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Practical Guide to Clinical Trial Accessibility: Making Trial Participation a Standard of Care

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OVERVIEW

Despite being a cornerstone of cancer treatment advancement, clinical trials remain inaccessible for many patients because of structural, socioeconomic, and systemic barriers. In this multidisciplinary perspective piece, stakeholders from patient advocacy, community oncology, industry, and academic medicine offer a collaborative overview of key challenges and practical solutions to improve trial accessibility. Patient advocates highlight the need to address language barriers, financial toxicity, and underrepresentation through community engagement and patient-centered trial design. Community oncologists underscore infrastructure limitations, generalist practice burdens, and misaligned trial offerings, calling for eligibility reform and cooperative trial models. Industry partners examine how overly restrictive criteria and inconsistent protocol practices hinder diversity and propose portfolio-wide strategies, such as protocol watch lists, for inclusive design. Academic oncologists focus on trial complexity, investigator burden, and limited generalizability, advocating for pragmatic and decentralized trial paradigms. Together, these perspectives underscore the shared responsibility across sectors to modernize clinical trial design, reduce access barriers, and ensure that trial participation becomes a standard and equitable component of cancer care.

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INTRODUCTION

Clinical trials are the foundation of advancing cancer treatment, yet they remain inaccessible and burdensome for many patients. There are multiple entities that influence the design of clinical trials, and each entity can additionally play a role in increasing accessibility and relieving burden. In recent years, the oncology community, including ASCO, the US Food and Drug Administration (FDA), and advocacy organizations, has increasingly prioritized the need to modernize trial eligibility, reduce patient burden, and enhance diversity in trial participation.^{1,2}

In this article, representatives from patient advocacy, industry, community practice, and academia have collaborated to offer commentary on ongoing challenges in making clinical trials more broadly available. Each group has offered strategies and potential solutions to these dilemmas, reflecting the unique lens and operational realities of their respective domains.

To synthesize these insights, [Figure 1](#) highlights the stakeholder-specific barriers identified by each group. By integrating these perspectives, we aim to provide a comprehensive and practical approach to refining the current clinical trial landscape and improving accessibility.

PERSPECTIVE OF THE PATIENT ADVOCATE

General Access Issues

A major obstacle in clinical trial participation is accessibility. Many patients, especially in community settings, lack access to trials, which are concentrated in academic centers.³ This creates disparities in participation, particularly among racially and socioeconomically marginalized groups.⁴ Moreover, trial protocols and consent forms are often available only in English, further excluding non-English speakers. Bias in health care also limits access. Some physicians may be hesitant to discuss trials with their patients because of misconceptions about risk, lack of institutional support, or fear of losing patients to larger institutions. Additionally, communities of color are underrepresented in clinical research because of both historical mistrust and systemic barriers that limit their inclusion.⁵ Expanding outreach, improving physician education, and providing multilingual resources can help address these inequities.

Participation and Navigation Issues

Even after enrollment, trial participation presents significant challenges. Financial toxicity is a major barrier as trials often require frequent travel, parking fees, unpaid work

PRACTICAL APPLICATIONS

- Enhancing clinical trial access requires collaboration across stakeholders, including patient advocates, community oncologists, industry sponsors, and academic investigators.
- Broadening eligibility criteria and decentralizing trial designs can improve the inclusion of real-world patient populations often underrepresented in research.
- Patient advocacy organizations play a critical role in improving education, trust, and trial navigation for historically excluded communities.
- Community oncology practices can increase accrual by leveraging infrastructure partnerships, using trial navigators, and prioritizing pragmatic trial models.
- Industry and academic sponsors can promote more inclusive research by aligning design with real-world care delivery.

time, and added childcare costs. Many patients cannot afford these costs, limiting participation to those with the financial means to absorb the burden. Sponsors should provide financial assistance for transportation, lodging, and other related expenses to ensure equitable access. Logistical challenges also arise from unmanageable testing and treatment schedules. Many trials require frequent hospital visits for scans, blood draws, and treatment infusions, which can be physically and emotionally exhausting. Decentralized clinical trials (DCTs; discussed subsequently) would help alleviate this burden. Telemedicine and digital health tools could further streamline participation, making trials more convenient and patient friendly.

Trial Design and Outputs

Clinical trial design must evolve to prioritize patient-centered outcomes. Traditional end points do not always capture what matters most to patients, including quality of life, treatment tolerability, and the ability to maintain daily activities. Future trials must increasingly incorporate patient-reported outcomes to ensure that new treatments improve not just survival but also overall well-being.⁶ Additionally, trial results should be analyzed with greater granularity. Tracking outcomes separately for underrepresented populations, such as people of color, or for patients with atypical responses to treatment would provide more meaningful insights into how different populations respond to treatment. This could help refine future trial designs and ensure that treatments are effective for all patients.

The Role of Patients and Advocacy Organizations

Patients and advocacy organizations play a crucial role in improving trial accessibility, education, and participation. They can educate patients, address misconceptions, and provide support throughout the trial process. They can also assist in recruitment and retention efforts by acting as trusted sources of information within patient communities. Moreover, patients themselves must have a voice in shaping clinical trial design. Engaging patients in the development of trial protocols ensures that trials reflect real-world patient needs. Patient input can help simplify consent forms, reduce unnecessary procedures, and make trials more patient friendly overall.

PERSPECTIVE OF THE COMMUNITY ONCOLOGIST

Defining Community Oncology

Community-based oncology practices play a critical role in delivering cancer care to patients close to home. Although many research advancements take place in academic centers, most patients receive cancer care in the community setting. Despite prior studies revealing that more than 70% of patients are willing to participate in clinical trials, fewer than 5% ultimately enroll.⁷

The definition of what represents a community oncologist is evolving. Decades ago, there was a binary distinction between academic medical centers and physician-owned practices. Now, many self-described community oncologists are employed by major academic centers or larger health care entities. Running clinical trials requires not only scientific collaboration but also operational infrastructure to support care delivery, regardless of ownership. For the oncology community to continue to improve care, it is vital that clinical trials are accessible to patients in any setting. There are specific challenges to implementing clinical trials in a community practice. Key barriers include oncologists who are more likely to be generalists, limited economies of scale to support robust clinical trial infrastructure, a lack of appropriate trials tailored to community settings, and eligibility issues when enrolling unselected patient populations.

Accrual at Community Centers: Weighing the Benefits

Most academic oncologists are single-disease specialists. By focusing on one disease type, they have more awareness and insight into which trials are appropriate for patients with specific conditions or those whose disease harbors a certain pathogenic mutation. By contrast, generalists in a community setting manage a broad range of cancers across diverse patient populations. In the context of a busy clinic without a dedicated research enterprise, managing clinical trial eligibility criteria, educating patients about a trial, and discussing indirect costs poses a significant challenge for community-based practitioners.^{8,9}

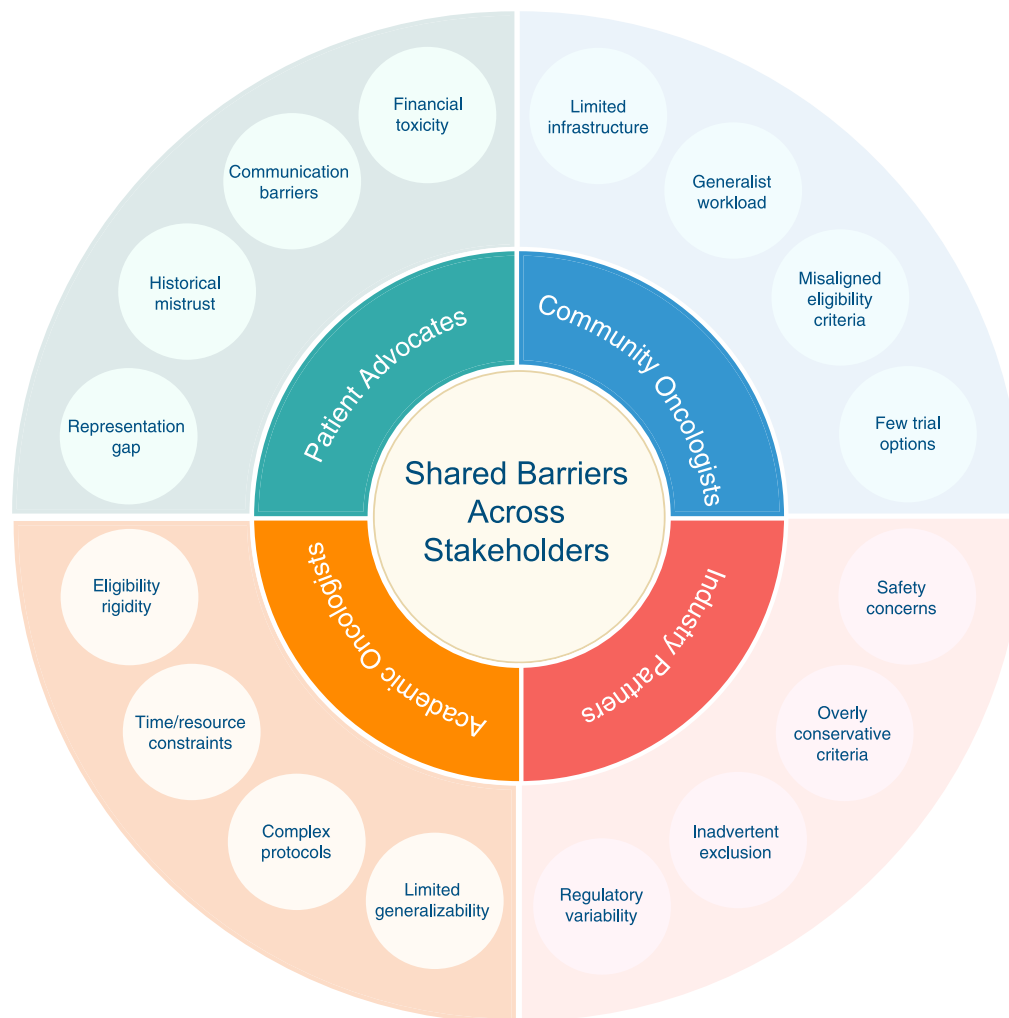


FIG 1. Barriers to clinical trial access identified by four key stakeholder groups: patient advocates, community oncologists, industry partners, and academic oncologists. Each quadrant reflects stakeholder-specific challenges that contribute to underenrollment or limited accessibility in oncology clinical research (created in [BioRender.com](https://www.biorender.com). Ebrahimi [2025]).

Community practices face financial pressure and operational costs more directly than larger organizations. Offering salaries to research staff can be cost prohibitive without economies of scale. Running trials effectively and safely, while ensuring regulatory compliance, requires resources and infrastructure. These demands are difficult to manage in small practices and often need to be shared across a group of practices or between a large owner and its satellite locations.

Most early-phase clinical trial enrollees receive treatment at academic centers where complex care can be provided in specialized phase I units. Opening trials appropriate for community infusion units, where staff often manage multiple roles, presents logistical challenges. These challenges are compounded by a shift away from large cooperative group phase III trials toward industry-sponsored early-phase trials, which are less accessible to community sites.

These trials have stricter eligibility requirements, have fewer slots for patients, and often require more advanced laboratory and imaging than what many community sites may not be able to accommodate. Studies show that the number of industry-sponsored trials available to community oncology centers is far below what is seen in academic and larger sites.¹⁰ Previous studies demonstrated that frontline and early-phase trials are less commonly available in community settings.¹¹ Selecting trials appropriate for community practices requires careful consideration of local patient needs and available staffing resources.

Patients receiving care in the community often face challenges to enrollment, as they are not part of a highly selected group of individuals like those seen at academic medical centers. Health literacy and social determinants of health can play a pivotal role in discussing clinical trials with eligible patients. Many patients seek care closer to home because

TABLE 1. Summary of Barriers and Aligned Solutions by Stakeholder Group

Stakeholder Group	Challenges	Proposed Solutions
Patient advocates	Linguistic barriers	Develop multilingual resources and streamline informed consent materials
	Financial toxicity from travel, time off work, and caregiving responsibilities	Provide funding support for transportation, lodging, and dependent care
	Historical mistrust and structural inequities	Engage trusted community leaders and advocacy groups to build trust and improve outreach
	Lack of patient involvement in trial design and limited relevance and acceptability	Integrate patient input into protocol development to ensure alignment with patient priorities
Community oncologists	Limited infrastructure and staffing to support clinical trial operations	Develop shared research resources through partnerships or networks
	Broad generalist scope limits time and focus on trial eligibility and protocol familiarity	Provide decision support tools and dedicated research staff
	Eligibility criteria often exclude patients with comorbidities common in community populations	Broaden eligibility criteria to better reflect real-world patient populations
	Financial constraints make it difficult to sustain research programs without economies of scale	Collaborate with larger institutions or sponsors
Industry partners	Overly restrictive eligibility criteria	Adopt inclusive trial design practices, including ASCO/FCR recommendations
	Protocol designs can inadvertently exclude specific subgroups	Use internal watch lists to aid in protocol writing and review
	Concerns about early-phase safety can lead to overly conservative eligibility criteria that remain in later phases	Use accumulated safety data from prior phases to broaden eligibility criteria in later-phase trials
	Global regulatory variability complicates protocol harmonization	Collaborate with regulators across regions to align on inclusive trial frameworks
Academic oncologists	Trial designs are often complex and resource intensive, limiting scalability and feasibility	Promote pragmatic and simplified designs that reduce data collection and procedural burden
	ISTs require significant time, funding, and administrative effort	Allocate protected time and provide institutional support for trial development and oversight
	Strict eligibility criteria limit generalizability to real-world patients	Integrate inclusive eligibility standards
	High documentation and safety monitoring burdens slow implementation	Streamline trial operations using risk-based monitoring and minimal data collection frameworks
	Limited trial accessibility beyond academic centers hinders equitable participation	Expand use of decentralized and hybrid models

Abbreviations: FCR, Friends of Cancer Research; ISTs, investigator-sponsored trials.

they are older or have comorbidities leading to ineligibility for trials.^{12,13}

Strategies to Enhance Accrual in Community Centers

Strategies to improve clinical trial enrollment in the community setting include enhancing general patient education about clinical trials, fostering collaboration among physicians and their employers to support research infrastructure, and opening trials that are feasible and appropriate for a

community setting. Additionally, improving screening processes and engaging study sponsors to broaden eligibility criteria to include real-world patients may increase participation.

Patient education about clinical trials in both early disease and after multiple lines of standard therapy is essential. A qualitative analysis of medical oncologists (24 academic and 20 from the community) demonstrated key differences in perceived barriers to accrual. Community oncologists

were more likely to report that patient understanding and caregiver burden as obstacles, compared with academic oncologists.¹⁴

Community physicians need stronger infrastructure to improve patient enrollment in clinical trials. Effective patient screening for eligibility can increase efficiency, facilitate trial-related discussions during clinical visits, and improve care coordination, including follow-up scheduling and toxicity monitoring.¹⁵

Partnerships between community practices and larger health care organizations or research networks have strengthened the infrastructure for the National Cancer Institute (NCI) Community Clinical Oncology Program (CCOP).¹⁶ This partnership between research institutions and community-based physicians enabled phase III cancer prevention, control, and treatment trials to be conducted in community-based settings. In 2007, the NCI expanded its community-targeted efforts by launching the NCI Community Cancer Centers Program (NCCCP), a public-private partnership with 21 community hospitals in 16 states. The program aimed to expand access and improve cancer care by building infrastructure for basic, clinical, and population-based research. This program helped increase the availability of phase III trials, provided the necessary infrastructure, and increased patient accrual at the NCCCP sites.^{17,18}

In 2014, the NCI Community Oncology Research Program (NCORP) replaced the CCOP and NCCCP programs in community-based settings. These programs serve as successful models of academic-community partnership, demonstrated by increased trial enrollment, and their structure can inform future industry-sponsored and investigator-initiated trials. Finally, expanding eligibility criteria to better reflect patients seen in community practices would allow more real-world patients to enroll in trials.¹⁹ NCORP respondents listed broadening eligibility as the top solution for improving clinical trial accrual.^{20,21}

PERSPECTIVE OF THE INDUSTRY PARTNER

Representation in Clinical Trials

Clinical trial populations should be representative of the intended-use population to facilitate understanding of variability in drug exposure, safety, and efficacy. This also helps develop confidence in dosing while improving the generalizability and external validity of research findings.²² Discussions on improving representation within clinical research often focus on the patient (socioeconomic disparities, language and cultural barriers, knowledge, and trust) and site level (capabilities, resources, and training).²³ While reducing patient and site barriers is critical, efforts in these areas are likely to fail to improve representation in line with disease prevalence and incidence if sponsors inadvertently prevent particular subpopulations from being randomly assigned because of protocol design.

Clinical trials that enroll only a narrow, highly selected subset of study participants may not adequately inform the broader patient population in whom the drug will ultimately be used once regulatory authorities approve it. Enrolling both early and late-phase trial cohorts that are more representative of the intended-treatment population has been identified as an important goal in oncology trials for more than 30 years. Organizations such as ASCO and the Friends of Cancer Research (FCR) have supported this through developing statements in support of broadening trial eligibility criteria.^{24,25} Patients with CNS metastases, adolescents and the elderly, patients with HIV, individuals with low-functioning performance status (often because of the underlying neoplasm itself), and patients with common comorbidities or minor laboratory abnormalities are often unnecessarily excluded from participation because of overly restrictive trial eligibility criteria.²⁶ Given that the generalizability of a study is influenced by the degree to which study participants mirror the characteristics of the patient population for whom the intervention was developed, maximizing generalizability should be an important goal for all stakeholders.

There are several reasons why oncology clinical trials continue to have restrictive eligibility criteria. In early phases, when there is limited knowledge of the safety profile, an overly conservative approach to safety can lead teams to be too restrictive in terms of the patient population to be included in the trial. In later phases, this conservatism within eligibility criteria can perpetuate, transferring from protocol to protocol despite improved knowledge of the safety profile. Trials are also increasingly complex, and even early-phase trials are now routinely conducted in multiple countries and assessed by numerous regulatory bodies that may be perceived to have different views on eligibility criteria.

Case Study of Eligibility Modification

A real-world case study may help illustrate some of the potential benefits of designing trials that enroll a more representative patient population. An early-phase study of a novel agent was developed for patients with a common neoplasm. Preclinical testing indicated that the study drug was likely to be primarily hepatically metabolized. The median age of the study population was in the 70s, and in this cohort, a reduced estimated glomerular filtration rate (eGFR) is common, especially in Black patients.²⁷ Working collaboratively with regulators and consistent with FDA guidance to industry, Institutional Review Boards, and clinical investigators about abnormal laboratory values and organ dysfunction in cancer clinical trial eligibility, the trial protocol proposed allowing enrollment of patients with a moderately reduced eGFR level below the typical threshold of >60 mL/min/1.73 m². Investigational New Drug clearance was achieved, and a proportion of enrolled patients in the trial had eGFRs in the 50–60 mL/min range. These patients achieved clinical benefit with no apparent adverse effects from their mild laboratory abnormality. If the study team

had retained the original threshold of >60 mL/min, these patients would not have been eligible for the study.

The FDA and ethics committees worldwide recommend that sponsors critically examine eligibility criteria for clinical trials as a method to facilitate the enrollment of a representative population that reflects those who may use the medicine if approved. Sponsors aiming to do this consistently across a large portfolio can benefit from tools, processes, and safeguards to avoid unnecessary or inadvertent exclusion of subpopulations.

Beyond individual trial designs, broader enterprise-level strategies can also help institutionalize inclusive eligibility practices. One sponsor was looking to ensure an inclusive clinical trial protocol design across multiple therapeutic areas at the enterprise level. A centralized team was formed and worked with clinical development physicians and scientists to create disease-specific eligibility criteria watch lists containing criteria that may inadvertently prevent the random assignment of subpopulations. These lists comprised of three sections: (1) principles of inclusive design, such as writing the criteria anew each time; (2) common subgroup exclusions, such as pregnancy, lactation, and HIV status; and (3) disease-specific laboratory values, clinical cutoffs, and related comorbidities. Trial teams were required to use the watch lists as tools to inform their protocol writing. The same lists are planned to be used retrospectively by protocol review committees to assess eligibility criteria. If a protocol contains criteria on a watch list, owing to safety or clinical end points, a detailed medical or clinical rationale is discussed and documented. This two-fold approach to standardizing the creation of eligibility criteria reduces the likelihood of protocols inadvertently excluding subpopulations. It also mitigates the variability introduced by personnel changes and provides a readily available resource and forum to evaluate overly conservative decision making. Importantly, discussions around potential subgroup exclusion at the protocol review stage provide an opportunity for clinical operations teams to factor the potential for low enrollment into feasibility and consider mitigations through site selection, engagement, and support.

PERSPECTIVE OF THE ACADEMIC ONCOLOGIST

Accrual at Academic Centers: Weighing the Benefits

Accrual to clinical trials is an expectation for many faculty members at academic centers. The term “physician-scientist” was traditionally used for individuals who did bench-to-bedside research but has now also come to encompass those with expertise in specific disease types and build clinical trial programs around these interests. The advantage of having clinical investigators positioned at academic centers includes the ability to build robust programs focused around individual diseases. Often times, these investigators are allocated protected time for trial development and oversight. Among the various types of trials

(investigator-sponsored, cooperative group, and industry), investigator-sponsored studies (ISTs) require the most significant effort. Curricula have been developed by ASCO and other organizations to aid investigators in skills such as protocol writing, consent generation, and trial oversight. Without appropriate education and adequate protected time (as offered by most academic centers), it is challenging to envision how investigators might develop effective IST programs.

For some time, efforts have been made to integrate community-based centers more optimally in research. Community-based centers are where most patients with cancer receive care in the United States. Careful selection of clinical trials to implement in this setting is of paramount importance. Trials that require intensive correlative studies or rigorous adverse event monitoring may be less ideal for most clinical practices. Such studies may also be paired with complex data collection, which requires significant staffing. Although it is challenging to generalize, cooperative group studies may be particularly well suited to community-based practices. These trials are often larger randomized phase II or phase III studies using therapeutic modalities. Although there are exceptions to the rule, the data collection requirements are more modest than most comparable industry-led clinical trials. A trade-off, however, is the lower budget that generally accompanies cooperative group studies. Of note, many cooperative groups are making specific efforts to develop pragmatic clinical trials that ease the regulatory and data burden of studies to an even greater extent (discussed subsequently).

Modernizing Eligibility

As emphasized by previous colleagues, a key element of trial development in oncology is the establishment of appropriate eligibility criteria. These criteria often reflect an intricate balance of science and safety. From a scientific perspective, contemporary studies may have increasingly complex screening requirements on the basis of disease biology. Genomic testing, assessment of circulating disease, and radiographic imaging using novel tracers represent just some of the new strategies that have been incorporated into patient selection. As these methods increase in complexity, the investigative community must consider the accessibility of these screening tools for these studies.

There has also been an evolution in safety criteria incorporated in oncology clinical trials. As noted previously, the ASCO-FCR guidance document provides key insights into how eligibility criteria may be refined, pooling the expertise of both investigators and patients. The ASCO-FCR recommendations have been assessed formally in the context of current studies for specific disease types. In renal cell carcinoma, a detailed exploration of 112 clinical trials showed that 74.1%, 53.6%, and 33.0% of studies excluded patients with HIV, hepatitis B virus (HBV)/hepatitis C virus (HCV) infections, and brain metastases, respectively.²⁸ A similar

analysis of trials in bladder cancer found that in 37 studies, HIV and HBV/HCV infections were exclusionary criteria in 89.2% and 56.8% of studies, respectively.²⁹ These analyses underscore the significant work that must be conducted to revise the trial design.

A New Generation of Studies

The US FDA launched Project Pragmatica in 2022 to “introduce functional efficiencies and enhance patient centrality by integrating aspects of clinical trials with real-world routine clinical practice through appropriate use of pragmatic design elements.”³⁰ A key example of this approach is the recently completed Southwest Oncology Group (SWOG) Pragmatica-Lung study, a randomized, phase III comparison of ramucirumab with pembrolizumab with standard-of-care therapy in patients with non–small cell lung cancer. The study explores the primary end point of overall survival.³¹ Eligibility criteria reflect a bare minimum, and data collection on the study is limited to several variables, including stage of disease, previous therapy, performance status, and vital status. While safety data are collected, only high-grade adverse events (grade 3 or 4) are recorded. The study was planned to accrue 800 patients over 24 months and closed 3 months ahead of the projected deadline.³² While pragmatic study designs do have many potential deficiencies (eg, lack of central scan review and absence of detailed biomarker work), they are well suited to answer some straightforward clinical questions.

Another novel trial design strategy that may ease regulatory and resource burden is the DCTs. Decentralized studies operate through a limited number of coordinating centers but engage patients from wide geographic catchment areas. A recent example of this is a phase I study assessing the role

of exercise in patients with localized prostate cancer ahead of prostatectomy, led by investigators at the Memorial Sloan Kettering Cancer Center.³³ In this study, patients consented to participate verbally, received exercise equipment and monitoring devices at their homes, and worked virtually with exercise physiologists throughout the conduct of the trial. Travel to the coordinating center was minimal, and clinician time required for study oversight was also limited.³⁴ Exercise assessment is but one of many examples of phenomena that can be explored through a decentralized design. As oncology centers expand to have regional and national footprints, DCTs may be of increasing utility. [Table 1](#) outlines a practical, stakeholder-aligned map of challenges and corresponding solutions across sectors.

CONCLUSION

Across four distinct groups (patient advocates, community oncologists, industry partners, and academic oncologists), multiple common themes emerge in the quest to increase trial accessibility. The inclusion of more representative trial populations in the clinical development of new therapies in oncology can lessen the risk of failure, decrease the time to trial completion, and reduce the likelihood of identifying a new safety signal in the postmarketing setting in a patient population that was not included or well represented in the development process.³⁵ In tandem with this, implementing novel trial paradigms (eg, pragmatic or decentralized designs) may alleviate the substantial regulatory burden and increase the ability of motivated patients to participate in clinical research. It is important to acknowledge that no single entity will be able to reform current issues with clinical trial design and implementation—it will require a concerted effort from all stakeholders, as reflected in this article, and as a shared priority for the oncology community moving forward.

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REFERENCES

- Kim ES, Uldrick TS, Schenkel C, et al: Continuing to broaden eligibility criteria to make clinical trials more representative and inclusive: ASCO-Friends of Cancer Research Joint Research Statement. *Clin Cancer Res* 27:2394-2399, 2021
- Cancer Clinical Trial Eligibility Criteria: Laboratory Values. Guidance for Industry, IRBs, and Clinical Investigators. FDA Guidance Documents 2024. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-laboratory-values>
- Ebrahimi H, Megally S, Plotkin E, et al: Barriers to clinical trial implementation among community care centers. *JAMA Netw Open* 7:e248739, 2024
- Murthy VH, Krumholz HM, Gross CP: Participation in cancer clinical trials: Race-sex-and age-based disparities. *JAMA* 291:2720-2726, 2004
- Rivers D, August EM, Sehovic I, et al: A systematic review of the factors influencing African Americans' participation in cancer clinical trials. *Contemp Clin Trials* 35:13-32, 2013
- Calvert M, Kyte D, Mercieca-Bebber R, et al: Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: The SPIRIT-PRO extension. *JAMA* 319:483-494, 2018
- Comis R, Miller J, Aldige C, et al: Public attitudes toward participation in cancer clinical trials. *J Clin Oncol* 21:830-835, 2003
- Wong A, Sun V, George K, et al: Barriers to participation in therapeutic clinical trials as perceived by community oncologists. *JCO Oncol Pract* 16:e849-e858, 2020
- Mahmud A, Zalay O, Springer A, et al: Barriers to participation in clinical trials: A physician survey. *Curr Oncol* 25:119-125, 2018
- Hamel L, Penner L, Albrecht TL, et al: Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. *Cancer Control* 23:327-337, 2016
- Sateren W, Trimble E, Abrams J, et al: How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *J Clin Oncol* 20:2109-2117, 2002
- Unger J, Cook E, Tai E, et al: The role of clinical trial participation in cancer research: Barriers, evidence, and strategies. *Am Soc Clin Oncol Educ Book* 35:185-198, 2016
- Unger J, Vaidya R, Hershman D, et al: Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. *J Natl Cancer Inst* 111:245-255, 2019
- Sedrak M, Mohile S, Sun V, et al: Barriers to clinical trial enrollment of older adults with cancer: A qualitative study of the perceptions of community and academic oncologists. *J Geriatr Oncol* 11:327-334, 2020
- Nightingale G, Burhenn P, Puts M, et al: Integrating nurses and allied health professionals in the care of older adults with cancer: A report from the International Society of Geriatric Oncology Nursing and Allied Health Interest Group. *J Geriatr Oncol* 11:187-190, 2020
- Minasian L, Carpenter W, Weiner B, et al: Translating research into evidence-based practice: The National Cancer Institute Community Clinical Oncology Program. *Cancer* 116:4440-4449, 2010
- Clauser S, Johnson M, O'Brien D, et al: Improving clinical research and cancer care delivery in community settings: Evaluating the NCI Community Cancer Centers Program. *Implement Sci* 4:63, 2009
- Copur M: Inadequate awareness of and participation in cancer clinical trials in the community oncology setting. *Oncology (Williston Park)* 33:54-57, 2019
- Minasian L, Unger J: What keeps patients out of clinical trials? *JCO Oncol Pract* 16:125-127, 2020
- Hopkins J, Braun-Inglis C, Guidice S, et al: Enrolling older adults onto National Cancer Institute-funded clinical trials in community oncology clinics: Barriers and solutions. *J Natl Cancer Inst Monogr* 2022:117-124, 2022
- Unger J, Hershman D, Fleury M, et al: Association of patient comorbid conditions with cancer clinical trial participation. *JAMA Oncol* 5:326-333, 2019
- Corneli A, Hanlen-Rosado E, McKenna K, et al: Enhancing diversity and inclusion in clinical trials. *Clin Pharmacol Ther* 113:489-499, 2023
- Yousafi S, Rangachari P, Holland ML: Barriers to recruitment and retention among underrepresented populations in cancer clinical trials: A qualitative study of the perspectives of clinical trial research coordinating staff at a cancer center. *J Healthc Leadersh* 16:427-441, 2024
- George SL: Reducing patient eligibility criteria in cancer clinical trials. *J Clin Oncol* 14:1364-1370, 1996
- Kim ES, Bruinooge SS, Roberts S, et al: Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. *J Clin Oncol* 35:3737-3744, 2017
- Beaver JA, Ison G, Pazdur R: Reevaluating eligibility criteria—Balancing patient protection and participation in oncology trials. *N Engl J Med* 376:1504-1505, 2017
- Derosé SF, Rutkowski MP, Crooks PW, et al: Racial differences in estimated GFR decline, ESRD, and mortality in an integrated health system. *Am J Kidney Dis* 62:236-244, 2013
- Castro DV, Prajapati SR, Feng M, et al: Assessment of eligibility criteria in renal cell carcinoma trials evaluating systemic therapy. *BJU Int* 133:297-304, 2024
- Mercier BD, Govindarajan A, Castro DV, et al: Eligibility criteria in advanced urothelial cancer clinical trials: An assessment of modernization and inclusion. *Cancer Med* 14:e70696, 2025
- Commissioner O of the. Project Pragmatica. FDA. <https://www.fda.gov/about-fda/oncology-center-excellence/project-pragmatica>
- Sankar K, Redman MW, Dragnev KH, et al: Pragmatism in cancer clinical trials. *Am Soc Clin Oncol Educ Book* 44:e100040, 2024
- Pragmatica-lung closes, PROSPECT-lung opens. SWOG. <https://www.swog.org/news-events/news/2024/12/13/pragmatica-lung-closes-prospect-lung-opens>
- Jones LW, Moskowitz CS, Lee CP, et al: Neoadjuvant exercise therapy in prostate cancer: A phase 1, decentralized nonrandomized controlled trial. *JAMA Oncol* 10:1187-1194, 2024
- Underwood WP, Michalski MG, Lee CP, et al: A digital, decentralized trial of exercise therapy in patients with cancer. *Npj Digit Med* 7:304, 2024
- Su Q, Cheng G, Huang J: A review of research on eligibility criteria for clinical trials. *Clin Exp Med* 23:1867-1879, 2023

Decoding Clinical Trials in Metastatic Breast Cancer: Practical Insights for Optimal Therapy Sequencing

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OVERVIEW

The art of sequencing therapy in the management of breast cancer is a multifaceted challenge that demands the careful integration of clinical trial data, real-world evidence, and individualized patient factors to guide treatment decisions. As the therapeutic landscape evolves rapidly with new agents and combinations, clinicians are confronted with critical decisions on how best to order treatments to maximize benefit, minimize toxicity, and preserve future options. For patients with estrogen receptor–positive (ER+) disease, this review discusses how emerging resistance patterns after cyclin-dependent kinase 4 and 6 inhibitors require careful re-evaluation of subsequent endocrine and targeted therapies, as well as chemotherapy, emphasizing the need for evidence-based strategies and ethical crossover designs in clinical trials. In addition, for both ER+ and ER– metastatic breast cancer (MBC) with nonoverexpressed human epidermal growth factor receptor 2 (HER2), this review highlights pivotal trials investigating antibody-drug conjugates (ADCs)—including trastuzumab deruxtecan, sacituzumab govitecan, and datopotamab deruxtecan—and the challenges related to control arm selection and crossover that may affect outcome interpretation. Finally, for patients with HER2–positive disease, the review explores first-line and maintenance strategies—including insights from landmark trials like CLEOPATRA and PATINA—and addresses the impact of brain metastases on sequencing decisions. By critically appraising current data and identifying gaps in biomarker-guided and sequencing-specific strategies, this review provides practical insights to inform clinical practice and optimize personalized treatment plans for patients with MBC.

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INTRODUCTION

Therapy sequencing in metastatic breast cancer (MBC) is challenging, requiring integration of clinical trial and real-world data, as well as individualized patient factors.¹ As the therapeutic landscape rapidly evolves, clinicians face critical decisions on how best to sequence treatments to maximize benefit, minimize toxicity, and preserve future options. This review offers practical insights into interpreting trial results for real-world applications, emphasizing a data-driven approach to personalized care. Key themes include sequencing challenges after cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i), where emerging resistance, specific targets, and subsequent treatment options require careful evaluation; the strategic placement of antibody-drug conjugates (ADCs), which have reshaped outcomes in all subtypes of MBC; and the evolving treatment paradigm in human epidermal growth factor receptor 2–positive (HER2+) disease, where the integration of targeted therapies and maintenance strategies plays a pivotal role.

CDK4/6i AND THEIR IMPACT ON TREATMENT PARADIGMS IN ENDOCRINE-SENSITIVE MBC

Timing of CDK4/6i: First- Versus Second-Line Strategies With Endocrine Therapy

Phase III trials demonstrated progression-free survival (PFS) benefits with CDK4/6i—palbociclib, ribociclib, and abemaciclib—in both first- and second-line MBC.¹ Overall survival (OS) significantly improved with ribociclib in combination with either an aromatase inhibitor (AI) or selective estrogen receptor modulators (MONALEESA-2, MONALEESA-7) and the selective estrogen receptor degrader (SERD) fulvestrant (MONALEESA-3) and abemaciclib plus fulvestrant (MONARCH-2).^{2–5} Notably, no OS benefit was seen with abemaciclib plus AI (MONARCH-3) or palbociclib with letrozole (PALOMA-2) or fulvestrant (PALOMA-3).^{6–8} Differing OS outcomes in these trials—with no OS improvement for palbociclib—raise questions about the comparability of the three agents.^{9,10} In this context, a US-based real-world study of 9,146 patients with estrogen

PRACTICAL APPLICATIONS

- Optimal therapy sequencing integrates clinical trial data, real-world evidence, and patient-specific factors to guide personalized treatment in metastatic breast cancer (MBC).
- The study highlights challenges in sequencing therapy after cyclin-dependent kinase 4 and 6 inhibitors, optimal antibody-drug conjugate placement for patients with estrogen receptor–positive (ER+) and ER– MBC, and tailored treatment strategies for human epidermal growth factor receptor 2–positive disease.
- Key challenges include biases from control arm selection, crossover design, and heterogeneous post-progression treatments, all of which may complicate interpretation of end points like overall survival and progression-free survival 2.
- Outcome interpretation may be further complicated by differences in pre- and post-treatment access across international study sites.
- Future practice should be shaped by sequencing-specific trials and biomarker integration, enabling more precise and personalized strategies.

receptor–positive (ER+)HER2– MBC receiving first-line AI plus CDK4/6i found no significant differences in OS among the three CDK4/6i.¹¹ A sensitivity analysis, including patients who initiated treatment in 2017 or later, also found no significant differences in OS between groups.¹¹

CDK4/6i can be added to AI or fulvestrant either in the first- or second-line setting.¹ However, first-line use has shown greater PFS improvements than second-line, and most guidelines recommend it as the preferred strategy.^{1,12} Yet, some patients may experience durable disease control with AI alone in the first line.¹³ Although crossover is ethically important when testing drugs earlier after later-line efficacy is established, only a few patients in the control arms of CDK4/6i-based first-line studies received a CDK4/6i in the second line.¹⁴

Within this framework, SONIA (phase III, N = 1,050) challenged the need for immediate CDK4/6i initiation with endocrine therapy (ET).⁹ The trial included pre- and postmenopausal women with ER+HER2– MBC, no previous systemic therapy for MBC, and no visceral crisis.⁹ Patients were randomly assigned to CDK4/6i plus AI in the first line or AI alone. Patients in the CDK4/6i-first group received fulvestrant on progression, whereas those in the AI-first group received CDK4/6i plus fulvestrant in the second line.⁹ The

primary end point was progression-free survival 2 (PFS2, time from the start of first-line therapy to progression on the second line).

The statistical method had an 89% power to detect the superiority of the CDK4/6i-first strategy over the CDK4/6i-second in PFS2. A clinically relevant difference was defined as a ≥ 3 -month median PFS2 improvement, with the lower bound of the 95% CI for the hazard ratio (HR) ≤ 0.65 . If superiority was not established, noninferiority was tested, with a noninferiority margin of 1.54 (reciprocal of 0.65).⁹

After a median follow-up of 37.3 months, the median PFS2 was 31.0 months in the CDK4/6i-first group and 26.8 months in the second-line group (HR, 0.87 [95% CI, 0.74 to 1.03]; $P = .10$). Superiority of the first-line CDK4/6i strategy was not established.⁹ Noninferiority testing showed that the second-line strategy was noninferior, with the upper limit of the 95% CI (1.35) within the noninferiority margin (1.54).⁹ The trial showed comparable quality of life (QoL) between groups, fewer adverse events with the CDK4/6i-second strategy, and lower costs.⁹

Some caveats should be noted for SONIA. First, while all three CDK4/6i were permitted, palbociclib dominated usage (91% in both strategies). Although differences exist between trials comparing drugs and those assessing sequencing like SONIA, the similar PFS across CDK4/6i in first- and second-line landmark trials suggests that a different distribution would unlikely alter progression rates. Second, since the start of SONIA, new targeted therapies including capivasertib, alpelisib, and, most recently, inavolisib—which improve PFS for patients with AKT pathway alterations and *PIK3CA* mutations—have entered clinical practice for ER+HER2– MBC.^{1,15–18} Finally, while in SONIA, the second-line approach showed noninferiority—with a shorter treatment duration and fewer associated toxicities—the prespecified margin of 1/0.65 may be too generous to exclude a clinically relevant outcome.⁹

The SONIA trial has not significantly affected global standard practice—especially in private payer-based systems—as it does not support up-front ET monotherapy for all patients while reserving CDK4/6i for second-line treatment.⁹ However, these results may offer evidence for prioritizing and allocating expensive treatments in national health care systems and may provide justification for using ET alone in selected frail patients where CDK4/6i could pose a concern.¹⁹

A key challenge remains the lack of robust biomarkers to identify patients who could benefit equally well from ET monotherapy. For now, the combination of ET and CDK4/6i remains the preferred first-line strategy in the United States. However, SONIA highlights the need for trials that optimize treatment sequencing with mandatory crossover when evaluating a cancer drug already proven to be effective in a later line of therapy and then tested in an earlier setting.¹⁴

Sequencing of Therapy Post-CDK4/6 Inhibition

Strategic Sequencing Insights From CDK4/6i-Post-CDK4/6i Clinical Trials

The optimal treatment sequence for ER+HER2– MBC after first-line ET with a CDK4/6i remains unclear.^{1,20} While postMONARCH and MAINTAIN suggest that continuing CDK4/6i beyond progression is feasible, most patients in these trials received first-line palbociclib, potentially limiting the applicability of these findings to current practice where ribociclib may be more common.¹ Notably, in post-MONARCH, the small subset pretreated with ribociclib did not appear to benefit.²¹

In greater detail, in MAINTAIN (phase II, N = 120), patients progressing on previous CDK4/6i and ET were randomly assigned to ribociclib or placebo, with ET switch.²² The ribociclib-ET arm showed a significant improvement in median PFS (mPFS, primary end point, 5.29 v 2.76 months, HR, 0.57 [95% CI, 0.39 to 0.95]; $P = .006$).²² At 12 months, the PFS rate was 24.6% with ribociclib, compared with 7.4% with placebo.²² PACE (phase II, N = 220) randomly assigned patients to receive palbociclib with fulvestrant, placebo with fulvestrant, or a triplet regimen of palbociclib, fulvestrant, and avelumab.²³ Although PACE enrolled a population similar to MAINTAIN (approximately 90% with previous palbociclib exposure and 76% with CDK4/6i use >12 months), it demonstrated no benefit of continuing palbociclib after progression on a CDK4/6i.²³ The mPFS was 4.6 months in the experimental arm compared with 4.8 months in the control arm (HR, 1.11 [95% CI, 0.79 to 1.55]; $P = .62$). In PALMIRA (phase II, N = 198), continuing palbociclib with a different ET after progression on first-line palbociclib plus ET did not improve PFS compared with ET alone. However, the 6-month clinical benefit rate was higher in the combination arm (41.9% v 27.4%).²⁴ Finally, postMONARCH (phase III, N = 368) randomly assigned patients to fulvestrant plus abemaciclib/placebo after either progression on a CDK4/6i plus AI for MBC or recurrence on/after adjuvant CDK4/6i plus ET. The 6-month investigator-assessed PFS (primary end point) was 50% versus 37%, whereas the mPFS was 6.0 months in the experimental arm versus 5.3 in the control arm (HR, 0.73 [95% CI, 0.57 to 0.95]; $P = .02$).²¹

Key trials evaluating CDK4/6i-based combinations after previous CDK4/6i and ET are described in Table 1. Exploratory biomarker analyses showed that *ESR1* and *PIK3CA* mutations were linked to reduced benefit from CDK4/6i combinations in TRINITI-1 (ribociclib, everolimus, exemestane) and MAINTAIN (ribociclib-based regimens).^{22,25} By contrast, PACE found that *ESR1* and *PIK3CA* mutations are associated with improved outcomes in the palbociclib arm.²³ Biomarker data for PALMIRA, ELAINE-II, and postMONARCH are pending; encouraging ELAINE-I (phase II, N = 103) data showed that lasofoxifene monotherapy reduced *ESR1* minor allele frequency more than fulvestrant, whereas postMONARCH documented consistent benefits from

abemaciclib combinations across genomic subgroups, including *ESR1* and *PIK3CA* mutations.²¹

Elacestrant and Positioning of Oral SERDs in the Treatment Landscape

Although some patients may benefit from continuing CDK4/6i, second-line treatment after progression is largely guided by genomic testing.¹ The SERD elacestrant is approved for *ESR1*-mutated (*ESR1m*) ER+HER2– MBC after ≥1 previous ET(s), based on EMERALD (phase III, N = 477), which showed improved 6- and 12-month PFS compared with investigator's ET choice (41% v 19%; 26.8% v 8.2%; mPFS 3.8 v 1.9 months, HR, 0.55 [95% CI, 0.39 to 0.77]; $P = .0005$), though without superior PFS in patients without circulating tumor (ct)DNA-detectable *ESR1m* (HR, 0.86 [95% CI, 0.63 to 1.19]; $P = .308$).^{26,27} Eligible patients had received 1–2 lines of ET for MBC and previous CDK4/6i with fulvestrant or AI. A maximum of one previous chemotherapy (ChT) for MBC was permitted. The primary end point was PFS in the intention-to-treat (ITT) population and in the *ESR1m* subset, addressing a known resistance mechanism under ET (Table 2).²⁸

However, the modest mPFS improvement in *ESR1m* (<2 months), lack of OS benefit in the final analysis, and suboptimal control raised questions. Despite the modest mPFS benefit, PFS survival curves, including the *ESR1m* subset, showed early drops—indicating additional ET resistance mechanisms beyond *ESR1m* (present in 47.8% of patients)—followed by later separation, likely reflecting a more ET-sensitive subgroup.²⁶ In this mixed ET-sensitive and ET-resistant population, the HR may better capture treatment outcomes than the small differences in mPFS.

EMERALD's control arm was limited to four options: fulvestrant (69%) and the AIs anastrozole, letrozole, and exemestane (31%). This design allowed suboptimal choices in some cases. For instance, patients previously treated with a CDK4/6i and fulvestrant should not receive fulvestrant again at progression. Similarly, those treated with a CDK4/6i should not receive AI monotherapy at progression. Patients progressing after both an AI and fulvestrant should also not receive the same therapy that failed.²⁹ Within the subset of 239 patients treated with elacestrant and compared with the 165 receiving fulvestrant control in EMERALD, the HR for PFS was 0.68 (95% CI, 0.52 to 0.90, $P = .0049$), with 12-month PFS rates of 22.3% versus 10.2%, respectively.²⁶ In *ESR1m*, the HR for PFS was 0.50 (95% CI, 0.34 to 0.74, $P = .0005$), with 12-month PFS rates of 26.8% versus 8.4%. A subanalysis that excluded six patients pretreated with fulvestrant before receiving it again in the study favored elacestrant over ET in both the ITT and *ESR1m* cohorts (mPFS 2.8 v 1.9 and 3.8 v 1.9 months, respectively; 12-month PFS 22.3% v 9.5% and 26.8% v 8.3%, respectively).²⁶ However, only comparisons with the investigator's choice ET were shown, leaving it unclear whether elacestrant is superior to fulvestrant in fulvestrant-naïve patients.²⁶

TABLE 1. Key Prospective Clinical Trials Evaluating CDK4/6 Inhibitor–Based Combinations After Previous Treatment With CDK4/6 Inhibitors and Endocrine Therapy

Characteristic	TRINITI-1	MAINTAIN	postMONARCH	PACE	PALMIRA	ELAINE II
Trial phase	I/II	II	III	II	II	II
Reporting year	2021	2022	2024	2023	2023	2023
Study population	ER+HER2– MBC, PD on 1-2 previous CDK4/6i + ET, 0-1 ChT lines	ER+HER2– MBC, PD on 1 previous CDK4/6i + ET, 0-1 ChT lines	ER+HER2– MBC, PD on 1L previous CDK4/6i + AI. No other previous tx for MBC	ER+HER2– MBC, PD on 1 previous CDK4/6i + AI, up to 2 previous ET lines, 0-1 ChT lines	ER+HER2– MBC, PD on 1L palbociclib + ET but CR/PR/SD ≥24 weeks, or recurrence on ≥12 months adjuvant palbociclib; no previous ChT for MBC	ER+HER2– MBC, <i>ESR1</i> m, PD on ET with or without CDK4/6i; previous ChT for MBC allowed
Sample size	96	120	368	220	198	29
First CDK4/6i	Palbociclib (100%), ribociclib (13%)	Palbociclib (86%), ribociclib (12%), abemaciclib (2%)	Palbociclib (59%), ribociclib (33%), abemaciclib (8%)	Palbociclib (91%), ribociclib (5%), abemaciclib (4%), unknown (1%)	Palbociclib (100%)	28/29 patients received 1-3 previous CDK4/6i: Palbociclib (90%), abemaciclib (14%), ribociclib (7%), unknown (3%)
Second CDK4/6i	Ribociclib	Ribociclib	Abemaciclib	Palbociclib	Palbociclib	Abemaciclib
Partner drug to second CDK4/6i	Everolimus + exemestane	ET, different from first-line ET	Fulvestrant	Fulvestrant with or without avelumab	ET, different from 1L ET (letrozole or fulvestrant)	Lasofoxifene
Control arm	NA (single arm)	Alternate ET + placebo	Fulvestrant + placebo	Fulvestrant monotox	Alternate ET alone	NA (single arm)
mPFS of second CDK4/6i combination	5.7 months. CBR week 24 (primary end point), 41.1% (95% CI: 31.1-51.6)	5.29 (exp.) v 2.76 months (ctrl.) (HR, 0.57 [95% CI, 0.39 to 0.95]; <i>P</i> = .006)	6.0 (exp.) v 5.3 months (ctrl.; HR, 0.73 [95% CI, 0.57 to 0.95]; <i>P</i> = .02)	4.8 (fulvestrant monotox) v 4.6 months (doublet) (HR, 1.11 [90% CI, 0.79 to 1.55]; <i>P</i> = .62), 9.1 months (triplet) (HR v monotox, 0.75 [90% CI, 0.50 to 1.12]; <i>P</i> = .23)	4.2 (exp.) v 3.6 (ctrl.) months (HR, 1.01 [95% CI, 0.78 to 1.30]; <i>P</i> = .96)	13.9 months (95% CI, 7.9 to NE)
Explored biomarkers	<i>ESR1</i> m and <i>PIK3CA</i> m a/w decreased benefit from combo	Baseline ctDNA-detected <i>ESR1</i> m a/w decreased benefit from the exp. arm	Not yet available. Consistent effect across baseline <i>ESR1</i> m and <i>PIK3CA</i> m groups	Baseline ctDNA-detected <i>ESR1</i> m and <i>PIK3CA</i> m a/w benefit in the palbociclib arm	Not yet available	Not yet available. Combo a/w decreased <i>ESR1</i> MAF in 21 of 26 patients

Abbreviations: 1L, first-line; a/w, associated with; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; combo, combination; CR, complete response; ctDNA, circulating tumor DNA; ctrl., control; ER, estrogen receptor; *ESR1*m, estrogen receptor gene one mutant; ET, endocrine therapy; exp., experimental; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MAF, mutation allele frequency; MBC, metastatic breast cancer; monotox, monotherapy; mPFS, median progression-free survival; NA, not applicable; NE, not evaluable; PD, progression of disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PIK3CA*m, *PIK3CA* mutations; PR, partial response; SD, stable disease; tx, therapy.

TABLE 2. Key Prospective Clinical Trials Evaluating Oral Selective Estrogen Receptor Degraders in ER+HER2– MBC

Characteristic	EMERALD	SERENA-2	AMEERA-3	acELERA	EMBER-3
Treatment	Elacestrant	Camizestrant	Amcenestrant	Giredestrant	Imlunestrant with or without abemaciclib
Control arm	Fulvestrant (165/238, 69%) or AI (73/238, 31%)	Fulvestrant (73, 100%)	Fulvestrant (89.8%), AI (6.8%), or tamoxifen (3.4%)	Fulvestrant (75%) or AI (25%)	Fulvestrant or exemestane
Phase	III (N = 477)	II (N = 240)	II (N = 290)	II (N = 303)	III (N = 874)
Patient population	Men or postmenopausal women	Postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)	Men or postmenopausal women
Primary end point	PFS in the overall population and in <i>ESR1</i> m	PFS	PFS	PFS	PFS, imlunestrant v standard ET in <i>ESR1</i> m and overall cohorts; PFS, imlunestrant-abemaciclib v imlunestrant in the overall cohort
<i>ESR1</i> m	115/239 (48%, elacestrant), 113/239 (47.2%, ctrl.)	29.7% (C75), 35.6% (C150), 47.9% (fulvestrant)	65/143 (45%, amcenestrant), 55/147 (37.4%, ctrl.)	51/151 (33.8%, giredestrant), 39/152 (25.7%, ctrl.)	138/331 (41.7%, imlunestrant), 67/213 (31.5%, imlunestrant-abemaciclib), 118/330 (35.8%, standard ET)
Previous CDK4/6i	Required (100%)	Allowed (51%)	Allowed (79%)	Allowed (42%)	Allowed (59% imlunestrant; 65% imlunestrant-abemaciclib)
Previous fulvestrant	Allowed (29.3% exp. v 31.5% ctrl.)	Not allowed	Allowed (10.4% exp. v 10.2% ctrl.)	Allowed (20% exp. v 18% ctrl.)	Not allowed
Previous ChT in MBC	Allowed (20.1% exp. v 24.4% ctrl.)	Allowed (C75, 21.6%; C150, 12.3%; ctrl., 26%)	Allowed (9.8% exp. v 12.9% ctrl.)	Allowed (31% exp. v 32% ctrl.)	Not allowed
Visceral disease	68.2% exp. v 71% ctrl.	58.1% (C75), 58.9% (C150), 58.9% (ctrl.)	63.6% exp. v 63.9% ctrl.	69% exp. v 68% ctrl.	41.7% imlunestrant, 55.9% imlunestrant-abemaciclib, 53.6% standard ET
Results (primary end point)	Positive (ITT: 6-month PFS: 34.3% v 20.4%; 12-month PFS: 22.3% v 9.4%; mPFS HR, 0.70 [95% CI, 0.55 to 0.88]; <i>P</i> = .002; <i>ESR1</i> m: 6-month PFS: 41% v 19%; 12-month PFS: 26.8% v 8.2%; HR, 0.55 [95% CI, 0.39 to 0.77]; <i>P</i> = .0005)	Positive (ITT: C75 mPFS: 7.2 months; C150 mPFS: 7.7 months; fulvestrant mPFS: 3.7 months; HR C75 v fulvestrant: 0.59 [90% CI, 0.42 to 0.82]; <i>P</i> = .017; HR C150 v fulvestrant: 0.64 [90% CI, 0.46 to 0.89]; <i>P</i> = .009)	Negative (mPFS: 3.6 v 3.7 months; stratified HR, 1.051 [95% CI, 0.789 to 1.4]; one-sided <i>P</i> = .643)	Negative (mPFS: 5.6 v 5.4 months; INV-PFS HR, 0.81 [95% CI, 0.60 to 1.10]; <i>P</i> = .1757)	Positive (mPFS imlunestrant v ET in <i>ESR1</i> m: 5.5 v 3.8 months [restricted mean survival time difference, 2.6 months; 95% CI, 1.2 to 3.9; <i>P</i> < .001]; mPFS imlunestrant v ET in ITT: 5.6 v 5.5 months; HR, 0.87 [95% CI, 0.72 to 1.04]; <i>P</i> = .12; mPFS imlunestrant-abemaciclib v imlunestrant in ITT: 9.4 v 5.5 months; HR, 0.57 [95% CI, 0.44 to 0.73]; <i>P</i> < .001)

NOTE. Adapted from the study by Corti C et al (2023).³²

Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; ChT, chemotherapy; ctrl., control arm; ER, estrogen receptor; *ESR1*m, estrogen receptor gene 1 mutant; ET, endocrine therapy; exp., experimental arm; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; INV, investigator-assessed; ITT, intention-to-treat; MBC, metastatic breast cancer; mPFS, median PFS; PFS, progression-free survival.

As a benchmark for fulvestrant performance post-CDK4/6i, with the understanding of its limitations, plasmaMATCH (phase IIa, N = 1,051; *ESR1m* cohort n = 84) data demonstrated that fulvestrant monotherapy in *ESR1m* patients yielded a mPFS of 2.2 months (95% CI, 1.8 to 3.6), with 8% (6 of 74) achieving partial response (median duration: 7 months) and 16% (12 of 74) showing clinical benefit.³⁰ In VERONICA (phase II, N = 103), post-CDK4/6i treatment with fulvestrant plus venetoclax (a B-cell lymphoma 2 inhibitor) versus fulvestrant alone showed a mPFS of 2.69 versus 1.94 months.³¹

Considerations on Oral SERDs in Combination With CDK4/6i

The data on CDK4/6i in the post-CDK4/6i setting and elacestrant's role in advancing oral SERDs could mark in the near future a shift from combining CDK4/6i with traditional ET—the first-line standard for ER+HER2– MBC—to combining them with oral SERDs in first-line therapy or after progression on previous CDK4/6i.^{1,32,33}

In this framework, EMBER-3 (phase III, N = 874; Table 2) evaluated imlunestrant, standard ET, or imlunestrant plus abemaciclib in patients with ER+HER2– MBC who recurred or progressed after AI with or without CDK4/6i.³⁴ Primary end points included PFS with imlunestrant versus standard ET in *ESR1m* and overall cohorts and PFS with imlunestrant-abemaciclib versus imlunestrant monotherapy in the overall cohort. The trial was positive, showing a mPFS of 5.5 versus 3.8 months for imlunestrant versus standard ET in *ESR1m* patients (restricted mean survival time difference, 2.6 months [95% CI, 1.2 to 3.9]; $P < .001$). No significant PFS benefit was observed for imlunestrant versus standard ET in the overall cohort (mPFS 5.6 v 5.5 months; HR, 0.87 [95% CI, 0.72 to 1.04]; $P = .12$). However, imlunestrant-abemaciclib showed superior mPFS compared with imlunestrant (9.4 v 5.5 months; HR, 0.57 [95% CI, 0.44 to 0.73]; $P < .001$).³⁴ Although EMBER-3 did not require previous CDK4/6i—unlike EMERALD and post-MONARCH—65% of patients in the imlunestrant-abemaciclib group had received one. The treatment effect (HR, 0.51) in this subgroup was consistent with that in the overall population, with a mPFS of 9.1 months.³⁴ However, the trial lacked a direct comparison between imlunestrant-abemaciclib and fulvestrant-abemaciclib, limiting conclusions about the relative and absolute benefits of this oral SERD in combination with a CDK4/6i.³⁴ If suboptimal control arm choices raised concerns for EMERALD, one might question whether fulvestrant or AI monotherapy is adequate in trials like EMBER-3, especially when evaluating doublet treatments such as imlunestrant-abemaciclib.³⁵ At publication, OS comparing imlunestrant-abemaciclib with imlunestrant monotherapy showed a HR of 1.34 (95% CI, 0.81 to 2.21), with 36 events in the combination arm versus 28 in the monotherapy group, each comprising 213 patients. This likely reflects immature data, and longer follow-up is needed to determine whether HR will decrease.³⁶

Finally, a press release reported a statistically significant and clinically meaningful improvement in PFS (primary end

point) in SERENA-6 (phase III, N = 315).³⁷ This trial investigates switching from an AI to the SERD camizestrant—while maintaining the same CDK4/6i—on detecting *ESR1* mutations in ctDNA before clinical progression on first-line therapy in ER+HER2– MBC.³⁸ This preprogression switch, echoing the early intervention strategy in PADA-1—switching from an AI plus palbociclib to fulvestrant plus palbociclib, which significantly prolonged PFS—may represent a paradigm shift.^{37,39} Consequently, key secondary end points—PFS2 and OS, which require longer follow-up—will be critical to determine whether early switching truly improves long-term outcomes.

OPTIMIZING ADC SEQUENCING IN ER– AND ENDOCRINE-REFRACTORY ER+ MBC

Currently, two ADCs are available for metastatic triple-negative breast cancer (mTNBC)—sacituzumab govitecan (SG) and trastuzumab deruxtecan (T-DXd) for HER2-low disease—and with datopotamab deruxtecan (Dato-DXd), three are available for ER+ MBC with nonoverexpressed HER2.^{40,41} In patients with pretreated mTNBC (HER2–0 or HER2-low), the efficacy of the topoisomerase I inhibitor-based TROP2-directed SG was compared with treatment of physician's choice (TPC) after ≥ 2 previous ChT lines, at least one for MBC. SG showed significant improvement in PFS and OS (HR, 0.41 and 0.51, respectively, in the final analysis).^{42,43} An exploratory analysis of 58 patients with ER-HER2-low MBC included in DESTINY-Breast04 showed a numerical improvement in PFS and OS with the topoisomerase I inhibitor-based HER2-targeted T-DXd compared with TPC (Table 3).^{1,43} For patients eligible for both TROP2- and HER2-targeted ADCs, it remains uncertain which should be administered first and whether sequential ADC therapy offers additional benefits.^{44–46}

Integrating ADCs and ChT in First-Line Treatment of Endocrine-Refractory ER+ MBC

For patients with ER+ MBC and nonoverexpressed HER2 who have exhausted ETs and become endocrine-refractory, the first cytotoxic option may be either traditional ChT (eg, capecitabine) or T-DXd. In DESTINY-Breast06 (phase III, N = 866), T-DXd achieved a mPFS of 13.2 versus 8.1 months with ChT in HER2-low (defined as immunohistochemistry 1+ or 2+/in situ hybridization nonamplified) patients (HR, 0.62 [95% CI, 0.52 to 0.75]; $P < .001$), with consistent results observed in the exploratory HER2-ultralow (ie, faint, incomplete membrane staining in $\leq 10\%$ tumor cells) group (mPFS of 13.2 v 8.3 months; HR, 0.78 [95% CI, 0.50 to 1.21]).^{41,47,48} Notably, patients who progressed within 6 months of first-line ET and CDK4/6i experienced a greater benefit, with a mPFS of 14.0 versus 6.5 months (HR, 0.38 [95% CI, 0.25 to 0.59]), compared with those with progression between 6 and 12 months (mPFS, 13.2 v 6.9 months; HR, 0.69 [95% CI, 0.43 to 1.12]) and those with progression after 12 months (mPFS, 12.9 v 8.2 months; HR, 0.67 [95% CI, 0.51 to 0.88]).⁴⁹

TABLE 3. Key Prospective Clinical Trials Supporting the Use of Antibody-Drug Conjugates in MBC With Nonoverexpressed HER2

Trial Name	ASCENT	Destiny-Breast04	TROPiCS-02	Destiny-Breast06	TROPION-Breast01
Drug name (experimental arm)	SG	T-DXd	SG	T-DXd	Dato-DXd
Target	TROP2	HER2	TROP2	HER2	TROP2
Linker	CL2A (cleavable via the disulfide bond in the reducing environment)	Tetrapeptide (cleavable by lysosomal enzymes)	CL2A (cleavable via the disulfide bond in the reducing environment)	Tetrapeptide (cleavable by lysosomal enzymes)	Valine-citrulline (cleavable by lysosomal enzymes)
Payload	SN-38 (TOPO1 inhibitor)	DXd (TOPO1 inhibitor)	SN-38 (TOPO1 inhibitor)	DXd (TOPO1 inhibitor)	DXd (TOPO1 inhibitor)
DAR	7.6:1	8:1	7.6:1	8:1	4:1
Phase (sample size)	III (468)	III (557; 494 ER+ and 63 ER−)	III (543)	III (866)	III (732)
Breast cancer subtype	TNBC	HER2-low (88.7% ER+; 11.3% TNBC)	ER+HER2−	ER+HER2−low or ER+HER2−ultralow	ER+HER2−
Patient population	PD ≥2 ChT lines for MBC, including taxane (any setting)	1-2 previous ChT lines for MBC	2-4 previous ChT lines for MBC (1 previous tx allowed if PD ≤12 months after (neo)adj tx). Must have received ≥1 taxane, CDK4/6i, and ET (any setting)	PD on ≥2 previous ET lines for MBC (1 previous ET line allowed if recurrence occurs within 24 months of adj ET or PD within 6 months of ET + CDK4/6i); no previous ChT for MBC	PD on ET, 1-2 previous ChT lines for MBC
Control arm	Single-agent ChT (eribulin, vinorelbine, capecitabine, gemcitabine)	Single-agent ChT (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel)	Single-agent ChT (eribulin, vinorelbine, capecitabine, or gemcitabine)	Single-agent ChT (capecitabine, nab-paclitaxel, or paclitaxel)	Single-agent ChT (eribulin, vinorelbine, capecitabine, gemcitabine)
Primary end point	PFS	PFS in the ER+ cohort	PFS	PFS in ER+HER2-low	PFS and OS
Results	mPFS 5.6 v 1.7 months; HR, 0.41; 95% CI, 0.32 to 0.52, <i>P</i> < .001 mOS 12.1 v 6.7 months; HR, 0.48; 95% CI, 0.38 to 0.59, <i>P</i> < .001	ER+: mPFS 10.1 v 5.4 months; HR, 0.51; 95% CI, 0.40 to 0.64, <i>P</i> < .001 ER+: mOS 23.9 v 17.5 months; HR, 0.64, 95% CI, 20.8 to 24.8, <i>P</i> = .003 ER− (subgroup analysis): mPFS 8.5 v 2.9 months; HR, 0.46; 95% CI, 0.24 to 0.89; mOS 18.2 v 8.3 months; HR, 0.48; 95% CI, 0.24 to 0.95	mPFS 5.5 v 4.0 months; HR: 0.66; 95% CI, 0.53 to 0.83; <i>P</i> = .0003 mOS 14.4 v 11.2; HR, 0.79; 95% CI, 0.65 to 0.96; <i>P</i> = .020	mPFS 13.2 v 8.1 months; HR, 0.62; 95% CI, 0.52 to 0.75; <i>P</i> < .001 mOS (approximately 40% maturity in HER2-low): HR, 0.83, 95% CI, 0.66 to 1.05 HER2-ultralow (exploratory): mPFS 13.2 v 8.3; HR, 0.78; 95% CI, 0.50 to 1.21	mPFS 6.9 v 4.9 months; HR, 0.63; 95% CI, 0.52 to 0.76; <i>P</i> < .0001 mOS: 18.6 v 18.3 months; HR, 1.01, 95% CI, 0.83 to 1.22. (post hoc) mOS adjusted for subsequent ADC therapy: 19.1 v 17.5 months; HR, 0.86, 95% CI, 0.70 to 1.06

Abbreviations: (neo)adj, (neo)adjuvant; ADC, antibody-drug conjugate; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; ChT, chemotherapy; DAR, drug-to-antibody ratio; Dato-DXd, datopotamab deruxtecan; DXd, deruxtecan; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; m, median; MBC, metastatic breast cancer; OS, overall survival; PD, progression of disease; PFS, progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; TOPO1, topoisomerase 1; TROP2, trophoblast cell surface antigen; tx, therapy.

Importantly, about 20.1% of patients in the TPC group within the HER2-low subgroup received T-DXd after treatment discontinuation, compared with 17.9% in the overall TPC population (HER2-low and HER2-ultralow). While optional (not mandatory) crossover is sometimes permitted in multinational trials with uneven access to novel drugs, its absence can obscure the investigational treatment's true effect on OS, which was only 40% mature at the data cutoff.⁴⁷ At present, T-DXd is an effective post-ET option. However, its higher toxicity compared with TPC, current absence of OS benefit, and lack of QoL data suggest that a one-size-fits-all T-DXd approach may not be optimal.

Optimizing ADCs in Subsequent-Line Therapy for Endocrine-Refractory ER+ MBC

After ≥ 1 previous line(s) of ChT, T-DXd is appropriate for patients with ER+HER2-low MBC who have not received it before as it significantly improves mPFS (10.1 v 5.4 months; HR, 0.51 [95% CI, 0.40 to 0.64]) and median OS (mOS, 23.9 v 17.5 months; HR, 0.64 [95% CI, 0.48 to 0.86]) compared with TPC as seen in DESTINY-Breast04 (phase III, N = 494).⁵⁰ Similarly, SG is approved for patients who have progressed on ≥ 1 previous ET(s), a taxane, a CDK4/6i in any setting, and 2-4 previous ChT regimens for MBC. This approval is based on TROPiCS-02 (phase III, N = 543), where SG improved mPFS (5.5 v 4.0 months; HR, 0.66 [95% CI, 0.53 to 0.83]) and mOS (14.4 v 11.2 months; HR, 0.79 [95% CI, 0.65 to 0.95]) compared with TPC.^{51,52}

Recently, in TROPION-Breast01 (phase III, N = 732), Dato-DXd—another topoisomerase I inhibitor-based TROP2-directed ADC—improved mPFS (primary end point; 6.9 v 4.9 months; HR, 0.63 [95% CI, 0.52 to 0.76]) versus TPC after previous ET and 1-2 lines of ChT, though without mOS benefit (coprimary end point, mOS: 18.6 v 18.3 months; HR, 1.01 [95% CI, 0.83 to 1.22]).⁵³ During TROPION-Breast01, the evolving treatment landscape—with approvals of ADCs like T-DXd and SG—created an imbalance in subsequent ADC use. Among 365 patients who received Dato-DXd, 12% (n = 45) later received an ADC (9% T-DXd, 4% SG, 1% both), compared with 24% (n = 88) in the TPC arm (22% T-DXd, 7% SG, 5% both).⁵³ A post hoc sensitivity analysis of OS adjusted for subsequent ADC therapy, using inverse probability censoring weighting, showed a mOS of 19.1 months in the experimental arm versus 17.5 months in the control arm (HR, 0.86 [95% CI, 0.70 to 1.06]).⁵³ In addition, PFS2 (11.7 v 10.4 months; HR, 0.76 [95% CI, 0.63 to 0.93]) and the time to first and second subsequent treatments (TFST: 8.0 v 5.2 months; HR, 0.58 [95% CI, 0.50 to 0.68] and TSST: 13.7 v 12.3 months; HR, 0.83 [95% CI, 0.70 to 0.98]) were extended in the Dato-DXd arm, indicating benefits beyond the first progression.⁵³ Finally, patient-reported outcomes showed delayed deterioration in Global Health Status/QoL, favoring Dato-DXd with 9.0 versus 4.8 months (HR, 0.76 [95% CI, 0.58 to 0.98]) in the ADC versus TPC arm.

Considering the three ADCs, DESTINY-Breast04 and TROPION-Breast01 had similar patient populations

regarding previous treatments. In this context, T-DXd showed a better PFS HR compared with Dato-DXd and improved OS, whereas in TROPiCS-02—a more pretreated population—the PFS HR was similar to that of Dato-DXd, with SG improving OS. Notably, at the time of TROPiCS-02, no other ADCs were approved, so immediate postprogression treatment with another ADC was not possible. A real-world study of 272 patients with ER+HER2- MBC previously treated with T-DXd found that those receiving ChT (capecitabine, eribulin, or a taxane) had longer PFS than those receiving SG ($P < .004$).⁵⁴ This finding may align with TROPION-PanTumor01, where Dato-DXd produced deep responses and favorable mPFS only in ADC-naïve patients.⁵⁵

In conclusion, until new biomarkers enable optimal treatment sequencing, Dato-DXd may be a viable option for ET-refractory ChT-pretreated ER+HER2- MBC. However, the significant PFS and OS improvements in DESTINY-Breast04 support T-DXd as the preferred ADC for pretreated HER2-low patients without contraindications. In this regard, the benefit of Dato-DXd after progression on T-DXd remains unknown, and no robust data directly compare Dato-DXd and SG as TROPiCS-02 involved more heavily pretreated patients.

Design Limitations in ADC Trials: Restricted Control Arms and Crossover Challenges

Beyond the discussed ADC placement issues, current trials have intrinsic limitations. Trofuse-010, a phase III, randomized, open-label trial evaluating the topoisomerase I inhibitor-based TROP2-targeted ADC sacituzumab tirumotecan (with or without pembrolizumab) versus TPC in ER+HER2- MBC, includes an ET-refractory population not ChT-pretreated (ClinicalTrials.gov identifier: [NCT06312176](https://clinicaltrials.gov/ct2/show/study?term=NCT06312176)). Although patients on ChT may crossover to receive SG on progression, the protocol excludes T-DXd from the control arm—since it was not approved for first-line ET-refractory patients at the time—allowing only paclitaxel, nab-paclitaxel, capecitabine, or liposomal doxorubicin.

Most of the discussed trials investigating ADCs in MBC have not allowed crossover, with the exception of ASCENT-03 and ASCENT-04, investigating SG versus TPC in patients with previously untreated PD-L1-negative (Combined Positive Score [CPS] < 10) mTNBC and investigating SG and pembrolizumab versus TPC and pembrolizumab in patients with untreated PD-L1-positive (CPS ≥ 10) mTNBC, respectively.

SEQUENCING OF THERAPIES IN HER2-POSITIVE MBC

First-Line Therapy Considerations

CLEOPATRA (phase III, N = 808) established the first-line standard for HER2+ MBC by adding pertuzumab to docetaxel and trastuzumab (THP), compared with placebo plus docetaxel and trastuzumab (THP), with ChT administered for at least six cycles.⁵⁶ The prespecified OS analysis showed

a mOS of 56.6 months versus 40.8 months (HR, 0.68 [95% CI, 0.56 to 0.84]; $P < .001$), and the 99-month follow-up confirmed these findings with a mOS of 57.1 versus 40.8 months (HR, 0.69 [95% CI, 0.58 to 0.82]) and 8-year OS rates of 37% versus 23% in the pertuzumab and control arms, respectively.⁵⁷

Although approximately 388 patients in CLEOPATRA were ER+, the trial did not allow ET alongside dual HER2 blockade. In triple-positive MBC (both hormone receptors and HER2-positive), standard practice adds ET to maintenance anti-HER2 treatment. PERTAIN (phase II, N = 258) supports this approach, showing improved PFS with trastuzumab plus an AI and pertuzumab (20.6 v 15.8 months; HR, 0.67 [95% CI, 0.50 to 0.90]) and a mOS of 60.2 versus 57.2 months (not statistically significant).⁵⁸ Notably, half of the patients received 18–24 weeks of induction taxane-based therapy before ET. In this subgroup, the mPFS was 16.9 months regardless of pertuzumab addition; however, among patients not receiving induction ChT, the mPFS was 26.6 months with pertuzumab versus 12.5 months without pertuzumab (unstratified HR, 0.68 [95% CI, 0.44 to 1.03]).⁵⁸

Preclinical data show that the cyclin D1-CDK4 axis is vital for initiating *ERBB2*-driven mammary carcinomas, that its persistent activity drives resistance to HER2 blockade, and that combined CDK4/6 and HER2 inhibition has synergistic antitumor effects in HER2+ breast cancer models.^{59–62}

Accordingly, palbociclib—already approved for ER+HER2–MBC—was evaluated in PATINA (phase III, N = 518) as an addition to anti-HER2 therapy (trastuzumab with or without pertuzumab) and ET versus anti-HER2 therapy, ET, and placebo for first-line maintenance after 6–8 induction cycles (including trastuzumab with or without pertuzumab and a taxane or vinorelbine). At a median follow-up of 52.6 months, the mPFS was 44.3 months in the experimental arm versus 29.1 months in the control arm (HR, 0.74 [95% CI, 0.58 to 0.94]), with 5-year OS rates of 74.3% versus 69.8% (HR, 0.86 [95% CI, 0.6 to 1.24]; mOS not reached), potentially setting a new standard of care.⁶³ While CLEOPATRA's limitation was the exclusion of ET despite some patients being hormone receptor-positive, PATINA's design—focusing on maintenance treatment and excluding early progressors—creates a more homogeneous group with potentially better outcomes but may limit generalizability by excluding patients with early treatment failure.⁶⁴

Optimizing Treatment Sequencing With T-DXd and Beyond

T-DXd improved survival compared with the antitubulin HER2-targeted trastuzumab emtansine (T-DM1) in pretreated HER2+ MBC and is now being compared with THP as first-line therapy in DESTINY-Breast09 (phase III).^{1,65} After previous HER2-based treatment in metastatic or (neo)adjuvant settings—with recurrence during or within 6 months of therapy—T-DXd significantly improved survival versus

T-DM1 in DESTINY-Breast03 (phase III, N = 524), establishing it as the preferred second-line regimen (PFS HR, 0.30 [95% CI, 0.24 to 0.38]; OS HR, 0.73 [95% CI, 0.56 to 0.94]).^{65,66}

Tailoring Second-Line Treatment in the Case of HER2+ Brain Metastases

Until recently, the optimal second-line regimen for brain metastases (BMs) was debated. In DESTINY-Breast03, only stable, pretreated BMs were allowed, excluding active lesions.⁶⁵ In HER2CLIMB, adding tucatinib (oral HER2 tyrosine kinase inhibitor [TKI]) to trastuzumab plus capecitabine in patients previously treated with HP and T-DM1—including those with stable or active BMs—improved mPFS and reduced the risk of new BMs, regardless of baseline BM status (HR, 0.52 [95% CI, 0.33 to 0.82]).^{67,68}

Among patients with active or treated stable BMs (47.5% of the study population), the tucatinib-based regimen improved mPFS (7.6 v 5.4 months; HR, 0.48 [95% CI, 0.34 to 0.69]),^{69,70} intracranial PFS (9.9 v 4.2 months; HR, 0.32 [95% CI, 0.22 to 0.48]),⁶⁷ and mOS (18.1 v 12.0 months; HR, 0.58 [95% CI, 0.40 to 0.85]). In a subgroup with active BMs and measurable intracranial disease at baseline (n = 75), the intracranial objective response rate (ORR) was 47.3% versus 20.0%.⁷⁰

Limited data for T-DXd in HER2+ MBC with active BMs had shown an intracranial ORR of 46.2% (95% CI, 19.2 to 74.9) in patients with asymptomatic untreated (n = 4) or progressing BMs after local therapy (n = 9) in DEBBRAH (phase II)⁷¹ and 73.3% (95% CI, 48.1 to 89.1) in patients with active BMs and no indication for immediate local therapy (N = 15) in TUXEDO-1 (phase II).⁷² A meta-analysis reported an intracranial ORR of 60.0% (95% CI, 48 to 72) with active BMs across 10 studies (N = 319).⁷³

Recently, DESTINY-Breast12 (phase IIb/IV; N = 504; BMs, n = 263 [stable, n = 157; active, n = 106]; no BMs, n = 241) was the largest prospective study to investigate T-DXd's intracranial activity in patients with HER2+ MBC and stable or active BMs who had received ≥ 1 previous anti-HER2 regimens (PFS, primary end point).⁷⁴ In the overall BM cohort, the 12-month PFS was 61.6% (95% CI, 54.9 to 67.6) and the 12-month CNS-PFS was 58.9% (95% CI, 51.9 to 65.3).⁷⁴ In the non-BM cohort, the ORR was 62.7% (95% CI, 56.5 to 68.8), demonstrating T-DXd's substantial and durable overall and intracranial activity (overall CNS-ORR: 71.7%; 62.3% in active BMs, including 82.6% in untreated and 50% in previously treated/progressing BMs), thereby supporting its use in patients with previously treated HER2+ MBC regardless of baseline BM status. HER2CLIMB04 (phase II, N = 70) will evaluate tucatinib plus T-DXd in patients with HER2+ MBC with or without BMs (stable, progressing, or untreated without the need for immediate local treatment; NCT04539938).

Based on current data, T-DXd is poised to be the preferred second-line treatment for HER2+ MBC, regardless of BMs, moving HER2CLIMB to third line. However, T-DXd's lung toxicity may necessitate alternative options. In addition, patients should also be informed about the risks of alopecia and the need for IV infusions. While the HER2CLIMB regimen may lead to more hand-foot syndrome and hair thinning, it is less associated with alopecia.

Predicting patient benefit will become crucial as new agents emerge and sequencing challenges increase. Real-world data suggest that while drugs like T-DXd maintain favorable activity in MBC, real-world PFS may be shorter than that in trials.⁷⁵⁻⁷⁷ Future approaches may use quantitative assays, which could more accurately evaluate HER2 and predict T-DXd benefits across the HER2 spectrum.^{78,79}

Treating Patients With HER2+ MBC After T-DXd Failure

With limited data after T-DXd progression, treatment decisions should consider patient characteristics (therapy response, tolerance, disease extent, BMs) and regimen toxicity. Third-line options and beyond include T-DM1 or tucatinib with capecitabine and trastuzumab (if not previously received) although none has been trial-tested post-T-DXd failure.^{1,80-82}

Although crossover was not planned in DESTINY-Breast03, patients received various systemic therapies after progression, which varied by country based on drug approval status. For example, in the T-DM1 group, 48.0% received HER2-directed TKIs and 11.6% received other new HER2-targeted agents, potentially affecting OS.⁶⁶ Ongoing real-world

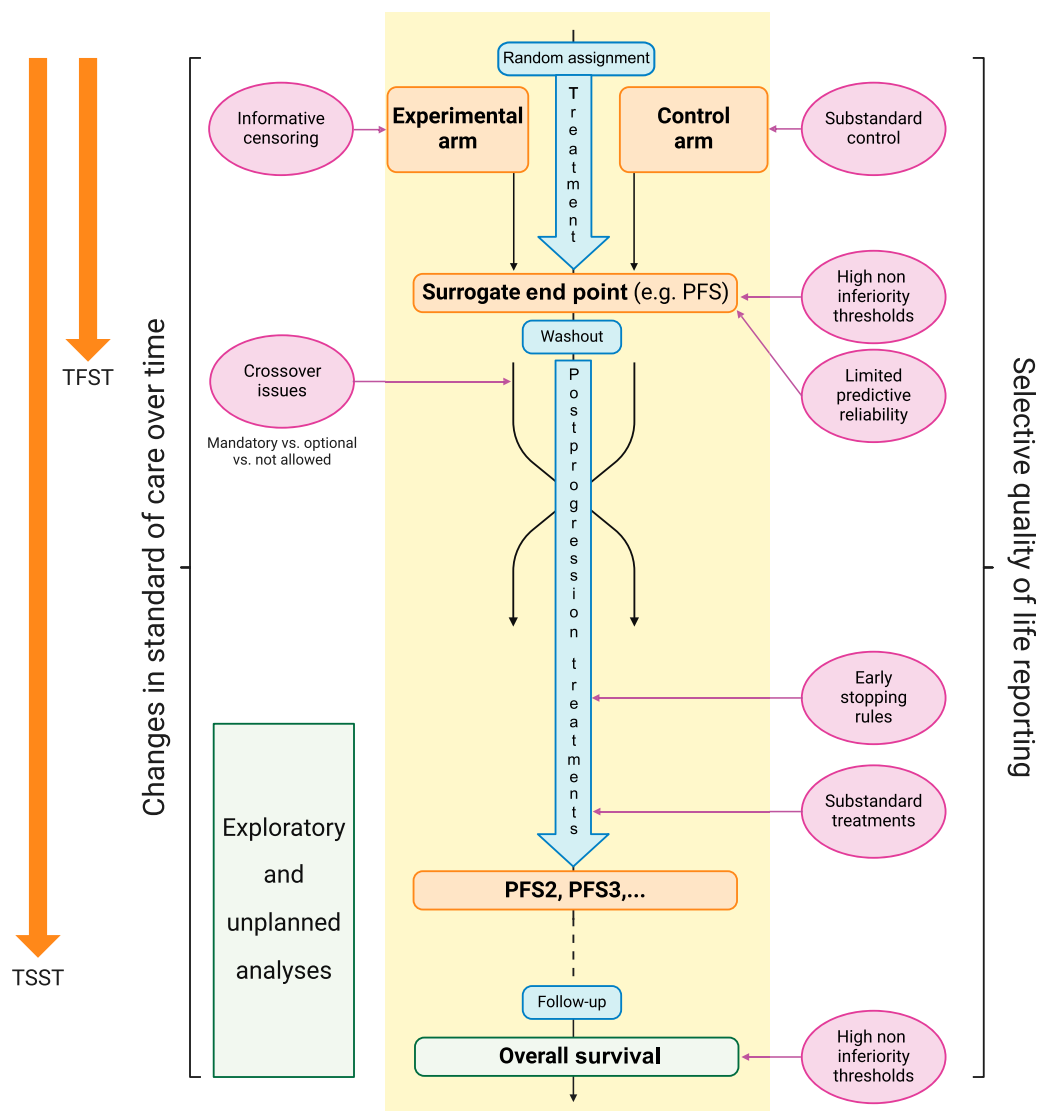


FIG 1. Potential issues in study design, implementation, and data analysis that may affect study outcomes. Adapted from the study by Gyawali et al.⁸⁸ Created in BioRender. Corti, C. (2025) <https://BioRender.com/c79i054>. PFS, progression-free survival; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

studies—including EUROPA T-DXd (ClinicalTrials.gov identifier: [NCT05458401](#)), DB RESPOND (ClinicalTrials.gov identifier: [NCT05592483](#)), and PROVIDENCE (ClinicalTrials.gov identifier: [NCT05573893](#))—will further clarify treatment patterns, time to treatment discontinuation, responses after progression, and optimal sequencing.⁸³ The first interim analysis of EUROPA T-DXd (n = 84, 44% >3 previous lines) showed that 40.5% of patients discontinued T-DXd at data cutoff, with 31% being due to disease progression. The median real-world time to treatment discontinuation was 21.4 months (95% CI, 17.6 to not evaluable), and median real-world PFS was not reached.⁸⁴

Neratinib plus capecitabine improved outcomes versus lapatinib plus capecitabine although the efficacy of sequential HER2 TKIs (eg, post-tucatinib) remains uncertain.⁸⁵ Reinitiating trastuzumab (with or without pertuzumab) with an alternative cytotoxic agent is another option, albeit with limited data.⁸⁶ The Fc-engineered anti-HER2 antibody margetuximab modestly improved outcomes compared with trastuzumab plus ChT in SOPHIA.⁸⁷ Novel agents—including new HER2-directed ADCs, TKIs, zanidatamab, and other bispecific antibodies—are under development.^{80,81}

Recent real-world data post-T-DXd progression in HER2+ MBC show the longest PFS with anti-HER2 monoclonal antibody with or without TKI (7.3 months, n = 34), followed by ChT plus anti-HER2 treatment (5.3 months, n = 56); capecitabine, trastuzumab, tucatinib (4.7 months, n = 95); and T-DM1 (4.1 months, n = 27), although sample sizes are small.⁵⁴

CONCLUSION

Understanding clinical trial results is crucial yet complex (Fig 1).⁸⁸ Trials are designed to answer specific questions, such as whether a new therapy improves survival compared with the current standard of care. However, many factors can introduce bias into the results and overestimate benefits. For example, a suboptimal control arm may exaggerate the

experimental treatment's effect, misleading clinicians and policymakers.

Another issue is crossover, where control patients receive experimental treatment after progression. While it is ethically appropriate when the experimental drug becomes part of standard care, it also complicates OS interpretation. Without proper design, it becomes difficult to discern whether benefit is due to early or delayed administration of a new therapy. Regulatory guidelines therefore call for careful crossover planning.

The handling of postprogression therapies further influences trial outcomes. After the initial treatment phase, patients often receive subsequent therapies that can affect OS. If these treatments are not standardized or evenly distributed between arms, the experimental benefit may be obscured.

Moreover, reliance on surrogate end points, such as PFS or ORR, rather than OS or QoL, adds complexity. While surrogate end points can indicate biological activity and offer early insights into a drug's efficacy, they do not always correlate with meaningful long-term benefits or cost-effectiveness. This discrepancy can be amplified if trials are stopped early because of promising interim results as early stopping rules may overestimate the magnitude of benefit.

In conclusion, it is important to approach clinical trial results with a critical eye.⁸⁸ Recognizing the potential biases and limitations in design not only improves one's understanding of the data but also ensures that treatment decisions are based on reliable evidence. More broadly, optimal sequencing should combine evidence-based and real-world data with individual patient factors—preferences, comorbidities, residual toxicity, and global access—to personalize treatment plans. Future directions call for sequencing-specific trials to uncover resistance mechanisms and the integration of biomarkers to guide decision making.

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REFERENCES

1. Corti C, Batra-Sharma H, Kelsten M, et al: Systemic therapy in breast cancer. *Am Soc Clin Oncol Educ Book* 44:e432442, 2024
2. Hortobagyi GN, Stemmer SM, Burris HA, et al: Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med* 386:942-950, 2022
3. Lu YS, Im SA, Colleoni M, et al: Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in pre- and perimenopausal patients with HR+/HER2- advanced breast cancer in MONALEESA-7: A phase III randomized clinical trial. *Clin Cancer Res* 28:851-859, 2022
4. Slamon DJ, Neven P, Chia S, et al: Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med* 382:514-524, 2020
5. Sledge GW, Toi M, Neven P, et al: The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: A randomized clinical trial. *JAMA Oncol* 6:116-124, 2020
6. Goetz MP, Toi M, Huober J, et al: Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2- advanced breast cancer: Final overall survival results of MONARCH 3. *Ann Oncol* 35:718-727, 2024
7. Slamon DJ, Diéras V, Rugo HS, et al: Overall survival with palbociclib plus letrozole in advanced breast cancer. *J Clin Oncol* 42:994-1000, 2024
8. Turner NC, Slamon DJ, Ro J, et al: Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med* 379:1926-1936, 2018
9. Sonke GS, van Ommen-Nijhof A, Wortelboer N, et al: Early versus deferred use of CDK4/6 inhibitors in advanced breast cancer. *Nature* 636:474-480, 2024
10. Provenzano L, Dieci MV, Curigliano G, et al: Real-world effectiveness comparison of first-line palbociclib, ribociclib or abemaciclib plus endocrine therapy in advanced HR+/HER2- BC patients: Results from the multicenter PALMARES-2 study. *Ann Oncol* 10.1016/j.annonc.2025.03.023 [epub ahead of print on April 7, 2025]
11. Rugo HS, Layman RM, Lynce F, et al: Comparative overall survival of CDK4/6 inhibitors plus an aromatase inhibitor in HR+/HER2- metastatic breast cancer in the US real-world setting. *ESMO Open* 10:104103, 2025
12. Gennari A, André F, Barrios CH, et al: ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 32:1475-1495, 2021
13. Kümler I, Knoop AS, Jessing CA, et al: Review of hormone-based treatments in postmenopausal patients with advanced breast cancer focusing on aromatase inhibitors and fulvestrant. *ESMO Open* 1:e000062, 2016
14. Gyawali B: Problematic crossovers in cancer drug trials. *Nat Rev Clin Oncol* 20:815-816, 2023
15. Turner NC, Im S-A, Saura C, et al: Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. *N Engl J Med* 391:1584-1596, 2024
16. Turner NC, Oliveira M, Howell SJ, et al: Capivasertib in hormone receptor-positive advanced breast cancer. *N Engl J Med* 388:2058-2070, 2023
17. André F, Ciruelos EM, Juric D, et al: Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: Final overall survival results from SOLAR-1. *Ann Oncol* 32:208-217, 2021
18. Rugo HS, Lerebours F, Ciruelos E, et al: Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): One cohort of a phase 2, multicentre, open-label, non-comparative study. *Lancet Oncol* 22:489-498, 2021
19. Masurkar PP, Prajapati P, Canedo J, et al: Cost-effectiveness of CDK4/6 inhibitors in HR+/HER2- metastatic breast cancer: A systematic review and meta-analysis. *Curr Med Res Opin* 40:1753-1767, 2024
20. dos Anjos CH, Razaavi P, Herbert J, et al: A large retrospective analysis of CDK 4/6 inhibitor retreatment in ER+ metastatic breast cancer (MBC). *J Clin Oncol* 37, 2019 (suppl 15; abstr 1053)
21. Kalinsky K, Bianchini G, Hamilton EP, et al: Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on a prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the phase 3 postMONARCH trial. *J Clin Oncol* 42, 2024 (suppl 17; abstr LBA1001)
22. Kalinsky K, Accorino MK, Chiuzan C, et al: Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: MAINTAIN trial. *J Clin Oncol* 41:4004-4013, 2023
23. Mayer EL, Ren Y, Wagle N, et al: Pace: A randomized phase II study of fulvestrant, palbociclib, and Avelumab after progression on cyclin-dependent kinase 4/6 inhibitor and aromatase inhibitor for hormone receptor-positive/human epidermal growth factor receptor-negative metastatic breast cancer. *J Clin Oncol* 42:2050-2060, 2024
24. Ilombart-cussac A, Harper-wynne C, Perello A, et al: Second-line endocrine therapy (ET) with or without palbociclib (P) maintenance in patients (pts) with hormone receptor-positive (HR [+]) human epidermal growth factor receptor 2-negative (HER2[-]) advanced breast cancer (ABC): PALMIRA trial. *J Clin Oncol* 41, 2023 (suppl 16; abstr 1001)
25. Bardia A, Hurvitz SA, DeMichele A, et al: Phase I/II trial of exemestane, ribociclib, and everolimus in women with HR+/HER2- advanced breast cancer after progression on CDK4/6 inhibitors (TRINITI-1). *Clin Cancer Res* 27:4177-4185, 2021
26. Bidard FC, Kaklamani VG, Neven P, et al: Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase III EMERALD trial. *J Clin Oncol* 40:3246-3256, 2022
27. Ascione L, Castellano G, Curigliano G, et al: Endocrine therapy for early breast cancer in the era of oral selective estrogen receptor degraders: Challenges and future perspectives. *Curr Opin Oncol* 36:465-473, 2024
28. Jeselsohn R, Buchwalter G, De Angelis C, et al: ESR1 mutations—A mechanism for acquired endocrine resistance in breast cancer. *Nat Rev Clin Oncol* 12:573-583, 2015
29. Olivier T, Prasad V: Elacestrant in metastatic breast cancer: Is the “standard of care” meeting standard requirements? *Transl Oncol* 15:101273, 2022
30. Turner NC, Kingston B, Kilburn LS, et al: Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): A multicentre, multicohort, phase 2a, platform trial. *Lancet Oncol* 21:1296-1308, 2020
31. Lindeman GJ, Fernando TM, Bowen R, et al: VERONICA: Randomized phase II study of fulvestrant and venetoclax in ER-positive metastatic breast cancer post-CDK4/6 inhibitors—Efficacy, safety, and biomarker results. *Clin Cancer Res* 28:3256-3267, 2022
32. Corti C, De Angelis C, Bianchini G, et al: Novel endocrine therapies: What is next in estrogen receptor positive, HER2 negative breast cancer? *Cancer Treat Rev* 117:102569, 2023
33. Apostolidou K, Zografos E, Papatheodoridis MA, et al: Oral SERDs alone or in combination with CDK 4/6 inhibitors in breast cancer: Current perspectives and clinical trials. *Breast* 75:103729, 2024
34. Jhaveri KL, Neven P, Casalnuovo ML, et al: Imlunestrant with or without abemaciclib in advanced breast cancer. *N Engl J Med* 392:1189-1202, 2025
35. Rossi A, Aïmar G, Audisio M, et al: Analysis of the adequacy of control arms in oncology randomised clinical trials published between 2017 and 2021: A meta-research study. *Eur J Cancer* 189: 112920, 2023
36. Jhaveri KL, Lim E, Jeselsohn R, et al: Imlunestrant, an oral selective estrogen receptor degrader, as monotherapy and in combination with targeted therapy in estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Phase Ia/Ib EMBER study. *J Clin Oncol* 42:4173-4186, 2024
37. AstraZeneca—Camizestrant demonstrated highly statistically significant and clinically meaningful improvement in progression-free survival in 1st-line advanced HR-positive breast cancer with an emergent ESR1 tumour mutation in SERENA-6 Phase III trial. <https://www.astrazeneca.com/media-centre/press-releases/2025/camizestrant-improved-pfs-in-1st-line-breast-cancer.html>
38. Turner N, Huang-Bartlett C, Kalinsky K, et al: Design of SERENA-6, a phase III switching trial of camizestrant in ESR1-mutant breast cancer during first-line treatment. *Future Oncol* 19:559-573, 2023

39. Bidard FC, Hardy-Bessard AC, Dalenc F, et al: Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): A randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 23:1367-1377, 2022
40. Corti C, Antonarelli G, Valenza C, et al: Histology-agnostic approvals for antibody-drug conjugates in solid tumours: Is the time ripe? *Eur J Cancer* 171:25-42, 2022
41. Ascione L, Guidi L, Prakash A, et al: Unlocking the potential: Biomarkers of response to antibody-drug conjugates. *Am Soc Clin Oncol Educ Book* 44:e431766, 2024
42. Bardia A, Rugo HS, Tolane SM, et al: Final results from the randomized phase III ASCENT clinical trial in metastatic triple-negative breast cancer and association of outcomes by human epidermal growth factor receptor 2 and trophoblast cell surface antigen 2 expression. *J Clin Oncol* 42:1738-1744, 2024
43. Bardia A, Hurvitz SA, Tolane SM, et al: Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med* 384:1529-1541, 2021
44. Pomeaud F, Morisseau M, Cabel L, et al: PS08-02 efficacy of sacituzumab-govitecan (SG) post trastuzumab-deruxtecan (T-DXd) and vice versa for HER2-low advanced or metastatic breast cancer (MBC): A French multicentre retrospective study. *San Antonio Breast Cancer Symposium*, 5-9 Dec 2023, San Antonio, TX
45. Huppert LA, Mahtani RL, Fisch SC, et al: PS08-04 Multicenter retrospective cohort study of the sequential use of the antibody-drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2-low metastatic breast cancer (MBC). *San Antonio Breast Cancer Symposium*, 5-9 Dec 2023, San Antonio, TX
46. Abelman RO, Spring L, Fell G, et al: Sequential use of antibody-drug conjugate after antibody-drug conjugate for patients with metastatic breast cancer: ADC after ADC (A3) study. *J Clin Oncol* 41, 2023 (suppl 16; abstr 1022)
47. Bardia A, Hu X, Dent R, et al: Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med* 391:2110-2122, 2024
48. Giugliano F, Carnevale Schianca A, Corti C, et al: Unlocking the resistance to anti-HER2 treatments in breast cancer: The issue of HER2 spatial distribution. *Cancers (Basel)* 15:1385, 2023
49. Bardia A, Hu X, Dent R, et al: LB1-04. Efficacy and safety of trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) by pace of disease progression on prior endocrine-based therapy: Additional analysis from DESTINY-Breast06. Dec 10-13, 2024. *San Antonio Breast Cancer Symposium* 2024. San Antonio, TX
50. Modi S, Jacot W, Yamashita T, et al: Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med* 387:9-20, 2022
51. Rugo HS, Bardia A, Marmé F, et al: Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPICS-02): A randomised, open-label, multicentre, phase 3 trial. *Lancet* 402:1423-1433, 2023
52. Rugo HS, Bardia A, Marmé F, et al: Primary results from TROPICS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer. *J Clin Oncol* 40, 2022 (suppl 17; abstr LBA1001)
53. Pistilli B, Jhaveri K, Im S-A, et al: VP1-2025: Datopotamab deruxtecan (Dato-DXd) vs chemotherapy (CT) in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer (BC): Final overall survival (OS) from the phase III TROPION-Breast01 trial. *Ann Oncol* 36:348-350, 2025
54. Tarantino P, Lee D, Foldi J, et al: P1-08-08: Efficacy of immediate subsequent lines of therapy after T-DXd in patients with metastatic breast cancer: Retrospective study from a nationwide real-world database. *San Antonio Breast Cancer Symposium* 2024
55. Bardia A, Krop IE, Kogawa T, et al: Datopotamab deruxtecan in advanced or metastatic HR+/HER2- and triple-negative breast cancer: Results from the phase I TROPION-PanTumor01 study. *J Clin Oncol* 42:2281-2294, 2024
56. Baselga J, Cortés J, Kim SB, et al: Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 366:109-119, 2012
57. Swain SM, Baselga J, Kim SB, et al: Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 372:724-734, 2015
58. Arpino G, de la Haba Rodríguez J, Ferrero JM, et al: Pertuzumab, trastuzumab, and an aromatase inhibitor for HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer: PERTAIN final analysis. *Clin Cancer Res* 29:1468-1476, 2023
59. Mochizuki N, Yamashita S, Kurokawa K, et al: Spatio-temporal images of growth-factor-induced activation of Ras and Rap1. *Nature* 411:1065-1068, 2001
60. Yu Q, Sicsinska E, Geng Y, et al: Requirement for CDK4 kinase function in breast cancer. *Cancer Cell* 9:23-32, 2006
61. Choi YJ, Li X, Hydbring P, et al: The requirement for cyclin D function in tumor maintenance. *Cancer Cell* 22:438-451, 2012
62. Goel S, Wang Q, Watt AC, et al: Overcoming therapeutic resistance in HER2-positive breast cancers with CDK4/6 inhibitors. *Cancer Cell* 29:255-269, 2016
63. Metzger O, Mandrekar S, DeMichele A, et al: AFT-38 PATINA: A randomized, open label, phase III trial to evaluate the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy vs. Anti-HER2 therapy + endocrine therapy after induction treatment for hormone receptor-positive (HR+)/HER2-Positive metastatic breast cancer. December 10-14, 2024. *San Antonio Breast Cancer Symposium* 2024, San Antonio, TX
64. Lam C, Varghese D, Collins J, et al: Treatment patterns and associated outcomes among patients with HER2+ metastatic breast cancer in the United States: An observational cohort study. *Oncologist* 30:oyae280, 2025
65. Cortés J, Kim SB, Chung WP, et al: Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med* 386:1143-1154, 2022
66. Cortés J, Hurvitz SA, Im SA, et al: Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: Long-term survival analysis of the DESTINY-Breast03 trial. *Nat Med* 30:2208-2215, 2024
67. Murthy RK, Loi S, Okines A, et al: Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med* 382:597-609, 2020
68. Criscitiello C, Corti C, De Laurentiis M, et al: Tucatinib's journey from clinical development to clinical practice: New horizons for HER2-positive metastatic disease and promising prospects for brain metastatic spread. *Cancer Treat Rev* 120:102618, 2023
69. Bachelot T, Lin NU, Murthy RK, et al: Impact of tucatinib on progression free survival in patients with HER2+ metastatic breast cancer and stable or active brain metastases. *Ann Oncol* 31: S348-S395, 2020
70. Lin NU, Borges V, Anders C, et al: Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol* 38:2610-2619, 2020
71. Pérez-García JM, Vaz Batista M, Cortez P, et al: Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: The DEBBRAH trial. *Neuro Oncol* 25:157-166, 2023
72. Bartsch R, Berghoff AS, Furner J, et al: Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: A single-arm, phase 2 trial. *Nat Med* 28:1840-1847, 2022
73. Michelson I, Vilbert M, Marinho AD, et al: Trastuzumab deruxtecan in human epidermal growth factor receptor 2-positive breast cancer brain metastases: A systematic review and meta-analysis. *ESMO Open* 9:102233, 2024
74. Harbeck N, Ciruelos E, Jerusalem G, et al: Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: A phase 3b/4 trial. *Nat Med* 30:3717-3727, 2024
75. Tarantino P, Lee D, Foldi J, et al: Outcomes with trastuzumab deruxtecan (T-DXd) by HER2 status and line of treatment in a large real-world database of patients with metastatic breast cancer. *J Clin Oncol* 42, 2024 (suppl 16; abstr 1077)
76. Cheng A, Frank S, Baines K, et al: Real world experience of trastuzumab deruxtecan for the treatment of metastatic breast cancer in the UK. *J Clin Oncol* 42, 2024 (suppl 16; abstr 1024)
77. Botticelli A, Caputo R, Scagnoli S, et al: Real-world outcomes of trastuzumab deruxtecan in patients with HER2+ metastatic breast cancer: The DE-REAL study. *Oncologist* 29:303-310, 2024
78. Kapil A, Spitzmüller A, Brieu N, et al: HER2 quantitative continuous scoring for accurate patient selection in HER2 negative trastuzumab deruxtecan treated breast cancer. *Sci Rep* 14:12129, 2024
79. Moutafi M, Robbins CJ, Yaghoobi V, et al: Quantitative measurement of HER2 expression to subclassify ERBB2 unamplified breast cancer. *Lab Invest* 102:1101-1108, 2022
80. Antonarelli G, Corti C, Tarantino P, et al: Management of patients with HER2-positive metastatic breast cancer after trastuzumab deruxtecan failure. *ESMO Open* 8:101608, 2023
81. Antonarelli G, Giugliano F, Corti C, et al: Research and clinical landscape of bispecific antibodies for the treatment of solid malignancies. *Pharmaceuticals (Basel)* 14:884, 2021
82. Corti C, Criscitiello C: Tucatinib approval by EMA expands options for HER2-positive locally advanced or metastatic breast cancer. *ESMO Open* 6:100063, 2021
83. Hurvitz SA, Curigliano G, Egorov A, et al: DESTINY-Breast03 trial: Some questions remain—Authors' reply. *Lancet* 401:1653-1654, 2023
84. De Laurentiis M, García-Sáenz JA, Bianchini G, et al: Abstract PO3-16-12: European real-world experience of patients with HER2+ advanced/metastatic breast cancer accessing trastuzumab deruxtecan through a named patient program: First interim analysis of EUROPA T-DXd. *Cancer Res* 84:PO3-16-12, 2024 (suppl 9)
85. Saura C, Oliveira M, Feng YH, et al: Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Phase III NALA trial. *J Clin Oncol* 38:3138-3149, 2020
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87. Rugo HS, Im SA, Cardoso F, et al: Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: A phase 3 randomized clinical trial. *JAMA Oncol* 7: 573-584, 2021
88. Gyawali B, de Vries EGE, Dafni U, et al: Biases in study design, implementation, and data analysis that distort the appraisal of clinical benefit and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scoring. *ESMO Open* 6:100117, 2021

Driving Knowledge to Action: Building a Better Future With Artificial Intelligence–Enabled Multidisciplinary Oncology

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OVERVIEW

Artificial intelligence (AI) is transforming multidisciplinary oncology at an unprecedented pace, redefining how clinicians detect, classify, and treat cancer. From earlier and more accurate diagnoses to personalized treatment planning, AI’s impact is evident across radiology, pathology, radiation oncology, and medical oncology. By leveraging vast and diverse data—including imaging, genomic, clinical, and real-world evidence—AI algorithms can uncover complex patterns, accelerate drug discovery, and help identify optimal treatment regimens for each patient. However, realizing the full potential of AI also necessitates addressing concerns regarding data quality, algorithmic bias, explainability, privacy, and regulatory oversight—especially in low- and middle-income countries (LMICs), where disparities in cancer care are particularly pronounced. This study provides a comprehensive overview of how AI is reshaping cancer care, reviews its benefits and challenges, and outlines ethical and policy implications in line with ASCO’s 2025 theme, *Driving Knowledge to Action*. We offer concrete calls to action for clinicians, researchers, industry stakeholders, and policymakers to ensure that AI-driven, patient-centric oncology is accessible, equitable, and sustainable worldwide.

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THE AI-ENHANCED TUMOR BOARD CASE

(Scene: A bustling multidisciplinary tumor board. Radiologists, pathologists, medical oncologists, radiation oncologists, surgeons, and genetic counselors gather around a large screen displaying patient data.) (Fig 1).

Welcome to a typical tumor board in an oncology center worldwide. Today, we are discussing Mrs Elena Ramirez, a 63-year-old woman recently diagnosed with non-small cell lung cancer (NSCLC). Mrs Ramirez, a former light smoker who quit 20 years ago, initially presented with a persistent cough. A routine chest X-ray revealed a 4-cm nodule in her right upper lobe. Subsequent computed tomography (CT) imaging confirmed a Stage III NSCLC, clinically staged T2N2M0. Let’s review the case.

Radiologist

“On her screening chest X-ray, in retrospect, a subtle density was easily missed. The diagnostic CT clearly shows a spiculated nodule with mediastinal lymphadenopathy. PET-CT confirms tumor uptake in the primary lesion and but no lymph nodes or distant metastases. Early-stage lung cancers can appear very subtle, and standard screening often fails to catch them. With AI-driven screening, we could flag these minor signs more consistently, shifting more patients like Mrs. Ramirez to potentially curative stages. The AI calculates a high

probability of non-small cell adenocarcinoma histology based on imaging alone. We also utilized AI for analyzing the CT and PET/CT images, and interestingly, the results highlight mediastinal nodal involvement based on the morphology of the smaller lymph nodes, even though they don’t meet size criteria. This would be consistent with Stage III disease.”

Pathologist

“The biopsy of the lung lesion confirms adenocarcinoma, moderately differentiated. However, some areas show necrosis, and morphological variations are noted. Even with digital pathology workflows, interpreting these features can be subjective. We then used AI to quantify these patterns and detect prognostic biomarkers. The AI predicted that there’s a high chance of *EGFR* mutation based on H&E slide staining alone.”

Medical Oncologist

“Genomic testing confirmed an *EGFR* exon 21 L858R mutation, without *ALK* rearrangements or high PD-L1 expression. *EGFR* TKIs are standard, but resistance often develops. With the explosion of genomic data, synthesizing all potential therapeutic targets and pathways becomes more challenging. An AI system that abstracts and

PRACTICAL APPLICATIONS

- Clinicians can use artificial intelligence (AI)-supported screening and imaging triage to detect cancers earlier and reduce diagnostic errors.
- Real-time adaptive radiation planning, powered by AI, can optimize treatment delivery and minimize toxicity.
- AI-enhanced digital pathology streamlines diagnostic workflows, improving efficiency in biomarker detection and tissue analysis.
- Automated clinical trial matching systems expand patient access to targeted research studies, accelerating therapy development.
- Integrating AI in low- and middle-income settings can help address workforce shortages and narrow global disparities in cancer care.

summarizes imaging, pathology, genomics, and clinical data could guide optimal treatment sequencing. It might even predict which patients could benefit from immunotherapy after TKI failure by analyzing complex multimodal data.”

Radiation Oncologist

“For Stage III disease, concurrent chemoradiation is a prime consideration along with *EGFR* TKI therapy. AI has now automated my ability to contour targets and organs at risk with a high degree of precision, and I can now rapidly plan an intensity modulated radiation therapy plan based on the initial diagnostic CT and PET scans. I’m anticipating

the tumor shrinking in size during treatment, and we’ll be able to adapt therapy in real-time based on daily imaging.”

Surgeon

“Surgery might be an option in select Stage III cases after neoadjuvant or targeted therapies. Predicting which patients truly benefit from surgery can be difficult. I am anticipating that AI, integrating radiomics and genomics, will forecast which tumors respond well to trimodality therapy or which might be better managed with even just a single modality of therapy alone.”

Clinical Trial Coordinator

“Mrs. Ramirez is open to clinical trials, but the sheer volume of trials and complex criteria make matching patients manually daunting. AI-powered trial matching systems allowed me to parse trial databases quickly, linking her to the most relevant options, even in resource-constrained settings.”

While the clinicians are discussing the case, the AI is pulling up relevant information on a shared screen, with associated pathways, recommendations, and probabilities. These discussions highlight how AI could reduce diagnostic delays, personalize therapy, predict outcomes, and expand trial access. Beyond immediate care, AI can address global disparities in settings with limited oncology resources.

INTRODUCTION: A NEW ERA OF AI IN ONCOLOGY

Cancer remains a formidable global challenge. Lung cancer alone accounts for approximately 1.8 million deaths annually.¹ In high-income countries, five-year lung cancer survival rates can reach 20%–25%, whereas in many low- and middle-income countries (LMICs), these rates languish at 5%–10%.² Moreover, while nearly all eligible patients in high-income nations have access to radiation therapy, only 20%–30% in LMICs receive it.³

ASCO’s 2025 theme, “Driving Knowledge to Action: Building a Better Future,” underscores the need to translate emerging technologies into clinical impact. AI holds considerable promise in achieving this goal, providing supportive tools to help address radiologist and pathologist shortages, synthesizing complex genomic data, and introducing potential adjunctive tools to assist with clinical coordination and clinical decision making. AI’s potential can be fully realized only through interdisciplinary collaboration and implementation with a safety and quality mindset.⁴

FOUNDATIONS OF AI

Artificial intelligence (AI) has been conceptualized in various ways, often anthropomorphizing human-like sensory perception, reasoning, and behaviors to machines. In 1950,



FIG 1. AI in a multidisciplinary tumor board workflow. A conceptual figure showing how AI integrates data from radiology, pathology, genomics, and clinical information into a decision support system, providing treatment recommendations, trial options, and outcome predictions that inform tumor board discussions. AI, artificial intelligence.

Alan Turing notably created the foundation for AI by asking “Can machines think?”⁵ Marvin Minsky expanded on this by suggesting that the goal of AI is not merely to construct intelligent machines, but rather to develop systems capable of learning to become intelligent.⁶ Ultimately, AI is anticipated to surpass human cognitive abilities, performing complex, high-dimensional reasoning tasks rapidly, reliably, and at scale, while accurately predicting future outcomes. Machine learning (ML) serves as a pivotal component in realizing AI, enabling systems to learn from data and improve over time.⁷ As such, the European Union’s AI Act provides a comprehensive definition of AI systems⁸:

‘AI system’ means a machine-based system that is designed to operate with varying levels of autonomy and that may exhibit adaptiveness after deployment, and that, for explicit or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments.

ML is a distinct branch of AI that embodies the concept of self-teaching algorithms that refine their ability to analyze and interpret data autonomously^{9–15} (Fig 2A). These ML or statistical learning algorithms possess the capability to identify patterns that may elude human detection. With exposure to an increasing volume of new data, these algorithms progressively improve their ability to learn and interpret data. ML is categorized into two primary methodologies: supervised learning, where the algorithm is trained with known, labeled outcome data, and unsupervised learning, which operates without predefined outcome data.¹⁶ Both methods use pattern recognition to facilitate predictions of various outcomes, such

as cancer detection, survival rates, or classification into risk groups.

More recent research advances have focused on deep learning (DL), which is a type of ML.^{17,18} DL is a subset of ML that uses models built on deep neural networks to detect patterns with minimal human involvement. These algorithms classify information in ways much like the human brain does. DL tools use artificial neural networks (ANNs) that mimic how our brain cells take in, process, and react to signals from the rest of our body.^{19–23}

These layers can get more and more complex. An increasingly used tool in oncology is OpenAI’s ChatGPT.^{24,25} ChatGPT is an example of a Generative Pre-Trained Transformer, which, in turn, is a type of a large language model (LLM). LLM is an example of generative AI, a DL subdivision (Fig 2B).

Numerous AI applications in oncology use DL architecture, which we will describe in more detail before discussing representative examples.

DEEP LEARNING

Traditional ML techniques often rely on manual feature engineering, where domain experts define features to optimize model performance. This approach is computationally efficient and works well with smaller data sets as it allows for the selection of predictive features based on expert knowledge and statistical methods.^{26,27} By contrast, DL models automate feature extraction through layered architectures such as convolutional neural networks (CNNs), enabling them to

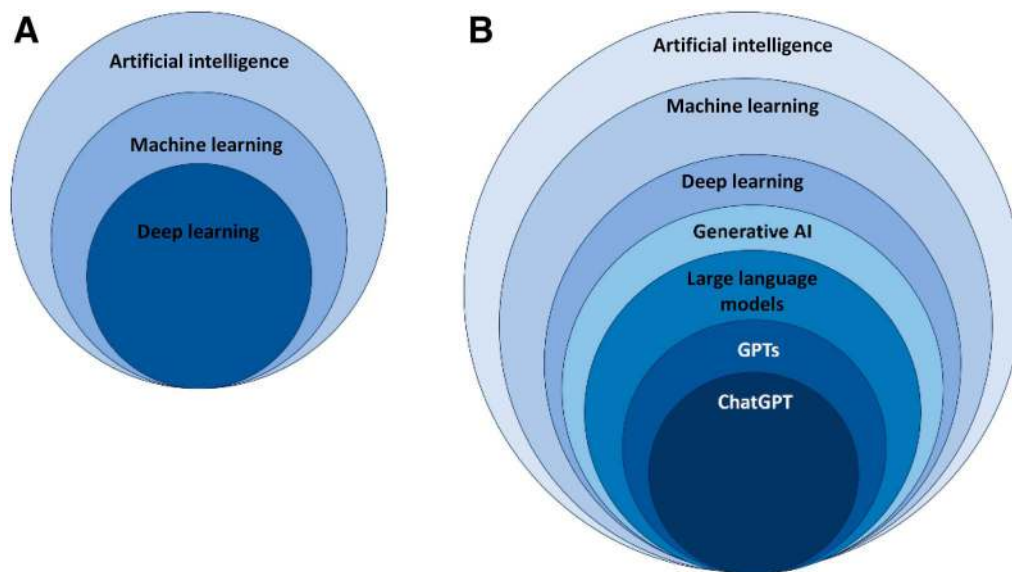


FIG 2. Evolution and hierarchy of AI technologies. (A) illustrates the foundational relationship between AI, ML, and DL, with each field nested within the broader one. (B) expands this hierarchy to include advancements in Generative AI, LLMs, and the development of GPTs, culminating in ChatGPT as a specialized implementation, for example. AI, artificial intelligence; DL, deep learning; GPTs, generative pretrained transformers; LLMs, large language models; ML, machine learning.

process raw, high-dimensional data like images or text without extensive preprocessing.²⁸ While DL excels in tasks requiring complex pattern recognition, it demands larger data sets and higher computational resources.

The distinction between ML and DL lies in their approaches to feature engineering and data representation, rather than the necessity for annotations or region of interest (ROI) segmentation. Both ML and DL can be applied in supervised or unsupervised learning paradigms, depending on whether labeled data are available.²⁹ Generally, DL outperforms ML in unstructured data analysis, such as image recognition, whereas ML remains effective for structured data tasks requiring simpler automation.³⁰

Artificial Neural Networks

At their core, ANNs are composed of three key components: (1) an input layer, (2) one or more hidden layers where multiple nodes apply weights to the input and introduce a bias, and (3) an output layer that uses an activation function to derive predictions. DL is characterized by the presence of multiple hidden layers. For DL development, training, and evaluation, several Python-based platforms are available, including Meta's PyTorch and Google's TensorFlow. In addition, Google offers Google Colaboratory, a free cloud-based Jupyter Notebook environment that facilitates Python programming and access to graphic processing units without needing local software installation.

DL models have generally ranged in complexity from shallow models, or less than two hidden layers, to more complex DL models with tens or even hundreds of hidden layers, each containing nonlinear functions (ie, deep neural networks). Combining a sufficient number of layers can represent arbitrarily complex relationships among data. As the number of layers has increased, so too has the capacity of these networks to discern patterns and make predictions from high-dimensional data.³¹

Convolutional Neural Networks

Several early cancer diagnosis models have exploited CNN architectures, which led to a revolution in computer vision research by allowing the use of color images as input data.³²⁻³⁴ While the downstream fully connected layers resemble those of an ANN as described above, the input data are processed by kernels that slide over image channels and extract features, such as color gradients and edges. Multiple imaging series, such as T1, T2, DWI, and others for magnetic resonance imaging (MRI) scans, can each be represented by their channel. These inputs are pooled and flattened before passing to the fully connected layer. There is an activation function such as SoftMax to convert the output to a probability. Numerous prominent CNN architectures have achieved significant accuracy improvements in computer vision tasks owing to their unique network designs.³⁵⁻³⁸ These designs are distinguished by the number of layers,

the connections between these layers, and the fundamental designs of the individual units within the network. These include AlexNet, EfficientNet, InceptionNet, VGGNet, ResNet, Inception, and DenseNet.

Transformers

Transformers were first designed in the field of natural language processing (NLP) as a novel architecture to handle sequences of data. They excel particularly at tasks that require understanding the context and relationships between words in a sentence, regardless of their position. Unlike previous models that processed words in order or with limited context, transformers use self-attention mechanisms to weigh the influence of different parts of the input data, enabling the model to simultaneously consider the entire sequence of words for more nuanced and contextually aware language understanding and generation. This architecture has significantly advanced the performance of NLP systems in tasks such as translation, summarization, and question-answering.

These have more recently been adapted for computer vision by transforming the spatial dimensions of input images into a sequence of features. These sequences are then processed using self-attention mechanisms within an encoder-decoder architecture, allowing the model to capture global dependencies across the entire input. These models have been used in medical image analysis, including classification, image registration, segmentation, image-to-image detection, and video-based applications.³⁹ However, because of the high computational demand of self-attention, this method is typically reserved for inputs with smaller spatial dimensions to ensure efficiency. Transformers and attention mechanisms have transformed AI tools, with the advent of LLMs, such as OpenAI's ChatGPT (Fig 2).⁴⁰ Their reliability, however, is hindered by medical hallucinations—fabricated or misleading content—necessitating robust detection, mitigation strategies, and ethical guidelines to safeguard patient safety and clinical integrity.⁴¹

AI-ENHANCED DIGITAL PATHOLOGY

Digital pathology, coupled with AI, is revolutionizing cancer diagnosis and treatment by enabling more accurate, efficient, and personalized approaches to oncologic care. This transformation is rapidly redefining traditional pathology practices while opening new frontiers in cancer research and clinical management.

The Evolution of Digital Pathology in Oncology

The digitization of pathology has emerged as a cornerstone of modern oncologic practice, extending far beyond merely offering correct diagnoses to playing an increasingly critical role in determining treatment strategies and prognoses for patients with cancer. Digital pathology, powered by whole-slide imaging (WSI) technology, has the potential to

transform the landscape of cancer research and diagnosis by converting traditional histopathologic specimens into high-resolution digital images.^{42,43} This technological advancement has paved the way for computer-aided analysis and opened new horizons for the integration of AI and ML.⁴⁴ The advent of whole-slide imaging, coupled with faster networks and cheaper storage solutions, now makes it considerably easier for pathologists to manage digital slide images and share them for clinical use.⁴⁵

The integration of digital slides into the pathology workflow enables advanced algorithms and computer-aided diagnostic techniques to extend the frontiers of pathology beyond what is visible through a microscope, facilitating true utilization and integration of knowledge beyond human limits.⁴⁵ This is particularly significant considering the immense complexity of digital pathology images, which can reach sizes of $100,000 \times 100,000$ pixels, contain color information from hematoxylin and eosin (H&E) staining and immunohistochemistry, lack apparent anatomic orientation unlike radiology images, and offer information at multiple scales and z-stack levels.⁵ The sheer volume and complexity of this visual information cannot be fully extracted by human reviewers alone, making AI applications increasingly valuable.⁴⁶

Transformative Potential of WSI

WSI has revolutionized pathology by digitizing glass slides into high-resolution images, enabling AI applications that extend diagnostic capabilities beyond traditional microscopy.^{42,43} This technology allows pathologists to store, access, and share digital slides, fostering remote collaboration and enhancing diagnostic accuracy.⁴⁷ By digitizing slides, WSI facilitates advanced computational tools for analyzing complex tissue patterns and biomarkers, marking a paradigm shift in cancer diagnosis.⁴⁸

Despite challenges like high initial costs and workflow adjustments, WSI adoption continues to grow as computing power advances, networks improve, and storage solutions become more affordable. These developments support telepathology and clinical applications while paving the way for AI integration into pathology workflows.^{42,49}

AI-Driven Advancements in Cancer Diagnosis

AI-powered deep neural networks have demonstrated remarkable capabilities in analyzing digital pathology images. These algorithms extract precise information, recognize tissue patterns, and identify biomarkers such as PD-L1 and human epidermal growth factor receptor 2 (HER2) with diagnostic accuracy comparable with human experts.^{47,50} AI's diagnostic potential is supported by substantial evidence. A meta-analysis of over 152,000 whole-slide images revealed a mean sensitivity of 96.3% and a specificity of 93.3%, demonstrating AI's ability to match or exceed pathologists' performance in certain tasks.⁵⁰ In addition, AI-driven tools have successfully detected ductal carcinoma

in situ using H&E-stained biopsies by partitioning slides into superpixels for analysis at specific magnifications.⁴⁷

AI extends beyond visual diagnostics by identifying molecular features imperceptible to human reviewers. Emerging platforms can detect microsatellite instability (MSI) and other genomic signatures directly from histopathology images, aiding personalized treatment strategies for patients with colorectal cancer.⁵¹ AI-driven immune assays like Immunoscore have improved reproducibility in assessing tumor immune contexture compared with traditional methods, enhancing cancer diagnosis and prognosis.⁴⁸

Enhancing Clinical Workflows Through Digital Integration

Integrating digital pathology with AI streamlines workflows by automating tasks such as tissue structure identification, tumor quantification, disease staging, and routine procedures like counting tumor-infiltrating lymphocytes. AI-assisted reporting accelerates turnaround times by generating preliminary diagnostic reports for pathologists to review and confirm, improving both consistency and accuracy.⁴⁹ Digital pathology enables remote consultations, allowing pathologists to access slides from virtually anywhere. This capability is particularly valuable in resource-limited settings where subspecialty support may be lacking. Real-time second opinions and expert consultations enhance diagnostic accuracy for complex cases.^{42,47} Digital pathology improves specimen-archiving efficiency while reducing physical storage needs. It also enables integration with clinical information systems for comprehensive patient care. Furthermore, AI-powered analysis of composite biomarkers like CD8 and PD-L1 has shown promise in predicting patient outcomes for immunotherapies.⁵¹

AI IN RADIATION ONCOLOGY

The integration of AI into radiation oncology has revolutionized clinical workflows, enhancing precision, efficiency, and personalization of cancer care. A primary application lies in automated tumor and organ-at-risk segmentation, where DL algorithms analyze multimodal imaging data to delineate anatomic structures with expert-level accuracy. For instance, transformer-based models have reduced contouring time by 65% while minimizing interobserver variability, enabling rapid treatment planning (Kawamura et al, PMID: 37996085). Similarly, AI-driven treatment planning systems, such as Varian Ethos and Elekta MOSAIQ, optimize beam configurations and dose distributions in minutes—a task traditionally requiring hours—by leveraging historical data to balance tumor coverage and organ-sparing (Parkinson et al, PMID: 34493445). These advancements streamline workflows, allowing clinicians to focus on complex decision making rather than repetitive tasks.

Adaptive radiation therapy (ART) exemplifies AI's transformative potential in real-time treatment delivery. AI

algorithms integrated with magnetic resonance linear accelerators (MR-Linacs) dynamically adjust radiation doses based on daily anatomic changes, tumor motion, and patient positioning. For example, DL models predict intrafraction tumor displacement with submillimeter accuracy, enabling beam gating systems to synchronize radiation delivery with respiratory motion (Fu et al, PMID: 38507259). Such innovations improve targeting precision, reduce toxicity, and support personalized dose modulation, particularly in thoracic and abdominal malignancies where motion management is critical.

Predictive analytics powered by AI are reshaping prognostic assessments and toxicity management. ML models analyze radiomic features, genomic data, and treatment histories to forecast outcomes such as local recurrence, radiation pneumonitis risk, and survival rates. Furthermore, AI-driven decision-support tools like IBM Watson for Oncology synthesize clinical guidelines and real-world evidence (RWE) to recommend personalized therapies although their efficacy remains contingent on rigorous validation across diverse populations.

AI IN MEDICAL ONCOLOGY

Chemotherapy

AI is increasingly used to tailor chemotherapy by predicting which patients will benefit or experience resistance.⁵² For instance, ML models analyzing pathology, imaging, or clinical data aim to identify patients, such as those with early-stage colorectal cancer, who might safely avoid adjuvant chemotherapy or predict neoadjuvant chemotherapy response in tumor types like gastroesophageal junction adenocarcinoma based on CT scan features.^{52,53} These approaches aim to spare unnecessary toxicity and focus treatment on likely responders⁵² although ongoing prospective validation is crucial. Early experiments evaluating LLMs for oncology decision support found generally high concordance (approximately 86% for adjuvant therapy recommendations in early breast cancer) with multidisciplinary expert recommendations.⁵⁴ However, performance varied for chemotherapy suggestions, and a tendency to overestimate the need for radiotherapy was noted in some scenarios.⁵⁴ This underscores that although promising, AI should currently augment, not replace, clinical judgment in chemotherapy planning.

Immunotherapy

AI-driven tools are enhancing patient selection and inspiring novel strategies in immunotherapy. US-based researchers developed a logistic regression AI score (LORIS) using six routine clinical factors (eg, age, albumin, tumor mutational burden) that predicted checkpoint inhibitor response and survival across 18 tumor types, reportedly outperforming some standard biomarkers.⁵⁵ Concurrently, multimodal AI models integrating pathology images and clinical text, such as

Stanford's MUSK model, have shown high accuracy in predicting prognosis and identifying which patients with lung and gastroesophageal cancer may benefit from immunotherapy, exceeding predictions based on PD-L1 expression alone.⁵⁶ AI-powered pathology analysis is also yielding actionable insights; a collaborative study using Lunit's AI slide analysis found that AI-detected changes in tumor-infiltrating lymphocytes and tumor content after treatment correlated strongly with improved survival outcomes from PD-1 blockade in patients with rare cancers.⁵⁷ Highlighting global efforts, initiatives like MIT's Team MATCHMAKERS, funded through Cancer Grand Challenges, are leveraging ML to analyze T-cell receptor interactions, aiming to build tools for designing personalized T-cell therapies.⁵⁸ While clinical validation for many newer AI applications is ongoing, these developments showcase AI's significant potential to personalize and improve immunotherapy.

Targeted Therapy

AI and LLM technologies are driving advancements in targeted cancer therapies, from improving drug selection to accelerating drug design. In clinical decision support, LLMs like GPT-4 demonstrated high accuracy (around 86% agreement with experts) in generating appropriate recommendations for targeted therapies, such as anti-HER2 or endocrine treatments, in early breast cancer cases based on patient records.⁵⁴ This suggests potential for LLMs to assist multidisciplinary teams. These examples illustrate how AI and LLMs are beginning to refine the application of existing targeted therapies and invent the next generation of precision agents.

AI FOR CLINICAL TRIALS

AI analytics are significantly enhancing oncology clinical trials, particularly by addressing critical bottlenecks in patient recruitment and enrollment through sophisticated matching algorithms. AI platforms leverage ML and NLP to rapidly screen vast amounts of patient data—from electronic health records (EHRs), genomic reports, and imaging—against complex trial eligibility criteria.⁵⁹ This automated matching aims to identify suitable candidates more efficiently and accurately than manual methods. For instance, one AI-enabled multitrial matching system demonstrated a 1.82-fold increase in potential trial matches per patient and reduced the matching time by 99.9% compared with manual efforts.⁶⁰ The concept is being advanced through digital prescreening hubs, which use AI and real-world data to proactively identify potential trial participants across broader populations before they even reach specific sites.⁶¹ Such proactive identification, combined with AI-driven matching, enables more efficient trial operations, including just-in-time activation of trial sites—opening them rapidly only when suitable, matched patients are ready to enroll, significantly reducing startup delays.⁶² Complementing these technological approaches are nationwide efforts aimed at improving trial access and infrastructure.

The American Cancer Society's programs provide crucial patient support alongside exploring tailored clinical trial options,⁶³ whereas initiatives like ARPA-H focus on building the tools and infrastructure necessary for decentralized trials, including improved participant identification and engagement methods accessible to a wider range of patients across the country.⁶⁴ Together, these AI-driven matching techniques, prescreening hubs, just-in-time processes, and national support systems strive to increase the speed, efficiency, and equity of clinical trial enrollment, ultimately accelerating the development of new cancer therapies.

AI IN CANCER DRUG DISCOVERY

AI is revolutionizing cancer drug discovery by addressing the inefficiencies of traditional methods, which are often time-consuming and costly and yield low success rates. This transformation is inherently multidisciplinary, combining expertise from computational biology, structural chemistry, pharmacology, and clinical oncology. AI-driven platforms leverage high-dimensional data from genomics, proteomics, and chemical libraries to accelerate the identification of novel drug candidates and optimize therapeutic regimens. For instance, tools like AlphaFold have redefined protein structure prediction, enabling researchers to design drugs that target previously intractable molecules with unprecedented precision. By integrating ML with experimental techniques, such as molecular docking and *in silico* simulations, researchers can rapidly screen millions of compounds for efficacy and safety before advancing to preclinical trials.

The success of AI in this field highlights the importance of interdisciplinary collaboration. Computational scientists develop algorithms capable of modeling complex biological systems, whereas biologists and chemists provide critical insights into molecular interactions and disease mechanisms. For example, AlphaFold's application in hepatocellular carcinoma demonstrated how AI could predict protein structures for novel targets, leading to the discovery of effective drug candidates within weeks—a process that traditionally takes years. In addition, RWE from wearable devices and patient registries complements clinical trial data, allowing regulatory bodies to expedite drug approvals. This convergence of AI technologies with experimental and clinical expertise underscores the potential for a holistic approach to precision oncology, paving the way for innovative therapies tailored to individual patients.

MULTIDISCIPLINARY APPLICATIONS OF AI IN ONCOLOGY

AI/ML has numerous promising applications throughout the continuum of oncology care (Table 1). The clinical context begins with screening and ends with ongoing monitoring and surveillance. Early applications of AI in early cancer detection have included the following: early symptom detection, radiology, pathology, medical images and videos, biomarker

testing, recurrence detection, remote monitoring, and risk stratification, among other emerging applications (Fig 3).

Screening for Early Cancer Detection

AI has the potential to leverage multimodal data to identify at-risk populations for better targeted screening initiatives, thereby enabling public health entities to optimize their screening and preventive strategies.^{65,66}

As NLP algorithms improve, EHR data can be mined with AI tools to predict the likelihood of developing cancer based on a patient's medical history, genetics, and lifestyle factors. For example, a recent study shows that AI can accurately assess pancreatic cancer risk using unstructured clinical notes within EHRs.⁶⁷ This allows for early intervention and personalized screening plans; AI algorithms have demonstrated increased detection rates for colorectal cancer by incorporating nontraditional risk factors such as environmental exposures.⁶⁸ Furthermore, AI-powered chatbots and virtual assistants help individuals monitor symptoms like pain or fatigue, prompting timely medical attention.^{69,70} By analyzing patient data—including genetic information, family history, and lifestyle factors—AI models could provide comprehensive risk assessments that guide clinicians in recommending regular screenings for high-risk individuals.⁷¹

AI has the potential to directly assist in cancer diagnosis by triggering investigations or referrals based on clinical parameters in individuals undergoing screening. Numerous studies have shown the potential benefits of cancer screening in terms of early detection and reduced mortality rates. However, even in diseases like breast cancer, where screening programs are well-established using routine mammography and/or MRI,⁷²⁻⁷⁴ ongoing debates persist regarding how to select the right patients and balance the risks and benefits. Concerns have arisen about the one-size-fits-all approach, which aligns differently from the principles of personalized medicine.^{74,75}

For example, the US Preventative Services Task Force (USPSTF) recommends annual low-dose CT (LDCT) for lung cancer screening for adults age 50–80 years with a 20+ pack-year history of smoking, who currently smoke or have quit within the past 15 years.⁷⁶ In 2021, only approximately 6% of those eligible were screened, possibly because of a lack of access to screening centers, poor documentation of smoking status, insufficient time during provider visits, and other socioeconomic factors.⁷⁷ Investigators recently trained a CNN model that incorporated minimal EHR data elements, including age, sex, current smoking status plus chest X-ray data from >10,000 patients on two major clinical trials—the Prostate, Lung, Colorectal, and Ovarian trial (PLCO) and National Lung Screening Trial (NLST).⁷⁸ Interestingly, CNN predicted 12-year lung cancer incidence better than CMS eligibility criteria (AUC 0.755 vs 0.634).

TABLE 1. Major AI Applications in Oncology

Application	Oncologic Focus	Example Tools/Algorithms	Potential Benefits	Key Challenges	Level of Evidence
Radiology	Automated lesion detection, radiomics (breast, lung, skin, brain)	CNN-based segmentation, DL models, mammography AI, dermoscopy classification, CT nodule detection, MRI gene prediction	Reduced reading time, improved diagnostic accuracy, earlier detection, fewer false positives	Variability in image acquisition, scanner differences	Prospective trials, observational studies
Pathology	WSI analysis (general pathology)	CNN-based classification, xAI, TIL quantification, automated biomarker detection, MSI analysis	Objective grading, biomarker detection, faster screening	Quality of digital slides, standardization issues	Retrospective validations, pilot RCTs
Radiation oncology	Automated planning, adaptive RT (RT for various cancers)	DL contouring, ART, AI auto-contouring, real-time dose reoptimization	Reduced planning time, consistent dosing, adaptive RT for changing anatomies	High computational demands, workflow integration	Observational, feasibility studies
Medical oncology	Decision support, clinical trial matching, personalized chemotherapy (systemic therapy)	NLP-based systems, LLM (OncoGPT), predictive drug sensitivity models	Personalized regimens, increased trial accrual, fewer side effects, reduced bias	EHR limitations, data integration challenges	Prospective observational studies, pilot RCTs
Intratumoral heterogeneity analysis	Treatment planning	Genetic/phenotypic clustering via AI	Target aggressive tumor subpopulations, monitor disease progression	Complex data interpretation, computational complexity	Observational, early clinical validations
AI-driven drug discovery	Novel and repurposed agents	Recursion, in silico medicine (in silico pipelines)	Faster compound screening, synergy identification, virtual trials	High initial computational investment, validation complexity	Preclinical validations, early-stage trials
Multidisciplinary collaboration	Virtual tumor boards	Integrated dashboards (EHR, imaging, genomic data)	Comprehensive data integration, real-time remote specialist input	Technical interoperability, clinician adoption	Case studies, pilot implementations
AI in low-resource settings	Global oncology	Cloud-based or smartphone-based triaging	Bridging specialist shortages, quicker triage, cost-effectiveness	Infrastructure limitations, data privacy concerns	Pilot studies, observational implementations

Abbreviations: AI, artificial intelligence; ART, adaptive radiotherapy; CNN, convolutional neural network; CT, computed tomography; DL, deep learning; EHR, electronic health record; LLM, large language model; MRI, magnetic resonance imaging; MSI, microsatellite instability; NLP, natural language processing; RCT, randomized controlled trial; RT, radiotherapy; TIL, tumor infiltrating lymphocytes; WSI, whole-slide imaging; xAI, explainable AI.

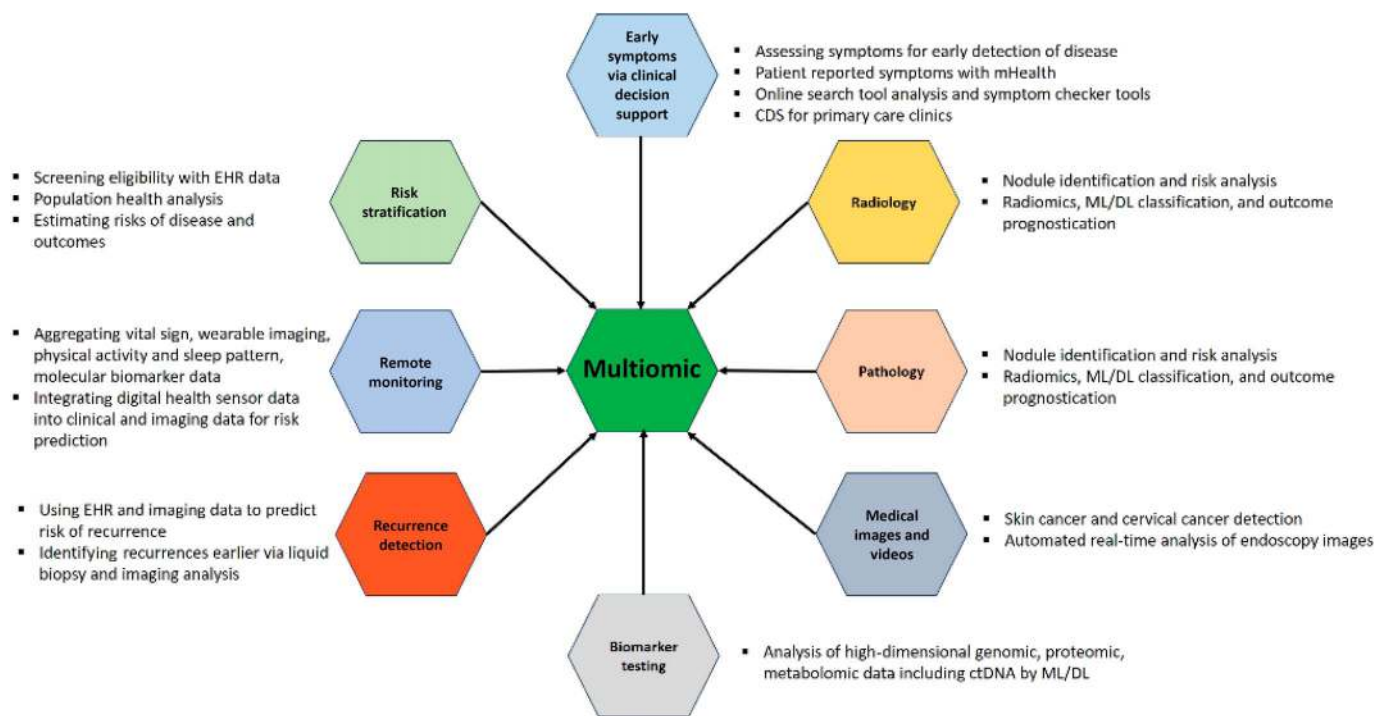


FIG 3. Applications of multiomic data integration in cancer detection and management. Multiomic data serve as a central hub supporting diverse clinical applications in oncology. These include early symptom detection via clinical decision support, risk stratification, remote monitoring, recurrence detection, and biomarker testing. Integration with radiology, pathology, and medical imaging enables advanced ML/DL analytics for risk prediction and prognostication. Together, these components enhance precision medicine by enabling earlier diagnosis, better treatment planning, and improved patient outcomes. CDS, clinical decision support; ctDNA, circulating tumor DNA; DL, deep learning; EHR, electronic health record; ML, machine learning.

Similarly, Gould et al⁷⁹ developed a ML model using non-imaging EHR data to predict lung cancer. The model, trained on a data set of 6,505 patients with lung cancer and 189,597 controls, achieved an AUC of 0.86, outperforming the PLCO Cancer Screening Trial criteria in predicting lung cancer within 9–12 months.^{79,80} This study demonstrated that AI can enhance the assessment of routine clinical data to better identify patients for lung cancer screening programs. It suggests that AI's role in improving patient selection for screening could be a valuable approach to achieving early diagnosis of lung cancer in the future.

AI may also help predict the risk of future pancreatic cancer. Pancreatic cancer is a low-incidence but high-mortality cancer diagnosis, and Placido et al⁶⁷ used the time sequence of disease events to assess the ability to predict cancer risk for increasing intervals between the end of the disease trajectory used for risk prediction and cancer occurrence. They investigated six million patients from the Danish National Patient Registry (24,000 pancreatic cancer cases) and cross-applied their models to three million patients from US Veterans Affairs. They trained an ML model CancerRiskNet on the sequence of disease codes from the EHR, including International Classification of Diseases codes (ICD) diagnosis and billing codes in clinical histories, and tested the prediction of pancreatic cancer within 36 months. Their model had an AUC of 0.88 for the Danish cohort, whereas cross-application to the US-VA cohort had a slightly

lower AUC of 0.71. Retraining was needed to improve performance (AUROC = 0.78). This is an excellent example of a prediction–surveillance selection process in a real-world population. This study used real-world data such as ICD disease codes and billing codes, both a strength and a weakness. Such studies will benefit from incorporating more expansive data beyond disease codes, such as medications, laboratory results, clinical notes, and abdominal imaging (such as CT or MRI), as well as population-wide germline genetic profiles and health records from general practitioners and, in the future, patient-provided information about their health state from wearable devices.

Other studies on pancreatic cancer have also used ML models to sift through expansive EHRs using sophisticated pattern recognition and NLP to flag individuals exhibiting potential cancer indicators, those predisposed based on established risk factors, or particular health metrics linked to cancer. ML algorithms can be deployed to scrutinize specific health markers, such as newly developed hyperglycemia—a potential harbinger of pancreatic cancer—and other data such as age, body mass index, change in body mass index, smoking, use of proton pump inhibitors, antidiabetic medications, and hemoglobin A1C, cholesterol, hemoglobin, creatinine, and alkaline phosphatase levels.^{81,82} These models can also evaluate data from health surveys to stratify individuals into risk categories, thereby enriching the pool of individuals screened for pancreatic cancer, increasing the

yield and cost-effectiveness of early-stage screenings.^{82,83} Such stratification ensures a more focused and efficient allocation of screening resources, potentially catching malignancies at a more treatable stage.

The development of AI-enabled chatbot-based symptom checker apps in health care has been gaining traction.⁸⁴ These apps aim to provide users with potential diagnoses and assist in self-triaging using AI-driven human-like conversations. However, more research is needed to explore their functionalities and user experiences. Early studies suggest that current apps must catch up in replicating the diagnostic process experienced during an in-person medical visit.^{84,85} Users have reported that these apps lack in several areas: they do not adequately support a comprehensive medical history review, they have limitations in accepting flexible symptom input, the questions asked by the apps are often not easily understandable, and there is a lack of coverage for a wide range of diseases and user demographics. These studies suggest the need to enhance their conversational design and include features that address these gaps, aiming to improve these AI-driven health care tools' overall effectiveness and user experience.

Early detection is crucial for better survival outcomes. There is growing evidence that AI can enhance diagnostic accuracy across multiple tumor types.

Breast Cancer

The USPSTF currently recommends that women age 50–74 years at average risk of developing breast cancer undergo biennial screening mammography.⁸⁶ Significant issues with screening include false-positive and false-negative rates, overdiagnosis and overtreatment, psychologic impact, and cost, among other harms and benefits.^{74,87} Improved breast cancer risk models are needed to not only achieve earlier detection of early-stage breast cancers but also reduce overtreatment.

Yala and Barzilay et al from MIT incorporated both imaging factors with nonimaging risk factors, such as age and hormonal factors.^{88,89} When these factors were unavailable in the data, their algorithm would impute those expected values based on the image. Their model takes as input standard views of a mammogram, followed by four modules (1. AUC for all women, 2. AUC for white women, 3. AUC for African American women, and 4. Portion of breast cancers categorized in highest risk decile)—an image encoder and then an aggregator to combine information across views of the entire mammogram. Based on this rich representation of the mammogram, risk factors are then predicted and used if these values need to be imputed. Finally, an additive hazard layer predicts a patient's risk of breast cancer for each year over the next 5 years. Training and testing data were multi-institutional and multinational. Impressively, they found that 31% of patients who would develop cancer within 5 years were identified as high risk by their model, compared with

only 18% by the more commonly used Tyrer-Cuzick model ($P < .001$).

Investigators from Google curated a large representative data set from the United Kingdom and a large enriched data set from the United States.⁹⁰ Their model resulted in an absolute reduction of 5.7% and 1.2% (US and UK cohorts, respectively) in false positives and 9.4% and 2.7% in false negatives. The AI system outperformed six human radiologists, where the AUC-ROC for the AI system was greater than the AUC-ROC for the average radiologist by an absolute margin of 11.5%. Given the high false-positive and false-negative rates for screening mammography, mammograms may be double-read to reduce errors.⁹¹ The AI system maintained noninferior performance in the double-read setting and surprisingly reduced the workload of the second reader by 88%. These results significantly affect resource availability and utilization in radiology, particularly in environments with limited access to radiologists and double-read workflows.

Most recently, Lång et al⁹² conducted a randomized controlled trial to evaluate the clinical safety of an AI-supported mammography screening protocol compared with standard double reading by radiologists. The trial involved women age 40–80 years undergoing mammography screening at four sites in Sweden. Participants were randomly assigned to either AI-supported screening or standard double reading without AI. The AI system provided a malignancy risk score, guiding the radiologists in determining whether a screening examination required single or double reading. The study aimed to assess secondary outcome measures including cancer detection rate, recall rate, false-positive rate, positive predictive value (PPV) of recall, type of cancer detected, and screen-reading workload. The findings revealed that AI-supported screening resulted in a similar cancer detection rate compared with standard double reading, meeting the predefined safety threshold. The recall rates and false-positive rates were comparable between the two groups, whereas the PPV of recall was slightly higher in the AI-supported group. Notably, there was a 44.3% reduction in screen-reading radiologist workload.

Another study by Dembrower et al⁹³ compared double reading by one radiologist plus AI with standard-of-care double reading by two radiologists, as well as single reading by AI alone and triple reading by two radiologists plus AI. The findings revealed that double reading by one radiologist plus AI was noninferior for cancer detection compared with standard double reading by two radiologists. Similarly, single reading by AI alone and triple reading by two radiologists plus AI were also noninferior to standard double reading by two radiologists. Notably, replacing one radiologist with AI resulted in a 4% higher noninferior cancer detection rate. The study suggests that AI has the potential for controlled implementation in screening mammography, which would involve risk management and real-world follow-up of performance.

Numerous other studies are evaluating the ability of innovative methods such as transformers and CNNs to improve the performance of AI algorithms in reading multiview mammograms.⁹⁴⁻⁹⁷

Skin Cancer

AI algorithms use dermoscopic images to discern malignant melanomas from benign moles with high accuracy, sometimes on par with expert dermatologists. Esteva, Thrun, and their team at Stanford created an AI tool for diagnosing skin cancer based on 129,450 clinical images.⁹⁸ The complete taxonomy contained over 2,000 diseases and was organized based on conditions' visual and clinical similarities. The model takes in an image of a skin lesion (eg, melanoma), and the image is sequentially warped into a probability distribution over clinical classes of skin diseases using Google Inception v3 CNN architecture pretrained on the ImageNet data set (which, in turn, was trained on 1.28 million images over 1,000 generic object classes). The authors fine-tuned their data set of 129,450 skin lesions comprising 2,032 diseases. They calculated the probability of an inference class by summing the probabilities of the training classes according to that taxonomy structure. The investigators could visualize the high-dimensional data on the last hidden layer of the CNN, with different clusters of disease categories. Their model here achieved parity with 21 board-certified dermatologists.

However, <5% of their data set pertained to darker skin patients. Recent systematic analysis suggests that ethnicity data are available for only 1.3% of images in publicly available skin data sets.⁹⁹ State-of-the-art dermatology AI models exhibit substantial limitations on diverse dermatology images, particularly dark skin tones, and uncommon diseases.¹⁰⁰ Fine-tuning AI models on diverse data sets can close the performance gap between light and dark skin tones. These findings identify important weaknesses and biases in dermatology AI that should be addressed for reliable application to diverse patients and diseases.¹⁰¹ More prospective trials and external validation of these models are required to ensure generalizability. However, the continuous refinement of these AI systems, coupled with growing databases of medical images, is paving the way for more nuanced and widespread early cancer detection capabilities.

Lung Cancer

More than 1.5 million lung nodules are identified in patients in the United States each year.^{102,103} While modern technology has led to innovations in imaging, biopsy, and bronchoscopic techniques, these approaches are expensive and often invasive and may fail to distinguish between benign and malignant nodules. As previously described, LDCT for lung cancer screening improves lung cancer mortality although most eligible people are not being screened.¹⁰⁴ The NLST and NELSON trials showed that LDCT screening in

those older than 50 years with a 20-pack-year smoking history can result in a 20%–24% decrease in lung cancer mortality.^{105,106}

Ardila et al¹⁰⁷ from Google recently published a DL algorithm to enhance lung cancer screening. Current lung cancer screening might frequently have variable interpretations by different graders and high rates of false positives and negatives.^{76,108,109} The investigators created an end-to-end algorithm that evaluates the entire screening process into a single workflow, from nodule identification to ROI detection to classification and risk prediction (Fig 4A). Their DL model used current and previous CT scans to assess lung cancer risk. It demonstrated state-of-the-art performance, with an AUC of 94.4%, validated on 6,716 cases from the NLST trial and further confirmed on an independent set of 1,139 clinical patients. The model's efficacy was compared with that of radiologists through two reader studies. Notably, the model surpassed the performance of six radiologists in scenarios where previous CT images were unavailable, showing significant reductions in false positives (11% reduction) and negatives (5% reduction). When previous CT scans were available, the model's performance was comparable with that of the radiologists. This model's capability to enhance the accuracy and consistency of lung cancer screenings could lead to broader adoption and improved screening practices globally. This development is particularly significant considering the current low rates of lung cancer screening worldwide.

Another group of investigators from MIT (Mikhael et al¹⁰²) similarly hypothesized that a DL model assessing the entire volumetric LDCT data could be built to predict individual risk without requiring additional demographic or clinical data. Radiologists annotated suspicious lesions on NLST LDCTs using MD.ai¹¹⁰ although they had numerous exclusions for lack of follow-up data, thick slices (no thin slice images), and data load failure. They first extracted features from the LDCTs with a pretrained 3D Resnet-18 encoder, which computed a global feature vector for the volume through a Max Pooling layer and an attention-guided pooling layer. The resulting vectors were concatenated and passed through a hazard layer to produce a cumulative probability of developing lung cancer within 6 years. They trained the same algorithm architecture five times and averaged those risk predictions to create their new algorithm called Sybil. Bounding box annotations of visible cancer nodules were used to guide the model's attention during training but were not used during testing. Surprisingly, Sybil performed exceptionally well, with an AUC of 0.86–0.92 for predicting lung cancer at 1 year in three multinational and multi-institutional cohorts. Sybil can run in the background at a radiology reading station when LDCT images are available without inputting demographic or other clinical data and requiring radiologists to annotate areas of interest. Interestingly, LDCT can be used to predict clinical factors like smoking duration, weight, race, smoking status, sex, family history, and age.¹⁰²

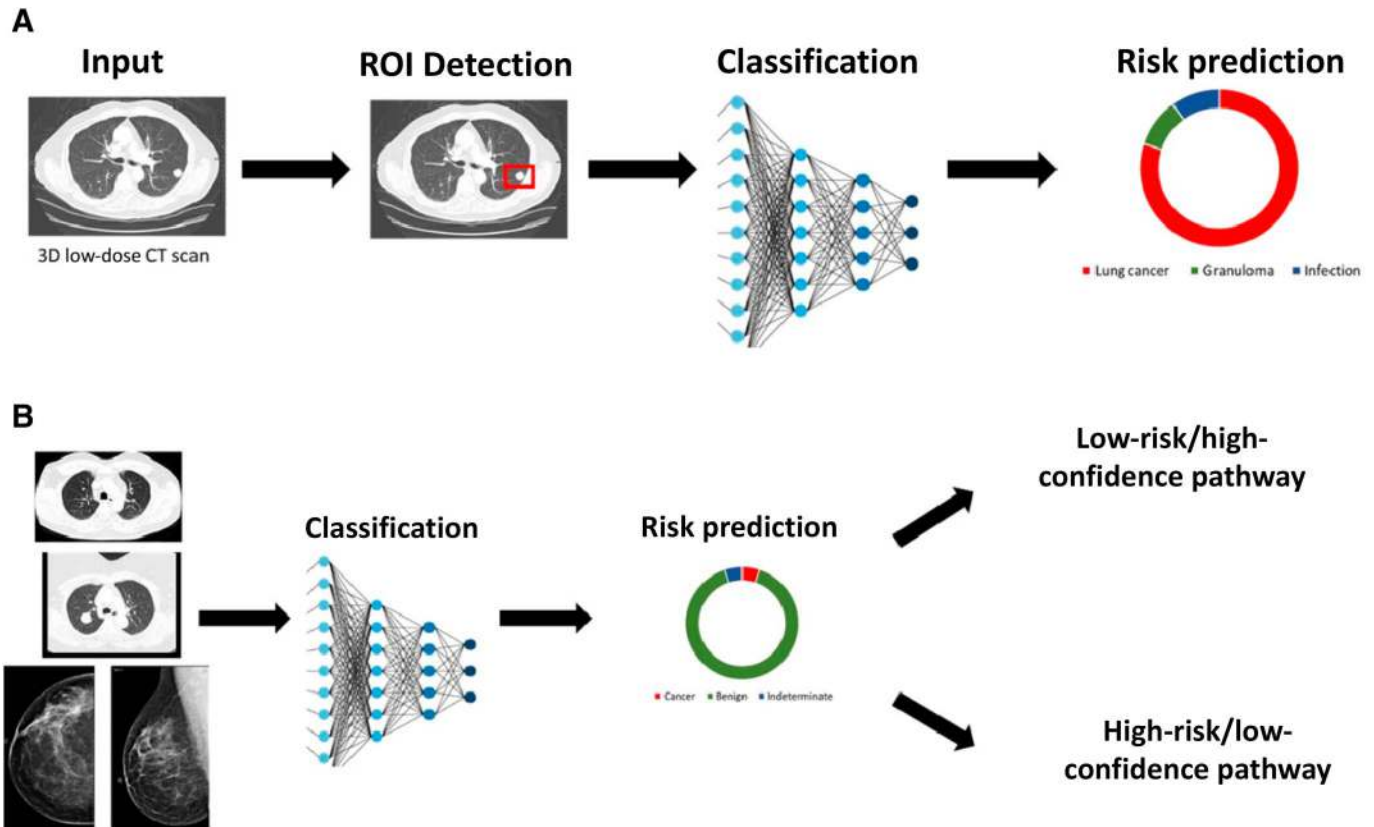


FIG 4. DL-based workflow for cancer risk prediction using medical imaging. AI-driven pipelines for lung and breast cancer detection. (A) In the top panel, a 3D low-dose CT scan undergoes ROI detection, classification through a neural network, and risk prediction for lung cancer, granuloma, or infection. (B) The bottom panel depicts a similar DL framework applied to mammograms and CT images, yielding risk predictions categorized as cancer, benign, or indeterminate. Depending on confidence levels, patients are triaged into low-risk/high-confidence or high-risk/low-confidence pathways, supporting more personalized and efficient clinical decision making. AI, artificial intelligence; CT, computed tomography; DL, deep learning; ROI, region of interest.

With such improvements in the performance of screening methodologies, the general diagnostic workflow for screening studies may evolve shortly; for standard screening procedures such as mammograms and LDCT, a threshold for patient risk, risk prediction, and confidence scores could be set a priori. If the risk is low and confidence is high, then the AI algorithm's analysis could serve as the primary read, with physician as a secondary review. Conversely, if risk is high or confidence in the AI evaluation is low, those cases would be escalated for physician review to supplement the AI evaluation (Fig 4B).

Chen et al¹¹¹ map radiomics features of subcentimeter solid nodules (SCSNs) to H&E-stained pathologic images. Radiomics features were extracted from noncontrast chest CT images preoperatively. The least absolute shrinkage and selection operator (LASSO) regression model was used for radiomics feature extraction and radiomics signature construction. Lung adenocarcinoma was significantly associated with an irregular margin and lobulated shape in the training and external validation sets. Their radiomics signature consisted of 22 features associated with lung adenocarcinomas of SCSNs, with AUCs of the combined model being

0.808–0.885. Such studies will provide more granular and interpretable information to clinicians evaluating these DL models' outputs.

Although an LDCT scan can be used for screening, diagnostic CT scans and more advanced imaging modalities such as PET/CT scans are commonly used for staging and surveillance. Biomarkers of non-small cell lung cancers (such as mutational status of the Epidermal Growth Factor Receptor (EGFR), ALK, ROS, PD-L1, and next-generation sequencing) direct systemic therapy decisions, such as cytotoxic chemotherapy, tyrosine kinase inhibitors, immune checkpoint inhibitors, and others. Currently, mutational analysis must be performed on biopsy tissue and cannot be conducted noninvasively. Mu and colleagues recently used unsupervised hierarchical clustering of DL features to identify significant associations between DL expression patterns and EGFR mutation, stage, smoke status, histology, and sex.¹¹² The EGFR-DL Score (EGFR-DLS) distribution varied among subgroups based on EGFR mutation status and histology type. There were notable differences between adenocarcinoma and squamous cell carcinoma for EGFR wild-type patients. EGFR-DLS was significantly and positively

associated with more prolonged progression-free survival (PFS) in patients treated with EGFR-TKIs. At the same time, EGFR-DLS is significantly and negatively associated with higher durable clinical benefit, reduced hyperprogression, and longer PFS among patients treated with ICIs. Thus, the EGFR-DLS provides a noninvasive method for precise quantification of EGFR mutation status in patients with NSCLC, which is promising for identifying patients with NSCLC sensitive to EGFR-TKI or ICI treatments.¹¹²

Brain Tumors

AI is also revolutionizing the detection and diagnosis of brain tumors, both primary and secondary, by enhancing accuracy, speed, and efficiency in various aspects of the diagnostic process. AI algorithms, particularly DL models, are being used to analyze MRI scans and other imaging modalities with remarkable accuracy. YOLOv7-based models have achieved up to 99.5% accuracy in detecting gliomas, meningiomas, and pituitary tumors in MRI images.¹¹³ Some AI models can detect brain tumors in MRI images almost as well as human radiologists, with accuracy rates around 85%.¹¹⁴

AI tools are enabling faster and more accurate molecular characterization of brain tumors. The DeepGlioma system can detect genetic mutations in brain tumors in under 90 seconds, potentially streamlining diagnosis and treatment planning.¹¹⁵ FastGlioma is a foundation model that rapidly detects glioma infiltration in unprocessed surgical tissue using label-free optical microscopy, achieving results in under 10 seconds with an AUC of over 92% in a multicenter study.¹¹⁶ Its performance surpasses that of traditional intraoperative imaging techniques, and it shows promising zero-shot generalization to other brain tumor subtypes, highlighting its potential as a versatile AI tool in neuro-oncology. ML models are being developed to differentiate pseudoprogression from true progression, a challenging clinical distinction that affects treatment decisions.¹¹⁷ These tools are also enhancing pathologic evaluation. DEPLOY, an AI tool, can analyze images of tumor slides to predict methylation states and infer tumor subtypes with an accuracy of 95%.¹¹⁸

Recent advances in AI-driven MRI analysis have demonstrated significant potential in noninvasively predicting IDH1/2 mutations and MGMT promoter methylation status in gliomas, enabling personalized treatment strategies. For IDH mutation prediction, transformer-based neural networks analyzing multiparametric MRI achieve an accuracy of up to 93% in internal test sets,¹¹⁹ with contrast-enhanced T1-weighted sequences proving to be most effective for radiomic feature extraction.¹²⁰ The integration of whole-tumor radiomics with clinical data through ensemble ML models yields an AUC value of 0.96 in external validations.¹²¹ Similarly, MGMT methylation prediction leverages combined radiomic features from tumor subregions across T1-Gd and T2-FLAIR sequences, with LASSO-optimized models

attaining an accuracy of 82% and an AUC of 0.81.¹²² These AI frameworks successfully correlate imaging phenotypes with molecular signatures by analyzing tumor heterogeneity patterns imperceptible to human observers, potentially reducing reliance on invasive biopsies. Clinically, this predictive capability allows treatment stratification—IDH-mutant gliomas may benefit from targeted therapies, whereas MGMT-methylated tumors show enhanced temozolomide response. However, challenges persist in standardizing imaging protocols and improving model generalizability across diverse patient populations,¹²³ necessitating multicenter validation studies to translate these techniques into routine neuro-oncologic practice. AI models are also being used to predict patient outcomes and guide treatment decisions. A recent study shows that AI can also predict whether adult patients with brain cancer will survive more than eight months after receiving radiotherapy treatment, helping to identify patients who may require early second-line treatment or clinical trial enrollment.¹²⁴

DL models, particularly CNNs, have shown promising results in automating and enhancing the accuracy of brain metastasis detection on MRI scans. Recent studies have demonstrated high sensitivity (85%–96%) in identifying brain metastases, potentially reducing the burden on radiologists and improving early detection rates.¹²⁵ In addition, AI tools are enhancing decision making in stereotactic radiosurgery by predicting local failure risks and optimizing radiation dosing.¹²⁶ Radiogenomics, which uses AI to correlate imaging features with genetic profiles, is also emerging as a noninvasive method to predict mutations like EGFR in brain metastases, potentially guiding targeted therapies without the need for invasive biopsies.¹²⁷ While these applications show great promise, challenges such as the need for larger data sets, external validation, and integration into clinical workflows remain areas for ongoing research and development.

Prostate Cancer

ML-based studies on the early detection of prostate cancer (PC) have increased significantly in recent years.¹²⁸ Numerous studies have focused on the use of AI in biopsy-based detection of PC, MRI-guided PC detection, CT scan-based PC detection, transrectal ultrasound-guided PC detection, 3D pathology-based PC detection, and genomics-based and proteomics-based PC detection.¹²⁸

Gleason grading is the most common system for grading PC. Urologic pathologists typically conduct grading during examination of prostate biopsy cores.¹²⁹ The Gleason score ranges from 6 to 10, with lower scores representing slower-growing and biologically less aggressive disease.¹³⁰ Nagpal et al developed a DL model using 112 million image patches from 1,226 slides annotated by pathologists and tested on 331 slides from 331 patients to improve the Gleason score for prostate cancer slides obtained during prostatectomies. Their model achieved a higher accuracy rate of 0.70

compared with the human eye detection method.¹³¹ Furthermore, another study used an AI-based algorithm trained on 698 biopsies, achieving a sensitivity of 100% in validation.¹³² Cross-validation and data set diversity were emphasized for reliable predictions. Another study used CNNs to enhance Gleason patterns and grading, training on 96 tissue specimens but noting the need for larger data sets.¹³³ A more extensive analysis of 838 biopsies showed that AI assistance improved pathologists' efficiency and reduced result inconsistencies, demonstrating the potential benefits of AI in prostate cancer diagnosis.¹³⁴

Recent advances have allowed DL techniques to be applied to advanced imaging modalities like multiparametric MRI,¹³⁵ which has emerged as an alternative to transrectal ultrasound-guided biopsies.^{136,137} For example, in a retrospective study by Schelb et al comparing clinical assessment with a U-Net DL system, both methods showed similar performance in detecting significant prostate cancer using T2-weighted and diffusion 3 T MRI.¹³⁸ The study involved 312 men, with U-Net achieving a sensitivity of 96% and a specificity of 31% at a probability threshold of ≥ 0.22 , comparable with PI-RADS cutoffs. The combination of PI-RADS and U-Net increased the PPV to 67%, demonstrating the effectiveness of integrating DL in clinical diagnostics for prostate cancer. Other studies have also shown improvement in detection when used with PI-RADS.^{139,140} Various CNN architectures, such as Alexnet, VGG, ResNet, and Googlenet, have also been developed to enhance prediction accuracy.¹⁴¹ In medical imaging, including prostate multiparametric MRI scan images, data augmentation may be necessary to create an ideal data set for CNN networks like VGG, leading to improved prostate cancer diagnosis, detection, and segmentation.¹⁴²

Similarly, improved technology has now allowed for whole pathology slide imaging, where high-resolution digital images are created from scanned pathology slides.^{143,144} First, the whole-slide images are segmented, then divided into tissue patches called tiling, and then undergo image adaptation, ROI extraction, classification, and the calculation of a confidence score. Predefined thresholds and levels of confidence can be set before analysis. After each step, the data are passed through a DL algorithm such as a CNN.¹⁴⁵

In 2021, the FDA authorized the first AI-based software to detect prostate cancer called Paige Prostate.¹⁴⁶ Paige Prostate resulted in the identification of four additional patients whose diagnoses were upgraded from benign/suspicious to malignant. In addition, this AI-based test provided an estimated 65.5% reduction in the diagnostic time for the material analyzed.

Interestingly, investigators are also working on nondestructive 3-dimensional computational pathology based on entire prostate biopsy cores, which may allow for volumetric segmentation of pathology tissues compared with a 2-dimensional pathology approach.¹⁴⁷ The risk assessment

for individuals with low- to intermediate-risk prostate cancers showed better results when considering the 3D glandular attributes of the cancer biopsies as opposed to the comparable 2D features.¹⁴⁷

Investigators across multiple institutions recently published a new foundation model called Virchow.^{148,149} This deep neural network foundation model comprises 632 million parameters, is designed explicitly for computational pathology, and leverages self-supervised learning based on a training data set of 1.5 million H&E-stained whole-slide images encompassing diverse tissue groups. This data set size is orders of magnitude larger than previous efforts. Virchow surpasses state-of-the-art systems when subjected to various downstream tasks, including tile-level pan-cancer detection, subtyping, and slide-level biomarker prediction, demonstrating its superior performance on internal data sets drawn from the same population as the pretraining data and external public data sets. Virchow achieves a balanced accuracy of 93% for pan-cancer tile classification, with impressive AUCs of 0.983 for predicting colon MSI status and 0.967 for predicting breast CDH1 status. These substantial performance improvements underscore the critical importance of pretraining on extensive pathology image data sets and suggest that even more significant performance enhancements can be achieved by pretraining on even larger data sets. This approach holds great potential for various high-impact applications, particularly in scenarios with limited training data, such as drug outcome prediction.¹⁴⁸

As detailed below, AI is also being used in the genomic and proteomic-based detection of PC and other cancers. Traditionally, prostate-specific antigen (PSA) level testing has aided in risk stratification, diagnosis, and surveillance of PC.^{150,151} Within the past several years, many new biomarkers have been introduced for prostate cancer.¹⁵²⁻¹⁵⁴ However, further multiomics integration with genomic, transcriptomic, metabolomic, radiomic, and pathomic data will likely drive further development, including improved performance prediction, discovery of new PC biomarkers, and enhanced PC detection and monitoring/surveillance.¹⁵⁵⁻¹⁵⁹

Image Analysis for Cervical Cancer and Colon Cancer

The integration of AI in analyzing medical images and videos from nonradiology and nonpathology domains is increasingly recognized for its potential in early cancer detection. A recent study in cervical cancer aimed to develop a DL-based algorithm for automatically detecting cervical precancer and cancer in women, particularly in low-resource settings where screening is lacking.¹⁶⁰ Using a longitudinal cohort of 9,406 women in Costa Rica and 60,000 digitized cervical images, the algorithm demonstrated high accuracy (AUC = 0.91) in identifying precancerous and cancerous cases, outperforming traditional cervigram interpretation and cytology by human experts. A single visual screening round for women age 25-49 years could identify over half of

precancer cases while referring only a small percentage for further evaluation. Health workers can use a cell phone or similar camera for this type of cervical screening. Other studies have similarly reported the benefits of DL-based models for automated visual evaluation during colposcopy.^{161–163} This advancement is particularly promising for improving cancer care in low-resource settings, where access to skilled specialists is limited, thereby expanding the reach of life-saving early detection methods.

DL is also being used during endoscopies, such as colonoscopy.¹⁶⁴ Colonoscopy is the gold standard for colorectal cancer screening although 25% of colorectal neoplasia may be missed at screening colonoscopy.^{165,166} AI has been shown to improve real-time polyp detection, differentiate between benign and malignant lesions, and increase adenoma detection rate (ADR).^{167,168} A recent systematic review and meta-analysis of 33 trials showed impressive improvements with AI during colonoscopy, with an incidence rate ratio of 1.39 for ADR using AI-aided systems.¹⁶⁹ Future efforts will focus on the ability of AI algorithms to classify polyps into premalignant vs nonpremalignant, a process called computer-aided diagnosis.¹⁷⁰ Cost-effectiveness, long-term benefits, and reduction in overdiagnosis are all future research areas for this technology. However, this tool may ultimately become a copilot for endoscopists.

Liquid Biopsies

Currently, screenings are organ-specific and limited to five cancer types (breast, lung, colon, cervical, and prostate) for the general population.¹⁷¹ These tests, however, do not provide information about other cancer types in different body parts. Multicancer early detection tests could detect over 50 different types of cancer through a single blood draw, including many cancers that currently lack screening methods.¹⁷² Ideally, such a test would be used in patients at elevated risk, can detect a maximal number of cancers, has a low false-positive rate, limits overdiagnosis localizing the tissue of origin, and is easy to use.^{172,173} Cancer detection through a blood sample is possible because tumor cells shed DNA fragments into the bloodstream. These fragments, known as cell-free DNA (cfDNA), originate from the genome, which contains all the instructions for cellular functions. Other biomarkers can also be detected in the blood, such as circulating tumor cells (CTCs) or tumor nucleic acids.¹⁷⁴ Peripheral blood can be sampled to detect these changes during screening, after treatments, and over time. By sequencing and analyzing these cfDNA fragments, it is possible to determine whether cells in the body are normal or have undergone malignant changes by recognizing differences in DNA methylation patterns in cfDNA.¹⁷⁵

ML algorithms are adept at sifting through the vast and complex data produced by liquid biopsies, identifying disease signatures with higher accuracy and efficiency. These advanced computational methods enhance the detection of cancer-specific signatures from minimal samples, like

blood, by effectively analyzing molecular data, which includes the genetic and epigenetic information of CTCs and DNA. For instance, the Galleri test evaluates over one million methylation sites in cfDNA and applies ML and pattern recognition to identify abnormal methylation patterns that could signal the presence of cancer. Both supervised and unsupervised approaches have been described.^{176–178}

FOCUS ON QUALITY AND SAFETY

While AI's potential in advancing cancer research and treatment is immense, there are a number of ongoing challenges with effective AI development and implementation, as summarized in [Table 2](#).

1. *Defining the purpose of the model and considering clinical integration at the point of model development:* Often, models are developed in isolation using the available data without consideration of how the model outputs will be integrated into the clinical workflow to assist and enhance the care and clinical decisions.^{179,180} Ideally, a multidisciplinary team should work together to clearly define the purpose of the model and how it would integrate clinically so that this purpose can drive what data are needed, what quality and frequency of data are needed, and how the model will be integrated into the clinical workflow.¹⁸¹
2. *Data quality:* While the phrase “garbage in garbage out” is often stated and data are heavily curated for training, the assessment of fit-for-purpose data quality is often overlooked in data used for model training and testing and at the point of implementation.¹⁸⁰ For example, imaging data with annotations from various publicly available data sets are commonly used for model training and testing without consideration of the quality of the images nor the consistency and quality of the annotations.¹⁷⁹ There are emerging studies that report more rapid training of models with smaller higher-quality data sets over larger noisier data sets. Beyond training and testing, the quality of the data that are fed into models once they are implemented can directly affect the performance of models and needs to be considered.¹⁸¹ This is true not only when initially evaluating models but also throughout its lifecycle as the nature and quality of data can evolve over time (eg, devices used to acquire the data can be updated over time).
3. *Addressing bias in data and models:* There has been attention to ensuring representative data sets from the perspective of having all populations included in model training to allow for generalizability and ensuring inclusiveness and equity.^{182–184} Beyond this source of potential bias, there are a number of other sources of bias in the data including but not limited to measurement bias, availability bias, confirmation bias, and confounding factors such as differences in practice across different clinics, regions, and countries. In addition to biases in the data, the model assumptions can also introduce bias in the model outputs. If these considerations of bias are not considered amid model training and use, these could lead

TABLE 2. Key Challenges, Ethical Considerations, and Mitigation Strategies for Effective AI Implementation in Oncology

Challenge	Description	Ethical/Practical Implications	Solutions/Mitigation Strategies
Defining clinical integration and purpose	Models often developed without clear clinical integration planning or defined purpose	Limits clinical utility, increases integration difficulties	Multidisciplinary team involvement, clear definition of clinical workflows and intended model use, early stakeholder engagement
Data quality	Inconsistent or poor-quality data used in training, testing, and postdeployment	Reduces model accuracy and reliability, affects patient care outcomes	Quality assessments; smaller, high-quality data sets over large noisy data sets; continuous data quality monitoring
Bias in data and models	Multiple biases (measurement, availability, confirmation, confounding factors) affecting model outputs	Potentially exacerbates health care disparities, affects clinical fairness	Federated adversarial debiasing, balanced training data sets, continuous bias audits, inclusive data collection strategies
Transparency, explainability, and accountability	Opaque AI decision processes (black box models)	Undermines clinician trust, complicates accountability for adverse outcomes	xAI techniques (attention maps, saliency overlays, Shapley values), clear liability frameworks, transparent AI model design
Implementation and lifecycle management	Challenges in deploying AI systems effectively across diverse clinical settings	Algorithmic bias, limited generalizability, poor health-IT integration, patient safety risks	Comprehensive AI lifecycle management framework, robust MLOps, interdisciplinary collaboration, ongoing validation and governance
Human-AI interaction and clinical decision making	Complex user interfaces, risk of clinician complacency or decision fatigue	May negatively affect clinician autonomy and patient involvement in decision making	User-centric AI interface design, transparent AI guidance, support for clinician-patient interactions, avoid over-reliance on AI recommendations
Privacy and security	Sensitive patient data exposure risk in AI applications	Risks patient confidentiality and public trust, compliance challenges across jurisdictions	Robust encryption, data deidentification, adherence to HIPAA/GDPR, strict governance frameworks
Economic considerations	High up-front and ongoing costs for AI infrastructure and maintenance	Accessibility challenges, particularly in resource-limited settings	Sustainable funding models, AI-as-a-service subscriptions, economic evaluations, demonstration of long-term value and cost-effectiveness
Regulatory and ethical frameworks	Lack of clear performance benchmarks, liability standards, and oversight protocols	Complicates AI approval and clinical integration; unclear accountability when AI errors occur	Dynamic regulatory frameworks, standardized performance benchmarks, comprehensive postmarket surveillance, clear liability delineation, global data standardization initiatives

NOTE. The table highlights critical issues affecting AI’s integration into clinical practice, emphasizing quality, safety, and equity considerations alongside practical solutions to ensure beneficial, transparent, and accountable deployment.

Abbreviations: AI, artificial intelligence; GDPR, General Data Protection Regulation; HIPAA, Health Insurance Portability and Accountability Act; IT, information technology; MLOps, machine learning operations; xAI, Explainable AI.

to a deleterious impact on clinical decisions using model outputs. Continuous bias monitoring is essential, and strategies like federated adversarial debiasing, balanced training sets, and routine audits mitigate bias.¹⁸⁵

4. *Transparency, explainability, and accountability:* The black box challenge can erode clinician trust. Explainable AI (xAI) techniques—attention maps, saliency overlays, and Shapley values—illuminate AI’s rationale.^{186,187} Clear liability frameworks are needed to determine accountability when AI-based recommendations cause adverse outcomes.^{188,189} Opaque DL models undermine clinician trust. xAI methods, like attention maps or saliency overlays, are critical.¹⁹⁰

5. *Model implementation and lifecycle management:* Implementation of AI solutions in an enterprise manner across a clinic, hospital, or health system faces several critical challenges, such as algorithmic bias, limited generalizability across diverse clinical contexts, insufficient real-world validation, patient safety concerns, immature ML operations practices, poor integration into existing Health-IT systems and workflows, and incomplete governance frameworks.¹⁹¹ An AI lifecycle management framework encompasses the entire AI development continuum, from initial concept and evaluation for implementation through to monitoring, maintenance, and decommissioning. Such a framework emphasizes

solution impact, safety, security, and model performance throughout each phase, ensuring successful outcomes and sustained benefits from enterprise AI solutions. It facilitates the rapid evaluation of an AI model's feasibility and suitability for addressing specific health care challenges, effectively mitigating associated risks. AI Lifecycle Management does not function as an isolated process; rather, it provides an overarching framework that incorporates an AI-specific perspective into established technology development methodologies, underscoring the essential role of interdisciplinary collaboration in effective operationalization of AI solutions.¹⁹²

6. *Human-AI interactions and clinical decision making:* There are growing recognition and interest in research around the nature of human-AI interaction and how to most effectively and safely introduce AI outputs to enhance decision making, while minimizing complacent dependency, alarm fatigue, or data overload. Complex user interfaces and limited EHR interoperability hinder adoption.^{193,194} For instance, AI systems should guide—not dictate—clinician-patient decisions, preserving informed consent and patient preference,¹⁹⁵ and enhance clinician-patient discussions, not replace them. Transparent communication about AI's role is vital to maintain trust, ensuring that patients remain central in decision making.^{195,196}
7. *Privacy and security:* Large amounts of sensitive data demand strict governance (eg, Health Insurance Portability and Accountability Act [HIPAA], General Data Protection Regulation [GDPR]) and robust encryption.¹⁹⁷ AI-driven solutions rely on large volumes of patient data. Encryption, deidentification, and compliance with HIPAA/GDPR are essential, particularly in cross-border collaborations.¹⁹⁸ This ensures patient privacy and builds public confidence in AI's role in health care.

CHALLENGES AND FUTURE DIRECTIONS

Despite the advancements discussed in this review, challenges persist in data standardization, algorithmic bias, and regulatory oversight. Heterogeneous imaging protocols and incomplete EHR data sets limit model generalizability, while under-represented populations risk exclusion from AI-driven care paradigms.^{199–201} Ethical frameworks advocating for transparent AI design and federated learning—training models on decentralized data without compromising privacy—are critical to equitable implementation.²⁰² Collaborative efforts among clinicians, data scientists, and policymakers will be essential to harness AI's full potential while safeguarding patient autonomy and safety in this rapidly evolving field.²⁰³

Economic considerations further complicate AI implementation in oncology.²⁰⁴ The substantial up-front investment for AI development, including infrastructure, expertise, and computing resources, creates barriers particularly for resource-limited settings. Ongoing costs for

algorithm updates, validation, and maintenance necessitate sustainable funding models although recent data suggest that cost savings are possible.²⁰⁵ The shift toward AI-as-a-service subscription models may improve accessibility but raises questions about cost-effectiveness, especially when demonstrating AI's value proposition remains challenging amid evolving reimbursement structures.²⁰⁴ Health care systems must balance these economic factors against potential long-term benefits such as improved diagnostic accuracy, reduced treatment delays, and optimized resource allocation.

Regulatory frameworks must evolve to address AI's unique characteristics in oncology care. Regulatory agencies need to establish clear performance benchmarks and data diversity thresholds while implementing dynamic postmarket surveillance systems to monitor algorithmic drift and adverse events.²⁰⁶ Liability frameworks must clearly delineate responsibility among clinicians, developers, and institutions when AI-driven errors occur. To address algorithmic bias, guidelines should mandate transparent data statements with detailed demographics for training sets, regular bias audits with predefined performance standards across population subsets, and incentives for collecting diverse data from under-represented areas.^{207,208} Moving forward, an ASCO AI Task Force could develop quality and safety checklists for AI model evaluation, whereas global efforts must focus on tackling interoperability through data standardization and harmonization to enable more effective development and implementation of AI technologies in cancer care.

CONCLUSION

AI stands as a cornerstone of future oncologic care—facilitating earlier detection, guiding personalized therapies, accelerating drug discovery, and enhancing multidisciplinary collaboration. The integration of AI into oncology workflows offers significant benefits, including improved diagnostic accuracy, customized treatment approaches, and efficient resource allocation. However, fully realizing AI's transformative potential requires addressing data quality, interpretability, privacy, regulatory oversight, and algorithmic bias. Ethical considerations—from maintaining patient autonomy to ensuring equitable implementation—must remain central.

In line with ASCO's 2025 theme, "Driving Knowledge to Action," this study calls for urgent, collective efforts from clinicians, researchers, industry, and policymakers to develop robust guidelines, global collaborations, and specialized training programs. By ensuring equitable access to advanced diagnostics and therapies, we can construct a future where AI-driven, patient-centric oncology is both accessible and impactful—improving outcomes and bridging global disparities so that patients like Mrs Ramirez, whether in Boston or rural Malawi, receive the best possible care.

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REFERENCES

- Thandra KC, Barsouk A, Saginala K, et al: Epidemiology of lung cancer. *Contemp Oncol (Pozn)* 25:45-52, 2021
- Institute of Medicine (US) Committee on Cancer Control in Low- and Middle-Income Countries, in Sloan FA, Gelband H (eds): *Cancer Control Opportunities in Low- and Middle-Income Countries*. Washington, DC, National Academies Press (US), 2007, pp 74-82. <https://www.ncbi.nlm.nih.gov/sites/books/NBK54018/>
- Anonymous: Advancing Access to Radiotherapy in Middle-And Low-Income Countries. 2022. <https://vcdnp.org/advancing-access-to-radiotherapy/>
- Chua IS, Gaziel-Yablowitz M, Korach ZT, et al: Artificial intelligence in oncology: Path to implementation. *Cancer Med* 10:4138-4149, 2021
- Anonymous: The Birth of Artificial Intelligence (AI) Research | Science and Technology. n.d. <https://st.llnl.gov/news/look-back/birth-artificial-intelligence-ai-research>
- News Q, Minsky M: The Brilliant AI Pioneer behind the Neural Network. 2024. <https://quantumzeitgeist.com/marvin-minsky/>
- Anonymous: What Is Machine Learning (ML)? | IBM. 2021. <https://www.ibm.com/think/topics/machine-learning>
- Anonymous: White Papers 2024 Understanding the EU AI Act. n.d. <https://www.isaca.org/resources/white-papers/2024/understanding-the-eu-ai-act>
- Krizhevsky A, Sutskever I, Hinton GE: ImageNet classification with deep convolutional neural networks, in Pereira F, Burges CJ, Bottou L, et al (eds): *Advances in Neural Information Processing Systems*. Red Hook, NY, Curran Associates, 2012, pp 1097-1105
- Hochreiter S, Schmidhuber J: Long Short-Term Memory | Neural Computation. 1997. <https://dl.acm.org/doi/10.1162/neco.1997.9.8.1735>
- Devlin J, Chang M, Lee K, et al: [1810.04805] BERT: Pre-training of Deep Bidirectional Transformers for Language Understanding. 2019. <https://arxiv.org/abs/1810.04805>
- Cortes C, Vapnik V: Support-vector networks. *Mach Learn* 20:273-297. 1995
- Breiman L: Random forests. *Mach Learn* 45:5-32, 2001
- Chen T, Guestrin C: XGBoost: A scalable tree boosting system, in *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*. Association for Computing Machinery, San Francisco, CA, August 13-17, 2016, pp 785-794. <https://doi.org/10.1145/2939672.2939785>
- Goodfellow IJ, Pouget-Abadie J, Mirza M, et al: Generative adversarial nets, in *Proceedings of the 27th International Conference on Neural Information Processing Systems—Volume 2*. Cambridge, MA, NIPS'14 MIT Press, 2014, pp 2672-2680. <https://dl.acm.org/doi/10.5555/2969033.2969125>
- Silva TC, Zhao L: Machine learning. In: Christiano Silva T, Zhao L (eds): *Machine Learning in Complex Networks*. Cham, Springer International Publishing, 2016. pp 71-91
- Goodfellow I: Deep Learning. 2016. <https://www.deeplearningbook.org/>
- Choudhary K, DeCost B, Chen C, et al: Recent advances and applications of deep learning methods in materials science. *NPJ Comput Mater* 8:59, 2022
- Paul D, Sanap G, Shenoy S, et al: Artificial intelligence in drug discovery and development. *Drug Discov Today* 26:80-93, 2021
- Futurside: Neural Networks: A Complete Overview and its Usefulness. n.d. <https://futurside.com/artificial-neural-networks/>
- Mahanama S: Introduction to Artificial Neural Networks (ANN). 2020. <https://medium.com/analytics-vidhya/introduction-to-artificial-neural-networks-ann-3109578d61ab>
- Surianarayanan C, Lawrence JJ, Chelliah PR, et al: Convergence of artificial intelligence and neuroscience towards the diagnosis of neurological disorders-A scoping review. *Sensors* 23:3062, 2023
- Sun T, Feng B, Huo J, et al: Artificial intelligence meets flexible sensors: Emerging smart flexible sensing systems driven by machine learning and artificial synapses. *Nanomicro Lett* 16:14, 2023
- OpenAI: ChatGPT. 2023. <https://openai.com/chatgpt>
- Longwell JB, Grant RC, Hirsch I, et al: Large language models encode medical oncology knowledge: Performance on the ASCO and ESMO examination questions. *JCO Oncol Pract* 19:511, 2023
- Norozi Z, Orooji A, Erfanian L: Analyzing the impact of feature selection methods on machine learning algorithms for heart disease prediction. *Sci Rep* 13:22588, 2023
- Roe KD, Jawa V, Zhang X, et al: Feature engineering with clinical expert knowledge: A case study assessment of machine learning model complexity and performance. *PLoS One* 15:e0231300, 2020
- Yousef M, Allmer J: Deep learning in bioinformatics. *Turk J Biol Turk Biyol Derg* 47:366-382, 2023
- Jiang T, Gradus JL, Rosellini AJ: Supervised machine learning: A brief primer. *Behav Ther* 51:675-687, 2020
- Zhang D, Yin C, Zeng J, et al: Combining structured and unstructured data for predictive models: A deep learning approach. *BMC Med Inform Decis Mak* 20:280, 2020
- Brownlee J: How to Control Neural Network Model Capacity with Nodes and Layers. 2019. <https://machinelearningmastery.com/how-to-control-neural-network-model-capacity-with-nodes-and-layers/>
- Hunter B, Hindocha S, Lee RW: The role of artificial intelligence in early cancer diagnosis. *Cancers* 14:1524, 2022
- Yamashita R, Nishio M, Do RKG, et al: Convolutional neural networks: An overview and application in radiology. *Insights Imaging* 9:611-629, 2018
- Shen D, Wu G, Suk H-I: Deep learning in medical image analysis. *Annu Rev Biomed Eng* 19:221-248, 2017

35. Sanders J, Frank S, Lewis G, et al: Multi-tasking neural networks for anatomy segmentation in prostate brachytherapy MRI. *Brachytherapy* 18:S16, 2019
36. Sanders JW, Frank SJ, Kudchadker RJ, et al: Development and clinical implementation of SeedNet: A sliding-window convolutional neural network for radioactive seed identification in MRI-assisted radiosurgery (MARS). *Magn Reson Med* 81:3888-3900, 2019
37. Sanders JW, Fletcher JR, Frank SJ, et al: Deep learning application engine (DLAE): Development and integration of deep learning algorithms in medical imaging. *SoftwareX* 10:100347, 2019
38. Sanders J, Bruno T, Frank S, et al: SeedNet for automated detection and localization of radioactive seeds in post-implant MRI: A comparison with and without the use of an endorectal coil for imaging. *Brachytherapy* 17:S80-S81, 2018
39. He K, Gan C, Li Z, et al: Transformers in medical image analysis. *Intell Med* 3:59-78, 2023
40. IBM: What Is an Attention Mechanism? | IBM. 2024. <https://www.ibm.com/think/topics/attention-mechanism>
41. Kim Y, Jeong H, Chen S, et al: Medical hallucinations in foundation models and their impact on healthcare. *medRxiv* 2025
42. Hanna MG, Parwani A, Sirintrapun SJ: Whole slide imaging: Technology and applications. *Adv Anat Pathol* 27:251-259, 2020
43. Hanna MG, Reuter VE, Hameed MR, et al: Whole slide imaging equivalency and efficiency study: Experience at a large academic center. *Mod Pathol* 32:916-928, 2019
44. Hijazi A, Bifulco C, Baldin P, et al: Digital pathology for better clinical practice. *Cancers* 16:1686, 2024
45. Niazi MKK, Parwani AV, Gurcan MN: Digital pathology and artificial intelligence. *Lancet Oncol* 20:e253-e261, 2019
46. Hutchinson JC, Picarsic J, McGenity C, et al: Whole slide imaging, artificial intelligence, and machine learning in pediatric and perinatal pathology: Current status and future directions. *Pediatr Dev Pathol* 28:91-98, 2025
47. Fatima G, Alhmadi H, Ali Mahdi A, et al: Transforming diagnostics: A comprehensive review of advances in digital pathology. *Cureus* 16:e71890, 2024
48. Hanna MG, Ardon D: Digital pathology systems enabling quality patient care. *Genes Chromosomes Cancer* 62:685-697, 2023
49. Baidoshvili A, Bucur A, van Leeuwen J, et al: Evaluating the benefits of digital pathology implementation: Time savings in laboratory logistics. *Histopathology* 73:784-794, 2018
50. McGenity C, Clarke EL, Jennings C, et al: Artificial intelligence in digital pathology: A systematic review and meta-analysis of diagnostic test accuracy. *NPJ Digit Med* 7:114, 2024
51. Salehi MA, Harandi H, Mohammadi S, et al: Diagnostic performance of artificial intelligence in detection of hepatocellular carcinoma: A meta-analysis. *J Imaging Inform Med* 37:1297-1311, 2024
52. Abdul Rasool Hassan B, Mohammed AH, Hallit S, et al: Exploring the role of artificial intelligence in chemotherapy development, cancer diagnosis, and treatment: Present achievements and future outlook. *Front Oncol* 15:1475893, 2025
53. Graf M, Ziegelmayer S, Reischl S, et al: CT-derived quantitative image features predict neoadjuvant treatment response in adenocarcinoma of the gastroesophageal junction with high accuracy. *Cancers* 17:216, 2025
54. Ah-Thiane L, Heudel P-E, Campone M, et al: Large language models as decision-making tools in oncology: Comparing artificial intelligence suggestions and expert recommendations. *JCO Clin Cancer Inform* 10.1200/CCI-24-00230
55. Chang T-G, Cao Y, Sfreddo HJ, et al: LORIS robustly predicts patient outcomes with immune checkpoint blockade therapy using common clinical, pathologic and genomic features. *Nat Cancer* 5: 1158-1175, 2024
56. Conger K: Unique Stanford Medicine-Designed AI Predicts Cancer Prognoses, Responses to Treatment. 2025. <https://med.stanford.edu/news/all-news/2025/01/ai-cancer-prognosis.html>
57. Waters JK: AI Shows Promise in Predicting Immunotherapy Response for Rare Cancer Patients, Unit Reveals at SITC 2024. 2024. <https://medcloudinsider.com/Articles/2024/11/18/AI-Shows-Promise-in-Predicting-Immunotherapy-Response-for-Rare-Cancer-Patients.aspx>
58. Schroeder B: Five MIT Faculty Members Take on Cancer Grand Challenges. 2024. <https://news.mit.edu/2024/mit-faculty-take-on-cancer-grand-challenges-0318>
59. Hunter E: AI Can Map Entire Patient Journey in Precision Oncology, from Clinical Trial Matching to Drug Matching. 2023. <https://www.pharmacytimes.com/view/ai-can-map-entire-patient-journey-in-precision-oncology-from-clinical-trial-matching-to-drug-matching>
60. Kurnaz S, Loaiza-Bonilla A, Carvallo Castañeda D, et al: Effect of a novel artificial intelligence (AI)-Enabled multi-trial matching system on patient matching using real-world data. *J Clin Oncol* 42, 2024 (suppl 16; abstr e13501)
61. BusinessWire: Massive Bio Recognized by White House Cancer Moonshot for First-Of-Their-Kind Pre-screening Hubs and AI-Powered Trial Matching, Launches \$15 Million Initiative at JPM 2025. 2025. <https://www.businesswire.com/news/home/20250115751663/en/Massive-Bio-Recognized-by-White-House-Cancer-Moonshot-for-First-of-Their-Kind-Pre-Screening-Hubs-and-AI-Powered-Trial-Matching-Launches-%2415-Million-Initiative-at-JPM-2025>
62. Gajra A, Mallahan S, Blau S, et al: Impact of Exigent Research Network's partnership with the tempus AI TIME program on the screening and matching of patients for clinical trials. *J Clin Oncol* 42, 2024 (suppl 16; abstr e13599)
63. American Cancer Society: Cancer Clinical Trials | Cancer Trials. 2025. <https://www.cancer.org/cancer/managing-cancer/making-treatment-decisions/clinical-trials.html>
64. American College of Radiology: New ARPA-H Initiative to Benefit ACR Clinical Trials Programs. 2025. <https://www.acr.org/News-and-Publications/New-ARPA-H-Initiative-to-Benefit-ACR-Clinical-Trials-Programs>
65. Zhang B, Shi H, Wang H: Machine learning and AI in cancer prognosis, prediction, and treatment selection: A critical approach. *J Multidiscip Healthc* 16:1779-1791, 2023
66. Cellina M, Cacioppa LM, Cè M, et al: Artificial intelligence in lung cancer screening: The future is now. *Cancers* 15:4344, 2023
67. Placido D, Yuan B, Hjaltekin JX, et al: A deep learning algorithm to predict risk of pancreatic cancer from disease trajectories. *Nat Med* 29:1113-1122, 2023
68. Lubell J: How AI Is Improving the Rate of Colon Cancer Risk Detection. 2025. <https://www.ama-assn.org/practice-management/digital/how-ai-improving-rate-colon-cancer-risk-detection>
69. Tabataba Vakili S, Haywood D, Kirk D, et al: Application of artificial intelligence in symptom monitoring in adult cancer survivorship: A systematic review. *JCO Clin Cancer Inform* 10.1200/CCI.24.00119
70. Thaker NG, Dicker AP, Loaiza-Bonilla A, et al: The role of artificial intelligence in early cancer detection: Exploring early clinical applications. *AI Precis Oncol* 1:91-105, 2024
71. Lee CI, Elmore JG: Cancer risk prediction paradigm shift: Using artificial intelligence to improve performance and health equity. *J Natl Cancer Inst* 114:1317-1319, 2022
72. Budh DP, Sapra A: Breast Cancer Screening. Treasure Island, FL, StatPearls Publishing, 2023
73. Eisemann N, Bunk S, Mukama T, et al: Nationwide real-world implementation of AI for cancer detection in population-based mammography screening. *Nat Med* 31:917-924, 2025
74. Lehman CD, Blume JD, Weatherall P, et al: Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer* 103:1898-1905, 2005
75. Esserman LJ, WISDOM Study and Athena Investigators: The WISDOM study: Breaking the deadlock in the breast cancer screening debate. *NPJ Breast Cancer* 3:34, 2017
76. US Preventive Services Task Force, Krist AH, Davidson KW, et al: Screening for lung cancer: US preventive services task Force recommendation statement. *JAMA* 325:962-970, 2021
77. American Lung Association: New Report: Critically Low Lung Cancer Screening Rates Reveal Opportunity to Save More Lives. 2023. <https://www.prnewswire.com/news-releases/new-report-critically-low-lung-cancer-screening-rates-reveal-opportunity-to-save-more-lives-301677370.html>
78. Lu MT, Raghu VK, Mayrhofer T, et al: Deep learning using chest radiographs to identify high-risk smokers for lung cancer screening computed tomography: Development and validation of a prediction model. *Ann Intern Med* 173:704-713, 2020
79. Gould MK, Tang T, Liu I-LA, et al: Recent trends in the identification of incidental pulmonary nodules. *Am J Respir Crit Care Med* 192:1208-1214, 2015
80. National Cancer Institute: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) | Division of Cancer Prevention. 2023. <https://prevention.cancer.gov/major-programs/prostate-lung-colorectal-and-ovarian-cancer-screening-trial-plco>
81. Boursi B, Finkelman B, Gintantonio BJ, et al: A clinical prediction model to assess risk for pancreatic cancer among patients with new-onset diabetes. *Gastroenterology* 152:840-850.e3, 2017
82. Singhi AD, Koay EJ, Chari ST, et al: Early detection of pancreatic cancer: Opportunities and challenges. *Gastroenterology* 156:2024-2040, 2019
83. Muhammad W, Hart GR, Nartowt B, et al: Pancreatic cancer prediction through an artificial neural network. *Front Artif Intell* 2:2, 2019
84. You Y, Gui X: Self-diagnosis through AI-enabled chatbot-based symptom checkers: User experiences and design considerations. *AMIA Annu Symp Proc* 2020:1354-1363, 2020
85. Reardon S: AI Chatbots Can Diagnose Medical Conditions at Home. How Good Are They? n.d. <https://www.scientificamerican.com/article/ai-chatbots-can-diagnose-medical-conditions-at-home-how-good-are-they/>
86. USPSTF: Recommendation: Breast Cancer: Screening | United States Preventive Services Taskforce. 2023. <https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-screening>
87. Welch HG, Passow HJ: Quantifying the benefits and harms of screening mammography. *JAMA Intern Med* 174:448-454, 2014
88. Yala A, Mikhael PG, Strand F, et al: Toward robust mammography-based models for breast cancer risk. *Sci Transl Med* 13:eaba4373, 2021
89. Brentnall AR, Harkness EF, Astley SM, et al: Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. *Breast Cancer Res* 17:147, 2015
90. McKinney SM, Sieniek M, Godbole V, et al: International evaluation of an AI system for breast cancer screening. *Nature* 577:89-94, 2020
91. Taylor-Phillips S, Stinton C: Double reading in breast cancer screening: Considerations for policy-making. *Br J Radiol* 93:20190610, 2020
92. Lång K, Josefsson V, Larsson A-M, et al: Artificial intelligence-supported screen reading versus standard double reading in the mammography screening with artificial intelligence trial (MASAI): A clinical safety analysis of a randomised, controlled, non-inferiority, single-blinded, screening accuracy study. *Lancet Oncol* 24:936-944, 2023

93. Dembrower K, Crippa A, Colón E, et al: Artificial intelligence for breast cancer detection in screening mammography in Sweden: A prospective, population-based, paired-reader, non-inferiority study. *Lancet Digit Health* 5:e703-e711, 2023
94. Chen X, Zhang K, Abdoli N, et al: Transformers improve breast cancer diagnosis from unregistered multi-view mammograms. *Diagnostics* (Basel, Switzerland) 12:1549, 2022
95. Betancourt Tarifa AS, Marrocco C, Molinara M, et al: Transformer-based mass detection in digital mammograms. *J Ambient Intelligence Humanized Comput* 14:2723-2737, 2023
96. Cantone M, Marrocco C, Tortorella F, et al: Convolutional networks and transformers for mammography classification: An experimental study. *Sensors* 23:1229, 2023
97. Matsoukas C, Haslum JF, Söderberg M, et al: Is it Time to Replace CNNs with Transformers for Medical Images? 2021
98. Esteve A, Kuprel B, Novoa RA, et al: Dermatologist-level classification of skin cancer with deep neural networks. *Nature* 542:115-118, 2017
99. Wen D, Khan SM, Ji Xu A, et al: Characteristics of publicly available skin cancer image datasets: A systematic review. *Lancet Digit Health* 4:e64-e74, 2022
100. Daneshjou R, Vodrahalli K, Novoa RA, et al: Disparities in dermatology AI performance on a diverse, curated clinical image set. *Sci Adv* 8:eabq6147, 2022
101. Zou J, Schiebinger L: AI can be sexist and racist—It's time to make it fair. *Nature* 559:324-326, 2018
102. Mikhael PG, Wohlwend J, Yala A, et al: Sybil: A validated deep learning model to predict future lung cancer risk from a single low-dose chest computed tomography. *J Clin Oncol* 41:2191-2200, 2023
103. Mazzone PJ, Lam L: Evaluating the patient with a pulmonary nodule: A review. *JAMA* 327:264-273, 2022
104. McDowell S: New Lung Cancer Screening Guideline Increases Eligibility. 2023. <https://www.cancer.org/research/acs-research-news/new-lung-cancer-screening-guidelines-urge-more-to-get-lcdt.html>
105. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al: Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 365:395-409, 2011
106. de Koning HJ, van der Aalst CM, de Jong PA, et al: Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med* 382:503-513, 2020
107. Ardila D, Kiraly AP, Bharadwaj S, et al: End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. *Nat Med* 25:954-961, 2019
108. Wood DE, Eapen GA, Ettinger DS, et al: Lung cancer screening. *J Natl Compr Cancer Netw* 10:240-265, 2012
109. Bartlett EC, Silva M, Callister ME, et al: False-negative results in lung cancer screening—Evidence and controversies. *J Thorac Oncol* 16:912-921, 2021
110. MD.ai: MD.ai | Center for Artificial Intelligence in Medicine & Imaging. 2023. <https://aimi.stanford.edu/shared-datasets/software-tools/mdai>
111. Chen X, Feng B, Chen Y, et al: A CT-based radiomics nomogram for prediction of lung adenocarcinomas and granulomatous lesions in patient with solitary sub-centimeter solid nodules. *Cancer Imaging* 20:45, 2020
112. Mu W, Jiang L, Zhang J, et al: Non-invasive decision support for NSCLC treatment using PET/CT radiomics. *Nat Commun* 11:5228, 2020
113. Abdulalov AB, Mukhiddinov M, Whangbo TK: Brain tumor detection based on deep learning approaches and magnetic resonance imaging. *Cancers* 15:4172, 2023
114. Rustom F, Moroze E, Parva P, et al: Deep learning and transfer learning for brain tumor detection and classification. *Biol Methods Protoc* 9:bpae080, 2024
115. Hollon T, Jiang C, Chowdury A, et al: Artificial-intelligence-based molecular classification of diffuse gliomas using rapid, label-free optical imaging. *Nat Med* 29:828-832, 2023
116. Kondepudi A, Pekmezci M, Hou X, et al: Foundation models for fast, label-free detection of glioma infiltration. *Nature* 637:439-445, 2025
117. Jang B-S, Jeon SH, Kim IH, et al: Prediction of pseudoprogression versus progression using machine learning algorithm in glioblastoma. *Sci Rep* 8:12516, 2018
118. Hoang D-T, Shulman ED, Turakulov R, et al: Prediction of DNA methylation-based tumor types from histopathology in central nervous system tumors with deep learning. *Nat Med* 30:1952-1961, 2024
119. Yu D, Zhong Q, Xiao Y, et al: Combination of MRI-based prediction and CRISPR/Cas12a-based detection for IDH genotyping in glioma. *NPJ Precis Oncol* 8:140, 2024
120. Kasap DNG, Mora NGN, Blömer DA, et al: Comparison of MRI sequences to predict IDH mutation status in gliomas using radiomics-based machine learning. *Biomedicines* 12:725, 2024
121. Truong NCD, Bangalore Yogananda CG, Wagner BC, et al: Two-stage training framework using multicontrast MRI radiomics for IDH mutation status prediction in glioma. *Radiol Artif Intell* 6:e230218, 2024
122. Restini FCF, Torfeh T, Aouadi S, et al: AI tool for predicting MGMT methylation in glioblastoma for clinical decision support in resource limited settings. *Sci Rep* 14:27995, 2024
123. Kim B-H, Lee H, Choi KS, et al: Validation of MRI-based models to predict MGMT promoter methylation in gliomas: BraTS 2021 radiogenomics challenge. *Cancers* 14:4827, 2022
124. Chelliah A, Wood DA, Canas LS, et al: Glioblastoma and radiotherapy: A multicenter ai study for survival predictions from MRI (GRASP study). *Neuro Oncol* 26:1138-1151, 2024
125. Cho SJ, Sunwoo L, Baik SH, et al: Brain metastasis detection using machine learning: A systematic review and meta-analysis. *Neuro Oncol* 23:214-225, 2021
126. Yarlagadda S, Zhang Y, Saxena A, et al: Development of a machine learning-based tool to predict local failure after stereotactic radiosurgery for small brain metastases. *Int J Radiat Oncol Biol Phys* 120:e292, 2024
127. Cao R, Fu L, Huang B, et al: Brain metastasis magnetic resonance imaging-based deep learning for predicting epidermal growth factor receptor (EGFR) mutation and subtypes in metastatic non-small cell lung cancer. *Quant Imaging Med Surg* 14:4749-4762, 2024
128. Rabaan AA, Bakhrebah MA, AlSaihati H, et al: Artificial intelligence for clinical diagnosis and treatment of prostate cancer. *Cancers* 14:5595, 2022
129. Mattiuzzi C, Lippi G: Current cancer epidemiology. *J Epidemiol Glob Health* 9:217-222, 2019
130. Leslie SW, Soon-Sutton TL, Sajjad H, et al: Prostate Cancer. Treasure Island, FL, StatPearls Publishing, 2023
131. Nagpal K, Foote D, Liu Y, et al: Development and validation of a deep learning algorithm for improving Gleason scoring of prostate cancer. *NPJ Digit Med* 2:48, 2019
132. Marginean F, Arvidsson I, Simoulis A, et al: An artificial intelligence-based support tool for automation and standardisation of Gleason grading in prostate biopsies. *Eur Urol Focus* 7:995-1001, 2021
133. Lucas M, Jansen I, Savci-Heijink CD, et al: Deep learning for automatic Gleason pattern classification for grade group determination of prostate biopsies. *Virchows Arch* 475:77-83, 2019
134. Huang W, Randhawa R, Jain P, et al: Development and validation of an artificial intelligence-powered platform for prostate cancer grading and quantification. *JAMA Netw Open* 4:e2132554, 2021
135. Mottet N, Bellmunt J, Bolla M, et al: EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. *Eur Urol* 71:618-629, 2017
136. Kasivisvanathan V, Rannikko AS, Borghi M, et al: MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 378:1767-1777, 2018
137. Rouvière O, Puech P, Renard-Penna R, et al: Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): A prospective, multicentre, paired diagnostic study. *Lancet Oncol* 20:100-109, 2019
138. Schelb P, Kohl S, Radtke JP, et al: Classification of cancer at prostate MRI: Deep learning versus clinical PI-RADS assessment. *Radiology* 293:607-617, 2019
139. Greer MD, Brown AM, Shih JH, et al: Accuracy and agreement of PI-RADSv2 for prostate cancer mpMRI: A multireader study. *J Magn Reson Imaging JMIR* 45:579-585, 2017
140. Gaur S, Lay N, Harmon SA, et al: Can computer-aided diagnosis assist in the identification of prostate cancer on prostate MRI? A multi-center, multi-reader investigation. *Oncotarget* 9:33804-33817, 2018
141. Anwar A: Difference between AlexNet, VGGNet, ResNet, and Inception. n.d. <https://towardsdatascience.com/the-w3h-of-alexnet-vggnet-resnet-and-inception-7baaecccc96>
142. Li H, Lee CH, Chia D, et al: Machine learning in prostate MRI for prostate cancer: Current status and future opportunities. *Diagnostics* 12:289, 2022
143. Escobar Díaz Guerrero R, Carvalho L, Bocklitz T, et al: Software tools and platforms in digital pathology: A review for clinicians and computer scientists. *J Pathol Inform* 13:100103, 2022
144. Reder NP, Glaser AK, McCarty EF, et al: Open-top light-sheet microscopy image atlas of prostate core needle biopsies. *Arch Pathol Lab Med* 143:1069-1075, 2019
145. Ianni JD, Soans RE, Sankarapandian S, et al: Tailored for real-world: A whole slide image classification system validated on uncured multi-site data emulating the prospective pathology workload. *Sci Rep* 10:3217, 2020
146. da Silva LM, Pereira EM, Salles PG, et al: Independent real-world application of a clinical-grade automated prostate cancer detection system. *J Pathol* 254:147-158, 2021
147. Xie W, Reder NP, Koyuncu C, et al: Prostate cancer risk stratification via nondestructive 3D pathology with deep learning-assisted gland analysis. *Cancer Res* 82:334-345, 2022
148. Vorontsov E, Bozkurt A, Casson A, et al: Virchow: A Million-Slide Digital Pathology Foundation Model. 2023
149. Vorontsov E, Bozkurt A, Casson A, et al: A foundation model for clinical-grade computational pathology and rare cancers detection. *Nat Med* 30:2924-2935, 2024
150. Botchorishvili G, Matikainen MP, Lilja H: Early prostate-specific antigen changes and the diagnosis and prognosis of prostate cancer. *Curr Opin Urol* 19:221-226, 2009
151. Narain TA, Sooriakumaran P: Beyond prostate specific antigen: New prostate cancer screening options. *World J Mens Health* 40:66-73, 2022
152. Jin W, Fei X, Wang X, et al: Detection and prognosis of prostate cancer using blood-based biomarkers. *Mediators Inflamm* 2020:8730608, 2020
153. Farha MW, Salami SS: Biomarkers for prostate cancer detection and risk stratification. *Ther Adv Urol* 14:17562872221103988, 2022
154. McDonald AC, Vira M, Shen J, et al: Circulating microRNAs in plasma as potential biomarkers for the early detection of prostate cancer. *The Prostate* 78:411-418, 2018
155. Kim Y, Ignatchenko V, Yao CQ, et al: Identification of differentially expressed proteins in direct expressed prostatic secretions of men with organ-confined versus extracapsular prostate cancer. *Mol Cell Proteomics* 11:1870-1884, 2012
156. Sun Y, Zhu S, Ma K, et al: Identification of 12 cancer types through genome deep learning. *Sci Rep* 9:17256, 2019
157. Kim Y, Jeon J, Mejia S, et al: Targeted proteomics identifies liquid-biopsy signatures for extracapsular prostate cancer. *Nat Commun* 7:11906, 2016
158. Scher HI, Heller G, Molina A, et al: Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. *J Clin Oncol* 33:1348-1355, 2015
159. Wörheide MA, Krumsiek J, Kastenmüller G, et al: Multi-omics integration in biomedical research—A metabolomics-centric review. *Anal Chim Acta* 1141:144-162, 2021

160. Hu L, Bell D, Antani S, et al: An observational study of deep learning and automated evaluation of cervical images for cancer screening. *J Natl Cancer Inst* 111:923-932, 2019
161. Fu L, Xia W, Shi W, et al: Deep learning based cervical screening by the cross-modal integration of colposcopy, cytology, and HPV test. *Int J Med Inform* 159:104675, 2022
162. Yuan C, Yao Y, Cheng B, et al: The application of deep learning based diagnostic system to cervical squamous intraepithelial lesions recognition in colposcopy images. *Sci Rep* 10:11639, 2020
163. Xue Z, Novetsky AP, Einstein MH, et al: A demonstration of automated visual evaluation of cervical images taken with a smartphone camera. *Int J Cancer* 147:2416-2423, 2020
164. Joseph J, LePage EM, Cheney CP, et al: Artificial intelligence in colonoscopy. *World J Gastroenterol* 27:4802-4817, 2021
165. Issa IA, Noureddine M: Colorectal cancer screening: An updated review of the available options. *World J Gastroenterol* 23:5086-5096, 2017
166. Mayo Clinic: AI-assisted Colonoscopies Reduce Miss Rate by 50 Percent. 2023. <https://www.mayoclinic.org/medical-professionals/cancer/news/ai-assisted-colonosopies-reduce-miss-rate-by-50-percent/mac-20536196>
167. Quan SY, Wei MT, Lee J, et al: Clinical evaluation of a real-time artificial intelligence-based polyp detection system: A US multi-center pilot study. *Sci Rep* 12:6598, 2022
168. Mayo Clinic: Role of AI in Detection and Management of Colorectal Polyps and Cancer. 2023. <https://www.mayoclinic.org/medical-professionals/digestive-diseases/news/role-of-ai-in-detection-and-management-of-colorectal-polyps-and-cancer/mac-20479605>
169. Lou S, Du F, Song W, et al: Artificial intelligence for colorectal neoplasia detection during colonoscopy: A systematic review and meta-analysis of randomized clinical trials. *eClinicalMedicine* 66:102341, 2023
170. Chao W-L, Manickavasagan H, Krishna SG: Application of artificial intelligence in the detection and differentiation of colon polyps: A technical review for physicians. *Diagnostics (Basel)* 9:99, 2019
171. Deverka PA, Douglas MP, Phillips KA: Multicancer screening tests: Anticipating and addressing considerations for payer coverage and patient access. *Health Aff (Millwood)* 41:383-389, 2022
172. Ofman J, Hall M, Aravanis A: GRAIL and the quest for earlier multi-cancer detection. 2020
173. National Cancer Institute: Questions and Answers about MCD Tests | Division of Cancer Prevention. 2023. <https://prevention.cancer.gov/major-programs/cancer-screening-research-network-csrn/questions-and-answers-about-multi-cancer>
174. Ginghina O, Hudita A, Zamfir M, et al: Liquid biopsy and artificial intelligence as tools to detect signatures of colorectal malignancies: A modern approach in patient's stratification. *Front Oncol* 12:856575, 2022
175. Liu MC, Oxnard GR, Klein EA, et al: Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol* 31:745-759, 2020
176. Svensson C-M, Krusekopf S, Lücke J, et al: Automated detection of circulating tumor cells with naive Bayesian classifiers. *Cytometry A* 85:501-511, 2014
177. Kalantari S, Rutishauser D, Samavat S, et al: Urinary prognostic biomarkers and classification of IgA nephropathy by high resolution mass spectrometry coupled with liquid chromatography. *PLoS One* 8:e80830, 2013
178. Helzer KT, Sharifi MN, Sperger JM, et al: Fragmentomic analysis of circulating tumor DNA-targeted cancer panels. *Ann Oncol* 34:813-825, 2023
179. Brink L, Coombs LP, Kattil Veetil D, et al: ACR's Connect and AI-LAB technical framework. *JAMIA Open* 5:00ac094, 2022
180. Nair M, Svedberg P, Larsson I, et al: A comprehensive overview of barriers and strategies for AI implementation in healthcare: Mixed-method design. *PLoS One* 19:e0305949, 2024
181. Ennab M, Mcheick H: Enhancing interpretability and accuracy of AI models in healthcare: A comprehensive review on challenges and future directions. *Front Robot AI* 11:1444763, 2024
182. Farhud DD, Zokaei S: Ethical issues of artificial intelligence in medicine and healthcare. *Iran J Public Health* 50:i-v, 2021
183. World Health Organization: WHO Calls for Safe and Ethical AI for Health. 2023. <https://www.who.int/news/item/16-05-2023-who-calls-for-safe-and-ethical-ai-for-health>
184. World Health Organization: The WHO Released a Framework on the Ethical Use of AI in Medicine. Oncologists Must Adapt. 2023. <https://dailynews.ascopubs.org/doi/10.1200/ADN.23.201585/full>
185. Parikh RB, Teeple S, Navathe AS: Addressing bias in artificial intelligence in health care. *JAMA* 322:2377-2378, 2019
186. Harishbhai Tilala M, Kumar Chenchala P, Choppadandi A, et al: Ethical considerations in the use of artificial intelligence and machine learning in health care: A comprehensive review. *Cureus* 16:e62443, 2024
187. Pierce RL, Van Biesen W, Van Cauwenberge D, et al: Explainability in medicine in an era of AI-based clinical decision support systems. *Front Genet* 13:903600, 2022
188. Cestonaro C, Delicati A, Marcante B, et al: Defining medical liability when artificial intelligence is applied on diagnostic algorithms: A systematic review. *Front Med* 10:1305756, 2023
189. Maliha G, Gerke S, Cohen IG, et al: Artificial intelligence and liability in medicine: Balancing safety and innovation. *Milbank Q* 99:629-647, 2021
190. Habli I, Lawton T, Porter Z: Artificial intelligence in health care: Accountability and safety. *Bull World Health Organ* 98:251-256, 2020
191. Davis SE, Walsh CG, Matheny ME: Open questions and research gaps for monitoring and updating AI-enabled tools in clinical settings. *Front Digit Health* 4:958284, 2022
192. Daye D, Wiggins WF, Lungren MP, et al: Implementation of clinical artificial intelligence in radiology: Who decides and how? *Radiology* 305:E62-E563, 2022
193. Alkathiri MS: Artificial intelligence assisted improved human-computer interactions for computer systems. *Comput Electr Eng* 101:107950, 2022
194. Palojoki S, Lehtonen L, Vuokko R: Semantic interoperability of electronic health records: Systematic review of alternative approaches for enhancing patient information availability. *JMIR Med Inform* 12:e53535, 2024
195. Jiang T, Sun Z, Fu S, et al: Human-AI interaction research agenda: A user-centered perspective. *Data Inf Manag* 8:100078, 2024
196. Pataranutaporn P: Project Overview | Cyborg Psychology: The Art + Science of Designing Human-AI Systems that Support Human Flourishing. 2025. <https://www.media.mit.edu/projects/cyborg-psychology/overview/>
197. Price WN II, Cohen IG: Privacy in the age of medical big data. *Nat Med* 25:37-43, 2019
198. Wang C, Zhang J, Lassi N, et al: Privacy protection in using artificial intelligence for healthcare: Chinese regulation in comparative perspective. *Healthcare (Basel)* 10:1878, 2022
199. Cross JL, Choma MA, Onofrey JA: Bias in medical AI: Implications for clinical decision-making. *PLoS Digit Health* 3:e0000651, 2024
200. Deig CR, Kanwar A, Thompson RF: Artificial intelligence in radiation oncology. *Hematol Oncol Clin North Am* 33:1095-1104, 2019
201. Norori N, Hu Q, Aellen FM, et al: Addressing bias in big data and AI for health care: A call for open science. *Patterns (New York, NY)* 2:100347, 2021
202. Arora A, Alderman JE, Palmer J, et al: The value of standards for health datasets in artificial intelligence-based applications. *Nat Med* 29:2929-2938, 2023
203. ASCO: ASCO Sets Six Guiding Principles for AI in Oncology. 2024. <https://ascopost.com/issues/june-25-2024/asco-sets-six-guiding-principles-for-ai-in-oncology/>
204. Khanna NN, Maindarker MA, Viswanathan V, et al: Economics of artificial intelligence in healthcare: Diagnosis vs. Treatment. *Healthcare* 10:2493, 2022
205. Patel TA, Heintz J, Chen J, et al: Spending analysis of machine learning-based communication nudges in oncology. *NEJM AI* 1:Aloa2300228, 2024
206. Tang D, Xi X, Li Y, et al: Regulatory approaches towards AI medical devices: A comparative study of the United States, the European Union and China. *Health Policy* 153:105260, 2025
207. Chen F, Wang L, Hong J, et al: Unmasking bias in artificial intelligence: A systematic review of bias detection and mitigation strategies in electronic health record-based models. *J Am Med Inform Assoc* 31:1172-1183, 2024
208. Coots M, Linn KA, Goel S, et al: Racial bias in clinical and population health algorithms: A critical review of current debates. *Annu Rev Public Health* 46:507-523, 2025

Designing Clinical Trials for Patients With Rare Cancers: Connecting the Zebras

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OVERVIEW

The field of rare cancer research is rapidly transforming, marked by significant progress in clinical trials and treatment strategies. Rare cancers, as defined by the National Cancer Institute, occur in fewer than 150 cases per million people each year, yet they collectively represent a significant portion of all cancer diagnoses. Because of their infrequency, these cancers pose distinct challenges for clinical trials, including limited patient populations, geographical dispersion, and a general lack of awareness of treatment options. Economic limitations further complicate drug development, making initiatives such as the Orphan Drug Act essential for incentivizing research. The advent of next-generation sequencing (NGS) and precision medicine has been instrumental in identifying actionable genetic alterations in parallel with an explosion in the development of genomically targeted therapies, immunotherapies, and antibody drug conjugates. Advances in clinical NGS, precision medicine, and tumor-agnostic therapies have become central to the progress in rare cancer research. The development and approval of tumor-agnostic drugs, such as BRAF, NTRK, and RET inhibitors, and immunotherapy for mismatch repair deficient/microsatellite instability–high status cancers highlight the potential of personalized treatments across diverse cancer types and across the age spectrum. Collaborative trials from cooperative groups including SWOG DART, ASCO TAPUR, NCI-MATCH, pediatric COG-match, DRUP, IMPRESS, and innovative registrational basket and platform trials (eg, VE-Basket, ROAR, LIBRETTO-001, ARROW), along with patient advocacy group-run trials like TRACK, are enhancing access to clinical trials. In addition, artificial intelligence has the potential to improve the trial matching process. An integrated approach, combining these innovations in collaboration with multiple stakeholders, is crucial for advancing rare cancer research, offering hope for better patient outcomes and quality of life.

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INTRODUCTION

The National Cancer Institute (NCI) classifies rare cancers as those that occur in <150 cases per million people annually, which translates to about 15 cases per 100,000 individuals each year. In the United States, this equates to approximately 40,000 or fewer new cases annually.¹ In Europe, cancers are considered rare when they affect fewer than six individuals of every 100,000 each year.² The Oncology Center of Excellence at the US Food and Drug Administration (FDA) defines ultrarare cancers as those that occur in fewer than 1,000 people each year in the United States or as unique molecular variations within more common cancers.³ While individually each of these cancers are rare or ultrarare, together, they account for almost 25% of the total cancer cases. There are roughly over 200 distinct types of rare or ultrarare cancers.⁴ By definition, pediatric cancers are all rare cancers.

Rare cancers are complex and multifaceted diseases, and clinical trials are essential for developing new treatment

strategies and improving patient outcomes.^{5,6} Conducting clinical trials for rare cancers presents several significant challenges. First, the limited patient population makes accrual difficult. Second, the geographic dispersion of patients complicates logistics and coordination.^{7,8} Third, there is often a lack of awareness and expertise among clinicians, leading to delayed referrals and diagnosis. Fourth, regulatory and ethical considerations in combination with the limited population size pose challenges in designing trials that meet regulatory requirements; adaptive designs and next-generation novel end points require time and education to gain acceptance.^{9–11} Fifth, the heterogeneity among rare cancer types can itself present a problem. Finally, funding constraints further impact research efforts as rare cancers often receive less financial support compared with more common types. All these issues are further exacerbated in pediatric cancers.^{12,13}

Developing medications for rare cancers poses significant economic challenges for pharmaceutical companies because

PRACTICAL APPLICATIONS

- **Innovative Trial Designs:** Basket, umbrella, and platform trials streamline rare cancer research by testing multiple cancer types or mutations in one trial, allowing for comprehensive data collection and robust studies despite small populations.
- **Precision Medicine and Next-Generation Sequencing:** Harnessing next-generation sequencing, we can identify genetic alterations in rare cancers, facilitating the path for personalized treatments and customized trial enrollment, ultimately leading to improved outcomes.
- **Tumor-Agnostic Therapies:** These therapies target genetic alterations regardless of cancer origin, offering new treatment options for rare cancers with shared molecular traits, surpassing tissue-specific limitations.
- **Collaborative Research Efforts:** By uniting resources and expertise, cooperative groups and advocacy organizations advance rare cancer research, facilitate large-scale trials, improve access to new therapies, and influence policy changes.
- **Artificial Intelligence in Trial Matching:** Future artificial intelligence integration promises enhanced patient enrollment in rare cancer trials through improved screening and matching processes.

of the limited market size, resulting in few companies being motivated to invest in the research and development of treatments for these uncommon conditions. To address this issue, the US FDA introduced the Orphan Drug Act in 1983. This legislation aimed to incentivize the creation of drugs specifically designed for rare diseases, including rare cancers.¹⁴ Cooperative groups have been key to advancing rare cancer research through public funding and expanding access to clinical trial platforms.

Advances in clinical next-generation sequencing (NGS), precision medicine, and tumor-agnostic therapies have become crucial and have taken a center stage in moving the rare cancer field forward.^{15–18} In addition, innovative registrational basket and platform trials (eg., VE-Basket, ROAR, LIBRETTO-001); cooperative group trials in the United States such as SWOG-DART, ASCO TAPUR, and NCI-MATCH; system-wide trials such as DRUP and IMPRESS; and, more recently, patient advocacy group-run trials such as TRACK have played a significant role in facilitating rare cancer research (Table 1).^{19–26} With patients diagnosed with rare cancers spread across diverse locations, social media has become a powerful tool, bringing together patient groups to connect and support one another.²⁷ Decentralized trials may

also permit patients to stay near home while they are treated on a clinical trial.^{7,8} The future integration of artificial intelligence (AI) in screening and matching clinical trials holds promise for overcoming enrollment hurdles. This perspective explores these key areas and their impact on successfully enrolling patients with rare cancer in clinical trials.

PRECISION ONCOLOGY AND NGS

Precision oncology refers to the tailoring of medical treatment to the individual characteristics of each patient, particularly their genetic profile.^{16,28} This approach contrasts with the traditional one-size-fits-all model, where treatments are designed for the average patient without considering individual variability.²⁹ Precision medicine leverages genetic information, biomarkers, and other patient-specific data to design personalized treatment plans that can be more effective with fewer side effects. The era of precision oncology has been enabled by the advent of widespread availability of NGS. NGS is a powerful technology that allows for the rapid sequencing of the entire genome or targeted regions of DNA and RNA.³⁰ Unlike traditional sequencing methods, NGS can process millions of sequences simultaneously, making it a high-throughput and cost-effective solution for genetic analysis. By understanding the genetic landscape of a patient's cancer, clinicians can identify specific alterations that may be targeted by existing or experimental therapies, thus facilitating personalized treatment strategies. In rare cancers, identifying specific biomarkers is crucial for developing targeted therapy strategies.

PATIENTS WITH RARE CANCERS BENEFIT FROM ENROLLING IN CLINICAL TRIALS

Patients with rare cancers have significantly benefited from enrollment in clinical trials, which offer access to cutting-edge therapies and personalized treatment options that are not available through standard of care (Table 2).^{17,49} The advent of NGS has also been pivotal in identifying specific genetic alterations such as *NTRK* fusions or *BRAF* V600 mutations in a wide variety of cancers, thereby facilitating the enrollment of patients into trials that are most likely to benefit them. In parallel, emergence of basket trials (like NCI-MATCH) that are available for patients across many diseases benefits patients with rare cancer. For instance, a pooled analysis of the combination of the *BRAF* + *MEK* inhibitor ROAR basket trial, the *BRAF*V600 arm of the NCI-MATCH trial, and a pediatric brain tumor trial led to FDA approval of this combination across all tumors highlighting the potential of targeted therapies in rare cancers.^{20,23,50,51}

Studies such as the I-PREDICT study underscore the value of molecular profiling in enabling personalized combination therapy, with treatment tailored based on the unique genetic makeup of each patient's cancer.^{41–43} The SWOG DART trial exemplifies the success of immunotherapy in treating rare cancers.^{52–54} In addition, early-phase trials, especially those

TABLE 1. Clinical Trial Platforms That Have Identified Effective Therapies for Rare Cancer Populations

Study Name	Description	Outcomes	Reference
ASCO TAPUR	The Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a nonrandomized clinical trial that aims to describe the performance (both safety and efficacy) of FDA-approved, targeted anticancer drugs prescribed for treatment of patients with advanced cancer that has a potentially actionable genomic alteration	Multiple arms show clinical benefit with many targets like BRAF, HER2, and TMB	85
NCI Match	The NCI-MATCH (Molecular Analysis for Therapy Choice) trial (ClinicalTrials.gov identifier: NCT02465060) was launched in 2015 as a genomically driven, signal-seeking precision medicine platform trial—largely for patients with treatment-refractory, malignant solid tumors	Having completed in 2023, it remains one of the largest tumor-agnostic, precision oncology trials undertaken to date	23
SWOG/NCI DART	DART: Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors	DART was the US national immunotherapy trial (nivolumab and ipilimumab) for rare cancers. It enrolled 798 patients with rare cancers on 53 cohorts and was open at >1,000 sites across the United States. Multiple cohorts reached their efficacy end points, setting the stage for several NCCN guideline changes for patients with rare cancers	52
VE-Basket	VE-BASKET, a first-in-kind, phase II, histology-independent basket study of VEM in nonmelanoma solid tumors harboring <i>BRAF V600</i> mutations (V600m)	FDA approval in rare cancer ECD/LCH	22
LIBRETTO-001	Phase I/II, single-group, open-label, basket trial of selipercatinib in patients 18 years and older (or ≥12 years, where permitted by regulatory authorities) with <i>RET</i> -altered cancers	FDA approval in RET + adult and pediatric cancers	21
ROAR	ROAR study was designed to assess the activity and safety of dabrafenib plus trametinib in patients with <i>BRAFV600E</i> -mutated rare cancers	FDA approval in BRAF V600 + adult and pediatric cancers	20,61,62
ARROW	ARROW (ClinicalTrials.gov identifier: NCT03037385 , ongoing) was designed to evaluate pralsetinib efficacy and safety in patients with advanced <i>RET</i> -altered solid tumors	Tumor-agnostic clinical benefit in many rare cancers	79,86
DRUP	Prospective, nonrandomized clinical trial A Dutch National Study on behalf of the CPCT to facilitate patient access to commercially available, targeted anticancer drugs to determine the potential efficacy in treatment of advanced cancers with a known molecular profile	Real-world clinical access to many off-label drugs	87
SAMBA 101	Retrospective review of prospectively enrolled patients with sarcoma on early-phase trials	The ORR of 587 patients with sarcoma was 13.1% matched compared with 4.9% in unmatched ($P < .001$); the clinical benefit rate at 6 months was 43.9% v 19.9% ($P < .001$); PFS (median, 5.5 v 2.4 months; $P < .001$) and OS (median, 21.5 v 12.3 months; $P < .001$)	57
SAMBA 102	Retrospective review of prospectively enrolled patients with ultrarare sarcoma on early-phase trials	106 ultrarare sarcomas. The median OS on matched trials was 27.3 months (95% CI, 1.9 to 52.7) v unmatched with 13.4 months (95% CI, 6.3 to 20.6; $P = .291$)	56
NGS Rare Cancer Study	Retrospective review of prospectively enrolled patients with rare cancers on early-phase trials based on NGS	Clinical benefit in multiple rare cancers	55
MTB for unicorns	MTB-based N-of-1 therapies in rare cancers	112 rare/ultrarare cancers. Clinical benefit of matched therapy recommended by an MTB	88

Abbreviations: CPCT, Center for Personalized Cancer Treatment; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DRUP, The Drug Rediscovery Protocol; ECD, Erdheim-Chester disease; FDA, US Food and Drug Administration; Her2, human epidermal growth factor receptor 2; LCH, Langerhans cell histiocytosis; MTB, Molecular Tumor Board; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TMB, tumor mutational burden; VEM, vemurafenib.

TABLE 2. Trial Design Considerations for Patients With Rare Cancer

Study Design	Definition	Examples	Comments	Reference
Basket trials	Patients enrolled with different types of cancers that share a common genetic mutation or biomarker. Instead of focusing on a single cancer type, these trials group patients based on the presence of a specific molecular alteration, regardless of the tumor's tissue of origin. This design allows for the investigation of targeted therapies across multiple rare cancers simultaneously	MyPathway, VE-Basket ROAR, NCI-Match	VE-Basket—FDA approval of vemurafenib in ECD/LCH ROAR + NCI-Match—BRAF + MEK tumor-agnostic approval	22,31–34
Umbrella trials	Focus on a single type of cancer but investigate multiple targeted therapies within that cancer type, based on distinct genetic or molecular subgroups Patients assigned to different treatment arms depending on their tumor's specific characteristics. This design enables the evaluation of several targeted treatments within a single trial framework	Examples are the Lung-MAP trial for non–small cell lung cancer, which includes various sub-studies, and the MyeloMATCH for AML and myelodysplastic syndromes; both include multiple substudies with eligibility based on different genetic alterations	Having a nonmatch treatment substudy increases the proportion of participants who can be enrolled on a substudy	35,36
Adaptive trials	Adaptive trials use a flexible design that allows for modifications to the study protocol based on interim results. These modifications can include changes to the sample size, treatment arms, or end points. Adaptive trials are particularly useful for rare cancers as they can optimize resource use and improve the trial's efficiency by focusing on the most promising treatments	The I-SPY 2 trial for breast cancer is an example of an adaptive trial that adjusts treatment regimens based on ongoing results		37
Platform trials	Platform trials are a type of adaptive trial that allows for the continuous addition and removal of treatment arms as new therapies become available. This design is suitable for evaluating multiple treatments simultaneously and can adapt to emerging scientific knowledge	The STAMPEDE trial for prostate cancer is an example of a platform trial that has tested various therapeutic strategies over time		38
Registry-based trials/master observational trials (MOT)	Registry-based trials/MOTs leverage existing patient registries to identify eligible participants and collect data. These trials can be particularly efficient for rare cancers as they use pre-existing infrastructure and patient cohorts. The use of registries can facilitate rapid patient recruitment and real-world data collection	Examples include TAPROOT and European Organization for Research and Treatment of Cancer (EORTC) SPECTA rare platform, which integrates patient data from multiple registries to support rare cancer trials		39,40

(continued on following page)

TABLE 2. Trial Design Considerations for Patients With Rare Cancer (continued)

Study Design	Definition	Examples	Comments	Reference
N-of-1 trials	N-of-1 trials are trials that treat each patient with a customized regimen and evaluate the algorithm reflecting the matching of patients to drugs, often called a matching score (rather than evaluating a type of treatment in a group of patients with a disease) N-of-1 trials are uniquely patient-centered (patients are at the trial universe center, and drugs are matched to each patient), which differs from canonical trial types, which are drug-centered (the trial drugs are the center of the trial universe, and patients are found for the drugs)	I-PREDICT and WINHER are examples of N-of-1 trials that used NGS (or in the case of WINHER, NGS, or transcriptomics) to navigate toward therapy Single patient inpatient dose escalation studies are also N-of-1 studies	N-of-1 trials in the cancer field differ from the similarly named N-of-1 trials used in noncancer research, in which single patients serve as their own control and are alternatively given different therapeutic agents or placebos. These types of N-of-1 trials are generally not usable in the cancer field because cancer will progress if patients are off therapy for periods of time	41–45
Multi-arm, multi-stage (MAMS) trials	MAMS trials are designed to evaluate multiple treatments simultaneously and can progress through different stages based on interim analyses. This design allows for the efficient comparison of several therapies and the early discontinuation of ineffective treatments	An example is the FOCUS4 trial for colorectal cancer, which evaluates multiple targeted therapies in different subgroups of patients		46
Hybrid designs	Uses external control data sets and random assignment to experimental and control groups to effectively assess the impact of the experimental treatment	In silico trials in extended-stage small cell lung cancer, in silico glioblastoma trial, and ARROW synthetic real-world synthetic control arm trials	Uses synthetic control arms	47,48

Abbreviations: ECD, Erdheim-Chester disease; FDA, US Food and Drug Administration; LCH, Langerhans cell histiocytosis; MOT, master observational trials; NGS, next generation sequencing.

with eligibility based on biomarkers, and early-phase consortia play a crucial role in increasing the enrollment of patients with rare cancer by offering early access to novel treatments.^{55–58} Collectively, these advances underscore the importance of clinical trials in improving outcomes for patients with rare cancers.

CASE STUDY OF RARE CANCERS AND CLINICAL BENEFIT WITH BRAF INHIBITORS

One of the prime examples of biomarker-driven drug development that benefited patients with rare cancers is BRAF inhibitors. BRAF V600 mutations appear in over 60% of melanomas and are also present in numerous other cancer types, including rare cancers such as salivary gland cancer, anaplastic thyroid cancer, appendiceal cancer, Erdheim-Chester disease, Langerhans cell histiocytosis, cranio-pharyngioma, and pediatric glioma.^{50,59,60} Initially developed for melanoma, broader application of the BRAF inhibitor vemurafenib was evaluated through a histology-independent basket trial, VE-BASKET trial, which revealed the actionable potential of BRAF V600 mutations across multiple cancer types.^{22,31} This trial included basket arm

cohorts for rare cancer including Langerhans Cell Histiocytosis (LCH) and Erdheim-Chester disease (ECD) harboring BRAFV600 mutations. The trial's high response rates in these ultrarare diseases led to the FDA approval of vemurafenib for Erdheim-Chester disease based on data from just 22 patients in a single-arm study.³² In this study, 26 patients from the VE-BASKET trial were included, comprising 22 with ECD and 4 with LCH. The overall response rate (ORR) was 61.5% (95% CI, 40.6% to 79.8%), whereas for patients with ECD, it was 54.5% (95% CI, 32.2% to 75.6%).³²

As the combination of BRAF + MEK inhibitors became standard of care in melanoma, the Rare Oncology Agnostic Research (ROAR) was designed as the first prospective investigation of the combination of dabrafenib and trametinib for patients with advanced, rare cancers harboring the BRAFV600E mutation that included cohorts for anaplastic thyroid cancer, biliary tract cancer (BTC), appendiceal cancer, GI stromal tumor, gliomas, and hairy cell leukemia.²⁰ The trial's success, particularly in the anaplastic thyroid cancer cohort, resulted in the first targeted therapy approval for one of the most lethal cancers based on the initial data set

of <25 patients.^{61,62} Demonstrating pan-cancer efficacy across 21 histologies, the study adopted a basket design, treating tumors with the same driver mutation with the same combination of drugs mirroring the VE-BASKET study.^{63,64} After ROAR's initiation, the NCI launched the MATCH study, exploring dabrafenib plus trametinib in various BRAFV600E-mutated malignancies.¹⁹ ROAR's findings corroborated those of the NCI-MATCH trial, which reported a 38% overall response rate with dabrafenib plus trametinib in patients with BRAF mutation-positive solid tumors and lymphomas.¹⁹ These studies, alongside a pediatric glioma trial and case reports, further affirmed the effectiveness of BRAF + MEK inhibition in diverse BRAFV600E mutation-positive tumors, including ultrarare cancers such as histiocytic sarcoma and ameloblastoma.²⁰ A pooled analysis of all the studies (ROAR + NCI-MATCH + pediatric glioma) led to the FDA approval of the BRAF + MEK inhibitor as the first combination therapy to receive approval as a tumor-agnostic therapy.²⁰ The assessment of safety and efficacy involved 131 adult participants enrolled in open-label, multigroup studies, BRF117019 (ClinicalTrials.gov identifier: [NCT02034110](#)) and NCI-MATCH (ClinicalTrials.gov identifier: [NCT02465060](#)). In addition, 36 pediatric participants were evaluated in study CTMT212X2101 (ClinicalTrials.gov identifier: [NCT02124772](#)).⁶⁵ Further evidence was drawn from the findings of COMBI-d, COMBI-v, and BRF113928, which are studies focusing on melanoma and lung cancer harboring BRAFV600 mutations.⁶⁵

TUMOR-AGNOSTIC APPROVALS AND THEIR IMPACT ON RARE CANCERS

Rare cancers have significantly benefited from tumor-agnostic drug development. Tumor-agnostic therapies are treatments that target specific genetic alterations or biomarkers regardless of the cancer's tissue of origin.^{12,66} This approach is based on the understanding that certain genetic alterations can drive cancer growth across different types of tumors.¹⁵ Tumor-agnostic therapies offer a new paradigm in cancer treatment, allowing for the use of the same targeted therapy in multiple cancer types that share the same genetic alteration and has benefited patients with rare cancer.¹⁵ Since 2017, the world of oncology has been revolutionized by the emergence of tumor-agnostic therapies since the approval of an immunotherapy pembrolizumab for all cancers harboring an MSI-H/dMMR signature.¹⁵

The shift toward tumor-agnostic therapies is particularly crucial for rare cancers. Many molecular alterations occur in a small fraction of tumors, often <5%. Given that rare tumors affect fewer than six in 100,000 people, these molecular changes might be present in just one in a million individuals with a specific rare cancer diagnosis. Conducting clinical trials for such a narrowly defined subset of approximately 200 rare tumor types is not feasible. Importantly, because these molecular alterations drive the cancer, therapies that target them can provide effective treatment options for patients with rare malignancies, a

group that has historically been underserved. As of date, immunotherapy, targeted therapy, and an antibody drug conjugates have been approved in a tissue-agnostic manner. In most cases, the targets span the adult and pediatric population.¹²

TISSUE-AGNOSTIC IMMUNOTHERAPY FOR SOLID TUMORS

MSI-H-/dMMR-Positive Cancers

Pembrolizumab, an anti-PD-1 therapy, was the first immunotherapy to receive FDA approval in 2017 for use based on a genomic biomarker and represented the marriage of the field of genomics and immunology.^{28,67} The approval is in solid tumors with MSI-H/dMMR, found in around 3% of cancers. In a clinical trial involving 149 patients, pembrolizumab achieved an ORR of 39.6%, with sustained responses lasting six months or more in 78% of responders. Dostarlimab, another anti-PD-1 therapy, received FDA approval in 2021 for treating dMMR solid tumors, affecting about 3% of cancers.⁶⁸ In a trial with 209 patients, the ORR was 41.6%, with a median response duration of 34.7 months.

High Tumor Mutational Burden Tumors

High tumor mutational burden (TMB) has proven to be a powerful biomarker for immunotherapy, even in the absence of microsatellite instability.⁶⁹⁻⁷¹ In 2020, pembrolizumab was also approved for treating tumors with high TMB, ≥ 10 mutations/mb, affecting approximately 14% of cancers.⁷² Among 102 patients, the ORR was 29%, with 57% experiencing response durations of at least 12 months.⁷³

TISSUE-AGNOSTIC GENE-TARGETED THERAPY

NTRK Fusions

NTRK fusions are ultrarare, occurring in about 1 in 300 adults or children with cancer.⁷⁴ Even so, targeting them results in remarkably high response rates. Indeed, there are now three NTRK inhibitors with tumor-agnostic FDA approvals. Larotrectinib, an NTRK inhibitor approved in 2018, targets solid tumors with NTRK gene fusions, present in roughly 0.3% of cancers.⁷⁵ It demonstrated an ORR of 75% in 55 patients across various cancer types. Entrectinib, approved in 2019, also targets NTRK gene fusions and showed an ORR of 57% in 54 adult patients. It is additionally approved for ROS1-positive non-small cell lung cancer.⁷⁶ Repotrectinib, receiving FDA approval in 2024, targets NTRK gene fusion-positive tumors.⁷⁷ In 88 adult patients, the ORR was between 50% and 58%, with a median response duration of 9.9 months.

RET Fusions

Selpercatinib, approved in 2022, targets RET fusion-positive tumors and demonstrated an ORR of 44% in 41 patients,

with responses lasting 24.5 months on average.^{21,78} Pralsetinib, another RET inhibitor, also has tissue-agnostic activity, but is not yet approved as a pan-cancer therapeutic. It is listed now in National Comprehensive Cancer Network (NCCN) guideline for BTC with RET fusion as category 2B.^{79,80}

BRAF V600E Mutations

The combination of dabrafenib and trametinib, approved in 2022, targets *BRAF V600E* mutations found in about 3% of cancers.²⁰ In clinical trials, the ORR was 41% for adults and 25% for pediatric patients.⁷⁹

FGFR1 Rearrangement in Hematologic Cancers

Pemigatinib, approved in 2022, targets *FGFR1*-rearranged myeloid/lymphoid neoplasms, an ultrarare blood cancer. In a trial with 28 patients, the complete cytogenetic response rate was 79%.⁸¹

Hypoxia-Inducible Factor-2 Alpha in VHL-Altered Tumors

Although only partially a tissue-agnostic approval, belzutifan, a hypoxia-inducible factor inhibitor, falls into the category of biomarker-based approvals that were applied to several cancers simultaneously. Indeed, belzutifan is approved for patients with von Hippel-Lindau disease who require therapy for associated renal cell carcinoma, CNS hemangioblastomas, or pancreatic neuroendocrine tumors.⁸² An ORR of 49%–83% was attained in the various malignancies approved, with the duration of response being over one year in more than half of the patients, reflecting the effectiveness of this agent across a variety of affected tumor types.

TISSUE-AGNOSTIC ANTIBODY-DRUG CONJUGATE

Trastuzumab deruxtecan, approved in 2024, targets HER2-positive (immunohistochemistry 3+ for HER2) tumors. In trials involving 192 patients, the ORR was approximately 50%, with response durations ranging from 6 to 19 months.⁸³

EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY TUMOR-AGNOSTIC CLASSIFIER AND SCREENER AND RARE CANCERS

The tumor-agnostic therapies represent a revolutionary shift in cancer treatment, offering hope and effective options for patients, especially those with rare cancers across all age groups.¹² By focusing on the genetic drivers of cancer, these treatments transcend traditional boundaries that benefit rare cancers more than ever, providing personalized and highly effective care. In response to the growing need for standardized approaches in tumor-agnostic drug development, the European Society for Medical Oncology (ESMO) Precision Medicine Working Group, alongside a

multidisciplinary team of international experts, has created the ESMO Tumor-Agnostic Classifier and Screener (ETAC-S).⁸⁴ This tool offers a straightforward set of minimum requirements for screening and verifying the tumor-agnostic potential of molecularly guided treatment options. ETAC-S is poised to redefine how we classify diseases within the broad category of cancer, shifting the focus to the molecular alterations driving tumor growth rather than the tumor's organ of origin. This methodology aims to mitigate the current delays plaguing drug development. Often, a drug initially designed for a specific cancer type is found to be effective in other tumors, especially many rare cancers, with the same molecular alterations only after several years. Given the rapidly increasing incidence of cancer that demands urgent action, streamlining the drug development process through a standardized framework can significantly expedite regulatory assessments, thereby improving access to effective therapies—particularly for rare cancers with limited treatment options.

STUDY DESIGNS FOR RARE CANCER TRIALS

Conducting clinical trials for rare cancers presents unique challenges because of the low incidence and heterogeneity of these diseases. To address these challenges, various innovative study designs have been tailored to the specific needs of rare cancer trials (Fig 1). These designs aim to optimize patient enrollment, enhance data collection, and improve the statistical power of the studies. Outlined in Table 2 are some of the common and emerging trial platforms and designs used in rare cancer trials.

Many areas of innovation in clinical trial design and conduct can particularly benefit research into rare cancer populations. Clinical trial designs that include more than one study within a single protocol or trial, including basket, umbrella, and platform designs, can increase efficiency through improved accrual and more efficient data entry, trial monitoring, and reporting through shared structures including data collection.^{5,7,89,90} The associated efficiencies can make it feasible to conduct rigorous trials in rare and ultrarare patient populations.

Decentralized and pragmatic designs exist on a spectrum, and elements of each can be incorporated into nearly all clinical trials to improve efficiency, expand access, and increase generalizability of results.^{91,92} The more decentralized and pragmatic elements a trial has, the more feasible accrual to the trial is, which, in particular, facilitates research in rare and ultrarare patient populations. In silico trials are computer simulations that model biological processes, including cancer treatment, instead of relying on real-world experiments or clinical trials.⁹³ They can be used in hybrid trial designs and can be helpful in rare cancers to explore different treatment strategies and predict their potential outcomes before conducting actual clinical trials (Table 2).

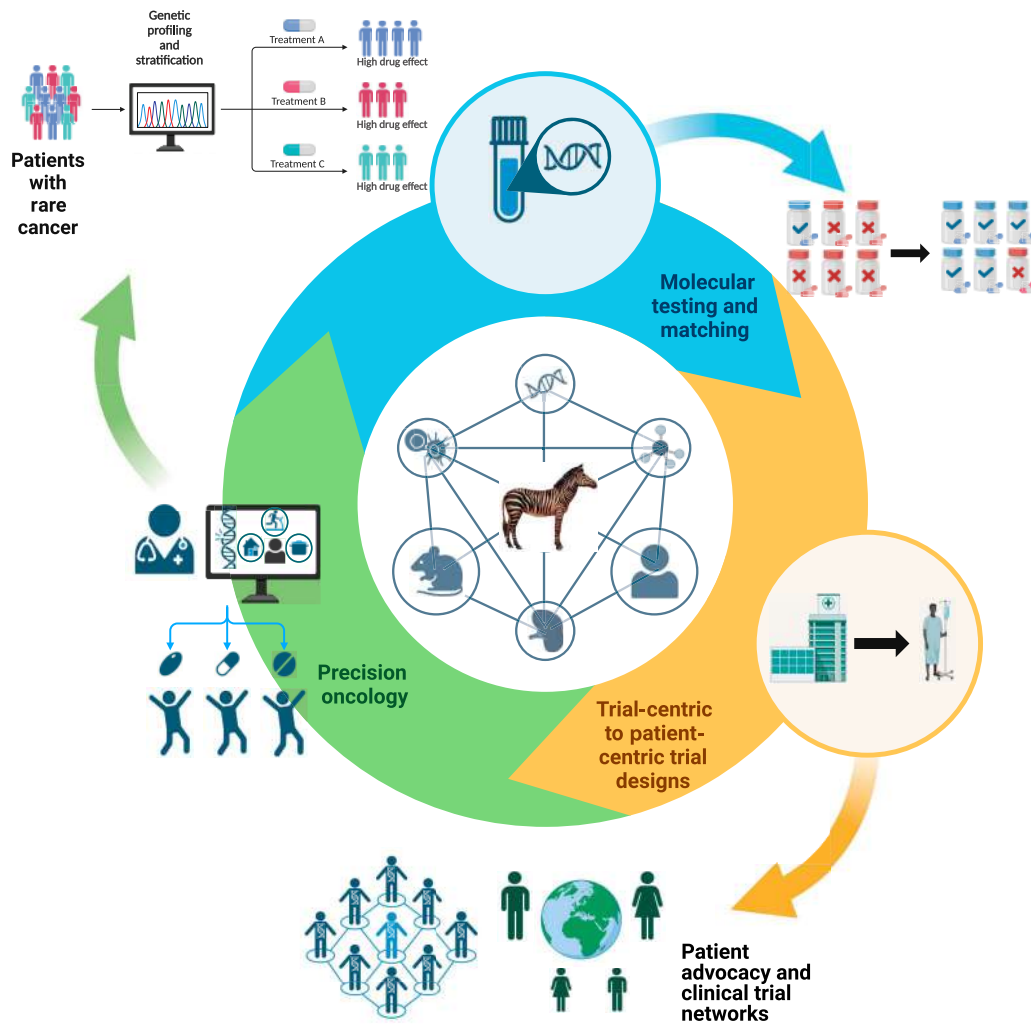


FIG 1. Rare cancer research connecting the zebras in the era of precision oncology. This figure illustrates the conceptual framework of using precision oncology to tackle rare cancers, metaphorically represented as zebras because of their uncommon nature. Created in [BioRender.com](https://www.biorender.com/).⁹⁷

As accrual is one of the primary challenges in conducting rare cancer trials, some study designs require adaptive elements to ensure that accrual can stop as early as possible when the research question has been convincingly answered.⁹⁴ Finally, N-of-1 trials look at patients as individuals, rather than as having a rare or ultrarare cancer. Each patient is given a therapy tailored to their biomarkers, and the algorithm governing therapy selection, rather than individual therapies, is assessed.^{41–44,95}

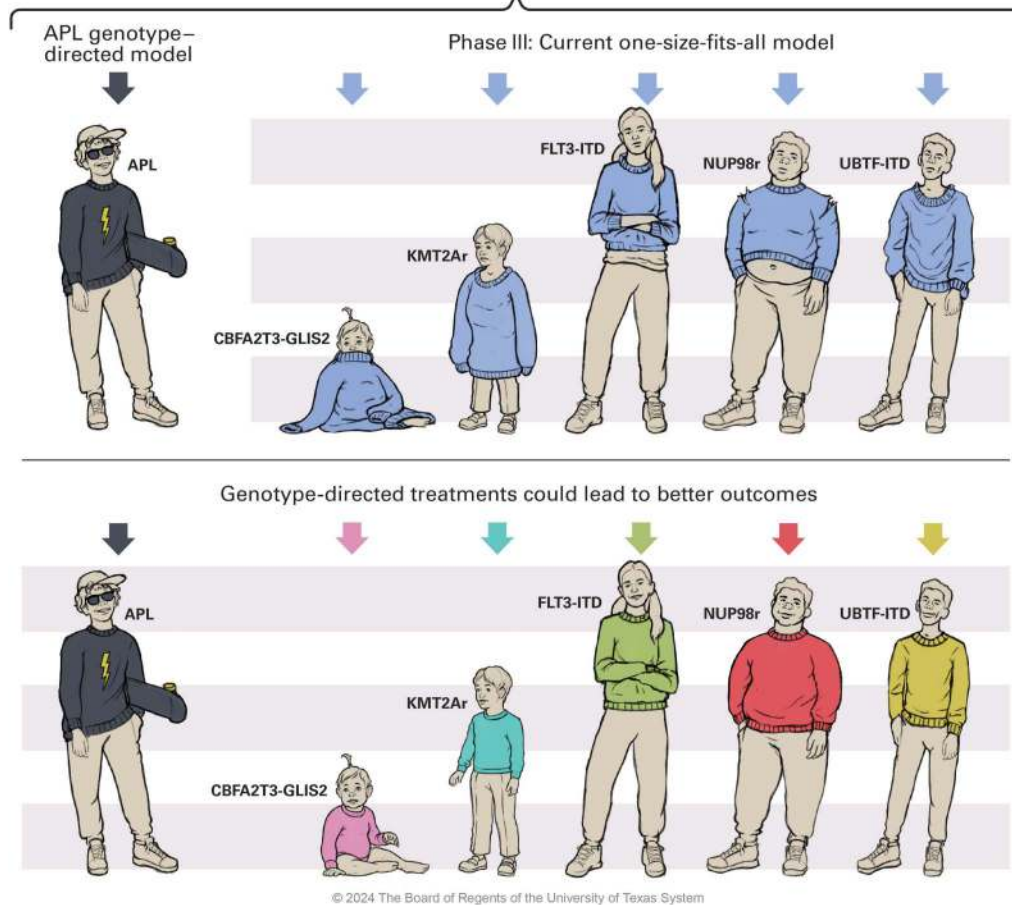
One of the significant challenges in drug development for rare diseases, such as sarcoma (comprising over 100 distinct diseases) and pediatric AML (P-AML, which is at least six different diseases), is the prevalent use of a one-size-fits-all approach in clinical trials. With the exception of acute promyelocytic leukemia, which is a rare variant of AML, all other types of AMLs are bunched together in randomized controlled trials.⁹⁶ As demonstrated earlier, adopting precision oncology trials, which tailor treatments to individual patient biomarkers, can lead to improved outcomes and

signify a necessary shift away from the conventional, uniform one-size-fits all strategy⁹⁶ (Fig 2).

CONSIDERATIONS FOR HEMATOLOGIC MALIGNANCIES

The landscape of hematologic malignancies, particularly rare cancers such as adult AML, is undergoing a transformative shift with the incorporation of targeted small-molecule inhibitors.⁹⁸ With an incidence of approximately 8 per million, adult AML stands as a rare but formidable challenge in oncology. Recent therapeutic advancements focus on the integration of small-molecule inhibitors, such as those targeting FLT3, IDH1, IDH2, and menin, into treatment regimens for both up-front and relapsed diseases.⁹⁸ These innovations are opening up the way for more personalized and effective approaches. Beyond AML, the area of rare hematologic malignancies extends to conditions like multiple myeloma (MM), AML, chronic lymphocytic leukemia, Hodgkin lymphoma, and various subtypes of non-Hodgkin lymphoma, including diffuse

Pediatric Myeloid Diseases



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FIG 2. Moving away from the one-size-fits-all approach to precision oncology in pediatric AML trials. This figure highlights the inadequacy of the one-size-fits-all approach in treating P-AML, where diverse subtypes, except for APL, are often grouped in clinical trials. It illustrates the genetic diversity of P-AML, showcasing the need for subtype-specific treatments, such as FLT3 inhibitors for FLT3-ITD patients and gemtuzumab ozogamicin or MENIN inhibitors for *KMT2A*-rearranged patients. The legend emphasizes the potential of personalized medicine in addressing these variations, advocating for tailored therapeutic strategies. It calls for a transition to precision medicine to improve treatment outcomes and cater to individual patient needs. APL, acute promyelocytic leukemia; ITD, internal tandem duplication; P-AML, pediatric AML; r, rearranged. Adapted from *Nat Rev Clin Oncol*.¹⁰²

large B-cell lymphoma with a frequency of 60 per million. While many of these diseases can be managed with current therapies, relapse remains a significant hurdle, often necessitating advanced interventions like autologous hematopoietic cell transplants or chimeric antigen receptor T-cell therapy. Despite these measures, relapse persists, underscoring the need for novel strategies and deeper molecular insights. MM, in particular, presents unique challenges as an incurable condition. Although numerous therapeutic agents exist, a substantial portion of patients exhaust available treatments. This highlights the urgency for designing studies that explore mutational analysis for those who have not yet undergone such testing, potentially unveiling new therapeutic avenues. The cautionary tales from trials, such as the use of venetoclax in relapsed MM without considering t(11;14)

status^{99,100} or the combination of pembrolizumab with immunomodulatory drugs, underscore the critical importance of precision medicine. Subsequent trials revealed inferior overall survival (OS) outcomes because of unanticipated toxicities, which could potentially be predicted and managed through advanced molecular testing in the future. The evolving treatment landscape for rare hematologic malignancies emphasizes the critical role of molecularly targeted therapies and the potential for personalized medicine to improve outcomes. Clinical development and FDA approval of agents such as tagraxofusp, a CD123-directed cytotoxin, for an ultrarare hematologic malignancy blastic plasmacytoid dendritic cell neoplasm in adults and in pediatric patients 2 years and older show the promise of precision therapies in rare cancers.¹⁰¹ As research advances, there is a compelling

need to refine our understanding of molecular profiles to predict toxicity and optimize therapeutic strategies (Fig 2).

ROLE OF COOPERATIVE GROUPS IN RARE CANCER RESEARCH

Cooperative groups are networks of researchers, hospitals, and institutions that collaborate to conduct large-scale clinical trials.¹⁰³ They are essential for advancing cancer research, particularly for rare cancers, where patient populations are small and dispersed. Some of the prominent cooperative groups include Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group—American College of Radiology Imaging Network (ECOG-ACRIN), Alliance for Clinical Trials in Oncology, and NRG Oncology. These groups bring together multidisciplinary teams to design and conduct clinical trials, share resources, and pool data to evaluate cross-trial populations and research questions. Such collaborative research is vital for rare cancer trials because of the limited number of patients and the need for specialized expertise.¹⁰³ Cooperative groups facilitate the pooling of resources and patient populations across multiple centers, enhancing the ability to conduct robust and meaningful studies, for example, the DART and ASCO TAPUR studies.

THE DART SWOG STUDY FOR RARE CANCERS

The DART (Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors) trial, conducted by the SWOG Early Therapeutics and Rare Cancers Committee, is an example of a successful collaborative effort to address the unmet needs of patients with rare cancer.⁵² DART investigated the efficacy of combining two immune checkpoint inhibitors, ipilimumab and nivolumab, in treating patients with various rare tumors. It was a national immunotherapy trial, conducted at >1,000 sites, and included 53 cohorts of patients with rare cancers as well as an “other” cohort. Total accrual was 798 patients.

The trial’s design allows for the inclusion of multiple rare cancer types, making it a highly innovative and inclusive study in rare cancer field. Preliminary results from DART have shown promising responses in multiple rare cancers including but not limited to angiosarcoma, neuroendocrine cancers, desmoid tumors, or ultrarare cancers like gestational trophoblastic neoplasia,^{52,53,104,105} demonstrating the potential of immunotherapy in these patient populations and highlighting the importance of collaborative research in advancing treatment options. DART aimed to provide new treatment options for patients with rare cancers who often had limited therapeutic choices because of the scarcity of specific research and clinical trials focused on their conditions. DART was a phase II clinical trial with a basket design, allowing the inclusion of multiple rare cancer types within a single study. This design as discussed above is particularly advantageous for rare cancers as it enables the investigation

of a common treatment approach across diverse tumor types. The primary end point was the ORR to the treatment. Secondary end points included progression-free survival, OS, and safety profiles.

While the DART trial has achieved notable successes, it also faced several challenges. Recruiting sufficient numbers of patients with ultrarare cancers was difficult because of the low incidence of these conditions even with the basket platform. In addition, the variability in tumor biology among different rare cancers may affect the treatment’s efficacy and complicate data interpretation. Despite these challenges, the trial’s basket design and collaborative approach have enabled researchers to gather valuable insights into the potential benefits of immunotherapy for rare cancers. The DART trial’s success has catalyzed further research into the use of immunotherapy for rare cancers. Future studies may explore additional combinations of immune checkpoint inhibitors, investigate the underlying mechanisms of response and resistance, and identify biomarkers to predict treatment outcomes. By using a basket trial design and focusing on a wide range of rare tumors, the DART trial has expanded treatment options for patients who previously had few alternatives.

ASCO TAPUR

The ASCO-TAPUR (Targeted Agent and Profiling Utilization Registry) study is a pragmatic clinical trial designed to evaluate the efficacy of FDA-approved targeted therapies in patients with advanced cancers that have specific genomic alterations.⁸⁵ The trial aims to provide real-world evidence on the use of these therapies in a broader range of cancer types, including rare cancers. TAPUR’s flexible design allows for the inclusion of multiple targeted agents and diverse patient populations including rare cancers, making it a valuable resource for understanding how these therapies perform outside of traditional clinical trial settings. The outcomes from TAPUR have provided important insights into the effectiveness of targeted therapies in various cancer types and have informed clinical practice.

DRUP TRIAL, DRUP-LIKE TRIALS, AND EU INITIATIVES

The Drug Rediscovery Protocol (DRUP) trial, conducted in the Netherlands, is another example of an innovative clinical trial model.⁸⁷ DRUP aims to identify new uses for existing cancer drugs by matching patients with rare or refractory cancers to targeted therapies based on their tumor’s molecular profile. The trial’s adaptive design allows for the rapid inclusion of new drugs and patient cohorts, making it highly scalable and flexible. DRUP has successfully enrolled patients with various rare cancers and has demonstrated the feasibility and benefits of repurposing existing drugs for new indications. DRUP-like trials (DLCTs), such as IMPRESS-Norway, are offering precision medicines to rare cancer

populations.^{106,107} Numerous precision cancer medicine (PCM) initiatives have proven the practicality and advantages of adopting PCM in individual nations. Two such EU-funded projects, PCM4EU (Personalized Cancer Medicine for all EU citizens) and PRIME-ROSE (Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials), aim to broaden fair and sustainable PCM access.¹⁰⁸ These initiatives, supported by EU4Health and Horizon Europe's EU Mission on Cancer programs, build upon successful national efforts with DRUP-like clinical trials to tackle crucial implementation challenges. The trial's model has the potential to be scaled and adapted in other countries, providing a framework for expanding treatment options for patients with rare cancer globally.

THE ROLE OF NCCN GUIDELINES IN STANDARDIZING CANCER TREATMENT

The NCCN guidelines are evidence-based recommendations that provide standardized protocols for the diagnosis, treatment, and management of various cancers. These guidelines are developed by panels of experts and are regularly updated to reflect the latest research and clinical practices. For some rare cancers, NCCN guidelines play a crucial role in ensuring that patients receive consistent and high-quality care, even in the absence of large-scale clinical trial data. By standardizing treatment protocols, the guidelines help to reduce variability in care and improve patient outcomes. NCCN guidelines are dynamic and continuously evolving to incorporate new research findings and emerging therapies. As new data from clinical trials, such as those from cooperative groups and innovative studies like SWOG's DART and ASCO TAPUR, become available, the guidelines are updated to reflect these results. This iterative process ensures that the guidelines remain current and relevant, providing clinicians with the most up-to-date information for making treatment decisions. The inclusion of novel therapies and personalized medicine approaches in the guidelines also helps to expand treatment options for patients with rare cancers.

PEDIATRIC RARE CANCER TRIALS AND CHILDREN'S ONCOLOGY GROUP

Pediatric cancers, which by definition are rare, have spurred various organizations to focus on specialized initiatives to address these challenges. Pediatric cancer, despite its classification as a rare disease, serves as a compelling case study in the power of collaborative research efforts. Over the past four decades, the effectiveness of cooperative groups has been vividly demonstrated in this field, primarily through the work of the Children's Oncology Group (COG) and its predecessor organizations, such as the Children's Cancer Group and the Pediatric Oncology Group (POG).¹⁰⁹ These groups pioneered a collaborative approach, uniting researchers, clinicians, and institutions across the nation and world to tackle the unique challenges of childhood cancers. By pooling resources, standardizing protocols, and

conducting large-scale clinical trials, they have significantly advanced our understanding and treatment of pediatric cancers.¹⁰⁹ This collective effort has led to remarkable improvements in survival rates and treatment outcomes, showcasing how cooperative groups can overcome the hurdles of rarity in disease research. The success of COG and its predecessors not only revolutionized pediatric oncology but also set a precedent for how collaboration can drive progress in other rare diseases.

Currently, the COG,¹¹⁰ the largest global consortium dedicated to pediatric and adolescent cancer research, has an extensive clinical trial portfolio that includes precision medicine trials, which is conducted through over 200 member institutions worldwide. The NCI collaborates with COG in the Pediatric MATCH program,¹¹¹ a pioneering effort operational in about 200 affiliated hospitals and centers across the United States and Australia, which matches targeted therapies to genetic mutations in patients age 1–21 years. In Europe, the Innovative Therapies for Children with Cancer organization accelerates the development of novel therapies through early-phase trials and translational research, working with academic institutions, industry partners, and patient advocacy groups. Meanwhile, the European Society for Pediatric Oncology coordinates efforts across Europe, focusing on rare cancers, and influences policies on childhood cancer research and treatment.¹¹²

ROLE OF RARE CANCER PATIENT ADVOCACY GROUPS IN HELPING RARE ENROLLMENT IN CLINICAL TRIALS

Rare cancer patient advocacy groups play a crucial role in supporting patients, raising awareness, and facilitating clinical trial enrollment (Fig 3). Organizations like the Target Cancer Foundation the International Cancer Advocacy Network, European Alliance for personalized medicine, International Cancer Patient Coalition, and many others work tirelessly to bridge gaps between patients, researchers, industry, and regulators.¹¹ Their efforts are instrumental in advancing research, providing patient support, and ensuring that patients with rare cancer have knowledge and access to the latest treatment options available through clinical trials. Rare cancer patient advocacy groups are crucial for enhancing clinical trial enrollment and advancing research by raising awareness, offering support and resources, connecting patients with trials, influencing policy, and collaborating with researchers.¹¹³ They conduct outreach programs and campaigns to educate patients, caregivers, and the public on rare cancers and the importance of clinical trials, leading to increased participation and robust data for researchers.¹¹ These groups provide personalized guidance, financial assistance, and emotional support, empowering patients to make informed treatment decisions. By maintaining trial databases and collaborating with researchers and institutions, they may facilitate patient access to relevant studies. Advocacy efforts also focus on policy changes to improve trial enrollment and patient outcomes, whereas

Solving the Rare Disease Puzzle Through Social Media

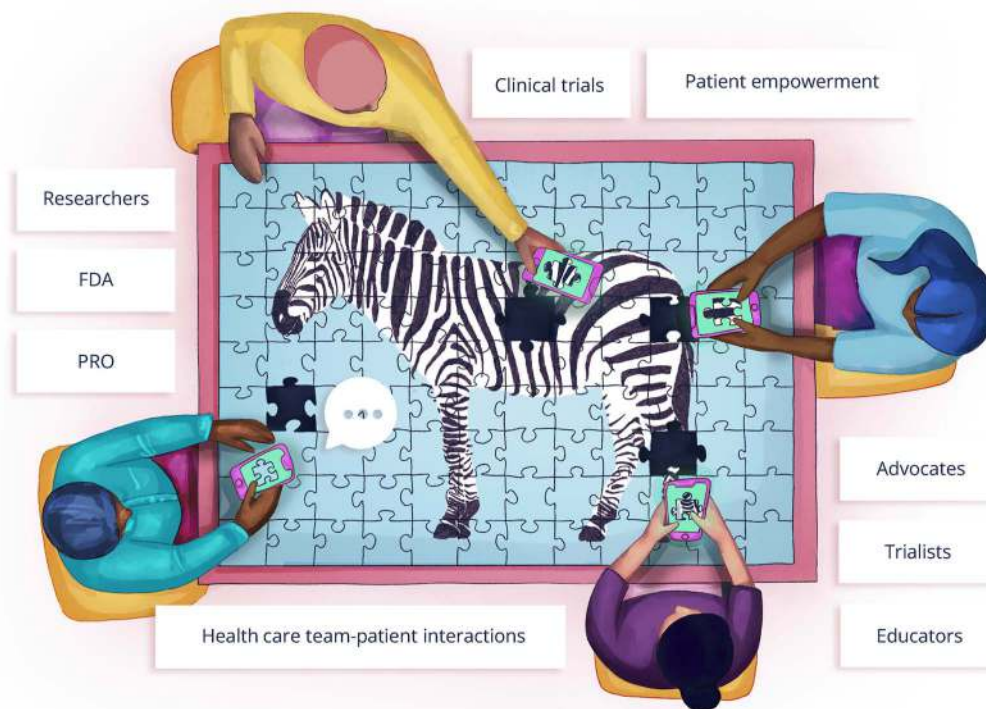


FIG. 3. Social media connecting the zebras. This figure illustrates how social media connects patients with rare diseases across the globe, creating a collaborative network to solve the zebra puzzle. It depicts individuals in diverse geographic locations using social media platforms to share experiences, insights, and support. The interconnected web symbolizes the collective effort to tackle the challenges of rare diseases. This approach highlights the power of digital communities in advancing understanding and solutions for rare conditions. FDA, US Food and Drug Administration; PRO, patient reported outcomes. Reprinted with permission from *Cancer*.¹¹⁹

partnerships with research institutions help develop patient-centered trials.¹¹³

The TRACK trial (ClinicalTrials.gov identifier: [NCT04504604](#)), spearheaded by TargetCancer Foundation, represents an innovative patient-centric initiative in rare cancer research.¹¹⁴ Known as the Target RAre Cancer Knowledge Trial (ClinicalTrials.gov identifier: [NCT04504604](#)), this fully remote and decentralized study leverages personalized genomic strategies, often referred to as N-of-1 trials.¹¹⁴ Driven by patient advocates, this unique, nonrandomized trial eliminates the need for participants to physically visit a facility for enrollment or treatment. It aims to assess the effectiveness of individualized molecular treatments based on clinical-grade NGS results, with guidance from a Molecular Tumor Board (MTB). With the goal of enrolling 400 participants, the study has received approval from a central Internal Review Board, and it uses remote methods for obtaining consent. Enrolled patients receive tissue and blood NGS at no cost. The team at TargetCancer Foundation is responsible for gathering medical records, facilitating communication with patients and their health care providers, managing the consent process, arranging mobile

phlebotomy for liquid biopsies, and accessing existing tissue samples. The trial kicked off in October 2020 during the peak of the pandemic.¹¹⁴ The MTB is composed of a diverse group of professionals, including oncologists, genomic experts, molecular pathologists, researchers, pharmacists, genetic counselors, regulatory experts, a scribe, an oncology fellow referred to as a mentern, and a specialist in medication procurement. Every week, members from eight different states connect virtually to review patient cases and provide treatment recommendations. At 4.5 years since its inception, the trial had successfully enrolled 223 eligible participants from 42 states, each diagnosed with one of over 50 rare or ultrarare cancers.²⁶

FUTURE ROLE OF AI IN SCREENING AND MATCHING CLINICAL TRIALS FOR RARE CANCERS

Matching patients to appropriate clinical trials, particularly for rare cancers, remains a significant challenge because of its often manual and labor-intensive nature.¹¹⁵ Clinicians and trial team personnel must navigate through extensive trial data and patient records, which can lead to delays and missed opportunities. The complex eligibility criteria of many trials

add another layer of complexity to the process. Moreover, the lack of standardized data formats and interoperability across different health care systems further complicates efficient patient-trial matching.

AI, although not ready yet, offers a promising solution to revolutionize the patient-trial matching process by using big data and machine learning.¹¹⁵ AI can potentially sift through vast data sets, such as electronic health records, genomic data, and clinical trial databases, to uncover patterns and correlations that might elude human screeners. Machine learning algorithms can be trained to understand eligibility criteria and match patients to trials based on their specific characteristics, including genetic mutations and medical history such as those outlined in TRIAL GPT. This automated approach can significantly expedite the matching process, enhance accuracy, and expand access to potentially life-saving trials for more patients. While AI's future in clinical trial matching appears to be promising, implementation challenges remain. Moreover, ethical considerations such as data privacy, security, transparency, and bias prevention must be addressed to ensure responsible and equitable integration into clinical research.

THE INTEGRATED APPROACH NEEDED TO IMPROVE ENROLLMENT IN RARE CANCER TRIALS

To improve the enrollment of patients with rare cancer in clinical trials, an integrated approach is essential (Table 3). First, this approach should combine the strengths of NGS, precision medicine, and tumor-agnostic therapies with collaborative research efforts and standardized guidelines. Second, a multistakeholder collaboration among researchers, clinicians, health care institutions, industry, patients and caregivers, and regulatory bodies is crucial for overcoming the challenges associated with rare cancer trials and maximizing their impact. Third, cooperative group trials, such as SWOG DART and ASCO TAPUR, should consistently be available and also incorporate novel agents and trials for patients with rare cancer. Fourth, innovative analyses to inform evidence, such as pooled analyses from multiple studies, should be encouraged to provide comprehensive evidence of the clinical benefits, such as the pooled analysis of the NCI-MATCH, ROAR, and pediatric trials that led to the FDA approval of BRAF + MEK therapies for all cancers. Fifth, the establishment of molecular tumor boards should be promoted at institutional, local, national, and international levels. Sixth, patient-centered patient advocacy, driven by social media, can significantly aid in the enrollment of patients with rare cancer. Seventh, we need to improve the harmonization of compassionate/expanded use and off-label use regulations, making it easier for patients and clinicians to access these drugs. Eighth, platform trials are extremely important in the rare cancer space. As an example, centers might have been hesitant to open a trial that focused on one cohort of rare cancers, because of the activation energy required, accrual limitations, and cost;

TABLE 3. Steps to Improve Trial Enrollment With Patients With Rare Cancers

Category/Domain	Steps
Integrated approach for enrollment	1. Enhance enrollment: improve enrollment by combining NGS, precision medicine, and tumor-agnostic therapies 2. Leverage technology: use AI to streamline the matching process for trial enrollment
Collaboration and network building	1. Establish reference networks: create virtual collaborative health care networks involving centers/clinicians of expertise 2. Multistakeholder collaboration: foster collaboration between researchers, clinicians, health care institutions, industry, patients/caregivers, and regulatory bodies 3. Cooperative group trials: ensure the existence of cooperative group trials like SWOG DART and ASCO TAPUR 4. Molecular tumor boards: promote the establishment of molecular tumor boards at various levels 5. Promote global collaborations: foster national and international collaborations for investigator-driven studies 6. Pathologic diagnosis review: ensure high-quality care through a central review of pathologic diagnoses. With digital path, this can be made virtual as well
Data collection and management	1. Enhance data collection: ensure long follow-ups and comprehensive data collection, including biological information 2. Maintain biobanks: centralize biobanks with dedicated personnel for quality control and regulatory compliance 3. Encourage clinical databases and registries: develop prospective clinical databases and registries specifically for rare cancers 4. Support cancer registries: maintain population cancer registries to provide vital data 5. Conduct observational studies: encourage observational studies on selected patient subgroups 6. Use patient-driven databases: support patient-driven efforts to feed databases and cancer registries 7. Innovative analysis: encourage pooled analysis of trials to inform the clinical benefit of treatments
Regulatory and policy framework	1. Incentivize orphan drug development: encourage pharmaceutical companies to develop new agents for rare cancers 2. Harmonize compassionate and off-label use regulations: standardize regulations for compassionate and off-label use of new drugs as monotherapy or in combinations 3. Engage regulatory bodies: facilitate regular consultations between regulatory bodies and rare cancer communities
Patient engagement and advocacy	1. Disseminate patient information: make trial information widely available and involve patient communities 2. Patient-centric advocacy: use patient-centric, social media-driven advocacy for rare cancer enrollment

Abbreviations: AI, artificial intelligence; NGS, next-generation sequencing.

however, using the DART trial as an example (immunotherapy for rare cancers sponsored by NCI/SWOG), the inclusion of 53 different rare cancer cohorts and an “other” cohort for miscellaneous rare cancers made this trial attractive to centers across the country, with over 1,000 sites activating. This also helped patients as it is likely that a site nearby would have the trial open, and hence, patients with

rare cancers could access cutting-edge immunotherapy without traveling far from home. It also permitted rapid enrollment and dissemination of data on a large number of rare and even ultrarare cancer cohorts, as well as incorporation of the treatment, where active, into NCI guidelines.^{105,116} One significant obstacle in organizing histology-independent basket trials is that most academic institutions are primarily centered around specific tumor types. Except for a few cancer centers like UT MD Anderson or Memorial Sloan Kettering, it is challenging to set up divisions or departments that operate independent of histologic classifications.¹¹⁷ This situation creates a logistical challenge in finding suitable sites to accommodate these trials. Many academic centers appoint site principal investigators or oncologists who specialize in rare cancer diseases to oversee these histology-agnostic trials.¹¹⁷ The MyPathway trial, facilitated by Sarah Cannon Research Institute's (SCRI) contract research organization, Sarah Cannon Development Innovations, was performed across both community and academic settings, proving that such comprehensive protocol collaborations are indeed possible.¹¹⁷ SCRI has adeptly used innovative models to enhance trial execution. The BRIDGE program is tailored for basket trials at community sites, whereas the Selected Trials for Accelerated Rollout (STAR) method is designed focusing on rare cancers or rare mutation studies for US Oncology network sites. When a facility identifies a potential STAR trial participant with a rare genetic alteration like *NTRK* fusion, the staff undergoes comprehensive training on the trial specifics. This preparation allows them to commence the study at the patient's treatment location within a swift two-week period. Finally, leveraging technology, as AI, to streamline the trial matching process can further enhance enrollment and ensure that more patients have access to cutting-edge treatments.

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CONCLUSIONS

The future of rare cancer clinical trials is hopeful, driven by ongoing advances in biomarker-based tumor-agnostic precision oncology.¹¹⁸ The tumor-agnostic paradigm for treatment is not only effective, because cancer is a disease of the genome, but the patients who benefit most may be those with one of the approximately 200 types of rare cancers, forming almost 25% of the cancer burden. It is highly unlikely that trials in each of these cancers would be feasible, especially for a rare alteration, such as an *NTRK* fusion, which occurs in about 0.3% of cancers. Even so, evidence strongly indicates that *NTRK* inhibitors, as an example, are active to tumors, regardless of organ of origin, and the FDA tumor-agnostic approval of three *NTRK* inhibitors provides therapy options for patients with the greatest unmet need—that is patients suffering from rare and ultrarare cancers bearing the ultrarare biomarker.

By adopting an integrated and collaborative approach, and moving away from the one-size-fits-all model to precision oncology, the oncology community can achieve significant progress in understanding and treating rare cancers. The application of AI and other innovative tools and the recognition that rare cancers, similar to common cancers, are often complex at the molecular level and individually distinct, necessitating personalized combination therapies, will be pivotal to overcoming existing challenges and ensuring that patients with rare cancer receive optimal care. As research advances and new therapies emerge, the prospects for patients with rare cancers will continue to improve, providing hope and a better quality of life for those facing these difficult diseases. This progress will enable us to deliver the right drug(s) to the right patient with rare cancer at the right time (Fig 3).

Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc.

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REFERENCES

- Greenlee RT, Goodman MT, Lynch CF, et al: The occurrence of rare cancers in U.S. adults, 1995–2004. *Public Health Rep* 125:28-43, 2010
- Gatta G, van der Zwan JM, Casali PG, et al: Rare cancers are not so rare: The rare cancer burden in Europe. *Eur J Cancer* 47:2493-2511, 2011
- US Food and Drug Administration, OCE Rare Cancers Program: Promoting development of new drug and biological products to treat patients with rare cancers, 2024. <https://www.fda.gov/about-fda/oncology-center-excellence/oce-rare-cancers-program>
- Surveillance, Epidemiology, and End Results National Institutes of Health: Rare Cancer Classification, 2024. <https://seer.cancer.gov/seerstat/variables/seer/raresiterecode/>
- Billingham L, Malottki K, Steven N: Research methods to change clinical practice for patients with rare cancers. *Lancet Oncol* 17:e70-e80, 2016
- Munoz J, Kurzrock R: Targeted therapy in rare cancers—adopting the orphans. *Nat Rev Clin Oncol* 9:631-642, 2012
- Adashek JJ, Kurzrock R: Home-run trials for rare cancers: Giving the right drug(s) to the right patients at the right time and in the right place. *NPJ Precis Oncol* 7:129, 2023
- Desai A, Subbiah V: Direct-to-patient clinical trials: One small step or a giant leap? *Clin Cancer Res* 29:2339-2341, 2023
- Subbiah V: The next generation of evidence-based medicine. *Nat Med* 29:49-58, 2023
- Horgan D, Hofman P, Buttner R, et al: Bridging the divide: Addressing discrepancies between clinical guidelines, policy guidelines, and biomarker utilization. *Diagnosis (Berl)* 12:94-107, 2024
- Horgan D, Tanner M, Aggarwal C, et al: Precision oncology: A global perspective on implementation and policy development. *JCO Glob Oncol* 10:1200/GO-24-00416
- Subbiah V, Kurzrock R: Precision oncology across the ages: Impact on children, adolescents, and young adults. *Cancer Cell* 42:1473-1479, 2024
- Braiteh F, Kurzrock R: Uncommon tumors and exceptional therapies: Paradox or paradigm? *Mol Cancer Ther* 6:1175-1179, 2007
- Christyani G, Carswell M, Qin S, et al: An overview of advances in rare cancer diagnosis and treatment. *Int J Mol Sci* 25:1201, 2024
- Subbiah V, Gouda MA, Ryll B, et al: The evolving landscape of tissue-agnostic therapies in precision oncology. *CA Cancer J Clin* 74:433-452, 2024
- Subbiah V, Kurzrock R: Challenging standard-of-care paradigms in the precision oncology era. *Trends Cancer* 4:101-109, 2018
- Subbiah V, Kurzrock R: Universal germline and tumor genomic testing needed to win the war against cancer: Genomics is the diagnosis. *J Clin Oncol* 41:3100-3103, 2023
- Horgan D, Pesapane F, Van der Buckle M, et al: From theory to practice: Implementing next-generation sequencing and public health genomics in healthcare systems. *Crit Rev Oncology/Hematology* 201:104433, 2024
- Salama AKS, Li S, Macrae ER, et al: Dabrafenib and trametinib in patients with tumors with *BRAF*^{V600E} mutations: Results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol* 38:3895-3904, 2020
- Subbiah V, Kreitman RJ, Weinberg ZA, et al: Dabrafenib plus trametinib in *BRAF*V600E-mutated rare cancers: The phase 2 ROAR trial. *Nat Med* 29:1103-1112, 2023
- Subbiah V, Wolf PJ, Konda B, et al: Tumour-agnostic efficacy and safety of selipatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): A phase 1/2, open-label, basket trial. *Lancet Oncol* 23:1261-1273, 2022
- Subbiah V, Puzanov I, Blay JY, et al: Pan-cancer efficacy of vemurafenib in *BRAF*^{V600}-mutant non-melanoma cancers. *Cancer Discov* 10:657-663, 2020
- O'Dwyer PJ, Gray RJ, Flaherty KT, et al: The NCI-MATCH trial: Lessons for precision oncology. *Nat Med* 29:1349-1357, 2023
- Othus M, Patel SP, Chae YK, et al: Correlation between tumor size change and outcome in a rare cancer immunotherapy basket trial. *J Natl Cancer Inst* 116:673-680, 2024
- Murciano-Goroff YR, Drilon A, Stadler ZK: The NCI-MATCH: A national, collaborative precision oncology trial for diverse tumor histologies. *Cancer Cell* 39:22-24, 2021
- Subbiah V, Groisberg R, Skefos C, et al: TCF-001 TRACK (Target Rare Cancer Knowledge): A national patient-centric precision oncology trial for rare cancers. *J Clin Oncol* 39, 2021 (suppl 15; abstr TPS3143)
- Morgan G, Subbiah V: Rare disease research powered by empowered patients: Solving the zebra puzzle through social media. *Cancer* 129:2128-2131, 2023
- Subbiah V, Kurzrock R: The marriage between genomics and immunotherapy: Mismatch meets its match. *Oncologist* 24:1-3, 2018
- Schwaederle M, Zhao M, Lee JJ, et al: Impact of precision medicine in diverse cancers: A meta-analysis of phase II clinical trials. *J Clin Oncol* 33:3817-3825, 2015
- Subbiah V, Kurzrock R: Universal genomic testing needed to win the war against cancer: Genomics IS the diagnosis. *JAMA Oncol* 2:719-720, 2016
- Hyman DM, Puzanov I, Subbiah V, et al: Vemurafenib in multiple nonmelanoma cancers with *BRAF* V600 mutations. *N Engl J Med* 373:726-736, 2015
- Diamond EL, Subbiah V, Lockhart AC, et al: Vemurafenib for *BRAF* V600-mutant Erdheim-Chester disease and Langerhans cell histiocytosis: Analysis of data from the histology-independent, phase 2, open-label VE-BASKET study. *JAMA Oncol* 4:384-388, 2018
- Sweeney CJ, Hainsworth JD, Bose R, et al: MyPathway human epidermal growth factor receptor 2 basket study: Pertuzumab + trastuzumab treatment of a tissue-agnostic cohort of patients with human epidermal growth factor receptor 2–altered advanced solid tumors. *J Clin Oncol* 42:258-265, 2024
- Hainsworth JD, Meric-Bernstam F, Swanton C, et al: Targeted therapy for advanced solid tumors on the basis of molecular profiles: Results from MyPathway, an open-label, phase IIa multiple basket study. *J Clin Oncol* 36:536-542, 2018
- Herbst RS, Gandara DR, Hirsch FR, et al: Lung Master Protocol (Lung-MAP)—A biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. *Clin Cancer Res* 21:1514-1524, 2015
- Little RF, Othus M, Assouline S, et al: Umbrella trial in myeloid malignancies: The Myelomatch National Clinical Trials Network Precision Medicine Initiative. *Blood* 140:9057-9060, 2022
- Wang H, Yee D: I-SPY 2: A neoadjuvant adaptive clinical trial designed to improve outcomes in high-risk breast cancer. *Curr Breast Cancer Rep* 11:303-310, 2019
- Gilson C, Ingleby F, Gilbert DC, et al: Genomic profiles of de novo high- and low-volume metastatic prostate cancer: Results from a 2-stage feasibility and prevalence study in the STAMPEDE trial. *JCO Precis Oncol* 10.1200/PO.19.00388
- Morfouace M, Stevovic A, Oliveira J, et al: Abstract 45: Screening somatic genomic alteration for rare adult cancers: The SPECTRA-ARCAGEN project of the EORTC/EURACAN. *Cancer Res* 82:45, 2022
- Dickson D, Johnson J, Bergan R, et al: The master observational trial: A new class of master protocol to advance precision medicine. *Cell* 180:9-14, 2020
- Sicklick JK, Kato S, Okamura R, et al: Molecular profiling of cancer patients enables personalized combination therapy: The I-PREDICT study. *Nat Med* 25:744-750, 2019
- Sicklick JK, Kato S, Okamura R, et al: Molecular profiling of advanced malignancies guides first-line N-of-1 treatments in the I-PREDICT treatment-naïve study. *Genome Med* 13:155, 2021
- Rodon J, Soria J-C, Berger R, et al: Genomic and transcriptomic profiling expands precision cancer medicine: The WINTHER trial. *Nat Med* 25:751-758, 2019
- Gouda MA, Buschhorn L, Schneeweiss A, et al: N-of-1 trials in cancer drug development. *Cancer Discov* 13:1301-1309, 2023
- Subbiah V, Velcheti V, Tuch BB, et al: Selective RET kinase inhibition for patients with RET-altered cancers. *Ann Oncol* 29:1869-1876, 2018
- Adams RA, Fisher DJ, Graham J, et al: Capecitabine versus active monitoring in stable or responding metastatic colorectal cancer after 16 Weeks of first-line therapy: Results of the randomized FOCUS4-N trial. *J Clin Oncol* 39:3693-3704, 2021
- Ventz S, Khozin S, Louv B, et al: The design and evaluation of hybrid controlled trials that leverage external data and randomization. *Nat Commun* 13:5783, 2022

48. Popat S, Liu SV, Scheuer N, et al: Addressing challenges with real-world synthetic control arms to demonstrate the comparative effectiveness of Pralsetinib in non-small cell lung cancer. *Nat Commun* 13:3500, 2022
49. Subbiah V, Kurzrock R: The best management for most patients with incurable cancer is on a clinical trial. *Ann Oncol* 36:240-243, 2025
50. Gouda MA, Subbiah V: Precision oncology for *BRAF*-mutant cancers with *BRAF* and *MEK* inhibitors: From melanoma to tissue-agnostic therapy. *ESMO Open* 8:100788, 2023
51. Gouda MA, Subbiah V: Expanding the benefit: Dabrafenib/trametinib as tissue-agnostic therapy for *BRAF*^{V600E}-positive adult and pediatric solid tumors. *Am Soc Clin Oncol Educ Book* 43: e404770, 2023
52. Patel SP, Mayerson E, Chae YK, et al: A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) SWOG S1609: High-grade neuroendocrine neoplasm cohort. *Cancer* 127:3194-3201, 2021
53. Wagner MJ, Othus M, Patel SP, et al: Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: A substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART). *J Immunother Cancer* 9:e002990, 2021
54. Patel SP, Othus M, Chae YK, et al: A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART SWOG 1609) in patients with nonpancreatic neuroendocrine tumors. *Clin Cancer Res* 26:2290-2296, 2020
55. Groisberg R, Hong DS, Roszik J, et al: Clinical next-generation sequencing for precision oncology in rare cancers. *Mol Cancer Ther* 17:1595-1601, 2018
56. Moyers JT, Pestana RC, Roszik J, et al: Examining stripes on a herd of zebras: Impact of genomic matching for ultrarare sarcomas in phase 1 clinical trials (SAMBA 102). *Clin Cancer Res* 29: 401-409, 2023
57. Carmagnani Pestana R, Moyers JT, Roszik J, et al: Impact of biomarker-matched therapies on outcomes in patients with sarcoma enrolled in early-phase clinical trials (SAMBA 101). *Clin Cancer Res* 29:1708-1718, 2023
58. Liu J, Farrow M, Seymour L, et al: Accelerating the future of oncology drug development: The role of consortia in the delivery of precision oncology early phase clinical trials. *J Clin Oncol* 43: 735-747, 2025
59. Adashek JJ, Menta AK, Reddy NK, et al: Tissue-agnostic activity of *BRAF* plus *MEK* inhibitor in *BRAF* V600-mutant tumors. *Mol Cancer Ther* 21:871-878, 2022
60. Gouda MA, Subbiah V: Expanding the benefit: Dabrafenib/trametinib as tissue-agnostic therapy for *BRAF* V600E-positive adult and pediatric solid tumors. *Am Soc Clin Oncol Educ Book* 43: e404770, 2023
61. Subbiah V, Kreitman RJ, Wainberg ZA, et al: Dabrafenib and trametinib treatment in patients with locally advanced or metastatic *BRAF* V600-mutant anaplastic thyroid cancer. *J Clin Oncol* 36: 7-13, 2018
62. Subbiah V, Kreitman RJ, Wainberg ZA, et al: Dabrafenib plus trametinib in patients with *BRAF* V600E-mutant anaplastic thyroid cancer: Updated analysis from the phase II ROAR basket study. *Ann Oncol* 33:406-415, 2022
63. Subbiah V, Lassen U, Elez E, et al: Dabrafenib plus trametinib in patients with *BRAF*(V600E)-mutated biliary tract cancer (ROAR): A phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol* 21:1234-1243, 2020
64. Wen PY, Stein A, van den Bent M, et al: Dabrafenib plus trametinib in patients with *BRAF*(V600E)-mutant low-grade and high-grade glioma (ROAR): A multicentre, open-label, single-arm, phase 2, basket trial. *Lancet Oncol* 23:53-64, 2022
65. US Food and Drug Administration: FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with *BRAF* V600E mutation, 2022. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dabrafenib-combination-trametinib-unresectable-or-metastatic-solid>
66. Munoz J, Swanton C, Kurzrock R: Molecular profiling and the reclassification of cancer: Divide and conquer. *Am Soc Clin Oncol Educ Book* 33:127-134, 2013
67. Marcus L, Lemery SJ, Keegan P, et al: FDA approval summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. *Clin Cancer Res* 25:3753-3758, 2019
68. André T, Berton D, Curigliano G, et al: Antitumor activity and safety of dostarlimab monotherapy in patients with mismatch repair deficient solid tumors: A nonrandomized controlled trial. *JAMA Netw Open* 6:e2341165, 2023
69. Jardim DL, Goodman A, de Melo Gagliato D, et al: The challenges of tumor mutational burden as an immunotherapy biomarker. *Cancer Cell* 39:154-173, 2021
70. Goodman AM, Kato S, Bazhenova L, et al: Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther* 16:2598-2608, 2017
71. Goodman AM, Sokol ES, Frampton GM, et al: Microsatellite-stable tumors with high mutational burden benefit from immunotherapy. *Cancer Immunol Res* 7:1570-1573, 2019
72. Subbiah V, Solit DB, Chan TA, et al: The FDA approval of pembrolizumab for adult and pediatric patients with tumor mutational burden (TMB) ≥ 10 : A decision centered on empowering patients and their physicians. *Ann Oncol* 31:1115-1118, 2020
73. Marabelle A, Fakih M, Lopez J, et al: Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: Prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 21:1353-1365, 2020
74. Okamura R, Boichard A, Kato S, et al: Analysis of NTRK alterations in pan-cancer adult and pediatric malignancies: Implications for NTRK-targeted therapeutics. *JCO Precis Oncol* [10.1200/P0.18.00183](https://doi.org/10.1200/P0.18.00183)
75. Moyers JT, Subbiah V: TRKing sarcomas for precision medicine: Seek, and ye shall find. *Cancer* 129:3694-3696, 2023
76. Doebele RC, Drilon A, Paz-Ares L, et al: Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. *Lancet Oncol* 21: 271-282, 2020
77. Chen MF, Yang S-R, Shia J, et al: Response to repotrectinib after development of NTRK resistance mutations on first- and second-generation TRK inhibitors. *JCO Precis Oncol* [10.1200/P0.22.00697](https://doi.org/10.1200/P0.22.00697)
78. Kurzrock R: Selpercatinib aimed at RET-altered cancers. 383:868-869, 2020
79. Subbiah V, Cassier PA, Siena S, et al: Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. *Nat Med* 28:1640-1645, 2022
80. NCCN: NCCN Guidelines Version 6.2024-Biliary Tract Cancers, 2025. <https://www.nccn.org>
81. Gotlib J, Kiladjian J-J, Vannucchi A, et al: A phase 2 study of pemigatinib (FIGHT-203; INCB054828) in patients with myeloid/lymphoid neoplasms (MLNs) with fibroblast growth factor receptor 1 (FGFR1) rearrangement (MLN FGFR1). *Blood* 138:385, 2021
82. Fallah J, Brave MH, Weinstock C, et al: FDA Approval Summary: Belzutifan for von Hippel-Lindau Disease-Associated Tumors. *Clin Cancer Res* 28:4843-4848, 2022
83. US Food and Drug Administration: FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors, 2024. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2>
84. Westphalen CB, Martins-Branco D, Beal JR, et al: The ESMO Tumour-Agnostic Classifier and Screener (ETAC-S): A tool for assessing tumour-agnostic potential of molecularly guided therapies and for steering drug development. *Ann Oncol* 35:936-953, 2024
85. Mangat PK, Halabi S, Bruinooge SS, et al: Rationale and design of the Targeted Agent and Profiling Utilization Registry study. *JCO Precis Oncol* [10.1200/P0.18.00122](https://doi.org/10.1200/P0.18.00122)
86. Subbiah V, Hu MI, Wirth LJ, et al: Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): A multi-cohort, open-label, registrational, phase 1/2 study. *Lancet Diabetes Endocrinol* 9:491-501, 2021
87. Hoes LR, van Berge Henegouwen JM, van der Wijngaart H, et al: Patients with rare cancers in the Drug Rediscovery Protocol (DRUP) benefit from genomics-guided treatment. *Clin Cancer Res* 28: 1402-1411, 2022
88. Louie BH, Kato S, Lim JS, et al: Molecular Tumor Board for Unicorns: Outcomes for rare and ultra-rare cancers using an N-of-One personalized treatment strategy. *iScience* 27:110465, 2024
89. Schott AF, Welch JJ, Verschraegen CF, et al: The National Clinical Trials Network: Conducting successful clinical trials of new therapies for rare cancers. *Semin Oncol* 42:731-739, 2015
90. Renfro LA, Sargent DJ: Statistical controversies in clinical research: Basket trials, umbrella trials, and other master protocols: A review and examples. *Ann Oncol* 28:34-43, 2017
91. US Food and Drug Administration: Conducting Clinical Trials with Decentralized Elements, 2024. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-clinical-trials-decentralized-elements>
92. Patel TH, Rivera DR, Singh H, et al: When less is more—Reducing complexity in cancer trials. *Lancet Oncol* 25:10-12, 2024
93. Creemers JHA, Ankan A, Roes KCB, et al: In silico cancer immunotherapy trials uncover the consequences of therapy-specific response patterns for clinical trial design and outcome. *Nat Commun* 14:2348, 2023
94. Chow S-C, Chang M: Adaptive design methods in clinical trials—A review. *Orphanet J Rare Dis* 3:11, 2008
95. Selukar S, Prince DK, May S: A framework for sequential monitoring of individual N-of-1 trials and combining results across a series of sequentially monitored N-of-1 trials. *Clin Trials* [10.1177/17407745241304284](https://doi.org/10.1177/17407745241304284) [epub ahead of print on January 2, 2025]
96. Cuglievan B, Subbiah V: Transforming paediatric AML trials: From failing one-size-fits-all methods to precision oncology. *Nat Rev Clin Oncol* 22:155-156, 2025
97. Subbiah V, 2025. <https://BioRender.com/128c938>
98. Kantarjian HM, DiNardo CD, Kadia TM, et al: Acute myeloid leukemia management and research in 2025. *CA Cancer J Clin* 75:46-67, 2025
99. Kumar S, Kaufman JL, Gasparetto C, et al: Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. *Blood* 130:2401-2409, 2017
100. Cliff ERS, Kaiser MF, Sborov DW, et al: Venetoclax in patients with multiple myeloma with or without t(11;14): A real-world analysis. *Blood* 144:3792.6, 2024

101. Pemmaraju N, Lane AA, Sweet KL, et al: Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. *N Engl J Med* 380:1628-1637, 2019
102. Cuglievan B, Subbiah V: Transforming paediatric AML trials: From failing one-size-fits-all methods to precision oncology. *Nat Rev Clin Oncol* 22:155-156, 2025
103. Bertagnolli MM, Blanke CD, Curran WJ, et al: What happened to the us cancer cooperative groups? A status update ten years after the Institute of Medicine report. *Cancer* 126:5022-5029, 2020
104. Chae YK, Othus M, Patel S, et al: Phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) SWOG S1609: The desmoid tumors. *J Immunother Cancer* 12:e009128, 2024
105. Patel SP, Othus M, Chae YK, et al: A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART SWOG 1609 Cohort 47) in patients with gestational trophoblastic neoplasia. *Clin Cancer Res* 30:33-38, 2024
106. Helland Å, Russnes HG, Fagereng GL, et al: Improving public cancer care by implementing precision medicine in Norway: IMPRESS-Norway. *J Transl Med* 20:225, 2022
107. Taskén K, Russnes HEG, Aas E, et al: A national precision cancer medicine implementation initiative for Norway. *Nat Med* 28:885-887, 2022
108. Taskén K, Haj Mohammad S F, Fagereng GL, et al: PCM4EU and PRIME-ROSE: Collaboration for implementation of precision cancer medicine in Europe. *Acta Oncol* 63:385-391, 2024
109. Reaman GH: Successful integration of cooperative groups: The origin of the Children's Oncology Group. *Am Soc Clin Oncol Educ Book* 32:149-151, 2012
110. Schultz KAP, Chintagumpala M, Piao J, et al: Children's Oncology Group's 2023 blueprint for research: Rare tumors. *Pediatr Blood Cancer* 70:e30574, 2023
111. Parsons DW, Janeway KA, Patton DR, et al: Actionable tumor alterations and treatment protocol enrollment of pediatric and young adult patients with refractory cancers in the National Cancer Institute-Children's Oncology Group Pediatric MATCH Trial. *J Clin Oncol* 40:2224-2234, 2022
112. Otth M, Brack E, Kearns PR, et al: Essential medicines for childhood cancer in Europe: A pan-European, systematic analysis by SIOPE. *Lancet Oncol* 23:1537-1546, 2022
113. Patterson AM, O'Boyle M, VanNoy GE, et al: Emerging roles and opportunities for rare disease patient advocacy groups. *Ther Adv Rare Dis* 4:26330040231164425, 2023
114. Palma J, Kato S, Nikanjam M, et al: On the right TRACK: Providing comprehensive genomic profiling (CGP) and molecular tumor board (MTB) for patients (pts) with rare cancers. *J Clin Oncol* 42, 2024 (suppl 16; abstr 3127)
115. Jin Q, Wang Z, Floudas CS, et al: Matching patients to clinical trials with large language models. *Nat Commun* 15:9074, 2024
116. Chae YK, Corthell L, Patel SP, et al: A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors SWOG S1609: Vulvar cancers. *Clin Cancer Res* 31:308-315, 2025
117. Subbiah V, Burris HA III, Kurzrock R: Revolutionizing cancer drug development: Harnessing the potential of basket trials. *Cancer* 130:186-200, 2024
118. Subbiah V, Horgan D, Subbiah IM: A vision for democratizing next-generation oncology clinical trials. *Cancer Discov* 14:579-584, 2024
119. Morgan G, Subbiah V: Rare disease research powered by empowered patients: Solving the zebra puzzle through social media. *Cancer* 129:2128-2131, 2023

Empowering the Next Generation of Cancer Research Advocates: Community Engagement Across the Research Continuum

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OVERVIEW

Community engagement represents a foundational strategy for advancing cancer research and improving health outcomes. This study examines advocacy as a form of community engagement across the cancer research continuum, aligning with ASCO’s 2024–2025 presidential theme of “Driving Knowledge to Action: Building a Better Future.” We present a comprehensive framework that promotes bidirectional learning, trust, and transparency at all stages of research, from conception to dissemination. The spectrum of engagement approaches is described, ranging from consultative models to fully collaborative partnerships, highlighting how each creates critical touchpoints throughout the research process. We identify significant challenges to meaningful community engagement—including institutional barriers, historical mistrust, and sustainability concerns—while offering practical solutions drawn from successful examples across diverse cancer research settings. This study concludes with actionable recommendations for advancing robust community engagement through diverse representation, mentorship programs, institutional support mechanisms, and dedicated funding channels. By integrating advocacy throughout the research continuum, we create pathways for patients, caregivers, community representatives, and emerging professionals to shape research agendas, inform study designs, and participate in translating findings into policy and practice, ultimately ensuring cancer research is inclusive, relevant, and accessible to all communities.

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INTRODUCTION

Overview of the Presidential Theme: Driving Knowledge to Action: Building a Better Future

ASCO’s 2024–2025 presidential theme, Driving Knowledge to Action: Building a Better Future, emphasizes the broad impact of developing and disseminating knowledge through community engagement to advance cancer research and clinical care. Dr Robin T. Zon’s vision rests on three fundamental pillars: harnessing emerging technologies, strengthening advocacy efforts, and embracing community engagement. This theme underscores that future real-world scientific impact in cancer care hinges on our ability to use a key strategy of advocacy: engagement with communities.

Purpose of the Study

This study examines the role of advocacy as community engagement across the cancer research continuum. As guided by the National Academy of Medicine (NAM), we define community engagement as a collaborative process

that integrates perspectives of affected populations into research priorities, programs, and policies, transforming community members from passive recipients to active participants in the research process.¹ This study first presents a community engagement framework that promotes bidirectional learning, trust, and transparency at all stages of research, from conception to dissemination. Next, we describe the spectrum of community engagement approaches, from consultative models to fully collaborative partnerships. We then detail how community engagement creates critical touchpoints throughout the research continuum, from question formulation and study design to implementation and policy translation. Challenges in community-engaged research (CER)—including institutional barriers, historical mistrust, and sustainability concerns—are then detailed, with practical solutions offered for consideration. Finally, the study concludes with recommendations for advancing robust community engagement in cancer research, emphasizing diverse representation, mentorship programs, institutional support mechanisms, and dedicated funding channels to ensure advocacy becomes a fundamental pillar of high-quality, equity-focused cancer research.

PRACTICAL APPLICATIONS

- Community engagement frameworks provide researchers with structured approaches to meaningfully involve patients and advocates throughout the cancer research process, from question formulation to policy translation.
- Effective community engagement requires dedicated resources, time, and institutional support to overcome historical barriers of mistrust and ensure sustainability of partnerships.
- Researchers should consider a spectrum of engagement approaches, selecting models that align with both community needs and research goals to maximize bidirectional knowledge exchange.
- Training the next generation of cancer researchers in community engagement principles creates a pathway for more relevant, accessible, and equitable research outcomes.
- Institutional policies that value and reward community-engaged research can help transform advocacy from an optional add-on to a fundamental component of high-quality cancer research.

COMMUNITY ENGAGEMENT OVERVIEW

Advocacy through community engagement can be a key strategy to mitigating variability in cancer outcomes experienced by different groups. Historically, cancer research has focused on technical advancements with limited integration of community perspectives, which has contributed to mistrust, particularly in historically under-resourced populations. The underperforming design of our policies and systems of care have resulted in higher cancer burdens and poorer outcomes for groups such as Black American individuals, rural residents, and individuals with lower financial means.² A key strategy in optimizing cancer outcomes for those worst off requires engagement and relationship building with affected communities to ensure research is relevant, accessible, and equitable.

Definition of Community Engagement

According to NAM, community engagement in cancer research is a collaborative process that integrates the perspectives of populations affected by cancer and other serious illnesses into research priorities, programs, and policies.¹ This approach ensures community members are active participants in the research process, characterized by power sharing, spaces for sharing lived experiences, and ongoing

relationships rather than one-time consultations. Moving beyond tokenism is essential for meaningful engagement and trust building between researchers and communities. Engagement creates a platform for diverse voices—including patients, caregivers, and siblings—to share their unique perspectives, enriching discussions about research priorities and addressing historical harms to prevent their repetition.^{1,3-6}

Community Engagement Framework

CER fosters bidirectional learning, trust, and transparency by involving stakeholders at all stages of the research process. The NAM's Community Engagement Framework emphasizes that meaningful advocacy necessitates true power-sharing relationships, where patients, caregivers, and local organizations actively shape research initiatives.¹ Their Achieving Health Equity and Systems Transformation through Meaningful Community Engagement (ACE) conceptual model outlines key principles for effective engagement, including trust building, bidirectional influence, cultural centeredness, and equitable financing. As guided by the ACE model, these principles drive four primary areas of impact: strengthened partnerships, expanded knowledge, improved health policies, and thriving communities. Sustainable involvement mechanisms and clear communication channels are critical to maintaining engagement throughout the research process.¹

This viewpoint is reinforced through the perspectives of long-standing patient advocates and coauthors (J.C.N. and D.M.): When researchers engage authentically, they address both cognitive and affective dimensions, effectively speaking to people's hearts rather than solely people's heads. This approach creates shared learning spaces characterized by reciprocity rather than unidirectional information transfer. Advocates function as independent intermediaries between institutions and communities, enhancing the research continuum with pragmatic perspectives that improve equity through meaningful accessibility.⁷

Different Types of Community Engagement

CER exists on a spectrum, ranging from consultative models, such as focus groups and advisory boards, to fully collaborative approaches such as community-based participatory research (CBPR), where community members serve as co-researchers. Effective engagement across all these levels requires selecting community partners who can provide constructive feedback and critique to research question objectives, enhance study design, and facilitate translation into clinical practice.^{4,5,8}

Several key organizations have developed extensive, detailed, and concrete guidance and resources on how to incorporate community engagement into the entire spectrum of research. Aligning these efforts with best practices from organizations such as the Patient-Centered Outcomes

Research Institute (PCORI),⁵ the Center for Disease Control,³ and the National Institutes of Health⁴ ensures that CER remains rigorous, equitable, and impactful in addressing disparities in cancer care and outcomes. These agencies have developed evidence-based toolkits to best practices in community engagement that are essential guides for researchers using these methods.

COMMUNITY ENGAGEMENT TOUCHPOINTS ACROSS THE RESEARCH CONTINUUM

Community engagement strategies can play a central role across the entire research continuum, from conception to dissemination.^{4,9} Figure 1 depicts how community partners can be engaged across the research continuum and to what specific aims and functions they can contribute. The downstream benefit of community engagement is the development of care, interventions, and policies that are more highly responsive to patients' and families' cancer care experiences, sensitive to the entire holistic context in which their cancer is being treated, including the larger policy setting. In the following sections, we elaborate on how to use community engagement strategies at different points of the research continuum and resulting benefits.

Research Question and Priority Setting

Eliciting direct feedback from community members, by asking them what problems and issues concern them the

most, can shape research priorities. Doing so can also help to refine and compellingly describe research problems and heighten significance by capturing the testimonials and lived experiences of the populations affected by cancer.^{10,11} Community members serve as subject matter experts, and they can draw on their first-person experiences with cancer to provide invaluable contextual knowledge that can often be overlooked, minimized, or completely missed.

Including diverse perspectives ensures nuanced understanding of health concerns across different populations, addressing differences in experiences from the outset. Beyond identifying priorities, communities make valuable contributions throughout the research development process by assisting with the identification of other key informants and community partners who should be included in discussions. Community members can also play a crucial role in validating that a final set of research priorities accurately reflects and addresses the real-world needs and challenges they face. As Price et al¹² described, this collaborative approach positions patients and their families as powerful sensors for shaping health care research, ensuring investigations deliver meaningful health improvements addressing communities' highest concerns.

Research Design and Protocol Development

Community engagement during the design and protocol development phase of a study can enhance the look and feel,

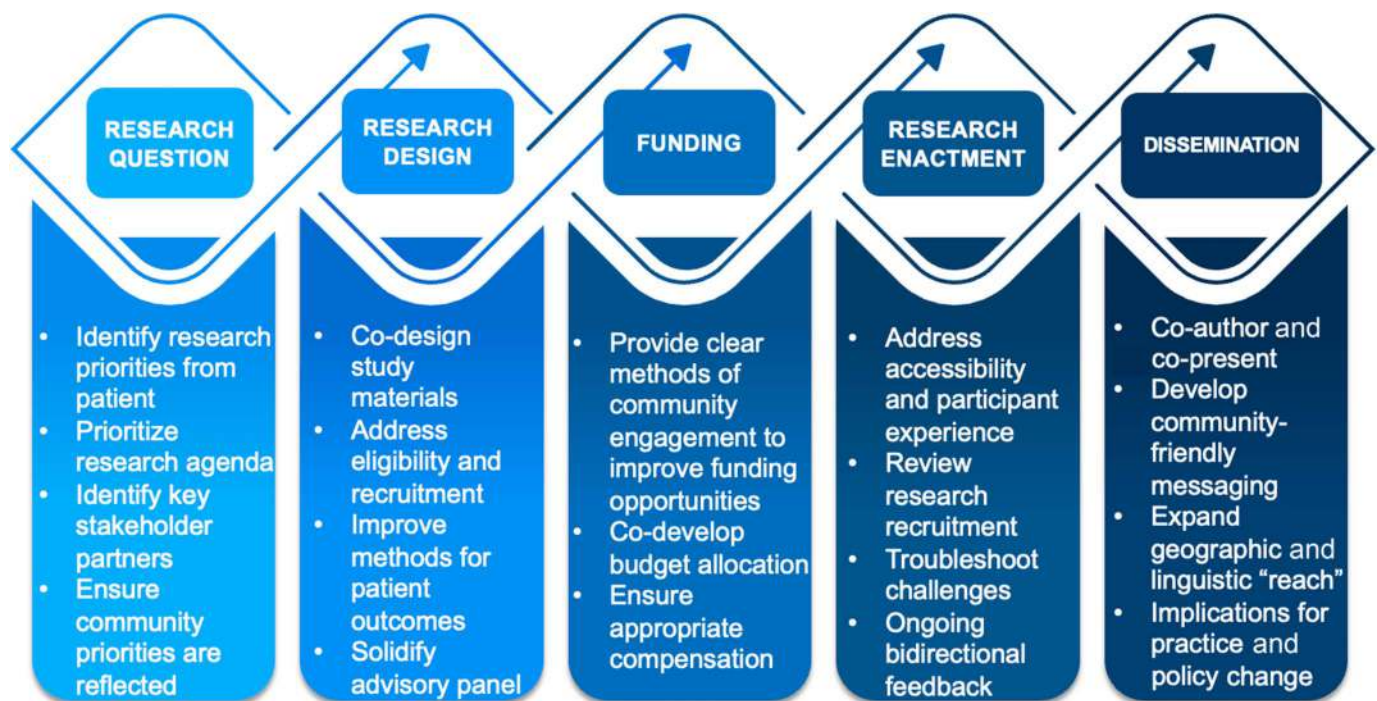


FIG 1. Considerations for community engagement across the research continuum.

efficiency, and success of a project.^{4,9} A foundational step in this process is building an advisory panel comprising community representatives with different backgrounds and experiences who can provide ongoing guidance throughout the research lifecycle. These advisory panels provide a formal way for community members to share their input on study decisions and how the project is conducted, ensuring their perspectives are considered throughout the project. A key aspect of this is ensuring study materials are clear, culturally relevant, and accessible. Community members help identify comprehension barriers, make language more familiar, and enhance how information is communicated to diverse populations.

For example, a community advisory group significantly influenced methodologic approaches in the Hindu Palliative Care Preferences Study—a CBPR project aimed at understanding how Hindu beliefs and values influence palliative care preferences among Hindu patients with cancer and their caregivers in the Charlotte metropolitan area.^{13–15} Led by a Hindu physician with backgrounds in hematology/oncology and hospice care, the study involves focus groups and surveys to develop culturally concordant interventions, addressing the gap where 40% of Hindu immigrants reported dissatisfaction with hospice experiences due to staff not understanding their end-of-life care preferences. In this study, a community advisory group significantly influenced methodologic approaches by recommending individual interviews rather than focus groups to ensure participant comfort in sharing experiences, advocating for the inclusion of caregivers who faced language barriers, and suggesting the incorporation of culturally specific questions about dietary considerations and ayurvedic medicine practices.

Likewise, community advocates affected research design in the American Indian Cancer Experience Study,^{16,17} which examined barriers to cancer care delivery among American Indian, rural, and frontier populations in South Dakota, an area where cancer mortality rates for American Indians are twice as high as those in other US regions. The goal of this study was to develop a culturally adapted, nurse-led palliative care intervention to address these significant health disparities. The American Indian Cancer Experience Study demonstrated how engagement with individuals possessing lived experience and collaboration with a Lakota cultural liaison led to culturally appropriate modifications in recruitment strategies and interview protocols, while the study's implementation at a rural oncology center featured dedicated space for Indigenous ceremonies, including smudging practices.

Funding and Resource Allocation

Community partners can increase the chances of funding success by aiding in the development of compelling lay summaries of proposals and affect statements that articulate real-world significance to funding agencies (eg,

American Cancer Society, PCORI). They help prioritize budgets that appropriately value community contributions and ensure resources are sufficient for engagement activities. Furthermore, fair compensation for community participants recognizes their expertise and acknowledges their value as partners in the research process and co-producers of the work. An important point by Price in this regard¹²: “Co-production does not imply equality in skills but equal respect, voice, and access to shared resources.” Community involvement can boost the argument to funders that a particular research study addresses a pressing health concern. Robust and detailed engagement plans can signal a genuine commitment to fair and inclusive research methods that give everyone an equal voice. Some studies suggest that there can be up to a 500-fold return on investment when community engagement is effectively implemented in the early stages of research design and protocol development,¹⁸ demonstrating the financial value alongside the scientific value for community engagement.

Research Implementation and Enactment

As a part of research enactment, community members can ensure studies are implemented in a way that optimizes participant recruitment and retention and maximizes the contribution of their participation. Their involvement is particularly critical in reaching disparate or historically underserved populations, as they can help address barriers such as mistrust, logistical challenges, and cultural or linguistic differences that may otherwise hinder participation.² When challenges arise, community guidance can provide insights into the causes of barriers to participation and help develop creative strategies to overcome them. Having regular monthly, quarterly, or annual check-ins with community advocates can provide ongoing, bidirectional feedback that allows for continuous quality improvement of study procedures. This collaborative implementation process of when recruitment and enrollment are ongoing further strengthens the study by building trust through transparency and shared ownership over the success of the project.^{4,9,10}

One aspect of community engagement that can widen the reach of research enactment is through optimizing research protocols, especially recruitment strategies. For example, the ProtecT trial, which followed 1,643 men with localized prostate cancer for a median of 15 years, comparing active monitoring, prostatectomy, and radiotherapy, demonstrates this value. Specifically, community input led to the redesign consent forms and renamed “watchful waiting” as “active monitoring,” which improved recruitment by 40%–70% while increasing participant satisfaction.¹⁹ Patient advocates can iteratively review assessment and consent documents to make them accessible for people with diverse backgrounds, abilities, and literacy levels, helping address the persistent challenge of underrepresentation in scientific research.

Dissemination and Translation Into Practice and Policy Change

Community engagement can greatly augment the strategies for broadcasting the results of a study on a wider scale, serving to bolster the real-world impact of scientific findings.^{20,21} Community members can help translate complex, technical findings into accessible language and relatable narratives that reflect the lived experiences of the target population, which can also help to make the results more actionable.

This key aspect of engagement is illustrated through the advocacy-driven legislative successes in pediatric oncology, which exemplify the transformative potential of strategic dissemination. Specifically, the Childhood Cancer Survivorship, Treatment, Access, and Research Act of 2018 (reauthorized in 2023) and the Childhood Cancer Data Initiative both emerged from effective storytelling that translated lived experiences into policy imperatives for enhanced research infrastructure and systematic data collection. Similarly, the New York City Regional Cancer Collaborative demonstrates an institutional approach to policy-driven dissemination, wherein community outreach and engagement cores from seven regional cancer centers collaborate with their respective Offices of Government Affairs to identify and advocate for multilevel policies that address cancer disparities through a structured policy work group that uses consensus-building technologies to prioritize community-identified concerns.

Community members can also assist with coauthoring publications and copresenting findings in a way that enhances credibility and relevance.^{9,20,21} This includes dissemination to diverse audiences through alternative media channels such as podcasts, newsletters, community forums, and town halls. Additionally, their input and advocacy activities can help bridge the gap between research and policy by contextualizing findings in ways that resonate with policymakers (many of whom they may already have relationships with), providing testimony or data-driven storytelling that underscores the urgency of action.

CHALLENGES AND SOLUTIONS IN ADVOCACY INTEGRATION

Challenges and Solutions in CER

While the benefits can be substantial, CER can present challenges, including power imbalances, resource constraints, conflicting priorities, and difficulty translating findings. [Table 1](#) outlines several challenges and corresponding solutions across six core domains: institutional barriers, trust and historical issues, resource and

sustainability concerns, training and expertise dynamics, operational challenges, and partner burnout.

Navigating Challenges and Solutions in CER

CER faces multiple interconnected challenges across six core domains. Institutional barriers stem from limited understanding of CER's value, with many academic centers failing to recognize its importance. Historical mistrust between research institutions and communities creates significant obstacles, rooted in past exploitative practices that have left lasting wounds. Sustainability challenges emerge when projects conclude without ongoing support, while training gaps and power imbalances persist when researchers and community members lack preparation for effective collaboration. Operational challenges arise from misaligned priorities and time lines, and the emotional labor required from all participants presents a real risk of burnout.^{21–24}

Addressing these challenges requires thoughtful, multifaceted solutions. Building authentic partnerships begins with mutual respect and consistent commitment—including, as our patient advocates state, “showing up when the iron is cold” rather than only when resources are needed. Successful CER practitioners demonstrate humility, recognizing diverse forms of expertise and ensuring work leads to tangible outcomes that benefit communities.

Institutional support forms the foundation for sustainable advocacy integration, requiring formal engagement structures, recognition in academic advancement decisions, and dedicated resources. This can be strengthened by developing frameworks demonstrating CER's value and incorporating its principles into institutional missions.¹ Technology helps overcome resource limitations by facilitating communication and enabling virtual participation, while strategic partnerships with community organizations provide additional support.²²

Financial sustainability demands multiple funding streams and planning from the project outset. Proper recognition of advocate contributions through compensation, acknowledgment in publications, and leadership opportunities helps build equitable partnerships. Educational programs that value lived experience as expertise and foster mutual learning environments help address training gaps.

Operationally, successful CER balances scientific rigor with community priorities, sets clear boundaries to prevent burnout, creates realistic workload distributions, and builds flexible time lines that acknowledge competing life commitments. Through these comprehensive approaches, CER can overcome historical mistrust, power imbalances, and resource constraints to create meaningful research partnerships that benefit all stakeholders.

TABLE 1. Challenges and Solutions for Community-Based Participatory Research Across Six Core Domains

Challenge Category	Challenges	Solutions
Institutional barriers	Limited understanding and appreciation of CER within institutions and funding agencies Lack of institutional support for community engagement	Increase institutional support through dedicated funding and protected time for researchers Develop clear frameworks showing CER value in research Include CER principles in institutional mission and priorities Create institutional mechanisms for sustained community partnerships Explore opportunities to diversify funding sources from foundation and philanthropy
Trust and historical issues	Historical mistrust due to past unethical research practices and discrimination Difficulty building authentic relationships	Invest time in relationship building and trust development Address and acknowledge past harms Maintain consistent, open communication Show up “when the iron is cold” (not just when you need something) Engage community members as equal research partners Demonstrate tangible outcomes and impact of work Follow through on commitments and promises
Resource and sustainability issues	Difficulty maintaining partnerships beyond initial funding period Challenge of creating meaningful and sustainable engagement Limited resources for long-term partnership maintenance	Plan for long-term sustainability from project outset Build funding for continued community involvement into grants Develop multiple funding streams Create lasting institutional-community partnerships Ensure each member recognizes their unique value through ongoing dialogue Set clear, shared goals yet be open to revisiting and modifying as changing needs arise Maintain transparent communication Regularly demonstrate and communicate project impact
Training and expertise dynamics	Lack of formal training in CER methods Power imbalances between academic and community partners Challenge of respecting different types of expertise	Provide comprehensive training for both researchers and community partners Develop educational programs on research methods for community members Train researchers in community engagement skills Practice humility and mutual respect Acknowledge that everyone is an expert in their field Value both lived experience and academic knowledge Create space for all voices to be heard Foster an environment of mutual learning
Operational challenges	Differences between academic and community priorities Misaligned timelines and expectations Community members' competing life commitments Difficulty maintaining consistent engagement	Balance scientific rigor with community needs and priorities Create clear processes for shared decision-making Build flexibility into partnership structure Be understanding and accommodating of schedule changes Create backup plans for participation Recognize that life happens and plan accordingly Establish realistic time lines that work for all partners Develop flexible meeting and participation options
Burnout and strain	High time commitment Emotional burden on researchers and community partners Stress from balancing multiple responsibilities	Set clear boundaries and expectations Provide adequate resources and support Create realistic workload distributions Build in time for relationship maintenance Maintain valuable partnerships through periods of change Acknowledge and plan for personal and professional challenges Create support systems for all partners

Abbreviation: CER, community-engaged research.

RECOMMENDATIONS FOR ADVANCING THE FUTURE OF ROBUST COMMUNITY ENGAGEMENT IN CANCER RESEARCH

As approaches to CER evolve and become more refined, measures are needed to offer the researcher training needed to engage communities, strengthen community engagement infrastructure in cancer centers, and prioritize community partnership as a cornerstone of cancer research strategic priorities. This section outlines key recommendations to this effect.

Offer Researcher Training Needed to Engage Communities

Strengthen the Advocacy Pipeline Through Mentorship and Training

Empowering the next generation of researchers and advocates necessitates structured mentorship programs that pair emerging leaders with experienced advocates. Mentorship fosters bidirectional learning, enabling young researchers to gain practical insights into advocacy while ensuring that patient perspectives remain central to scientific inquiry.^{25–28}

Several established programs demonstrate the efficacy of this approach, including the American Association for Cancer Research's Scientist-Survivor Program, which creates immersive environments where patient advocates interact directly with researchers at scientific conferences, facilitating bidirectional knowledge exchange and perspective sharing. Similarly, the National Breast Cancer Coalition's Project LEAD provides comprehensive scientific training in cancer biology, genetics, epidemiology, and research methodology for breast cancer advocates, equipping them with the expertise to participate meaningfully in research discussions, review panels, and policy forums. The Research Advocacy Network further exemplifies this model through training initiatives that emphasize evidence-based advocacy and develop participants' capacity to translate complex scientific concepts for diverse stakeholders, with graduates of these programs subsequently serving on institutional review boards, grant review panels, and research advisory committees at cancer centers nationwide.

Institutionalizing Early Exposure to Community Engagement and Research Collaboration

Introducing students and early-career researchers to advocacy-based research fosters long-term engagement and strengthens the pipeline of patient-centered scientists. Institutional initiatives should integrate advocacy principles into research training, ensuring that future oncology researchers are equipped with the skills to engage with diverse patient populations and translate findings into practice. Community co-led research projects, policy engagement

initiatives, and advocacy fellowships can serve as mechanisms for sustaining early exposure to advocacy-driven cancer research.

STRENGTHEN COMMUNITY ENGAGEMENT INFRASTRUCTURE IN CANCER CENTERS

Demonstrate Impact Through Evaluation Metrics Guided by Established Engagement Frameworks

To quantify and communicate the value of community partnerships in cancer research, investigators should leverage established evaluation frameworks rather than creating new ones. The NAM's Assessing Community Engagement (ACE) framework,¹ PCORI's Engagement Rubric,⁵ and the Community Engagement Assessment Tool from Community-Campus Partnerships for Health²⁹ all provide validated metrics for assessing partnership quality, process outcomes, and research impact. Additionally, the Robert Wood Johnson Foundation's Practical Guide for Engaging Stakeholders in Developing Evaluation Questions³⁰ offers structured approaches to collaborative evaluation design. By applying these established evaluation approaches, researchers can demonstrate how community-engaged partnerships influence research priorities, strengthen study design, and produce findings that meaningfully affect patients and communities. This evidence of impact is critical for making the case for institutional support and continued investment in community-engaged cancer research. Detailed guidance on implementing these frameworks is readily available through each organization's online resources, enabling researchers to select metrics most relevant to their specific partnership contexts.

Fund Community Partnership-Research Collaborations

Institutional commitment to equity-focused advocacy requires cross-sector collaboration among cancer center leadership, population health departments, and government affairs teams. Strategic partnerships can drive policy initiatives that incorporate community priorities and strengthen institutional support for advocacy-driven research. Sustainable funding mechanisms—through research grants, philanthropic investments, and National Cancer Institute-designated Comprehensive Cancer Center requirements—are critical to ensuring long-term integration of advocacy into cancer research.

Embed Community Engagement Training Programs in Cancer Center Infrastructure

Training programs should focus on equipping emerging advocates with the tools to navigate research, policy, and health care systems effectively, reinforcing the role of advocacy in driving patient-centered research priorities. As modeled by cancer centers with established community engagement programs,^{31,32} a training curriculum is integrated into the cancer center infrastructure to ensure access

and awareness. Two exemplary programs include the Community Scientist Institute at City College of New York³³ and the University of Florida's Citizen Scientist Program.³¹ These curricula ensure ease for new community members and researchers to undergo tailored training programs and participate in educational activities to enhance culturally sensitive cancer research.

PRIORITIZE COMMUNITY PARTNERSHIP AS A CORNERSTONE OF CANCER RESEARCH STRATEGIC PRIORITIES

Invite and Encourage Diversity of Perspectives Through Flexible, Empathetic Engagement

Regardless of depth of engagement, patient advocates (J.C.N., D.M.) value clear communication about research time lines and outcomes as fundamental to sustainable involvement. Traditional research can progress slowly from grant application to implementation, which often conflicts with communities' desire for more immediate results. For example, Mount Sinai's mobile prostate cancer screening unit demonstrates effective community engagement by providing immediate health services while collecting research data. They partner with local organizations to directly reach high-risk communities, creating tangible benefits alongside research progress. Similarly, their IMPACT (National Institute of Aging Imbedded Pragmatic Alzheimer's Disease [AD] and AD-Related Dementias [AD/ADRD] Clinical Trials) pilot study for patients with prostate cancer under active surveillance builds trust through respectful interaction and transparent communication, while simultaneously delivering immediate patient benefits and advancing research objectives. Being up-front with community partners about exactly when and how research will benefit their members is essential for maintaining productive, trust-based relationships.

Diverse representation in advocacy efforts is essential for addressing disparities in cancer outcomes. This requires intentional recruitment and engagement strategies that prioritize underrepresented groups, culturally responsive partnership development, and targeted efforts to eliminate participation barriers. Researchers must recognize that missing perspectives often result from competing demands on time and resources—not from lack of valuable insights.

Meaningful engagement necessitates flexibility and accessibility. Researchers should implement varied meeting schedules (including evenings/weekends) and multiple participation options (in-person, virtual, asynchronous) to accommodate diverse life circumstances. Fair compensation at professional consultation rates acknowledges community expertise, while practical support (childcare, transportation, and technology access) removes participation barriers.

Creative strategies include community-hosted research forums, embedding discussions within existing community

gatherings, using arts-based methods that transcend language barriers, and training community members as core-researchers. The Meharry-Vanderbilt Community Engaged Research Core and Penn Center for Community Health Workers offer successful models for integrating perspectives from underrepresented communities through trained liaisons who maintain authentic connections within their networks.

Integrating mentorship and training initiatives further bolsters advocacy efforts by equipping emerging leaders with skills for research engagement, always designed with cultural humility and awareness of historical research harms that may affect trust.

Embed Community Partnership Requirements in Research Grants and Initiatives

Incorporating advocacy components into research funding mechanisms can institutionalize community engagement within oncology research. This may include grant requirements for structured community engagement plans and dedicated funding for advocacy-driven activities and affect assessment metrics evaluating community participation. These structural incentives ensure that advocacy is not an ancillary component but a fundamental pillar of high-quality, equity-focused cancer research.

CONCLUSION

The integration of advocacy through community engagement throughout the research continuum represents a transformative approach to enhance the relevance, rigor, and impact of cancer science. As discussed in this study, community engagement is not merely a good thing to do but a scientific enhancement that bridges scientific findings and the lived experience of those affected by cancer.

Community engagement creates critical touchpoints across the research continuum—from question formulation and study design to implementation and policy translation—ensuring that cancer research addresses the priorities and needs of those it aims to serve. When properly implemented, these partnerships help mitigate historical inequities, build trust, and create pathways for translating scientific discoveries into meaningful improvements in patient care.

Despite the well-documented benefits, significant challenges persist in establishing and maintaining authentic community partnerships. Power imbalances, resource constraints, institutional barriers, historical mistrust, and sustainability concerns all threaten to undermine engagement efforts. However, as our analysis suggests, these challenges can be addressed through intentional strategies: institutional commitment, dedicated funding streams, flexible engagement mechanisms, comprehensive training, and transparent communication practices.

The future of robust community engagement in cancer research depends on our collective ability to implement the recommendations outlined in this study: demonstrating impact through established evaluation metrics, diversifying advocacy perspectives, strengthening the advocacy pipeline through mentorship, institutionalizing early exposure to community engagement, funding sustainable partnership-research collaborations, and embedding community partnership requirements in research initiatives. These approaches will help ensure that advocacy becomes a fundamental pillar of high-quality, equity-focused cancer research.

In alignment with ASCO's 2024-2025 presidential theme, Driving Knowledge to Action: Building a Better Future, community engagement and advocacy serve as critical mechanisms for transforming oncologic knowledge into meaningful action. By centering the voices and perspectives

of those affected by cancer, researchers can develop interventions that address the complex interplay of biological, social, and environmental factors influencing cancer outcomes. This collaborative approach not only enhances scientific validity but also builds the trust and shared ownership necessary to implement findings effectively in diverse communities.

As we look toward the future of cancer research and care, the integration of advocacy across the research continuum stands as an essential strategy for achieving equitable outcomes. Through meaningful partnerships between researchers, clinicians, patients, caregivers, and communities, we can build a research enterprise that is not only scientifically rigorous but also deeply responsive to the needs and priorities of those it aims to serve. This is the pathway to truly patient-centered cancer care—one where knowledge is consistently transformed into action that improves lives.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Aguilar-Gaxiola S, Ahmed SM, Anise A, et al: Assessing meaningful community engagement: A conceptual model to advance health equity through transformed systems for health: Organizing committee for assessing meaningful community engagement in health & health care programs & policies. *NAM Perspect* 1-12, 2022
2. Cyril S, Smith BJ, Possamai-Inesedy A, et al: Exploring the role of community engagement in improving the health of disadvantaged populations: A systematic review. *Glob Health Action* 8:29842, 2015
3. Clinical and Translational Science Awards Consortium: Principles of Community Engagement (ed 2). Bethesda, MD, National Institutes of Health, 2011
4. National Institutes of Health (NIH): Principles of Community Engagement (ed 3). Bethesda, MD, NIH, 2022
5. Patient Centered Outcomes Research Institute: PCORI Engagement Rubric. Washington, DC, Patient Centered Outcomes Research Institute, 2016
6. Polite BN, Adams-Campbell LL, Brawley OW, et al: Charting the future of cancer health disparities research: A position statement from the American Association for Cancer Research, the American Cancer Society, the American Society of Clinical Oncology, and the National Cancer Institute. *CA Cancer J Clin* 67:353-361, 2017
7. Trapl ES, Koopman Gonzalez S, Austin K: A framework for building comprehensive cancer center's capacity for bidirectional engagement. *Cancer Causes Control* 35:963-971, 2024
8. Kiss N, Jongbloed H, Baguley B, et al: Meaningful consumer involvement in cancer care: A systematic review on co-design methods and processes. *JNCI Cancer Spectr* 8:pkae048, 2024
9. Key KD, Furr-Holden D, Lewis EY, et al: The continuum of community engagement in research: A roadmap for understanding and assessing progress. *Prog Community Health Partnersh* 13: 427-434, 2019
10. Leader AE, Aplin AE: From the community to the bench and back again: The value of patient and community engagement in cancer research. *Cancer Discov* 11:2135-2138, 2021
11. Kale S, Hirani S, Vardhan S, et al: Addressing cancer disparities through community engagement: Lessons and best practices. *Cureus* 15:e43445, 2023
12. Price A, Clarke M, Staniszewska S, et al: Patient and public involvement in research: A journey to co-production. *Patient Educ Couns* 105:1041-1047, 2022
13. Patel RV, Patel VR, Patel DR, et al: Top ten things palliative care clinicians should know about caring for Hindus. *J Palliat Med* 23:980-984, 2020

14. Patel RV, Murali KP, Patel VR: Clarifying karma for culturally concordant care. *JCO Glob Oncol* 10.1200/GO.23.00259
15. Patel RV: Developing culturally concordant palliative care for Hindu patients and families. *Oncology Fellows*, 14, 2023
16. Varilek B, Mollman S: Healthcare professionals' perspectives of barriers to cancer care delivery for American Indian, rural, and frontier populations. *PEC Innov* 4:100247, 2024
17. Fitch M, Mollman S, Varilek B: Identifying the need for a nurse-driven palliative care intervention for American Indian and rural family. *Fam Syst Health* 10.1037/fsh0000931 [epub ahead of print on October 21, 2024]
18. Levitan B, Getz K, Eisenstein EL, et al: Assessing the financial value of patient engagement: A quantitative approach from CTTI's patient groups and clinical trials project. *Ther Innov Regul Sci* 52: 220-229, 2018
19. Hamdy FC, Donovan JL, Lane JA, et al: Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 388:1547-1558, 2023
20. McDavitt B, Bogart LM, Mutchler MG, et al: Dissemination as dialogue: Building trust and sharing research findings through community engagement. *Prev Chronic Dis* 13:E38, 2016
21. Holt CL, Chambers DA: Opportunities and challenges in conducting community-engaged dissemination/implementation research. *Transl Behav Med* 7:389-392, 2017
22. Ohmer ML, Mendenhall AN, Carney MM, et al: Community engagement: Evolution, challenges and opportunities for change. *J Community Pract* 30:351-358, 2022
23. Shultz J, Oneha MF, Magnussen L, et al: Finding solutions to challenges faced in community-based participatory research between academic and community organizations. *J Interprof Care* 20: 133-144, 2006
24. Irby MB, Moore KR, Mann-Jackson L, et al: Community-engaged research: Common themes and needs identified by investigators and research teams at an emerging academic learning health system. *Int J Environ Res Public Health* 18:3893, 2021
25. Salamone JM, Lucas W, Brundage SB, et al: Promoting scientist-advocate collaborations in cancer research: Why and how. *Cancer Res* 78:5723-5728, 2018
26. Jaffee EM, Dang CV, Agus DB, et al: Future cancer research priorities in the USA: A Lancet Oncology Commission. *Lancet Oncol* 18:e653-e706, 2017
27. Masterson D, Areskoug Josefsson K, Robert G, et al: Mapping definitions of co-production and co-design in health and social care: A systematic scoping review providing lessons for the future. *Health Expect* 25:902-913, 2022
28. Grindell C, Coates E, Croot L, et al: The use of co-production, co-design and co-creation to mobilise knowledge in the management of health conditions: A systematic review. *BMC Health Serv Res* 22:877, 2022
29. Community Scientist Program at Tisch Cancer Institute. New York, NY, Icahn School of Medicine at Mount Sinai. <https://icahn.mssm.edu/research/tisch/community/research/community-scientist-program>
30. CCNY Community Scientist Institute Course Webpage. New York, NY, City College of New York. <https://www.ccny.cuny.edu/cps/community-scientist-institute>
31. Community-Campus Partnerships for Health: Community Engagement Assessment Tool. Community-Campus Partnerships for Health, 2018
32. Preskill H, Jones N: Practical Guide for Engaging Stakeholders in Developing Evaluation Questions. Robert Wood Johnson Foundation, 2009
33. Citizen Scientist Cancer Curriculum UF Health Cancer Center. <https://citizenscientist.cancer.ufl.edu>

Oncology and Suffering: Strategies on Coping With Grief for Health Care Professionals

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OVERVIEW

This article comprises three integrated sections exploring the multidimensional suffering experienced in oncology—from the perspective of both patients and health care professionals. It explores how oncology clinicians can better understand, address, and accompany the suffering of patients with advanced illness and what resources the patients themselves may appeal to when facing a terminal diagnosis. Section 1 outlines a clinical framework for attending to patient suffering when there is no cure, emphasizing psychologic formulation, attunement, and countertransference as therapeutic tools. Section 2 addresses provider overwhelm and distress in response to patient grief, with strategies grounded in neuroscience, meaning making, and emotional regulation. Section 3 considers attending to suffering in oncology in the context of spirituality and focuses in particular on when patients and providers are unable to draw support from religious belief. Together, these insights offer a narrative-driven, psychologically attuned, and spiritually inclusive approach to care.

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SECTION 1: ATTENDING TO SUFFERING WHEN THERE IS NO CURE: A FRAMEWORK FOR PALLIATIVE ONCOLOGY

Suffering When There Is No Cure

Suffering in serious illness is multidimensional, extending far beyond physical symptoms to encompass psychologic, existential, social, and spiritual distress. The seminal work by Cassell defines suffering as “the distress associated with threats to the integrity of the person,” emphasizing that suffering arises when an individual perceives a fundamental loss of identity, autonomy, or meaning in life.¹ This conceptualization underscores that suffering is not merely about pain or symptom burden but about the disruption of one’s sense of self, purpose, and connection to others.

In psycho-oncology, systematic reviews have characterized suffering as a dynamic, evolving experience, frequently marked by alienation, helplessness, and profound existential distress.² Patients with advanced cancer often experience suffering not only from physical decline but also from the psychosocial ramifications of their illness, including changes in relationships, loss of independence, and anticipatory grief. The framework proposed by Tate further refines this understanding by defining suffering as “the experience of a gap between how things are and how things ought to be.” The gap itself is what is perceived, sensed, or experienced. This conceptualization highlights that suffering arises from this discrepancy between one’s current reality and an idealized state, whether in terms of health, relationships, autonomy, or existential meaning.³

Recognizing this gap offers oncology clinicians a point of entry for both empathic understanding and tailored interventions. Given its complexity, suffering calls for an inter-professional lens to engage with patients on a deeper, narrative-driven level. A biomedical approach alone is insufficient to address the existential weight of a life-limiting illness. Instead, patient narratives, values, and meaning making must be integrated.^{4,5} For example, a 68-year-old woman with metastatic pancreatic cancer expresses profound emotional distress over her inability to cook for her grandchildren—an activity that once defined her identity and sense of purpose. Her suffering is not solely about her prognosis or physical decline but about the loss of her role as a caregiver, which has been central to her self-concept. The distress she experiences is a threat to her personhood, eroding her sense of autonomy, connection, and generativity.

This patient case illustrates how suffering is not merely a function of disease progression but a deeply personal, relational, and existential experience. Oncology clinicians can explore how illness disrupts a patient’s sense of self and ways to restore or redefine meaning in life. This may also support patients in reclaiming agency or identity through spiritual, relational, or creative means—even as physical decline continues. Thus, a response to the patient’s suffering requires a holistic, patient-centered approach that is attuned to both visible and unspoken sources of distress. The multidimensional aspect of suffering calls not only for empathic listening but also a psychologically informed approach. The next section explores how a coping assessment (ie,

PRACTICAL APPLICATIONS

- Recognizing the multidimensional nature of suffering involving existential, psychologic, social, and spiritual distress is crucial for enhancing therapeutic responses and clinician attunement.
- Understanding and using clinician countertransference reactions can inform compassionate care and promote resilience.
- Through awareness and proactive strategies, providers can minimize burnout and foster a long-term, emotionally nourishing relationship with their work.
- When health care providers actively pursue joy, they reinforce their own emotional strength and build capacity to sustain them through the difficult moments of caregiving.
- Pursuing the goal of enabling patients, their families, and health care professionals to get on or move on in the face of terminal diagnosis and death, respectively, can have a self-undermining effect.

psychologic formulation) and attunement offer stepwise clinical methods to recognize, assess, and respond to suffering when there is no cure.

Coping Assessment: Psychologic Formulation, Attunement, and Personhood

Effectively addressing suffering in serious illness requires more than recognizing distress—it necessitates understanding the psychologic underpinnings that drive a patient's experience. Psychologic *formulation* provides a structured framework to explore the *why* behind a patient's thoughts, emotions, and behaviors, allowing clinicians to develop tailored, patient-specific therapeutic interventions.⁶ Unlike a diagnosis, formulation is not a fixed label but rather a working hypothesis, evolving as more data emerge from the patient's narrative, behavior, and clinician-patient interactions.⁷

Formulation, originally a foundational concept in psychotherapy, has been adapted to serious illness communication as a tool to enhance therapeutic effectiveness. It is a hypothesis—a flexible, evolving framework—meant to guide clinical reasoning and communication choices.⁶ Although different psychotherapeutic traditions conceptualize formulation uniquely, they share a common goal: to uncover the core struggle beneath a patient's presentation, thereby enabling a more precise and compassionate response.⁸

In serious illness care, a patient's outward behaviors—hesitation, withdrawal, and emotional distress—may

appear similar across different individuals but can stem from entirely different underlying struggles. Without formulation, a clinician may inadvertently respond generically rather than therapeutically, risking misalignment with the patient's actual needs.

Illustrating the Power of Formulation

A patient delaying an important medical decision could be doing so for any number of reasons, including:

1. Distrust of the medical system—perhaps because of prior negative health care experiences.
2. Regret from past medical decisions—fear of making the wrong choice again.
3. Family discord or external pressure—a misalignment between what the patient wants and what their loved ones expect.
4. A lifelong pattern of ambivalence—they have struggled with big decisions throughout their life.

If a clinician assumes all indecision stems from the same cause, their approach may be ineffective—or even countertherapeutic. A formulation-driven response, however, would adapt the clinician's strategy on the basis of the underlying psychologic drivers:

1. For medical distrust, focusing on transparency and relationship building would take priority: "I want to make sure you feel fully informed and supported every step of this journey. What questions or concerns do you have?"
2. For regret from previous decisions, clinicians might validate this distress and offer perspective taking: "It makes sense that you're feeling cautious. Can we talk about what might allow you to feel more confident and assured?"
3. For family discord, eliciting the patient's priorities and facilitating open conversations might be key: "It sounds like your family feels strongly about one path, while you're uncertain. Can we explore those two aspects together?"
4. For lifelong ambivalence, providing structured, stepwise guidance may be beneficial: "Would it help to break this decision into smaller parts?"

Each of these responses is uniquely tailored to the patient's psychologic landscape, on the basis of the specific formulation of what might be each patient's core inner struggle. Each formulation in [Table 1](#) underscores that patient behaviors are often rooted in distinct psychologic coping mechanisms. Clinicians who recognize these patterns can respond with nuance, reducing distress rather than inadvertently reinforcing maladaptive coping.

There are some key principles for understanding formulation:

1. Formulations are fluid—they evolve with new evidence. Unlike a diagnosis, formulations are working hypotheses that should be adjusted and refined as the clinician gathers more data from the patient's responses, verbal cues, and emotional shifts.⁶

TABLE 1. Patient Presentations With Dual Formulations and Differentiated Therapeutic Responses

Patient Presentation	Formulations	Therapeutic Response
Requests continued aggressive chemotherapy	A: Denial as protective coping	A: Introduce QOL conversations with sensitivity and empathy
	B: Family pressure to keep fighting	B: Facilitate family discussions about prognosis and focus of care
Withdraws from medical decision making	A: Fear of being a burden on loved ones	A: Encourage family discussions and patient autonomy when possible
	B: Overwhelmed existentially with the losses	B: Consistent support and accompaniment
Repeatedly seeks alternative therapies	A: Distrust in medical care	A: Transparent, consistent communication and follow-through to build trust
	B: Sustaining hoping for the best	B: Empathically introduce the dialectic of hoping for the best and preparing for all outcomes
Frequently changes decisions about care	A: Ambivalence	A: Discuss the various parts of self and the competing values the patient is holding
	B: Decision making is emotionally overwhelming	B: Preplan together the pacing and process for decisions; mobilize inner circle for support
Fixation on minor clinical details	A: Fear of losing control	A: Clear, frequent communication; anticipatory planning; providing agency when possible
	B: Intolerance of uncertainty	B: Structured approach; cognitive behavioral techniques; model being with uncertainty

Abbreviation: QOL, quality of life.

- Multiple data points inform a formulation—clinicians should incorporate not just what patients say, but how they say it, their body language, prior interactions, and even interdisciplinary team observations.⁸
- Formulation happens on multiple scales—it can apply to a moment of distress, an entire conversation, or a long-standing patient dynamic.⁷ Recognizing the level at which formulation is being applied prevents overgeneralization.
- Formulation guides clinicians to tailor and personalize their communication—by knowing *why* a patient is struggling, a clinician can shift their tone, pacing, level of directiveness, or choice of words to better align with the patient's needs.⁶
- Formulation enhances empathic attunement—instead of reacting solely to behavior, clinicians can engage with the deeper emotional experience beneath the behavior, fostering stronger therapeutic connections.^{5,9}

The Synergy of Formulation and Attunement

Attunement—the ability to recognize and validate both explicit and unspoken distress signals—is a critical skill that complements formulation. An attuned clinician does not rush to fix suffering but instead engages in deep listening, emotional presence, and validation.⁵

One simple yet powerful tool for fostering attunement is the patient dignity question framed by Chochinov: “What do I need to know about you as a person to give you the best care possible?” This question elicits aspects of personhood, reinforcing that the patient is more than their illness and that their values, fears, and identity remain central to their care. Evidence demonstrates that dignity-conserving care reduces existential distress and strengthens the clinician-patient relationship.¹⁰

Psychologic formulation is an indispensable tool in serious illness care, helping clinicians move beyond surface-level observations to understand the psychologic and existential roots of suffering. By integrating formulation with attunement, clinicians can tailor their communication strategies, adapt their therapeutic stance, and respond in ways that are deeply aligned with patient needs. Rather than relying on one-size-fits-all communication strategies, formulation guides the art and science of serious illness care, ensuring that every response is thoughtful, compassionate, and therapeutically precise.

Countertransference as Clinical Insight: Enhancing Patient Care and Clinician Well-Being

Countertransference—a clinician's emotional response and reactions to a patient—is often perceived as a challenge to be managed. However, when acknowledged, explored, and integrated into clinical reasoning, countertransference becomes a powerful diagnostic tool, offering deep insights into the patient's psychologic state, coping mechanisms, and underlying emotional struggles. Equally important, countertransference serves as a window into the clinician's own well-being, helping to promote sustainability, wellness, equity, and inclusion in clinical practice. By reflecting on their own reactions, clinicians can enhance both patient care and their own professional fulfillment, transforming countertransference from an unconscious liability into an intentional therapeutic asset.¹¹

Beyond its role in therapeutic attunement, countertransference is a valuable data point in psychologic formulation, offering clinicians deeper insight into the core psychologic drivers behind a patient's behaviors, emotions, and coping strategies. Strong, unusual, or disproportionate emotional

TABLE 2. Examples of Clinician Countertransference and Response Possibilities

Countertransference	Response Possibilities
Rescue fantasy	Accompany patient, rather than trying to fix it all
Emotional numbing	Self-awareness and self-reflection. Ensure equity of care for the patient. Self-care to protect from compassion fatigue
Moral distress	Name and validate the conflict and ethical tension. Case discussions and debriefs with interprofessional colleagues
Overidentification	Maintain professional boundaries. Avoid projecting personal fears/experiences by distinguishing the uniqueness of the patient. Use interprofessional team and process with trusted colleagues
Persistent worry	Contain the worry with boundaries. Distinguish what is within one's control. Grounding mantra to disrupt worry spiraling
Avoidance	Self-reflection. Mindfulness before encounters. Shifting perspective and reframing
Helpless and hopeless	Normalize and validate. Reframe role from fixing to supporting and accompanying. Redirect focus to small, meaningful actions to restore agency
Guilt or self-blame	Reframe from self-judgment to meaningful presence. Reality check with a trusted colleague. Acknowledge limits of medicine and health care systems
Anger or frustration	Pause and ground before responding. Shift to curiosity (rather than reactive judgment). Name and validate patient's experience without escalating

reactions—such as dread, frustration, or exhaustion—often mirror the patient's unspoken or suppressed distress, particularly in cases of demoralization, avoidance, or psychologic defenses. For example, a clinician who consistently feels hopeless and emotionally depleted when seeing a specific patient may be absorbing the patient's own demoralization, a syndrome marked by helplessness, loss of meaning, and emotional exhaustion, which can be highly contagious in clinical interactions. Recognizing this emotional response allows the clinician to move beyond frustration and instead implement interventions that restore meaning, dignity, and autonomy, rather than focusing solely on disease management.^{9,11}

In addition to illuminating the patient's emotional state, countertransference also serves as a critical tool in the formulation process, helping clinicians refine their understanding of a patient's coping mechanisms and core psychologic struggles. For example, if a clinician experiences frustration or urgency in response to a patient delaying a medical decision, this reaction may signal unresolved ambivalence, mistrust, or external conflict rather than simple indecisiveness. By incorporating countertransference as a diagnostic clue, clinicians can deepen their formulation process, enhancing their ability to tailor interventions effectively. [Table 2](#) outlines common countertransference reactions and provides ideas for response strategies to foster

TABLE 3. Clinician Strategies to Explore and Respond to Suffering

Exploring and Responding Strategies	Possible Phrases and Wording
Ask open-ended questions	"What's been some of the hardest parts of this for you?"
Explore meaning	"What worries you the most about the illness?"
Reflect emotion	"It sounds like this has been very heavy and draining"
Gentle naming	"It sounds like there is suffering—not simply in your body, but also in your heart, mind, and spirit"
Normalize the experience	"Many patients in this situation describe feeling similarly"
Validate the experience	"It makes sense you would feel this way; you have endured so much hardship"
Attend to silence and body language	[Pause—leaving space for silence and emotion]

self-awareness, therapeutic attunement, and sustainable patient care.

Countertransference elevates care by both providing insight into the patient's inner world and illuminating aspects of the clinician's well-being. Emotional responses such as excessive self-blame, compassion fatigue, or frustration toward specific types of patients may signal unacknowledged personal stressors, moral distress, or systemic challenges.

By incorporating countertransference not only as a clinical tool but as a self-reflective practice, clinicians can cultivate both patient-centered care and professional sustainability, ensuring that their own emotional well-being is as valued as the care they provide. Therefore, countertransference, when actively examined, serves as a dynamic tool for both patient care and clinician wellness. Rather than viewing strong emotional reactions as a burden, oncology clinicians can harness them as valuable clinical data, ultimately leading to more compassionate, psychologically informed care—for both their patients and themselves.

Therapeutic Approaches to Attending to Suffering

When cure is no longer possible, therapeutic attunement informed by personalized psychologic formulations provides a structured approach to mitigating suffering, helping patients reclaim a sense of meaning, dignity, and connection. The goal is not merely to alleviate distress but to foster a therapeutic space in which patients feel understood, validated, accompanied, and supported. [Table 3](#) offers strategies for providers to explore and respond to suffering. Moreover, approaches such as narrative interventions, meaning-centered therapies, attuned communication, and structured existential care help patients cope with existential uncertainty and loss of autonomy, guiding them toward psychologic integration, acceptance, and even post-traumatic growth.

Narrative and Meaning-Centered Therapies for Patients

One of the most profound interventions in palliative oncology is allowing patients to construct and share their life narratives. Narrative-based therapies, such as dignity therapy and managing cancer and living meaningfully (CALM), are examples of interventions that offer structured frameworks for patients to articulate their experiences, values, and legacy, often leading to enhanced psychologic well-being and reduced distress. Dignity therapy involves a structured conversation in which the patient reflects on life experiences, meaningful moments, and personal wisdom they wish to pass on to others. This intervention has been shown to reinforce identity, promote legacy building, and reduce existential distress in patients facing advanced cancer.¹²

CALM therapy, developed for patients with advanced cancer, focuses on enhancing resilience and acceptance by integrating psychologic, existential, and emotional elements.¹³ For example, a 45-year-old man with recurrent glioblastoma described intense anticipatory grief about missing future milestones with his young children. CALM therapy helped him reframe his legacy, emphasizing quality of presence over the quantity of time, allowing him to re-engage with his family with renewed purpose.

Meaning-centered psychotherapy (MCP) is another example of an intervention that fosters a deep exploration of personal values, legacy, and existential meaning. This therapy is particularly useful for patients struggling with a sense of futility or identity loss after a cancer diagnosis.¹⁴ MCP provides a structured framework to help patients reconstruct purpose, even in the face of terminal illness.

Finally, spiritual and existential concerns are deeply interwoven with suffering in advanced cancer. Even in nonreligious patients, questions of meaning, legacy, and life closure are prominent. Structured spiritual care provides an opportunity for patients to explore their fears, hopes, and beliefs, often leading to a sense of peace and acceptance. Incorporating chaplains, spiritual counselors, or existential therapists into oncology care has been shown to reduce anxiety, depression, and death-related distress, particularly in patients experiencing severe spiritual pain or unresolved guilt.¹⁶ For example, a 68-year-old atheist with end-stage multiple myeloma expressed intense fear of dying alone. When a palliative chaplain asked, “What has helped you through difficult times in the past?” the patient recalled the comfort of music and poetry, leading to the creation of a personalized playlist for his final days—transforming his distress into an intentional, comforting ritual.

Clinical Attunement and Communication Strategies for Clinicians

A clinician’s ability to attune to a patient’s unspoken fears, losses, and existential concerns is central to therapeutic efficacy. Attuned communication fosters emotional safety,

helping patients feel understood and emotionally contained in the face of profound uncertainty. Key strategies for attuned communication include:

1. **Active listening and validation:** Creating a space for emotional expression allows patients to process grief, fear, and uncertainty without feeling rushed or dismissed. For example, a 60-year-old woman with metastatic breast cancer voiced regret and unfinished business with her estranged sister. Instead of redirecting the conversation to symptom control, the oncologist paused, validated her emotions, and facilitated a discussion about whether reconciliation was important to her well-being.
2. **Exploratory questioning:** Open-ended inquiries, such as “What is weighing most on your mind?” or “How has your illness changed what matters most to you?” encourage patients to express their deeper concerns, often revealing underlying fears about loss of autonomy, relational conflict, or spiritual distress.
3. **Balancing realism with reassurance:** While false hope can be damaging, patients often benefit from a compassionate balancing of realism with emotional support. Holding a dialectic of “hoping for the best, while preparing for the worst or any outcome” models a balanced approach. For example, a patient asked, “Am I dying soon?” Instead of deflecting, the oncologist responded, “While your cancer is progressing, we are here to support you in living as well as possible while also knowing that time is likely more limited than we hoped. Are you interested in knowing what to expect in terms of time? What concerns you most about what’s ahead?” This approach acknowledged reality while reinforcing continued care and connection.

Attuned communication fosters trust, enabling patients to navigate existential distress with greater emotional stability and engagement in their care.

Section 1 Summary

Attending to suffering in serious illness requires a shift from a purely biomedical approach to one that is psychologically attuned, narrative-driven, and rooted in the patient’s lived experience. Suffering is deeply personal, shaped not only by physical decline but also by loss of identity, relational disconnection, existential distress, and fears about the future. Oncology clinicians must recognize that alleviating suffering is not about fixing or eradicating distress, but about witnessing, validating, and accompanying patients through it, fostering meaning, dignity, and autonomy in the face of serious illness.

By incorporating psychologic formulation, attunement, and countertransference awareness, clinicians can better understand why a patient is struggling, allowing for more personalized and effective therapeutic responses. Countertransference, when used skillfully, provides valuable insights into the patient’s emotional world, serving as a data point to refine clinical formulations and attune to unspoken suffering. Through narrative-based interventions, MCP, and dignity-conserving

care, clinicians can help patients reclaim agency and meaning, even in the setting of an incurable illness.

Ultimately, therapeutic presence is the foundation of alleviating suffering. By integrating psychologic insights with compassionate, attuned communication, clinicians can provide care that honors the patient's humanity, ensuring that suffering is not endured in isolation but met with deep understanding, empathy, and dignity.

SECTION 2: PRACTICAL TIPS FOR NOT BEING OVERWHELMED BY THE GRIEF OF THOSE FOR WHOM WE CARE

Understanding Why Overwhelm Happens

Focusing on the multidimensional and narrative aspects of suffering in oncology patients and providers is highly valuable. It informs the field; clarifies treatment plans; and fosters a meaningful, adaptive relationship with the work. The concept of a provider's therapeutic presence in the face of suffering has profound implications for both practice and self-care. One key aspect of therapeutic presence is the existential response to death and mortality salience, along with the defensive mechanisms providers develop to cope with constant exposure to their own vulnerability. Although there are thousands of ways that death could come for anyone, at any given moment in time, being wholly and fully connected to that feeling at all moments in time would be overwhelmingly impractical. Humans, in their sentience, have created adaptive space between intellectual awareness of mortality and a felt sense of its salience.^{17,18} When people become seriously ill, that space becomes threatened, and the ill person can no longer pretend like death is not near.

While the distress that arises from seriously ill patients contemplating their own mortality is somewhat obvious, the impacts of that awareness within patients on the empathic dyad between the patient and the provider can be less visible. When health care providers attune to people in these raw and vulnerable states and the sense of a shared humanity is felt, they can be reminded of their own mortality. Their carefully constructed protective space can become threatened, leading to distress and overwhelm. Defensive responses such as numbness, distancing, saviorism may emerge as a new baseline.¹⁸

This dynamic, reflective of the research on death anxiety, can also be understood in the context of grief. From an attachment lens, we can understand grief as a kind of mortal separation anxiety—a deeply felt fear and dysregulation that comes when safety objects (certain people, relationships, etc) are threatened or gone.¹⁹ In serious illness, the grief may begin as soon as there is a sense of an “after”: when symptoms become apparent, at diagnosis, at a shift in treatment plans, when prognoses change, in dying, or in bereavement.²⁰

Grief may be in patients or family members, as well as in providers who have developed long-standing relationships

or share unusually familiar personal circumstances. When providers either experience or bear witness to the underdefended, mortality-salient states that grief entails, they can trigger the same defensive responses in themselves.¹⁸ For providers who generally find their work personally satisfying, closing off the emotional availability to the work can lead to compassion fatigue, burnout, and pessimism.

Several research-based theories may help explain this dynamic. Terror management theory (TMT) touches on the existential elements of grief, suggesting that people experience existential anxiety when they are presented with reminders of their own mortality. In response, they develop structures to protect against dysregulation, which can range from psychologic distancing to engaging in culturally affirming, self-esteem boosting connections.¹⁷

Polyvagal theory addresses some of the physiologic and neurologic components of emotional distress in grief. It states that the safety-seeking elements of the nervous system exist in three states—beyond just fight/flight and rest/digest—helping to explain how we navigate emotional stress. From this perspective, grief can trigger a fight/flight (sympathetic) or shutdown (parasympathetic) response, moving away from an ideal baseline of social engagement and connectedness.²¹

Attachment theories further explore how early bonding patterns shape our blueprint for connection, safety, and threat, affecting providers' ability to navigate their connections with patients that they are losing to death.¹⁹ The balance between facing death while staying emotionally connected to the work is challenging. Providers must appreciate a patient's suffering enough to be driven to offer healing but not be so overwhelmed by the suffering that they become paralyzed.²¹ With constant exposure to mortality, cycles of nervous system overactivation and shutdown, and boundary struggles influenced by attachment styles, health care providers have much to process.

Understanding the emotional overwhelm that can arise from facing patient grief can help health care providers process their distress and build professional resilience. Additionally, practical interventions—based on deeper understandings of mortality salience, existential distress, and coping mechanisms—can be helpful. Providers who integrate cognitive, physiologic, and relational strategies like the ones below will be better prepared to sustain their well-being while providing compassionate care.

Finding Meaning in Care

MCP offers a constructivist approach to grief, considering that one's legacy comprises both inherited experiences and daily choices.²² Providers with a strong sense of why they work with mortality and how they understand their role—especially beyond merely avoiding death—will have greater resilience to death anxiety. From a TMT perspective,¹⁷ this aligns with

the concept of cultural self-esteem—seeing oneself as a valuable member of a community. Every person inherits a body vulnerable to illness and a health care system that often induces moral distress. However, providers can buffer against powerlessness by defining their role not just through specialization but also through their interpersonal approach to care.^{18,23} The more providers can explicitly articulate why they do what they do and how their efforts contribute to a legacy, the more resilience they can foster.

Creating Rituals

Rituals can serve multiple purposes, such as increasing mindful awareness and marking the transition between patient encounters. Rituals signal the nervous system to shift states, facilitating movement out of hyperaroused or hypoaroused responses. They can range from deep breaths between patients to lighting candles, meditating, memorializing, or engaging in movement-based practices. Establishing consistent rituals provides a sense of predictability and control, which can act as a psychologic buffer against emotional fatigue.

Recognize Physiologic States

Tracking one's nervous system state through a polyvagal framework aids mindfulness and self-regulation.²¹ Awareness of personal triggers—such as feeling powerless or overwhelmed—helps providers make informed self-care choices. This awareness also enhances understanding of how patients, families, and colleagues are coping.

Engage With Coregulation

Accessing the ventral vagal state, where social connection resides, can help calm the nervous system and prevent overwhelm. Peer support—through authentic, vulnerable sharing rather than venting from a place of burnout—is invaluable. Social connection signals safety, encouraging emotional engagement and reducing distress.^{21,23}

Somatic Strategies

Given that trauma is primarily a somatic experience, interventions targeting the body are essential. Common techniques include intentional breathwork, mindful movement, and sensory stimulation. These strategies should be approached with self-awareness, beginning with noticing current nervous system states and tracking shifts in response to interventions.²⁰

Self-Reflection Box (Box 1)

Boundaries as Self-Preservation

Many people in helping professions were socialized in families of origin or community to prioritize others' needs over their own. In a society that often praises personal boundary crossing

BOX 1. SELF-REFLECTION

1. How does my distress at work relate to past experiences in my life (eg, feeling alone, overwhelmed, or fearful of managing others' chaos)? Is my body responding to both current and past vulnerabilities?
2. What prevents me from addressing my emotional needs? Do I minimize, invalidate, or fear that expressing my needs will push others away?
3. Am I aware when I am overactivated or shut down, or do I mistakenly believe I'm always grounded? (Hint: no one is always grounded.)
4. What motivates me? Am I trying to avoid a specific fear, achieve a goal, or reach a certain feeling or outcome?
5. When am I most proud of myself?
6. When do I feel most alive?
7. What do I wish others understood about me that may not be obvious to others?²³

as a sign of commitment, individuals may lose sight of where their needs end and others' expectations begin. Setting boundaries can be challenging, stemming from the fear of conflict or disappointing others, the guilt of not meeting others' expectations, or even just a lack of practice. Boundaries can be external, such as declining additional responsibilities, time, or emotional labor, or internal, such as not internalizing patient suffering while still providing compassionate care.²⁴ When people protect their own time and energy, they are less likely to end up depleted and overwhelmed.

Joy

Moving toward something for the joy of moving toward it is a crucial piece of building resilience against death anxiety, grief, and existential overwhelm. It facilitates growth in a socially connected state and promotes creativity, rest, and insight development. Joy should be cultivated as a daily practice, whether through hobbies, moments of laughter, physical activity, or engaging in the arts. Engaging in joy does not mean ignoring suffering, but rather embracing the full spectrum of human emotion, allowing providers to experience and appreciate moments of connection and lightness amid the heaviness of their work. When health care providers actively pursue joy, they reinforce their own emotional strength and create access to a socially connected nervous system state²¹ that can sustain them through the difficult moments of caregiving.²⁴

Provider resilience strategies:

1. Clarify your *why*: Define your role and what gives it meaning.
2. Use rituals to mark transitions and ground yourself emotionally.

3. Track your nervous system state using polyvagal-informed tools.
4. Lean on peer support for coregulation and shared vulnerability.
5. Embrace joy and creativity as a counterbalance to grief.
6. Set boundaries intentionally—compassion does not require depletion.

Section 2 Summary

Health care providers' grief and existential distress extend beyond sadness. These emotions are tied to existential fears, nervous system regulation, and attachment bonds. A sustainable approach to managing patient grief combines cognitive meaning making, nervous system self-regulation, and secure emotional engagement within the provider. On a systemic level, managing provider grief should not be an individual burden but a supported process within workplace structures. Through awareness and proactive strategies, providers can minimize burnout and foster a long-term, emotionally nourishing relationship with their work. These techniques, although primarily aimed at providers, can also benefit patients by promoting self-reflection to manage the overwhelm of illness. Patients may find value in regulating their nervous systems, discovering purpose in their roles as patients and family members, and intentionally cultivating joy. Such interventions support the nervous systems of both patients and providers, as both are profoundly affected by the cancer experience. Ultimately, the shared humanity between a patient and a provider enhances the richness of this work.

SECTION 3: SHOULD WE MOVE ON? SPIRITUALITY, SUFFERING, AND GRIEF IN ONCOLOGY

Approaching Psychologic Suffering in Oncology: The Spiritual Support of Religious Belief

A cancer diagnosis is a heavy blow for anyone. It is something that will by itself often stop us in our tracks by making the end of life suddenly pellucid. The progression of the disease can make death anxiety acute in patients with advanced cancer considerably adding to their suffering.²⁵ For health care professionals working with these patients, this is a source of additional psychologic strain resulting from a sense of futility or helplessness. The two previous sections have discussed ways of coping with this strain both in health care professionals and patients. There is a further question, however, as to what the end goal of attending to suffering should consist in and how it relates to the broader context of a meaningful life. This will be the focus of this section.

In end-of-life situations in the clinical context, we may draw spiritual support from religion. In most religious traditions, consolation in the face of death comes from the belief that death is not the end. This belief is an important source of strength that allows those who have it to get on with life even despite being diagnosed as terminally ill.^{26,27} Likewise, when

we live through the terminal illness and death of others, religion is often fundamentally important in the grieving process.

The dead, although lost to us in some respects, in these traditions often continue to play a relevant part in our lives and remain a source of psychologic or moral support. In many cases, we hope to be reunited with the dead when it is time for us to join them and so we find it easier to move on when they are gone. It is natural that psychologic support in end-of-life care as well as that extended to health care providers who work with terminally ill patients often draws on the patient's and health care provider's religious beliefs.^{28,29}

Psychologic Suffering When Religious Belief Is Absent: How Can We Move On?

Death anxiety and loss pose a more complex challenge, however, when religious belief is not present. It is understandably harder to get on or move on when death is seen as annihilation. Without the spiritual support of religious belief, the threat death poses may undermine the meanings and values that structure our lives leading to depression and apathy. The absence of such support also makes it harder for health care providers to cope emotionally and psychologically when working with patients with advanced cancer.

Consequently, research on managing death anxiety in patients with cancer facing the dying process and the health care providers working with them often focuses on creating alternative frameworks of meaning and value that help protect against death anxiety. Strategies of achieving this include developing defensive psychologic systems such as the maintenance of a cultural worldview, the pursuit of self-esteem, or the formation of secure attachments outside of the religiously motivated beliefs that death does not equate with annihilation.^{30,31} These methods are meant to protect against death anxiety to enable both patients and their families and health care professionals, if not overcome, than at least cope with, the psychologic and emotional strain that comes with facing death.

As much as this work is extremely valuable and helps to make a significant change in the quality of life of patients with advanced cancer as well as their families and health care professionals, it is also at risk of sidestepping an important aspect of what makes death—our own and that of others—a source of anxiety. The issue is not simply that the psychologic methods of alleviating death anxiety and coping with grief attempt to bring the consolation, which religious traditions offer, without the crucial element of the belief that death is not the end. Rather it is that the goal of making it easier to go on in the face of death and move on in the face of loss is, in an important sense, the wrong end of the stick.

Focusing on the psychologic well-being of those facing death or loss and those caring for them relies predominantly

on accepting the finality of death and building meaning that does not rely on our own continued existence or presence of those we have lost. This presupposes a large degree of psychologic self-sufficiency, which, on this view, we might say, is undermined or supplanted by relationships with others. Reaffirming this (psychologic) self-sufficiency is hoped to lessen the anxiety about death and help those who have suffered a loss to move on.

The spiritual support we draw from religion, however, stems from the recognition that we are not psychologically, emotionally, or morally self-sufficient and makes provision for the dependence that we have on others to continue albeit in a transfigured form. Put simply, religious spirituality can be helpful in facing death and grief not because it allows us to move on but because it makes a place for those we have lost in our lives and gives us the hope, when facing death, that one day we will be present in the same way in the lives of others.

Can We Do Better Than Hope to Move On?

This issue has been taken seriously in the psychology of grief and has become widely recognized under the name of the continuing bonds model.^{32,33} Nonetheless, by and large, these approaches also focus on the psychologic well-being of the bereaved as a goal and treat the continued investment in the person who has been lost as instrumental to this.³⁴ If we cannot ultimately hope for emotional, psychologic, and moral self-sufficiency, as religious spirituality suggests, this approach is in danger of being self-defeating.

An investment in the dead, if taken seriously, must allow for a degree of psychologic discomfort to remain. This is unsurprising—someone who cannot be replaced died. To suppress the longing for that person and circumvent our dependency on them, it is to be left emotionally and existentially amputated as the cost of having moved on. In an important sense, the goal of moving on in the face of loss is a form of avoiding rather than facing its reality. The same, we believe, is true when we are brought into proximity with our own death as patients.

Nonetheless, there might be ways to maintain our attachments as a meaningful part of our life in both situations even without recourse to religious spirituality.³⁴ This approach is a valuable spiritual resource when we have to face our own death or that of someone close to us. An important question in the context of patients with advanced cancer and end-of-life care is whether a similar attitude might be possible and desirable to adopt.

Why We Should Accept Suffering

It might seem at first that maintaining a psychologic and emotional investment in others in the context of cancer treatment might put both professionals and patients under additional strain, rather than help coping with the

challenges it poses. After all, the relationships between health care providers and patients and their families are not typically close relationships of the kind that are the subject of research in psychology of grief and bereavement.

It is important to remember, however, that in the religious context, the consolation which comes from the belief that death is not the end is not limited only to those closest to us. The religious context admits degrees of personal investment in others while preserving the fundamental need for it in each case. Indeed, this is precisely why it is explicitly appealed to, when present, as a source of psychologic support when addressing death anxiety in patients with advanced cancer.

Similarly, affirming and maintaining psychologic and emotional attachments in the clinical context, which does not appeal to religious spirituality, will also admit degrees of investment in others. This will involve accepting a degree of psychologic and emotional discomfort caused by the strain illness puts on these attachments rather attempting to alleviate it. The discomfort experienced by patients, their families, and health care providers is, however, part of the reality of the situation, and maintaining the attachments which cause the discomfort in the first place is arguably an important part of maintaining our shared humanity as it implies our mutual interdependence rather than the illusion of self-sufficiency.

Section 3 Summary

It may seem advantageous when approaching death anxiety in patients as well as emotional strain in health care providers to facilitate ways of moving on in the face of terminal illness. The ability to move on in the face of loss and death relies on building a sense of self-sufficiency. This approach helps safeguard against suffering particularly when patients or health care providers cannot draw support from religious belief. However, at the same time, it contributes to a long-term erosion of the framework of meaning and value in which we function. This framework implies our mutual moral, psychologic, and emotional interdependence. Emphasizing this interdependence when facing death in the clinical context is an important spiritual resource in end-of-life care.

CONCLUSION

In serious illness, suffering arises not only from physical symptoms but from ruptures in meaning, identity, and relationship. This suffering touches patients, families, and clinicians alike. Across psychologic, emotional, and spiritual dimensions, we find that what heals is not fixing but accompanying. Through personalized formulation, attuned presence, countertransference awareness, and a shared search for meaning, oncology teams can provide care that honors the whole person. When providers also attend to their own emotional needs—through meaning making, nervous

system awareness, peer connection, and boundaries—they model sustainability and authenticity. Even in the absence of cure, spiritual frameworks—whether religious or secular—can help patients and clinicians hold onto the bonds that persist through loss, offering continuity, not closure, as a path to integration. In moments when cure is no longer possible, continuing to foreground the interpersonal

relationships that give meaning to our shared humanity will not only have a therapeutic effect in elevating suffering but will help establish meanings and values beyond those of a potential cure. The clinical context is where we most often encounter mortality in the modern world. It should therefore be as open as possible to an integrated approach to death and dying.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Cassel EJ: The nature of suffering and the goals of medicine. *N Engl J Med* 306:639-645, 1982
- Best M, Aldridge L, Butow P, et al: Conceptual analysis of suffering in cancer: A systematic review. *Psychooncology* 24:977-986, 2015
- Tate T: Objective suffering. *Camb Q Healthc Ethics*:1-9, 2025. <https://doi.org/10.1017/S0963180125000040>
- Puchalski C, Jafari N: Acknowledging the person in the clinical encounter: Whole person care for patients and clinicians alike. Commentary on Chochinov et al. *J Pain Symptom Manage* 49:973-974, 2015
- Jacobsen J, Brenner KO, Shalev D, et al: Defining clinical attunement: A ubiquitous but undertheorized aspect of palliative care. *J Palliat Med* 24:1757-1761, 2021
- Chammas D, Moment A, Rosenberg L, et al: Formulation in palliative care: Elevating our potential for therapeutic communication. *Am J Hosp Palliat Med*:10499091241300614, 2024. <https://doi.org/10.1177/10499091241300614>
- Owen G: What is formulation in psychiatry? *Psychol Med* 53:1700-1707, 2023
- Cabaniss DL: *Psychodynamic Psychotherapy: A Clinical Manual*. Chichester, England, John Wiley & Sons, 2016
- Shalev D, Rosenberg LB, Brenner KO, et al: Foundations for psychological thinking in palliative care: Frame and formulation. *J Palliat Med* 24:1430-1435, 2021
- Chochinov HM, McClement S, Hack T, et al: Eliciting personhood within clinical practice. *J Pain Symptom Manage* 49:974-980, 2015
- Rosenberg LB, Brenner KO, Jackson VA, et al: The meaning of together: Exploring transference and countertransference in palliative care settings. *J Palliat Med* 24:1598-1602, 2021
- Chochinov HM, Hack T, Hassard T, et al: Dignity therapy: A novel psychotherapeutic intervention for patients near the end of life. *J Clin Oncol* 23:5520-5525, 2005
- Rodin G, Lo C, Rydall A, et al: Managing cancer and living meaningfully (CALM): A randomized controlled trial of a psychological intervention for patients with advanced cancer. *J Clin Oncol* 36:2422-2432, 2018
- Breitbart W, Rosenfeld B, Gibson C, et al: Meaning-centered psychotherapy for patients with advanced cancer. *Cancer* 121:3754-3761, 2015
- Reference deleted
- Balboni TA, VanderWeele TJ, Doan-Soares SD, et al: The role of spirituality in serious illness and end-of-life care. *J Clin Oncol* 31:3076-3084, 2013
- Svet M, Portalupi LBB, Pyszczyński T: Applying terror management theory to patients with life-threatening illnesses. *BMC Palliat Care* 22:74-74, 2023
- Liechty D: Touching mortality, touching strength: Clinical work with dying patients. *J Relig Health* 39:247-258, 2000
- Brenk-Franz K, Strauss B, Tiesler F, et al: Attachment and health: The influence of adult attachment on patient self-management in primary care. *PLoS One* 10:e0136723, 2015
- DiBiase J, Nathanson A: Trauma-informed approaches and interventions in serious illness, in Hemphill M, Nathanson A (eds): *The Practice of Clinical Social Work in Healthcare*. Cham, Switzerland, Springer Press, 2023, pp 261-284
- Lynch JM, Stange KC, Dowrick C: The sense of safety theoretical framework: A trauma-informed and healing-oriented approach for whole person care. *Front Psychol* 15:1441493, 2025
- Breitbart W, Pessin H, Rosenfeld B, et al: Individual meaning-centered psychotherapy for the treatment of psychological and existential distress: A randomized controlled trial in patients with advanced cancer. *Cancer* 124:3231-3239, 2018
- Posada J, Griffith JL: Mobilizing hope with brief psychotherapeutic interventions that counter demoralization—Assessment, formulation, intervention in four steps. *Acad Psychiatry* 42:1-11, 2018
- Kenfield K: 5 self-care strategies that aren't f**king mani-pedis. <https://katekenfield.com/articles/5-self-care-strategies-that-arent-mani-pedis>
- Brown TL, Chown P, Solomon S, et al: Psychosocial correlates of death anxiety in advanced cancer: A scoping review. *Psychooncology* 34:e70068, 2025
- Hwang K, Hammer JH, Cragun RT: Extending religion-health research to secular minorities: Issues and concerns. *J Relig Health* 50:608-622, 2011
- Weber S, Pargament KI, Kunik ME, et al: Psychological distress among religious nonbelievers: A systematic review. *J Relig Health* 51:72-86, 2012
- Rego F, Gonçalves F, Moutinho S, et al: The influence of spirituality on decision-making in palliative care outpatients: A cross-sectional study. *BMC Palliat Care* 19:22, 2020
- Pentaris P, Tripathi K: Palliative professionals' views on the importance of religion, belief, and spiritual identities toward the end of life. *Int J Environ Res Public Health* 19:6031, 2022
- Burke BL, Martens A, Faucher EH: Two decades of terror management theory: A meta-analysis of mortality salience research. *Pers Soc Psychol Rev* 14:155-195, 2010
- Pyszczyński T, Greenberg J, Solomon S: A dual-process model of defense against conscious and unconscious death-related thoughts: An extension of terror management theory. *Psychol Rev* 106:835-845, 1999
- Klass D, Silverman PR, Nickman SL (eds): *Continuing Bonds: New Understandings of Grief*. London, United Kingdom, Routledge, 1996
- Klass D, Steffen EM (eds): *Continuing Bonds in Bereavement: New Directions for Research and Practice*. London, United Kingdom, Routledge, 2018
- Sławkowski-Rode M: Mourning and the second person perspective, in Sławkowski-Rode M (eds): *The Meaning of Mourning: Perspectives on Death, Loss, and Grief*. London, United Kingdom, Rowman and Littlefield, Lexington Books, 2023, pp 152-170

Financial Toxicity and Breast Cancer: Why Does It Matter, Who Is at Risk, and How Do We Intervene?

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OVERVIEW

Financial toxicity, or the financial burden patients experience because of medical costs, can lead to negative patient effects including lower quality of life, compromised clinical care, and worse health outcomes. People with cancer and survivors are more likely to have financial toxicity than those without cancer, and patients with breast cancer are uniquely at risk. Patients with breast cancer often require multimodal treatment (surgery, radiation, and/or systemic therapy) and adjuvant hormonal therapy can continue for years after primary treatment. With improved disease outcomes, patients with breast cancer have prolonged survivorship often lasting decades but may carry chronic toxicities from treatment; both ongoing treatment of metastatic disease and long-term surveillance include continued tests, imaging, and medical visits that add to the cumulative burden on patients and their families. Additionally, breast cancer predominately affects women, who are more likely to have dual caregiver responsibilities, and increasingly is diagnosed in younger patients, who may have fertility preservation expenses and are more likely to experience education and/or employment disruption. When faced with high costs, patients may face difficult decisions regarding what sacrifices they are willing to endure to receive care. Interventions designed to reduce financial toxicity are moving out of the pilot phase, and ongoing randomized trials are expected to provide evidence into the effectiveness of financial navigation programs. Further work to address financial toxicity in breast cancer at the patient-provider, institutional, and governmental levels is needed for comprehensively better financial outcomes and quality of life.

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INTRODUCTION

Thanks to the research-driven advances, more than 18 million people with a history of cancer were alive in the United States as of 2022, a number projected to rise to 26 million by 2040.¹ Given incredible new treatment developments and large overall survival gains, there has been a necessary shift in focus to quality of life and reducing acute and chronic side-effect burden. Physical treatment side effects, or toxicities, are not the only ones that patients experience. There are financial consequences of medical care that can create life-altering toxicities for patients in the form of distress, debt, and employment disruptions.^{2,3} The National Cancer Institute calls this financial toxicity, specifically defined as the “problems a patient has related to the cost of medical care.”⁴ Alternative terms include economic burden, economic hardship, financial burden, financial distress, financial hardship, and financial stress.⁴ Financial toxicity is influenced by costs of new, innovative treatments that are developed and recommended in medical guidelines, often regardless of their costs.⁵ In this chapter, we discuss financial toxicity in cancer care, with a focus on breast cancer in both the United States and globally.

FINANCIAL TOXICITY IN CANCER CARE

Financial toxicity is a phenomenon across all medical conditions. However, patients with cancer and their families are at an increased risk when compared with patients with other chronic diseases.⁶ Estimates range but up to one half of patients with cancer are estimated to experience financial toxicity, and survivors are more than twice as likely to declare bankruptcy than those without a history of cancer.^{7,8} Medical expenses include direct costs, such as copays for tests, imaging, and appointments during diagnosis, treatment, and survivorship, and indirect costs, including but not limited to transportation and loss of income for both patients and families.⁹ Cancer treatments are uniquely expensive, with costs continually rising as novel medications develop and survival increases, and oncologic care also requires frequent appointments that disrupt employment and caregiver responsibilities.^{9–11} Additionally, oncology guidelines and providers may recommend expensive treatments and frequent appointments with limited expected clinical benefit. This may unnecessarily increase patient financial burdens because of a lack of attention to the net health benefit of each recommendation that is made.¹²

PRACTICAL APPLICATIONS

- Financial toxicity describes the negative effects that medical costs have on patients and is associated with decreased quality of life and lower adherence to treatment; it can have lasting effects on both patients and families and lead to compromised physical and financial outcomes.
- The prevalence of financial toxicity varies within the breast cancer patient population and is higher for those who are younger, in marginalized racial/ethnic groups, and who have metastatic disease. Clinicians should familiarize themselves with financial toxicity screening tools and coordinate with their multidisciplinary team of social workers, financial counselors, nurses, and other oncology specialists to best implement the tools in their clinics' workflows to assess all patients, with awareness that some patients may be particularly at risk.
- Most patients with breast cancer report that clinicians do not discuss the financial implications of treatment despite patient desires for cost conversations. This may be due to poor clinician education about financial toxicity screening tools or lack of knowledge of the scope of the problem. Widespread implementation of an affordability curriculum would better prepare clinicians to address financial toxicity and allow clinicians to better meet patient needs.
- Providers, institutions, and societies should be cognizant of their roles in contributing to the financial toxicity of patients. When recommending care, clinicians should identify which clinical outcomes are most important to an individual patient and align treatment recommendations with patients' goals and values to be good stewards of their financial resources. Additionally, the value of breast cancer testing, imaging, and treatment should be considered when designing clinical trials and writing guidelines.
- As financial toxicity research has expanded to include randomized trials, this higher level of evidence will better inform approaches to reduce financial toxicity. Institutional investment in patient financial navigation and policy changes to improve affordability can ensure that financial toxicity is addressed proactively.

mortality among those who declare bankruptcy.¹³ Additionally, financial toxicity exacerbates health inequities, such as for those with low health literacy who have challenges with financial assistance applications and those in racial/ethnic minority groups.^{14–16} Cross-sectional surveys have also shown that increased financial toxicity is related to greater distress and worse quality of life and that general care satisfaction is lower when there is a high financial burden.^{17–19} Financial toxicity also contributes to patient behaviors that can negatively affect health outcomes, with financial distress and unanticipated high financial burdens increasing medication nonadherence and early treatment discontinuation.^{20–22} Financial burdens can affect the entire family unit as well; studies show that caregivers of patients with cancer may also struggle with lower quality of life and compromised medical care as a result of cost.^{23,24}

FINANCIAL TOXICITY RESEARCH REVIEWS

The concept of financial toxicity in cancer care was first introduced by Drs Zafar and Abernethy in 2013, and the number of publications on financial toxicity and cancer has been increasing annually, with over 200 articles published in 2023.^{25,26} National oncologic organizations have also highlighted the role of discussions about financial toxicity, with ASCO incorporating patient costs into their updated Value Framework and consistently featuring financial toxicity topics in the annual educational book.¹² Prior educational book and annual meeting sessions have covered the financial toxicity of clinical trials,²⁷ special populations (pediatrics and adolescent and young adult survivors),^{28,29} and the role of cost conversations³⁰ and multipronged interventions.^{27,31} ASCO's *Journal of Clinical Oncology: Oncology Practice (JCO OP)* published a 2025 special issue focused on financial toxicity in cancer care, including research on patient perspectives,³ patient-level needs,³² and financial toxicity in the global setting.^{26,33,34}

Various financial toxicity screening tools have been used in cancer research in the United States and globally, with the Comprehensive Score for Financial Toxicity (COST) tool, an 11-item survey covering both objective and subjective patient financial burden, being most common.^{35–38} It uses a five-point Likert scale (“not at all” to “very much”) and is scored from 0 to 44, with multiple studies using a score of ≤20 as the threshold for financial toxicity.³⁹ The COST tool has been used in clinical settings, but the large number of questions has been seen as a barrier to broad use.³⁹ An abbreviated two-question version of the COST tool was recently validated at an urban comprehensive cancer center and found to have a high predictive value to the full measure.³⁹ Table 1 outlines the questions used in the full and abbreviated COST tools.^{36–38} Screening can be effectively completed through an online patient portal or in person in the clinic waiting room (on paper or e-device), as was done in the validation study.³⁹ Clinicians can also normalize the discussion of costs and cost concerns and discuss universal financial toxicity screening to ensure all patients feel

WHY DOES FINANCIAL TOXICITY IN CANCER CARE MATTER?

The repercussions of financial toxicity for patients with cancer are unfortunately vast, including an increase in

TABLE 1. Components of the Full and Abbreviated Two-Item COST Screening Tools

Survey Item	Included in Abbreviated Tool (Y or N)
Q1: I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment	N
Q2: My out-of-pocket medical expenses are more than I thought they would be	N
Q3: I worry about the financial problems I will have in the future as a result of my illness or treatment	Y
Q4: I feel I have no choice about the amount of money I spend on care	N
Q5: I am frustrated that I cannot work or contribute as much as I usually do	N
Q6: I am satisfied with my current financial situation	Y
Q7: I am able to meet my monthly expenses	N
Q8: I feel financially stressed	N
Q9: I am concerned about keeping my job and income, including paid work at home	N
Q10: My cancer or treatment has reduced my satisfaction with my present financial situation	N
Q11: I feel in control of my financial situation	N
Q12: My illness has been a financial hardship to my family and me	N

NOTE. The full COST screening tool has commonly been used in research and includes 11 questions plus a summary measure. Response options use a five-point Likert scale³⁸ from “not at all” to “very much” and are in reference to the past 7 days. The abbreviated two-item COST screening tool was developed by Thom et al³⁹ and is the only financial toxicity tool that has been validated for use in screening a general oncology population in a clinical setting. The two items (Q3 and Q6) have a 0.922 correlation with the full tool, a positive predictive value of 74%-91%, and a negative predictive value of 91%-98% compared with the full tool. Note that some survey items are reverse scored (questions 2, 3, 4, 5, 8, 9, and 10).

Abbreviation: COST, Comprehensive Score for Financial Toxicity.

comfortable discussing concerns as they may arise. We recognize there may be challenges with incorporating cost conversations into clinic workflows, as time is often already limited, but even intermittent brief discussions can be beneficial to patients so that financial needs are not fully unnoticed or unaddressed.

Multiple other interventions have attempted to address financial toxicity for patients with cancer. Interventions have most commonly included financial navigation programs and specialty pharmacy assistance programs⁴⁰⁻⁴² as well as a

financial toxicity tumor board and direct assistance.⁴³ As we look to the future, long-term data from multi-institutional randomized trials will provide high-quality insight into the impact of financial navigation programs on financial, treatment, and quality of life outcomes of patients with cancer.^{40,44}

FINANCIAL TOXICITY IN BREAST CANCER: A LOOK AT THE UNITED STATES

Breast Cancer–Related Financial Toxicity: An Overview

Although financial toxicity can affect all patients with cancer, patients with breast cancer are particularly at risk of poor financial outcomes, warranting dedicated discussion.⁴⁵ The majority (approximately 99%) of patients with breast cancer are women, and women are more likely to have a higher caregiver burden as well as lower income than men, increasing their risk of financial toxicity.⁴⁶⁻⁴⁸ Breast cancer also requires multimodal treatments, with many patients undergoing a combination of surgery, radiation, systemic, and/or hormonal therapies.^{49,50} This requires care coordination, frequent appointments, complex insurance navigation, and high burden of out-of-pocket costs from copayments and/or coinsurance. In one single-institution retrospective survey study, over 70% of patients with breast cancer had experienced financial toxicity, requiring personal budget changes, the use of savings, and the reduction of spending.⁵¹ Additionally, although it is fortunate that most patients with breast cancer have a good clinical prognosis, the resulting long survivorship period may require ongoing medical care for treatment side effects, prolonging the accumulation of costs.⁵² The long survivorship period can also include activities (physical therapy, mental health care, support groups, advocacy events, etc) that add to long-term costs. Finally, patients with breast cancer include adolescents and young adults who may have costs related to fertility preservation or childcare for young children and who may be at increased risk of employment disruptions, which nearly doubles the risk of financial hardship.^{2,45,53}

Who Is Particularly at Risk?

Specific sociodemographic and clinical groups within the breast cancer population have higher risks of experiencing financial toxicity; these include younger patients and those of lower socioeconomic status and/or in marginalized racial/ethnic groups. A recent single-institution study used the COST tool and found that Black and Asian women had significantly higher financial toxicity compared with their White counterparts, including worse cost-related medication nonadherence.⁵⁴ Additionally, women younger than 45 years had higher financial toxicity, with intersectional additive burden seen for young Black women.⁵⁴ This is consistent with work focused on those younger than 40 years in a nationwide sample, which showed nearly half had worsening finances because of treatment costs,⁵⁵ as well as a secondary analysis of a randomized trial that showed

younger patients had higher financial toxicity after breast surgery and that non-White patients experience around 2–2.5 times more financial toxicity.⁵⁶ In one study, a cohort of Latino patients with breast cancer expressed that cultural norms and challenges with accessing financial support contributed to their poorly managed financial burden.⁵⁷ A cohort of Black women with breast cancer in the Carolina Breast Cancer Study experienced higher job/income loss and transportation barriers compared with White women, even after controlling for socioeconomic factors.⁵⁸ Black women have also been found to be at higher risk of housing or food insecurity as a result of breast cancer treatment costs.⁵⁹ Along with age and race/ethnicity, Area Deprivation Index (ADI) is an additional relevant socioeconomic factor. A retrospective study of patients with breast cancer showed a 1.2% higher risk of financial toxicity for each unit increase of ADI.⁶⁰

Certain clinical groups are also at notable risk of financial toxicity. This includes clinical trial participants, those with metastatic disease, and long-term survivors; this burden often also spills over to affect patient caregivers and/or partners. Clinical trials require patients to travel to specific centers for care, increasing transportation costs for those who participate and deterring others from participating even if they would benefit from trial regimens.^{27,61,62} A study on women with metastatic breast cancer found that financial toxicity was common, despite nearly all women being insured, and was associated with poorer quality of life and increased distress.⁶³ In a separate study with 30% uninsured patients with metastatic breast cancer, those without insurance were over twice as likely to have been contacted by debt collectors (92%) and around half were unable to meet their monthly expenses or did not have enough money to pay for treatment costs.⁶⁴ An interview-based study further supports these findings, with medication, travel, and parking costs and lost wages contributing to the financial burden of women with metastatic breast cancer.⁶⁵ Although financial distress is the highest during treatment, there are durable out-of-pocket and time costs throughout survivorship, especially for those with less social support.^{66,67} More specifically, breast cancer survivors may still have medical debt and experience financial decline for years after diagnosis.⁶⁸ This burden is shared within families, as a study focused on partners showed that 32% decreased work hours because of the cancer diagnosis and treatment, and a majority felt pressure to continue working and to avoid job changes to maintain health insurance coverage.⁶⁹

A Case Example of Financial Toxicity in Breast Cancer

Each aspect of breast cancer treatment uniquely contributes to financial toxicity. To illustrate the cumulative burden of cancer diagnosis and treatment, we present the case of Ms S (Table 2). Ms S is a 35-year-old woman working as a dental hygienist and a single mother to a 3-year-old son. She was diagnosed with locally advanced, node-positive, human epidermal growth factor receptor 2 overexpressed (HER2+) breast cancer.

Diagnostic Workup

Ms S first presented to her primary care physician (PCP) with a history of a left breast mass. Her PCP initially believed this mass was related to her menstrual cycle; however, it was persistent and increased in size over a period of 3 months. Her PCP eventually ordered a diagnostic mammogram and ultrasound and then subsequent magnetic resonance imaging (MRI) because of dense breast tissue, which cost her \$500 in US dollars (USD) out of pocket with her private insurance.^{70,71} Her two PCP visits and breast imaging workup required four half days off work.

An MRI-guided biopsy was recommended, requiring a visit to the main hospital over 1 hour away requiring her to miss an entire day of work. She was unable to get her mother to come and cover on short notice and had to pay a babysitter to watch her son, totaling \$2,000 (USD) in out-of-pocket costs for the biopsy and \$60 (USD) dollars for the babysitter.⁷¹ Pathology results showed invasive ductal carcinoma, estrogen receptor–positive, progesterone receptor–positive, HER2+ breast cancer, and she was found to have stage III disease on imaging.

Consultations

Ms S was referred to surgical, medical, and radiation oncologists and to a plastic surgeon. The surgery and medical oncology appointments were scheduled on the same day but 5 hours apart, requiring her to miss a full day of work and to pay a babysitter to take her son to his preschool in the morning. Her radiation oncology appointment was on a different day 1 week later, requiring an additional trip to the main hospital. Her plastic surgery appointment required a third trip to complete her consultation appointments.

Chemotherapy

The medical oncologist recommended neoadjuvant chemotherapy over the course of 5 months. It required two echocardiograms and port placement, as well as infusion visits and shots for ovarian suppression. Despite her best efforts to arrange her work schedule around treatment, she still missed a total of 12 days of work reducing her take-home pay by 20%. After evaluating the options, she decided against cold capping because of cost. Ms S's out-of-pocket costs for her chemotherapy were \$3,000 (USD).

Surgery

After repeat breast imaging, she subsequently underwent breast-conserving surgery with axillary lymph node dissection. Although she did not discuss surgery costs with her medical team, she chose breast-conserving treatment because of concerns about breast reconstruction costs, as she had a coworker who was still in debt because of breast reconstruction.^{72–74} Ms S's parents came to town to help with childcare during surgery and recovery. This required

TABLE 2. Case Example of Direct and Indirect Costs Associated With Breast Cancer and Potential Clinician and Health Care Team Member Interventions

Treatment Aspect	Direct Costs and Copays	Indirect Costs	Clinician Interventions	Team Member Interventions
Baseline medical care	Monthly health insurance premiums		Clinicians can advocate for policy changes to improve insurance coverage for oncologic care	Financial navigators can provide guidance to find the best insurance plan to fit needs, with assistance in applying for Medicaid or selecting a Medicare plan as appropriate
Diagnostic work-up	PCP Imaging (breast and full body) MRI-guided biopsy	Time off work/income loss Transportation to main center/ parking Babysitter	PCPs may ensure ordered imaging is guideline concordant and high value at the time of initial workup to avoid unnecessary costs	Social workers may assist with parking vouchers or rideshare as available Scheduling to prioritize sites both in network and near to the patient to minimize travel burden
Consultations	Medical, surgical, and radiation oncologist visits Plastic surgeon visit	Time off work/income loss Transportation to main center/ parking Food during all-day visit Babysitter	Standardized COST screening tool at the time of consultation with referral to patient financial assistance and/or social work when appropriate Clinicians can normalize discussions about treatment costs and institutional resources	Scheduling teams ask patient scheduling preferences and prioritize consult appointments on the same day (if desired) to minimize the need for multiple trips Up-front meetings with financial counselors at the time of consults for high-risk patients
Chemotherapy	Echocardiogram Port placement Chemotherapy Ovarian suppression injections Supportive care medications (antinausea) Over-the-counter medications (antidiarrheal, acetaminophen)	Time off work/income loss Transportation (parking is free during active treatment) Food during all-day visits	Prompt completion of FMLA paperwork High-value lens for repeat laboratory tests and imaging Repeat financial toxicity screening at regular intervals, referrals as appropriate	Social workers can inform patients about philanthropic organizations that help offset costs. Examples: Hair to Stay (cold cap costs), Family Reach (one time grants for utilities or basic needs), Cancer Care (financial counseling and assistance), Hope Lodge (housing), Road to Recovery (transportation), and local food banks Institutional advocacy for subsidized parking and meals while on treatment
Surgery	Preoperative imaging copay Surgical procedure copay	Parents' flights Parents' time off work/income loss Time off work/income loss	Coordination of surgical timing with patient and family needs Repeat financial toxicity screening at regular intervals, referrals as appropriate	Appropriate training of caregivers on physical needs and signs and symptoms of infection to minimize readmission risk
Radiation	Radiation treatment Over-the-counter medications (emollient cream, topical steroid)	Local housing Time off work/income loss Children's flights Food while staying away from home	Coordination of daily radiation treatments to maximize capacity for return to work Repeat financial toxicity screening at regular intervals, referrals as appropriate	Social workers to provide meal or parking vouchers as available and connect with philanthropic organizations as above for housing and/or transportation

(continued on following page)

TABLE 2. Case Example of Direct and Indirect Costs Associated With Breast Cancer and Potential Clinician and Health Care Team Member Interventions (continued)

Treatment Aspect	Direct Costs and Copays	Indirect Costs	Clinician Interventions	Team Member Interventions
Adjuvant HER2+ and hormone therapy	Adjuvant HER2+ therapies to complete 1 year Tamoxifen Supportive care medications (medications for peripheral neuropathy, hot flashes) Supportive care treatments (acupuncture)	Time off work/income loss	Generic prescriptions when available, pharmacy assistance (foundation, good Rx, cost plus drugs) when appropriate Repeat financial toxicity screening at regular intervals, referrals as appropriate	Optimized survivorship care with social work, supportive care, physical, occupational, and speech therapy as appropriate

Abbreviations: COST, Comprehensive Score for Financial Toxicity; FMLA, Family and Medical Leave Act; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; PCP, primary care physician.

\$800 (USD) in flights from out-of-state and income loss from their salaried jobs. Thankfully, she had reached her annual out-of-pocket max by this time; given this, she strongly advocated for her surgery to be scheduled before the end of the calendar year. Although this created additional personal burdens because of travel during the holidays for her family, she was grateful that her surgery was fully covered by insurance.

Radiation

Ms S's radiation oncologist recommended comprehensive adjuvant radiation therapy for 5 days a week with a boost; this was delivered over six weeks at the main hospital. Ms S became very concerned about associated costs and taking care of her son, as she learned she would have \$2,000 (USD) out-of-pocket costs for her radiation treatments.^{75,76} These concerns worried her more than potential physical side effects of radiation.⁷⁴ A social worker helped Ms S find reduced-cost housing near the main campus for the duration of radiation, but no children were allowed to stay in the apartment, and she had to use her savings to help cover the housing costs and was unable to work. Her son stayed with her parents out-of-state during her radiation treatments. Although he visited every weekend, being unable to see her son everyday caused Ms S notable psychologic distress during her many weeks of radiation, and she felt guilty about her friends paying for her son's flights home to visit her.

Adjuvant Hormone Therapy

After completing radiation therapy, Ms S was continued on adjuvant HER2+ therapies. After discussing and deciding against ovarian suppression and an aromatase inhibitor, she was started on tamoxifen, planned for 10 years. Unfortunately, she experienced significant symptom burden from the antiestrogen therapy including fatigue, headaches, and debilitating hot flashes. She was prescribed a number of different treatments including magnesium, venlafaxine, and acupuncture (for which she paid \$60 [USD] per session out of pocket). Willing to try anything, she paid \$540 (USD) out of pocket for fezolinetant after her insurance denied coverage; this medication did allow her to finally work full time. However, given high costs and already having used some of her savings during treatment, she discontinued the tamoxifen after 1 year when she completed her adjuvant HER2+-based therapies as she reasoned she had done enough. She did not discuss the fact she stopped tamoxifen with her medical oncologist for many months; when her oncologist finally learned she had stopped, she was offered tamoxifen dose reduction, but she ultimately declined.

Ms S's case represents the challenges some young women with breast cancer face in each aspect of treatment. The diagnostic workup, consultations, and each type of treatment have physical, psychologic, and financial consequences that can accumulate for patients and their families, worsening quality of life and emotional well-being. As presented

in [Table 2](#),⁷⁷ there are several interventions clinicians and other health care team members can use to help decrease the risk of financial toxicity and address contributors to financial burden for patients like Ms S. These include actions to prioritize patient-centered, efficient, and high-value care from diagnosis to survivorship. Interventions range from adding financial toxicity screening into routine workflow, understanding resources that are available so that referrals can provide the most benefit to patients, and optimizing scheduling for working patients to reduce travel burdens and time away from work. Team members can facilitate appropriate use of noninstitutional referrals for philanthropic help for specific items (wigs or cold caps) or direct financial assistance to meet basic needs (food, housing, transportation, and utilities).

FINANCIAL TOXICITY IN BREAST CANCER: THE GLOBAL SETTING

Although financial toxicity concerns for patients with breast cancer in the United States are the most studied, patient financial toxicity may be even higher for those living in other countries.⁷⁸ Internationally, financial toxicity rates range from 25% of patients with breast cancer in high-income countries to nearly 80% in low- and middle-income countries (LMICs)⁷⁹; one recent meta-analysis of the global burden from cancer found that over half of patients (56%) faced catastrophic health expenditures.⁸⁰ In Europe, breast cancer costs are the highest of all disease sites, and systemic therapy costs have been driving the cost increase over the past 20 years.⁸¹ Although breast cancer cytotoxic chemotherapies are usually fully reimbursed or have minimal copays in Europe, one study found that targeted HER2 agents are more likely to require high out-of-pocket costs in low- and middle-income European countries compared with high-income countries in Europe.⁸¹ Similarly, cancer medication costs have been rapidly increasing in Canada, with a total expenditure of 1.7 billion Canadian dollars on cancer medications in 2021–2022, a substantial burden on the national health care system.⁸² Travel burden and lost wages have been the most pressing financial toxicity drivers for Canadian patients, surprising many who believed that universal health care coverage would protect them from financial burdens.⁸³

Financial toxicity in breast cancer has also been studied in China. A single-center study in a low-middle income region showed that nearly 80% of patients with breast cancer decreased their nonmedical expenses because of high costs, and, alarmingly, one third decreased or stopped treatment owing to financial toxicity.²¹ Another study focused on those who completed chemotherapy demonstrated that a combination of high financial toxicity and poor social support reduced patients' social functioning.⁸⁴

Sadly, there has been less research in countries where patients and families may be at the greatest risk of financial toxicity because of an overall lack of resources. In a recent scoping review of cancer-related financial toxicity studies

that specifically defined and measured the concept in LMICs, only five of 68 studies were conducted in low-income countries (defined as gross national income per capita of \$1,135 (USD) or less).³³ Of the available LMIC-based financial toxicity studies, research shows that patients with breast cancer in Africa and Asia have incredibly high rates of financial toxicity. An interview-based study in Rwanda showed that financial toxicity was highest for patients with breast cancer compared with other cancers, with 70% asking for financial support from charity, 84% borrowing loans with interest, and 44% selling property, compared with 0%–21%, 2%–8%, and 3%–26%, respectively, for colorectal, cervical, Hodgkin, and non-Hodgkin lymphoma.⁸⁵ An interview-based study in Sri Lanka, a LMIC with free universal health care, also showed strikingly high financial toxicity among patients with breast cancer.⁸⁶ Specifically, travel costs, out-of-hospital tests, and consultation fees contributed to financial toxicity in over 80% of patients.⁸⁶ Further 30% made daily food compromises because of treatment costs.⁸⁶ A systematic review on financial toxicity in cancer in India identified three breast cancer-specific studies: One, with over 90% of patients being uninsured, found that 74% of patients with breast cancer had to use savings, 88% had to borrow money, 55% relied on social nets, and 30% sold assets to help with cancer care costs.⁸⁷ A second study in India also found 30% of patients with breast cancer had to sell assets or mortgage land, although 29% of the study population had medical insurance.⁸⁷ Moreover, a recent analysis of medical crowdfunding in India found that cancer was the number 1 reason for needing financial assistance.⁸⁸ Alternatively, a survey study of patients with breast cancer in Vietnam highlighted the importance of having a strong social network when financial support is needed, with over 75% of patients who could not afford their breast cancer treatments asking for financial assistance from family and/or friends (with no interest) versus 32% borrowing money from banks and/or lenders (with interest).⁸⁹

MITIGATING FINANCIAL TOXICITY: KEY INTERVENTIONS

It is critical that interventions work to decrease financial toxicity for patients with breast cancer through a multilevel approach. At the government and institutional levels, effective interventions may include patient assistant programs with minimal paperwork and clear instructions as well as increased health insurance options, medical debt forgiveness programs, and more nonprofit financial support options.^{11,14} Additionally, institutions should offer clinical trial enrollment at sites in geographically diverse areas to lower transportation costs; although some trials do reimburse some travel costs, for many patients it does not cover all indirect costs related to extra visits and requires a substantial up-front outlaying of funds, with delayed reimbursement.^{3,90} Governments, national societies, and institutions should also make careful cost/benefit considerations when investing in breast cancer care innovation to be good stewards of available resources, with oncology spending in the United States alone expected to nearly triple from 65 billion dollars in 2019 to 180 billion dollars in 2028.⁵

Individuals, panels, and committees who design clinical trials, write medical guidelines, and recommend testing and treatments should recognize their role in creating financial toxicity and identify ways to lower cancer costs. Clinical trials can be designed with the Common Sense Oncology approach of minimizing the use of outcomes that have small clinical benefits but high financial toxicity by using value frameworks.^{12,27,91,92} National and international guideline writers should consider financial toxicity when recommending treatments that have unjustifiable pricing that burden both patients and reimbursement systems. Furthermore, providers may speak out against pricing disconnected from treatment benefit and be price aware when ordering testing (such as repeating laboratory tests and extensive panels) and selecting treatments as to not blindly use options that may have minimal expected clinical benefit but cause significant financial toxicity, even if considered routine.⁷⁷ This includes understanding which outcomes matter most to individual patients and effectively communicating which treatment options best align with their values and goals, such as a patient's preference to pursue hospice over a fifth-line chemotherapy that has no overall survival or quality-of-life benefits and a higher cost.^{12,93}

At the patient-provider level, along with interventions discussed previously in relation to Ms S., clinicians should work to implement routine financial toxicity screening for all patients, screen near the time of diagnosis and at regular intervals, consult financial counselors to prepare patients for the range of treatment costs, and engage financial navigation services to understand patients' specific risks and to provide personalized resources.^{7,14,94–96} Previous work has unfortunately shown that patients with breast cancer desire financial discussions, but over 70% of clinicians are perceived to be unhelpful, and over 50% do not have the discussions with patients who desire them.⁵⁹ Improved clinician education about financial toxicity and value frameworks, starting in medical school and continued throughout training and beyond, is needed to prepare clinicians for such discussions.⁹⁷

CONCLUSIONS

Financial toxicity is prevalent among patients with breast cancer both in the United States and globally. Burdensome costs are attributable to the multimodality treatments needed for breast cancer, as well as indirect costs, such as related to transportation and loss of income. Those who are younger, in marginalized/racial ethnic groups, enrolled in clinical trials, or who have metastatic disease are at increased risk of financial toxicity. The financial burden continues for patients and their partners after treatments have been completed. Even in countries with free universal health care, some patients with breast cancer decrease spending on essential needs, such as food, because of high treatment costs. Continued interventions at the government, institutional, and patient-provider levels are needed to help clinicians do no financial harm when caring for those with breast cancer.

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REFERENCES

1. AACR Cancer Progress Report 2024. cancerprogressreport.org
2. Meernik C, Sandler DP, Peipins LA, et al: Breast cancer-related employment disruption and financial hardship in the sister study. *JNCI Cancer Spectr* 5:pkab024, 2021
3. Shanahan K: Debt or dying: The high costs of cancer care in America, one patient's perspective. *JCO Oncol Pract* 21:20-22, 2025
4. Institute NC: Financial Toxicity. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/financial-toxicity>
5. IQVIA: Global Oncology Trends 2024: Outlook to 2028: IQVIA Institute for Human Data Science. <https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-oncology-trends-2024>
6. Bernard DSM, Farr SL, Fang Z: National Estimates of out-of-pocket health care expenditure burdens among nonelderly adults with cancer: 2001 to 2008. *J Clin Oncol* 29:2821-2826, 2011
7. Smith GL, Banegas MP, Acquati C, et al: Navigating financial toxicity in patients with cancer: A multidisciplinary management approach. *CA Cancer J Clin* 72:437-453, 2022
8. Ramsey S, Blough D, Kirchhoff A, et al: Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. *Health Aff (Millwood)* 32:1143-1152, 2013
9. Abrams HR, Durbin S, Huang CX, et al: Financial toxicity in cancer care: Origins, impact, and solutions. *Transl Behav Med* 11:2043-2054, 2021
10. Khan HM, Ramsey S, Shankaran V: Financial toxicity in cancer care: Implications for clinical care and potential Practice solutions. *J Clin Oncol* 41:3051-3058, 2023
11. Yabroff KR, Doran JF, Zhao J, et al: Cancer diagnosis and treatment in working-age adults: Implications for employment, health insurance coverage, and financial hardship in the United States. *CA Cancer J Clin* 74:341-358, 2024
12. Schnipper LE, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. *J Clin Oncol* 34:2925-2934, 2016
13. Ramsey SD, Bansal A, Fedorenko CR, et al: Financial insolvency as a risk factor for early mortality among patients with cancer. *J Clin Oncol* 34:980-986, 2016
14. Shah K, Zafar SY, Chino F: Role of financial toxicity in perpetuating health disparities. *Trends Cancer* 8:266-268, 2022
15. Ragavan MV, Swartz S, Clark M, et al: Access to financial assistance programs and their impact on overall spending on oral anticancer medications at an integrated specialty pharmacy. *JCO Oncol Pract* 20:291-299, 2024
16. Swami N, Dee EC, Mahal BA, et al: Prevalence of financial toxicity among hispanic cancer survivors: A nationally representative pan-cancer analysis. *J Gen Intern Med* 38:1334-1337, 2023
17. Chino F, Peppercorn J, Taylor DH Jr, et al: Self-reported financial burden and satisfaction with care among patients with cancer. *Oncologist* 19:414-420, 2014
18. Chino F, Peppercorn JM, Rushing C, et al: Out-of-Pocket costs, financial distress, and underinsurance in cancer care. *JAMA Oncol* 3:1582-1584, 2017
19. Shankaran V, Li L, Fedorenko C, et al: Risk of adverse financial events in patients with cancer: Evidence from a novel linkage between cancer registry and credit records. *J Clin Oncol* 40:884-891, 2022
20. Bestvina CM, Zullig LL, Rushing C, et al: Patient-oncologist cost communication, financial distress, and medication adherence. *JCO Oncol Pract* 10:162-167, 2014
21. Jing J, Feng R, Zhang X, et al: Financial toxicity and its associated patient and cancer factors among women with breast cancer: A single-center analysis of low-middle income region in China. *Breast Cancer Res Treat* 181:435-443, 2020
22. Thom B, Friedman DN, Aviki EM, et al: The long-term financial experiences of adolescent and young adult cancer survivors. *J Cancer Surviv* 17:1813-1823, 2023
23. Kazzi B, Chino F, Kazzi B, et al: Shared burden: The association between cancer diagnosis, financial toxicity, and healthcare cost-related coping mechanisms by family members of non-elderly patients in the USA. *Support Care Cancer* 30:8905-8917, 2022
24. Ghazal LV, Abrahamse P, Ward KC, et al: Financial toxicity and its association with health-related quality of life among partners of colorectal cancer survivors. *JAMA Netw Open* 6:e235897, 2023
25. Zafar SY, Abernethy AP: Financial toxicity, Part I: A new name for a growing problem. *Oncology (Williston Park)* 27:80-81, 2013, 149
26. Chino F, Nipp R: Financial toxicity in cancer care: Where are we, and how did we get here? Introduction to a special series. *JCO Oncol Pract* 21:1-3, 2025
27. Chino F, Zafar SY: Financial toxicity and equitable access to clinical trials. *Am Soc Clin Oncol Educ Book* 39:11-18, 2019
28. Parsons SK, Castellino SM, Yabroff KR: Cost, value, and financial hardship in cancer care: Implications for pediatric oncology. *Am Soc Clin Oncol Educ Book* 38:850-860, 2018
29. Perez GK, Salsman JM, Fladeboe K, et al: Taboo topics in adolescent and young adult oncology: Strategies for managing challenging but important conversations central to adolescent and young adult cancer survivorship. *Am Soc Clin Oncol Educ Book* 40:e171-e185, 2020
30. Nipp RD, Sonet EM, Guy GP: Communicating the financial burden of treatment with patients. *Am Soc Clin Oncol Educ Book* 38:524-531, 2018
31. Zafar SY, Newcomer LN, McCarthy J, et al: How should we intervene on the financial toxicity of cancer care? One shot, four perspectives. *Am Soc Clin Oncol Educ Book* 37:35-39, 2017
32. Anant S, Jiang C, Doran J, et al: Social and legal needs in patients and families with cancer: Interaction with patient-level financial toxicity. *JCO Oncol Pract* 21:41-51, 2025
33. Raptis SG, Shkabari B, Banday S, et al: Defining and measuring financial toxicity in low- and middle-income countries. *JCO Oncol Pract* 21:57-68, 2025
34. Chan RJ, Ke Y, Carerra P, et al: Addressing financial toxicity from a global perspective: How to advance shared-learning to facilitate change?. *JCO Oncol Pract* 21:69-72, 2025
35. Peppercorn J, Gelin M, Masteralexis TE, et al: Screening for financial toxicity in oncology research and practice: A narrative review. *JCO Oncol Pract* 21:5-11, 2025
36. de Souza JA, Yap BJ, Hlubocky FJ, et al: The development of a financial toxicity patient-reported outcome in cancer: The COST measure. *Cancer* 120:3245-3253, 2014
37. de Souza JA, Yap BJ, Wroblewski K, et al: Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the COmprehensive Score for financial Toxicity (COST). *Cancer* 123:476-484, 2017
38. COST: A FACIT Measure of Financial Toxicity: FACIT Group. <https://www.facit.org/measures/facit-cost>
39. Thom B, Tin AL, Chino F, et al: Development and validation of a simplified financial toxicity screening tool for use in clinical Practice. *JCO Oncol Pract* 21:12-19, 2025
40. Wheeler SB, Thom B, Waters AR, et al: Interventions to address cancer-related financial hardship: A scoping review and call to action. *JCO Oncol Pract* 21:29-40, 2025
41. Ragavan MV, Swartz S, Clark M, et al: Pharmacy assistance programs for oral anticancer drugs: A narrative review. *JCO Oncol Pract* 20:472-482, 2024

42. Ragavan MV, Mora RV, Nipp R, et al: Band-Aids can still help heal: The role of patient financial assistance programs in addressing financial toxicity. *JCO Oncol Pract* 21:73-77, 2025
43. Raghavan D, Keith NA, Warden HR, et al: Levine cancer Institute financial toxicity tumor board: A potential solution to an emerging problem. *JCO Oncol Pract* 17:e1433-e1439, 2021
44. Bell-Brown A, Watabayashi K, Delaney D, et al: Assessment of financial screening and navigation capabilities at National Cancer Institute community oncology clinics. *JNCI Cancer Spectr* 7:pkad055, 2023
45. Huang H, Yang Z, Dong Y, et al: Cancer cost-related subjective financial distress among breast cancer: A scoping review. *Support Care Cancer* 32:484, 2024
46. Bureau of Labor Statistics, U.S. Department of Labor: Women's Earnings Were 83.6 Percent of Men's in 2023. <https://www.bls.gov/opub/ted/2024/womens-earnings-were-83-6-percent-of-mens-in-2023.htm>
47. Schrank B, Ebert-Vogel A, Amering M, et al: Gender differences in caregiver burden and its determinants in family members of terminally ill cancer patients. *Psychooncology* 25:808-814, 2016
48. Fox S, Speirs V, Shaaban AM: Male breast cancer: An update. *Virchows Arch* 480:85-93, 2022
49. National Cancer Institute, NIH, DHHS: Cancer Trends Progress Report. <https://progressreport.cancer.gov>
50. Schreuder K, Middelburg JG, Aarts MJ, et al: An actualised population-based study on the use of radiotherapy in breast cancer patients in The Netherlands. *Breast J* 25:942-947, 2019
51. Neilson T, Huynh V, Macdonald A, et al: Financial toxicity of breast cancer care: The patient perspective through surveys and interviews. *J Surg Res* 281:122-129, 2023
52. Storandt MH, Durani U, Stan D, et al: Financial hardship in breast cancer survivors: A prospective analysis of change in financial concerns over time. *Support Care Cancer* 31:62, 2022
53. Myers SP, Zheng Y, Dibble K, et al: Financial difficulty over time in young adults with breast cancer. *JAMA Netw Open* 7:e2446091, 2024
54. Myers SP, Aviki E, Sevilimedu V, et al: Financial toxicity among women with breast cancer varies by age and race. *Ann Surg Oncol* 31:8040-8047, 2024
55. Tangka FKL, Subramanian S, Jones M, et al: Insurance coverage, employment status, and financial well-being of young women diagnosed with breast cancer. *Cancer Epidemiol Biomarkers Prev* 29:616-624, 2020
56. Politi MC, Yen RW, Elwyn G, et al: Women who are young, non-white, and with lower socioeconomic status report higher financial toxicity up to 1 year after breast cancer surgery: A mixed-effects regression analysis. *Oncologist* 26:e142-e152, 2021
57. Chebli P, Lemus J, Avila C, et al: Multilevel determinants of financial toxicity in breast cancer care: Perspectives of healthcare professionals and Latina survivors. *Support Care Cancer* 28:3179-3188, 2020
58. Wheeler SB, Spencer JC, Pinheiro LC, et al: Financial impact of breast cancer in black versus white women. *J Clin Oncol* 36:1695-1701, 2018
59. Jaggi R, Ward KC, Abrahamse PH, et al: Unmet need for clinician engagement regarding financial toxicity after diagnosis of breast cancer. *Cancer* 124:3668-3676, 2018
60. Corkum J, Zhu V, Agbafé V, et al: Area deprivation Index and rurality in relation to financial toxicity among breast cancer surgical patients: Retrospective cross-sectional study of geospatial differences in risk profiles. *J Am Coll Surg* 234:816-826, 2022
61. Galsky MD, Stensland KD, McBride RB, et al: Geographic accessibility to clinical trials for advanced cancer in the United States. *JAMA Intern Med* 175:293-295, 2015
62. Virani S, Burke L, Remick SC, et al: Barriers to recruitment of rural patients in cancer clinical trials. *JCO Oncol Pract* 7:172-177, 2011
63. Rosenzweig M, West M, Matthews J, et al: Financial toxicity among women with metastatic breast cancer. *Oncol Nurs Forum* 46:83-91, 2019
64. Wheeler SB, Spencer JC, Manning ML, et al: Multidimensional financial hardship among uninsured and insured young adult patients with metastatic breast cancer. *Cancer Med* 12:11930-11940, 2023
65. Waters AR, Petermann VM, Planey AM, et al: Financial burden among metastatic breast cancer patients: A qualitative inquiry of costs, financial assistance, health insurance, and financial coping behaviors. *Cancer Causes Control* 35:955-961, 2024
66. Semin JN, Palm D, Smith LM, et al: Understanding breast cancer survivors' financial burden and distress after financial assistance. *Support Care Cancer* 28:4241-4248, 2020
67. Yabroff KR, Mariotto A, Tangka F, et al: Annual report to the nation on the status of cancer, Part 2: Patient economic burden associated with cancer care. *J Natl Cancer Inst* 113:1670-1682, 2021
68. Jaggi R, Pottow JA, Griffith KA, et al: Long-term financial burden of breast cancer: Experiences of a diverse cohort of survivors identified through population-based registries. *J Clin Oncol* 32:1269-1276, 2014
69. Veenstra CM, Wallner LP, Jaggi R, et al: Long-term economic and employment outcomes among partners of women with early-stage breast cancer. *JCO Oncol Pract* 13:e916-e926, 2017
70. Hunter SA, Morris C, Nelson K, et al: Digital breast tomosynthesis: Cost-effectiveness of using private and Medicare insurance in community-based health care facilities. *AJR Am J Roentgenol* 208:1171-1175, 2017
71. Kunst N, Long JB, Xu X, et al: Understanding regional variation in the cost of breast cancer screening among privately insured women in the United States. *Med Care* 59:437-443, 2021
72. Greenup RA, Rushing C, Fish L, et al: Financial costs and burden related to decisions for breast cancer surgery. *JCO Oncol Pract* 15:e666-e676, 2019
73. Ganesh Kumar N, Berlin NL, Hawley ST, et al: Financial toxicity in breast reconstruction: A national survey of women who have undergone breast reconstruction after mastectomy. *Ann Surg Oncol* 29:535-544, 2022
74. Williams CP, Gallagher KD, Deehr K, et al: Quantifying treatment preferences and their association with financial toxicity in women with breast cancer. *Cancer* 127:449-457, 2021
75. Wu VS, Khlopim M, Chadha M, et al: Out-of-Pocket cost modeling of adjuvant antiestrogen and radiation therapy after lumpectomy for early-stage breast cancer across Medicaid and Medicare plans. *Int J Radiat Oncol Biol Phys* 119:1379-1385, 2024
76. Wu VS, Khlopim M, Jaggi R, et al: Out-of-Pocket cost modeling of adjuvant radiation therapy duration in standard-of-care early stage breast cancer treatment across Medicaid and Medicare plans. *Pract Radiat Oncol* 14:24-27, 2024
77. Ragavan M, Parikh D, Patel M: Defining the clinician's role in mitigating financial toxicity: An exploratory study. *Support Care Cancer* 29:4835-4845, 2021
78. Çeli K Y, Çeli K SŞ, Sariköse S, et al: Evaluation of financial toxicity and associated factors in female patients with breast cancer: A systematic review and meta-analysis. *Support Care Cancer* 31:691, 2023
79. Ehsan AN, Wu CA, Minasian A, et al: Financial toxicity among patients with breast cancer worldwide: A systematic review and meta-analysis. *JAMA Netw Open* 6:e2255388, 2023
80. Kitaw TA, Tilahun BD, Zemariam AB, et al: The financial toxicity of cancer: Unveiling global burden and risk factors—A systematic review and meta-analysis. *BMJ Glob Health* 10:e017133, 2025
81. Trapani D, Curigliano G, Eniu A: Breast cancer: Reimbursement policies and adoption of new therapeutic agents by national health systems. *Breast Care (Basel)* 14:373-381, 2019
82. Del Paggio JC, Naipaul R, Gavura S, et al: Cost and value of cancer medicines in a single-payer public health system in Ontario, Canada: A cross-sectional study. *Lancet Oncol* 25:431-438, 2024
83. Fitch MI, Longo CJ: Emerging understanding about the impact of financial toxicity related to cancer: Canadian perspectives. *Semin Oncol Nurs* 37:151174, 2021
84. Lin L, Chen Q, Lai F, et al: The interaction of financial toxicity and social support on social functioning in post-chemotherapy breast cancer patients: A cross-sectional study. *Support Care Cancer* 31:583, 2023
85. Rubagumya F, Wilson B, Manirakiza A, et al: Financial toxicity: Unveiling the burden of cancer care on patients in Rwanda. *Oncologist* 29:e345-e350, 2024
86. Ranawaka S, Gunaratna S, Gunasekera S, et al: Breast cancer-related financial toxicity in Sri Lanka: Insights from a lower middle-income country with free universal public healthcare. *Oncologist* 29:e259-e265, 2024
87. Bobby JM, Rajappa S, Mathew A: Financial toxicity in cancer care in India: A systematic review. *Lancet Oncol* 22:e541-e549, 2021
88. Sra MS: Patterns of online medical crowdfunding in India. *JAMA Netw Open* 8:e2454855, 2025
89. Ngan TT, Van Minh H, Donnelly M, et al: Financial toxicity due to breast cancer treatment in low- and middle-income countries: Evidence from Vietnam. *Support Care Cancer* 29:6325-6333, 2021
90. Planey AM, Speers LP, Biddell CB, et al: The intersection of travel burdens and financial hardship in cancer care: A scoping review. *JNCI Cancer Spectr* 8:pkae093, 2024
91. Wilson BE, Sengar M, Tregear M, et al: Common Sense Oncology: Equity, value, and outcomes that matter. *Am Soc Clin Oncol Educ Book* 44:e100039, 2024
92. Gyawali B, Eisenhauer EA, van der Graaf W, et al: Common Sense Oncology principles for the design, analysis, and reporting of phase 3 randomised clinical trials. *Lancet Oncol* 26:e80-e89, 2025
93. Booth CM, Sengar M, Goodman A, et al: Common Sense Oncology: Outcomes that matter. *Lancet Oncol* 24:833-835, 2023
94. Roy N, Villavisanis DF, Taub PJ: Mitigating financial toxicity in breast cancer from diagnosis to treatment and reconstruction. *Clin Breast Cancer* 23:e32-e36, 2023
95. Gharzai LA, Ryan KA, Szczygiel L, et al: Financial toxicity during breast cancer treatment: A qualitative analysis to inform strategies for mitigation. *JCO Oncol Pract* 17:e1413-e1423, 2021
96. Gharzai LA, Liu YA, Sun Z, et al: Financial toxicity screening preferences in patients with breast cancer. *JCO Oncol Pract* 21:561-568, 2025
97. Bell L, Thom B, Chino F: Value-based health care: Evaluating the education of future radiation oncologists on costs and affordability. *J Am Coll Radiol* 20:59-62, 2023

Artificial Intelligence and Machine Learning Innovations to Improve Design and Representativeness in Oncology Clinical Trials

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OVERVIEW

The integration of artificial intelligence (AI) and machine learning (ML) in oncology clinical trials is rapidly evolving alongside the broader field. For example, AI-driven adaptive trial designs may allow for real-time modifications based on emerging safety and efficacy signals, enabling more responsive and efficient trials. AI-powered diagnostic tools, including radiomics, computational pathology, and spatial omics, can improve trial patient selection and response assessments. ML-based patient outcome simulations can similarly enhance patient stratification strategies and statistical power. Application of AI can also improve the accessibility of real-world data, including opportunities to enhance data extraction, standardization, and harmonization of data from routine clinical practice. Data generated from digital health technologies (eg, wearable devices, electronic sensors, computing platforms, software applications) may enable a more comprehensive understanding of patient populations to support clinical trials from enrollment to assessment. Automation of trial operations and data management can also improve data fidelity and decrease investigator burden, which has the potential to streamline trial execution and increase potential use of decentralization. There are ongoing efforts to enhance regulatory clarity, mitigate bias, and uphold ethical use of these novel technologies. In this article, we review use cases of AI and ML in oncology clinical trials, including their role in patient recruitment, trial design and operations, data management, and diagnostics. Although these technologies can have applications across all phases of drug development including early discovery, we focus on phase II and III trials, where AI and ML may have a pronounced ability to enhance trial efficiency, patient stratification, and regulatory decision making. By integrating AI and ML, clinical trials can become more adaptive, data-driven, and inclusive in the pursuit of improving patient outcomes.

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INTRODUCTION

Artificial intelligence (AI) refers to machine-based systems that analyze input data to generate predictions, recommendations, or decisions.¹ AI-based and machine learning (ML)-based technologies have advanced significantly with improvements in computational power and data availability (Fig 1), leading to increasingly sophisticated applications in medicine and oncology. Among these advancements, large language models (LLMs) have expanded the role of AI in drug development, from early target discovery to clinical implementation. AI-driven approaches hold particular promise for enhancing clinical trial design, enabling adaptive methods that support a precision medicine approach.

Clinical trials progress through multiple phases, each with distinct objectives. Phase I trials primarily focus on assessing safety, pharmacology, and tolerability of novel interventions. Phase II and III trials are typically larger trials to

evaluate efficacy and safety, with the former often including dose-finding and the latter often including a comparison with a standard of care. In this study, we explore AI applications across multiple domains of late-stage clinical trials, where AI may be applied to analyze large data sets and improve trial efficiency. While we focus on unique features in oncology clinical trials, similar applications of AI in clinical trials in other disciplines have been previously reviewed.²⁻⁴

Despite its promise, the integration of AI into clinical research raises important considerations. While a potential concern among clinicians is whether AI could replace physician roles,⁵ real-world applications suggest that AI serves as a complementary tool that enhances and does not replace human decision making.⁶ In clinical research, AI can automate administrative tasks and enhance opportunities to harness large-scale data sets for scientific application. Nevertheless, challenges remain, including understanding regulatory requirements, model bias mitigation, and the

PRACTICAL APPLICATIONS

- The application of artificial intelligence (AI) can allow for:
 - Rapid assessment of large data sets, including real-world data and data generated from digital health technologies, and facilitate the use of innovative diagnostic tools, such as radiomics and computational pathology.
 - Patient-trial matching models to enrich patient enrollment representativeness and incorporate dynamic variables, including genomic sequencing.
 - Adaptive trial design to enable prompt responses to safety and outcome signals, as well as simulate patient outcomes to enhance patient stratification and optimize trial design for statistical power.
 - Automation of trial operations and data management to improve trial efficiency, enhance data fidelity, and decrease investigator burden.
- Challenges persist in the deployment of AI technologies in oncology clinical trials, including the need for large-scale technical validation, the establishment of standard metrics to assess available tools, and safeguards for security and representativeness.

need for multi-disciplinary collaboration for implementation. While some inflated expectations of certain AI technologies have been tempered,⁷ many AI-driven technologies are already being applied to aspects of oncology clinical trials (Fig 2). As these technologies continue to evolve, we highlight emerging principles for ethical deployment and safeguards to ensure responsible implementation.

PATIENT RECRUITMENT AND RETENTION

Barriers to patient participation in clinical trials begin before trial enrollment. Matching patients to appropriate clinical trials is challenging due to heterogeneous eligibility criteria, geographic constraints of active clinical trial sites, and limited enrollment windows. Several AI technologies have been developed to address these challenges. TrialGPT, developed in collaboration with the National Institutes of Health, is an open-source program that prompts LLM to find appropriate trials for a patient based on a free-text description, using natural language processing methods.⁸ The program outputs a list of matched trials in rank order of best fit on the basis of the available criteria for each patient. The Patient Records Interpretation for Semantic Clinical Trial Matching system is another patient-trial matching algorithm that uses OncoLLM, the first federally funded clinical trial LLM.⁹ Additionally, other biotechnology leaders are developing a model that uses computer vision and natural language processing to match patients across multiple trials, integrating next-generation sequencing results.¹⁰ Other proprietary patient-trial matching programs are available, with features such as continuous patient-trial matching and patient-facing algorithms designed to enhance trial access.

There is a unique unmet need for improved patient-trial matching in early-phase trials. In the phase I trial setting, an estimated 30% of referred patients are trial eligible and 20% of enrolled patients discontinue a trial early because of disease progression, study-related toxicity, or other complications.¹¹ In this setting, AI models propose to augment matching by harnessing natural language processing,¹² such as an ML tool that uses free-text input to predict whether a patient is eligible and would complete the dose-limiting toxicity period.¹³ Another tool has been designed to predict

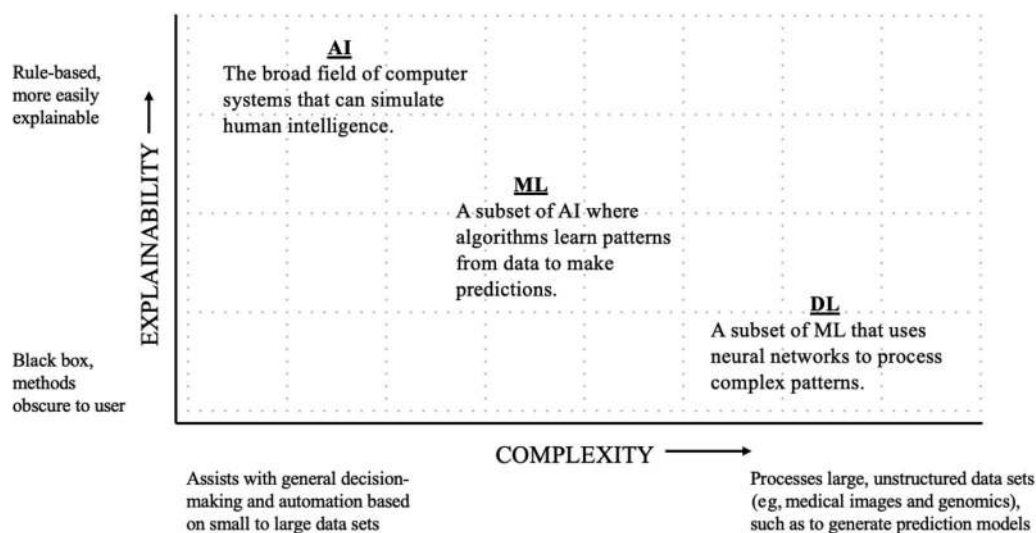


FIG 1. Relationship between complexity and explainability in AI, ML, and DL. AI, artificial intelligence; DL, deep learning; ML, machine learning. Definitions adapted from the FDA Digital Health and Artificial Intelligence Glossary,¹ and concepts discussed by Frasca et al.⁷¹

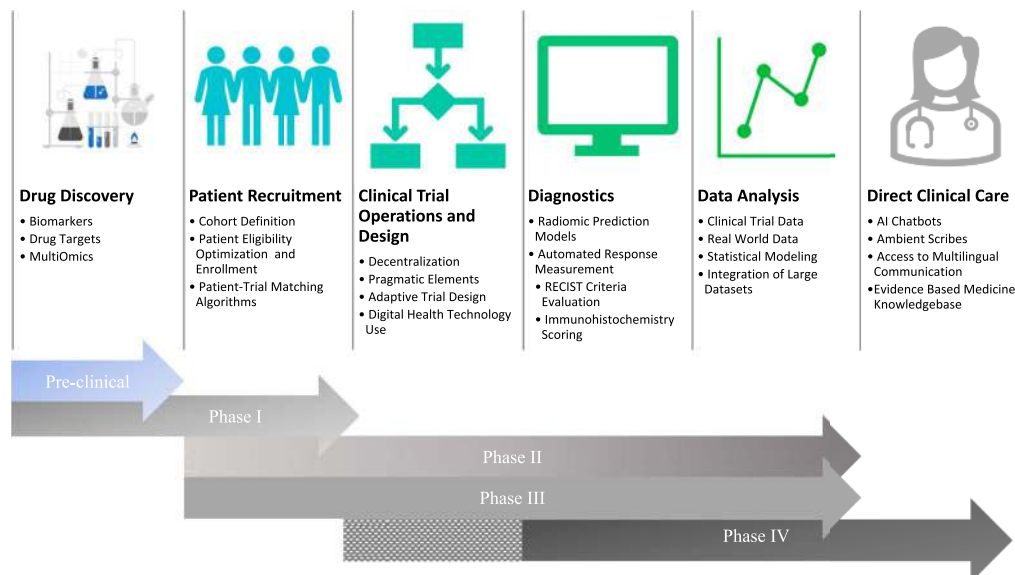


FIG 2. Integration of artificial intelligence across the spectrum of oncology clinical trial phases. AI, artificial intelligence.

whether a clinical trial is likely to meet its enrollment goal, helping sponsors assess feasibility before trial initiation.¹⁴ For models at every trial phase, training on nonrepresentative data sets may inadvertently exclude certain patient populations, leading to nonrepresentative reinforcement rather than mitigation. Ensuring external validation across representative populations and continuous monitoring of AI-driven recruitment tools is essential to prevent systematic biases.

Improving patient access to trial information may also be further improved by digital technologies. Platforms that allow direct trial data input range from social media recruitment to mobile phone applications.¹⁵ Among patient-facing technologies, use of a chatbot to respond to patient queries about trial enrollment may provide useful and easily accessible information to patients. For example, digital staff can screen, schedule, and follow up on trial participants through telephone, email, or text modalities.¹⁶ In a recent study on general health-related patient queries, chatbot responses were rated higher than physician responses in the domains of quality and empathy,¹⁷ although response length was a contributing variable to high scoring responses. Furthermore, chatbots may improve multilingual access to cancer and clinical trial information by automating translation, as shown in a European study including eight languages across seven publicly available LLMs.¹⁸ Further delineation of the appropriate role and limitations of such chatbot-patient interactions, particularly in clinical trial settings, is needed.

In addition to trial enrollment, AI technologies may aid in patient retention by predicting patient behavior or outcomes. For example, one AI model was developed to predict grade 3 or 4 adverse events in patients with breast cancer

treated with neoadjuvant therapy.¹⁹ Another ML platform, designed outside of clinical trials, was applied to predict 30-day unplanned readmission rates for patients with cancer on the basis of data from a publicly available cancer center database.²⁰ Identifying individualized risk potential for adverse events, trial attrition, or hospital admission can help investigators identify the need for dose adjustments, early interventions, or symptom management plans. Incorporation of AI to predict these outcomes requires ongoing validation across representative patient communities, cancer subtypes, treatment modalities, and trial environments to ensure reliability and generalizability.

TRIAL DESIGN, OPERATIONS, AND DATA MANAGEMENT

The application of AI presents opportunities to transform both interventional and noninterventional (observational) clinical trial designs. AI can also be implemented in pragmatic clinical trials with decentralized elements, where trial-related activities occur outside the clinic or traditional research setting. Decentralization is an approach to increase access to and generate data that may better reflect representative patients.^{21,22} Such studies can leverage telehealth and digital health technologies, enabling participation from patients in various geographic locations who might otherwise be unable to access a given trial.

Within trial design, AI may be useful to optimize patient selection to best represent target populations. Early detection of study end points and safety signals may empower adaptive trial designs, wherein a trial is modified to support patient safety and outcome targets. The potential use of ML-powered predictive models can further enhance understanding of the intended-use population for patient stratification before random assignment. Approaches such as

response-adaptive random assignment adjust patient allocation on the basis of predictive models to optimize patient-specific results.²³ Technologies are available to estimate how adjusting an inclusion criterion may affect trial outcomes using aggregated published trial results²⁴ and enter eligibility criteria to generate a corresponding patient database using Web-based interfaces.^{25,26} AI can also enhance representativeness in clinical trials by balancing cohorts with specific patient characteristics, as is appropriate for the epidemiology of the disease.²⁷ AI models are exploring virtual patient simulations, such as digital twins of enrolled patients, which may provide modeling approaches to increase statistical power and patient representation; the applicability for these approaches in drug development is nascent.^{28,29}

In addition to patient selection, ML-based models can also aggregate and interpret large data sets generated by digital health technologies. For example, wearable devices can record vital signs, physical states, drug adherence, and other behavioral parameters that may inform patient outcomes.^{30,31} The integration of such technologies and other decentralized elements in oncology trials still face many hurdles, including logistical challenges in shipment and administration of treatments, as well as trial coordination of clinical services across multiple locations.³²

AI and ML approaches can be implemented in clinical trial data management and analysis to standardize unstructured clinical data (eg, free-text notes); harmonize data across multiple variables, trial sites, or institutions; and deidentify personal health information to enhance privacy protections.³³ AI can also enable pharmacometrics analysis in large data sets, such as identifying optimal drug dose, drug-drug or drug-food interactions, and pharmacokinetic variability among subgroups.³⁴ To ensure data quality, ML algorithms have been proposed to detect and remove duplicate participants, impute missing data points, and validate novel data sets against existing reference databases.³⁵ These applications can process high-volume, multidimensional, and incomplete records, which can be common in real-world data. This, however, requires specific expertise in epidemiology, biostatistics, and data science to ensure it is done appropriately.

Overall, greater automation of trial components can increase efficiency and reduce investigator burden. For example, AI-based technologies may automate grading of adverse events. Ambient AI scribes have been implemented and demonstrated potential value in the outpatient care settings by reducing time spent on clinical documentation and increasing physician interaction.^{36,90} In clinical trials, AI scribes may summarize subjective reports, pend orders, and generate treatment plans according to trial protocols. LLMs can generate personalized patient education materials, which may be written in the patient's native language.^{37,38} LLMs already available to many physicians offer Health Insurance Portability and Accountability Act-compliant document generation.³⁹ From cohort definition to the clinic

visit, AI technologies are likely to be integrated into many existing clinician workflows with clinician supervision.

DIAGNOSTICS

AI and ML technologies are transforming diagnostic modalities that augment patient selection and assessment in clinical trials. For example, radiomics is the mining of quantitative image features applied to clinical decision support systems to improve diagnostic, prognostic, and predictive accuracy.⁴⁰ Machine and deep learning (DL) technologies in oncology have been widely applied to cancer screening image interpretation, such as low-dose computed tomography scan for lung or mammography for breast cancer screenings.⁴¹⁻⁴⁴ In clinical trials, these technologies may help automate the time-intensive and resource-intensive task of measuring radiographic response, such as through RECIST criteria.⁴⁵⁻⁴⁸ Comparisons between ML-generated and radiologists' RECIST measurements have highlighted inter-radiologist variation in target and measurable lesion selection.⁴⁹ Radiomics platforms are also being used for early prediction of toxicity, such as anticipating diagnosis and determining the etiology of an adverse event (eg, pneumonitis from either radiation or immune checkpoint blockade),⁵⁰⁻⁵² and patient outcomes, such as treatment response or survival.^{53,54} The ability to scale these tools depends largely on the availability of representative data sets for training and appropriate refinement of a model that is fit for use.

In parallel to advancements in radiology, computational pathology applies AI to data generated from anatomic and clinical pathology specimens.⁵⁵ Immunohistochemistry (IHC) assessment is one technique fit for AI innovation given the subjective and semiquantitative nature of manual interpretation. Several ML models have been developed to automate IHC grading. McKelvey et al⁵⁶ compared concordance among AI models that assess human epidermal growth factor receptor 2 (HER2) staining; discordance in HER2 measurement was highest among HER2 1+ or 2+, while higher agreement was observed for HER2 3+ and 0. Additionally, there was more agreement among samples assigned two or more HER2 scores apart (eg, 0-2, 1-3, 0-3), which is similar to interpathologist interpretation variability. Further ML-based platforms that are agnostic to tumor type and biomarker are ongoing development.⁵⁷

Digital pathology-based biomarkers represent a more complex assessment, in which ML models may be used to quantify a predictive biomarker for use in therapeutic selection. An example of this is quantitative continuous scoring (QCS), where measurement of an IHC target at the cellular level (eg, in the cell membrane versus the cytoplasm) can optimize patient selection for therapies. This can be applied for antibody-drug conjugates to estimate cellular internalization of treatment payload, whereas traditional histopathologic assessment has not been predictive. Several studies have already implemented QCS analysis for patient

selection and stratification of the appropriate population, such as with HER2 assessment for trastuzumab deruxtecan treatment in breast cancer⁵⁸ or TROP2 assessment for datopotamab deruxtecan treatment in lung cancer.⁵⁹

Another novel area of computational pathology is spatial transcriptomics.^{60–63} This method uses molecular profiling to map and quantify gene activity in a sampled tissue. Several commercial platforms for this technique are available, some with expression detection at the level of single cells.⁶⁴ These assays can depict the three-dimensional distribution of biomarkers and signaling networks within the tumor microenvironment, offering new avenues for precision oncology trials.

Use of AI and ML in patient data and tumor characterization may have the most feasible application to genomics, given the widespread generation of large genomic data sets and limited (though expanding) knowledge of the clinical implications of genomic findings.⁶⁵ Since the completion of the Human Genome Project in 2003, the field of oncology has embraced sequencing of DNA, RNA, and the epigenome from somatic tissues and peripheral blood (eg, cell-free DNA). ML applications are ongoing development to translate data to knowledge.⁶⁶ For instance, ML models may use whole-genome sequencing to generate mutational signatures, graph-based genome alignment (eg, for identification of polymorphisms), and genome-wide association studies. They may also interpret epigenomics by mapping chromatin states or enhancer sites and clarify regulatory sequence networks.⁶⁷ In clinical trials, these technologies can be applied to analyze existing sequencing data, evaluate genomic data from electronic medical records, and integrate insights from commercial sequencing platforms to increase understanding of patient outcomes through precision medicine approaches. To maximize the impact of these tools, the field will need to create and maintain representative training data sets, establish responsible frameworks for data sharing, and communicate early on appropriate regulatory pathways.

BIAS AND MISREPRESENTATION

While AI has the potential to mitigate certain types of biases in oncology clinical trials, AI approaches remain vulnerable to introducing other types of biases and measurement errors, paralleling many well described epidemiological biases (eg, selection bias, publication bias; [Table 1](#)). At the level of AI system development, models are subject to expertise bias, particularly when designed as tumor-agnostic or stage-independent tools.^{68,70} ML model training relies on the availability of high-quality training data sets, which may introduce bias through underrepresentation or overrepresentation of certain clinical features (eg, demographics and cancer stage), biologic parameters (eg, biomarker distribution), management decisions, or patient outcomes.⁶⁹ Clinical oncology is particularly susceptible to shifts in data set relevance over time—known as data drift—due to the rapid pace of drug development, including trial

TABLE 1. Bias Types and Mitigation Strategies for Use of AI Models in Clinical Oncology Data Sets

Bias type	Description
Expertise	Bias related to expertise among individuals involved in developing AI systems
Exclusion	Bias when group(s) are systematically left out of data collection and analysis
Environmental	Bias arises from the socioenvironmental context in which data are collected and used
Evidence	Bias resulting from the processes through which scientific evidence is generated, disseminated, and translated into practice
Empathy	Bias from the challenge to incorporate subjective experiences into AI systems
Mitigation strategy	Description
Collection	Enter data electronically with limited manual input to allow for consistent long-term data collection
Classification	Collect binary data when more detailed data are not possible or impractical to obtain
Capture	Include and analyze data on patient demographics and other relevant factors
Cross-check	Aggregate with parallel data sources to cross-check against other data parameters (eg, verification with state or government data sources that can verify data)
Class balance	Perform regular data quality checks for known sources of bias and class imbalance

NOTE. Adapted from Dankwa-Mullan et al⁶⁸ and Tasci et al.⁶⁹
Abbreviation: AI, artificial intelligence.

publication, drug approvals, and changing standards of care. Beyond the data available, evidence bias (often referred to as publication bias) also shapes the type of information available. For example, published trials are more likely to be funded and report positive trial results. To address these challenges, many techniques have been proposed, including regular data quality assurance processes for known sources of class imbalance and continuous updating of data sets for training⁶⁹ ([Table 1](#)). Additionally, AI and ML models may struggle to integrate subjective clinical experiences, which are often central to oncologic decision making and a foundational argument for the importance of clinician involvement in direct patient care, wherein AI tools are integrated.

ETHICAL PRINCIPLES

In addition to bias, AI in clinical care raises ethical concerns related to trust, transparency, and accountability. One key

challenge is the opacity problem, wherein AI, ML, and DL often operate in ways that are not transparent to users, making it difficult to interpret decision-making processes (Fig 1). Transparency is an important aspect of model development. Efforts to improve AI interpretability (the degree to which cause and effect can be seen inside a system) and explainability (the ability to provide explicit justifications or reasoning for model decisions) in health care and other areas are ongoing.⁷¹

Several ethical frameworks have been proposed to address these concerns, including those that outline the potential benefits and risks of AI-based technologies in health care, as well as responsibilities for stakeholders in ethical implementation.⁷² Multidisciplinary professional associations seeking to standardize ethical development and deployment of AI in medicine have also emerged, connecting leaders in the field in this evolving area and building best practices for AI applications in health care.^{73,74} Among ethical concepts, digital determinants of health—including access to technology tools, digital literacy, and community infrastructure such as broadband internet—are increasingly recognized as important to patient outcomes.⁷⁵

Within oncology, ASCO released an ethical framework for clinical oncology in 2024.⁷⁶ The framework can be summarized in the FAITH acronym: promoting fairness in model design and access; accountability in compliance with legal, regulatory, and ethical standards; informing stakeholders of AI use in clinical encounters; institutional oversight and transparency of AI technologies; and human-centered application (Table 2). Among these principles, ensuring human-centered AI deployment is critical, emphasizing that AI does not eliminate the need for human interaction in sensitive clinical interactions in oncology.

REGULATORY CONSIDERATIONS

The integration of AI into clinical care and research presents new questions for regulatory agencies, including the US Food and Drug Administration (FDA).⁷⁷ AI and ML technologies are predominantly software based. As software can be a device, AI-enabled innovations often meet the definition and are considered devices for regulatory purposes. Recognizing this, the FDA recently published draft guidance on the use of AI in regulatory decision making for drugs and biologics,⁷⁸ as well as for devices that include AI-enabled device software functions.⁷⁹ The guidance for drugs and biologics outlines a risk-based credibility framework that includes seven steps to establish and assess credibility (Fig 3). Defining the specific question of interest and context of use is essential to evaluating the clinical implications of AI use.

In a review of drug applications to the FDA over the past decade, integration of AI and ML approaches has steadily increased, exceeding 100 annual submissions across therapeutic areas by 2021, with the largest number for a therapeutic area in oncology (27%).⁸⁰ Additionally, the FDA has

TABLE 2. FAITH Acronym Summarizes Principles for the Responsible Use of AI in Oncology, as Outlined by ASCO 2024⁷⁶

Fairness and equity	Developers and users of AI should protect against bias in AI model design and implementation and ensure equitable access to AI tools
Accountability	AI systems must comply with legal, regulatory, and ethical requirements that govern the use of data. AI developers should assume responsibility for their AI systems, their decisions, and their adherence to legal, regulatory, and ethical standards
Informed stakeholders	Patients and clinicians should be notified when AI is used in clinical decision making and patient care
Institutional oversight	Decision-makers should establish institutional compliance policies that govern the use of AI, including protections that guard clinician and patient autonomy in clinical decision making and privacy of personal health information
Transparency	AI tools and applications should be transparent throughout their lifecycle
Human-centered application	Human interaction is a fundamental element of health care delivery. AI does not eliminate the need for human interaction and should not be used as a substitute for sensitive interactions that require it

Abbreviation: AI, artificial intelligence.

demonstrated experience in AI review, authorizing more than 1,000 medical devices since 1995 that use AI and/or ML.⁸¹ Transparency throughout the development process, alongside adoption of consensus standards, can facilitate appropriate use of these technologies. Early communication with regulatory agencies is encouraged.

Regulatory developments are also emerging internationally. The European Medicines Agency reflection paper on AI emphasizes the importance of risk-based regulatory frameworks to ensure patient safety and data integrity in drug development and clinical trials.⁸² Similarly, the UK Medicines and Healthcare products Regulatory Agency outlined a strategic approach to AI, focusing on international collaboration to develop guiding principles for AI-driven medical devices.⁸³ These initiatives reflect the potential of harmonizing AI regulation, ensuring that AI technologies meet consistent safety and performance standards across different regulatory jurisdictions and that developers have adequate clarity on regulatory requirements.

As the output of AI models rely on the quality of input data, the development of publicly available reference data sets for

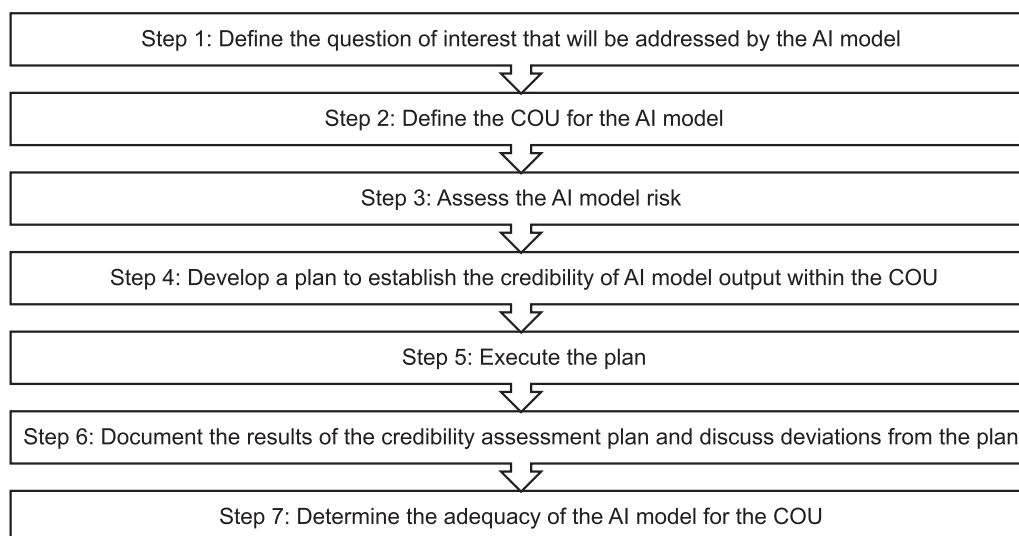


FIG 3. Risk-based credibility assessment framework to establish and assess the credibility of an artificial intelligence model output for a specific COU, as outlined by the FDA.⁷⁹ AI, artificial intelligence; COU, context of use; FDA, US Food and Drug Administration.

validation may be useful for oncology clinical trials.⁸⁴ These reference data sets could enable performance benchmarking across AI models and help mitigate bias from single-source data. Global regulatory agencies have all underscored the need for external validation using independent data sets, as aligned with Good ML Practices.⁸⁵ A coordinated effort, such as a public-private partnership, to establish comprehensive, multi-institutional reference data sets with detailed metadata could enhance AI transparency and reproducibility for patient, provider, and regulatory decision making. As AI adoption grows, various interested parties may contribute to appropriate uses of AI-based and ML-based technologies in clinical trials.

DATA SAFETY AND HARMONIZATION

Whether specific to a trial or at the broader health system level, sustainable deployment of AI and ML requires substantial infrastructural considerations to address data privacy, safety, and harmonization. Data collected by AI-driven systems may be vulnerable to software privacy concerns or model tampering, as they rely on infrastructure for data storage, encryption, and access.⁸⁶ Meanwhile, a major challenge in data harmonization is the lack of standardization in how unstructured clinical data are collected and stored within the electronic medical record or data repositories across institutions.⁸⁷ There are ongoing efforts to standardize health data elements and exchange throughout the United States,⁸⁸ as are already available in countries with national health systems, which may improve quality and access to valuable real-world data. Ensuring transparency in data ownership, access control, transformation, and storage policies is essential to support patient autonomy. There are ongoing patient, provider, legal, ethical, and data science efforts to better define patient rights in data ownership, particularly in clinical research settings.⁸⁹

CONCLUSIONS

AI-based technologies are increasingly being integrated into oncology clinical trials, yet widespread adoption lags behind technologic advancements. Digital technologies, including telehealth and wearable devices, have the potential to enhance patient engagement and retention, while enabling decentralization can reduce patient burden and collect data that better reflects patients' experiences in everyday life. ML models may improve cohort stratification, simulate trial outcomes, and enhance statistical power, while AI-assisted automation can streamline administrative tasks to optimize efficiency and reduce investigator burden. Realizing the potential of these innovations will require a multidisciplinary approach, including collaboration among patient advocates, clinicians, data scientists, epidemiologists, biostatisticians, and regulators.

Published regulatory guidance highlights a risk-based credibility assessment framework, along with the importance of early communication, when using AI in clinical research. This reinforces the importance of a multidisciplinary approach, integral to upholding the necessary high standards for AI and ML technologies in trials that both increase innovation and ensures patient safety. With careful oversight, these technologies may enhance trial efficiency, reduce clinician burden, and ultimately advance clinical research by bringing cancer care closer to clinical trials.

Nonetheless, several challenges persist in the integration of AI and ML technologies into existing systems. The heterogeneity of electronic health record systems, variability in multinational regulatory agency guidance, and availability of upfront implementation resources (eg, cost, staffing) present ongoing barriers. Questions around ownership of infrastructure development and system interoperability are

unresolved. Coordinated public-private partnerships as well as cross-institution collaborations are pivotal to advance these efforts. AI technologies are likely to be more widely integrated into physician workflows before direct patient

facing applications become routine. Enduring ethical debates highlight the need for human involvement in AI- and ML-model design, deployment, and system integration across the spectrum of clinical trials in oncology.

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REFERENCES

- FDA Digital Health and Artificial Intelligence Glossary—Educational Resource. <https://www.fda.gov/science-research/artificial-intelligence-and-medical-products/fda-digital-health-and-artificial-intelligence-glossary-educational-resource>
- Pontes CB, Valerio Netto A: The use of artificial intelligence algorithms in drug development and clinical trials: A scoping review. *Int J Med Inform* 195:105798, 2025
- Askin S, Burkhalter D, Calado G, et al: Artificial intelligence applied to clinical trials: Opportunities and challenges. *Health Technol (Berl)* 13:203-213, 2023
- Weissler EH, Naumann T, Andersson T, et al: The role of machine learning in clinical research: Transforming the future of evidence generation. *Trials* 22:537, 2021
- Budd K: Will artificial intelligence replace doctors? *AAMCNews*, 2019
- Lohr S: A.I. May Someday Work Medical Miracles. For Now, it Helps Do Paperwork 2023. <https://www.nytimes.com/2023/06/26/technology/ai-health-care-documentation.html>
- Zhang P, Shi J, Kamel Boulos MN: Generative AI in medicine and healthcare: Moving beyond the 'peak of inflated expectations'. *Future Internet* 16:462, 2024
- Jin Q, Wang Z, Floudas CS, et al: Matching patients to clinical trials with large language models. *Nat Commun* 15:9074, 2024
- Gupta S, Basu A, Nievas M, et al: PRISM: Patient records interpretation for semantic clinical trial matching system using large language models. *NPJ Digit Med* 7:305, 2024
- Kurnaz S-B, Castaneda AC, DarlaHuner OG, et al: Effect of a Novel Artificial Intelligence (AI)-Enabled Multi-Trial Matching System on Patient Matching Using Real-World Data. Chicago, IL, American Society of Clinical Oncology Annual Meeting 2024, 2024
- Douma JAJ, Buffart LM, Sedhom R, et al: Clinical predictors of early trial discontinuation for patients participating in phase I clinical trials in oncology. *Cancers (Basel)* 13:2304, 2021
- Ghosh S, Abushukair HM, Ganesan A, et al: Harnessing explainable artificial intelligence for patient-to-clinical-trial matching: A proof-of-concept pilot study using phase I oncology trials. *PLoS One* 19:e0311510, 2024
- Delorme J, Charvet V, Wartelle M, et al: Natural language processing for patient selection in phase I or II oncology clinical trials. *JCO Clin Cancer Inform* 10.1200/CCI.21.00003
- Bieganeck C, Aliferis C, Ma S: Prediction of clinical trial enrollment rates. *PLoS One* 17:e0263193, 2022
- Kasahara A, Mitchell J, Yang J, et al: Digital technologies used in clinical trial recruitment and enrollment including application to trial diversity and inclusion: A systematic review. *Digit Health* 10:20552076241242390, 2024
- Grove AI: Meet grace: The industry-leading digital staff for clinical trial operations 2025. <https://www.grovetrials.com/>
- Ayers JW, Poliak A, Dredze M, et al: Comparing physician and artificial intelligence Chatbot responses to patient questions posted to a public social media forum. *JAMA Intern Med* 183:589-596, 2023
- Menz BD, Modi ND, Abuhelwa AY, et al: Generative AI chatbots for reliable cancer information: Evaluating web-search, multilingual, and reference capabilities of emerging large language models. *Eur J Cancer* 218:115274, 2025
- Cai L, Deutsch TM, Sidey-Gibbons C, et al: Machine learning to predict the individual risk of treatment-relevant toxicity for patients with breast cancer undergoing neoadjuvant systemic treatment. *JCO Clin Cancer Inform* 10.1200/CCI.24.00010
- Stabellini N, Nazha A, Agrawal N, et al: Thirty-day unplanned hospital readmissions in patients with cancer and the impact of social determinants of health: A machine learning approach. *JCO Clin Cancer Inform* 10.1200/CCI.22.00143
- Khozin S, Coravos A: Decentralized trials in the age of real-world evidence and inclusivity in clinical investigations. *Clin Pharmacol Ther* 106:25-27, 2019
- US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), et al: Conducting Clinical Trials with Decentralized Elements 2024. <https://www.fda.gov/media/167696/download>
- Wang Y, Carter BZ, Li Z, et al: Application of machine learning methods in clinical trials for precision medicine. *JAMIA Open* 5:00ab107, 2022
- Liu R, Rizzo S, Whipple S, et al: Evaluating eligibility criteria of oncology trials using real-world data and AI. *Nature* 592:629-633, 2021
- Yuan C, Ryan PB, Ta C, et al: Criteria2Query: A natural language interface to clinical databases for cohort definition. *J Am Med Inform Assoc* 26:294-305, 2019
- Park J, Fang Y, Ta C, et al: Criteria2Query 3.0: Leveraging generative large language models for clinical trial eligibility query generation. *J Biomed Inform* 154:104649, 2024
- Craig KJ, Ji YJ, Zhang YC, et al: Real-world application of racial and ethnic imputation and cohort balancing techniques to deliver equitable clinical trial recruitment. *AMIA Annu Symp Proc* 2023: 319-328, 2023
- Vidovszky AA, Fisher CK, Loukianov AD, et al: Increasing acceptance of AI-generated digital twins through clinical trial applications. *Clin Transl Sci* 17:e13897, 2024
- Papachristou K, Katsakiori PF, Papadimitriou P, et al: Digital twins' advancements and applications in healthcare, towards precision medicine. *J Pers Med* 14:1101, 2024
- Birla M, Rajan, Roy PG, et al: Integrating artificial intelligence-driven wearable technology in oncology decision-making: A narrative review. *Oncology* 103:69-82, 2025
- Mason M, Cho Y, Rayo J, et al: Technologies for medication adherence monitoring and technology assessment criteria: Narrative review. *JMIR Mhealth Uhealth* 10:e35157, 2022
- Fu S, Gerber DE, Beg MS: Decentralized clinical trials in oncology: Are we ready for a virtual-first paradigm? *J Clin Oncol* 41:181-185, 2023
- Senthil Kumar K, Miskovic V, Blasiak A, et al: Artificial intelligence in clinical oncology: From data to digital pathology and treatment. *Am Soc Clin Oncol Educ Book* 43:e390084, 2023
- Johnson M, Patel M, Phipps A, et al: The potential and pitfalls of artificial intelligence in clinical pharmacology. *CPT Pharmacometrics Syst Pharmacol* 12:279-284, 2023
- Zhang X, Yan C, Gao C, et al: Predicting missing values in medical data via XGBoost regression. *J Healthc Inform Res* 4:383-394, 2020
- Tierney AA, Gayre G, Hoberman B, et al: Ambient artificial intelligence scribes to alleviate the burden of clinical documentation. *NEJM Catalyst* 5:1-13, 2024
- Hui G, Jiang J, Dommaraju S, et al: Artificial intelligence vs. physicians: Quality of oncology patient education materials. *JCO Oncol Pract* 20:408, 2024
- Hutson M: How AI is being used to accelerate clinical trials. *Nature* 627:S2-S5, 2024

39. Dashevsky J: The Impact of Doximity GPT on Physician Workflows 2023. <https://www.healthcarehuddle.com/p/impact-doximity-gpt-physician-workflows>
40. Lambin P, Leijenaar RTH, Deist TM, et al: Radiomics: The bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 14:749-762, 2017
41. Hickman SE, Woitek R, Le EPV, et al: Machine learning for workflow applications in screening mammography: Systematic review and meta-analysis. *Radiology* 302:88-104, 2022
42. Mikhael PG, Wohlwend J, Yala A, et al: Sybil: A validated deep learning model to predict future lung cancer risk from a single low-dose chest computed tomography. *J Clin Oncol* 41:2191-2200, 2023
43. Adams SJ, Mikhael P, Wohlwend J, et al: Artificial intelligence and machine learning in lung cancer screening. *Thorac Surg Clin* 33:401-409, 2023
44. Yala A, Mikhael PG, Strand F, et al: Multi-institutional validation of a mammography-based breast cancer risk model. *J Clin Oncol* 40:1732-1740, 2022
45. Arbour KC, Luu AT, Luo J, et al: Deep learning to estimate RECIST in patients with NSCLC treated with PD-1 blockade. *Cancer Discov* 11:59-67, 2021
46. Riaz IB, Ashraf N, Harris GJ, et al: Deep learning to estimate RECIST in patients with cancer treated in real-world settings. *J Clin Oncol* 41:1564, 2023
47. Gong A, Daly M, Melendez-Corres G, et al: Toward automating RECIST 1.1: Improving AI new lesion detection with longitudinal image data. *J Clin Oncol* 41:e13545, 2023
48. Hérent P, Philippe H, Ferreres E, et al: Promptable foundation model for automatic whole body RECIST measurement. *J Clin Oncol* 42:e13643, 2024
49. Tareco Bucho TM, Petrychenko L, Abdelatty MA, et al: Reproducing RECIST lesion selection via machine learning: Insights into intra and inter-radiologist variation. *Eur J Radiol Open* 12:100562, 2024
50. Kraus KM, Oreshko M, Schnabel JA, et al: Dosiomics and radiomics-based prediction of pneumonitis after radiotherapy and immune checkpoint inhibition: The relevance of fractionation. *Lung Cancer* 189:107507, 2024
51. Delasos L, Khorrami M, Viswanathan VS, et al: Novel radiogenomics approach to predict and characterize pneumonitis in stage III NSCLC. *NPJ Precis Oncol* 8:290, 2024
52. Naidoo J, Haakensen VD, Bar J, et al: Quantitative radiomics for the detection of symptomatic pneumonitis following chemoradiotherapy in patients with stage III unresectable NSCLC 2024. <https://oncologypro.esmo.org/meeting-resources/esmo-congress-2024/quantitative-radiomics-for-the-detection-of-symptomatic-pneumonitis-following-chemoradiotherapy-in-patients-with-stage-iii-unresectable-nsclc>
53. Braman N, Prasanna P, Bera K, et al: Novel radiomic measurements of tumor-associated vasculature morphology on clinical imaging as a biomarker of treatment response in multiple cancers. *Clin Cancer Res* 28:4410-4424, 2022
54. Somasundaram E, Wadhwa RR, Litzler A, et al: Clinical nomogram using novel computed tomography-based radiomics predicts survival in patients with non-small-cell lung cancer treated with stereotactic body radiation therapy. *JCO Clin Cancer Inform* 10.1200/CCI.22.00173
55. A Friends of Cancer Research White Paper: Supporting the Application of Computational Pathology in Oncology. https://friendsofcancerresearch.org/wp-content/uploads/Supporting_the_Application_of_Computational_Pathology_in_Oncology.pdf
56. McKelvey B, Torres-Saavedra PA, Li J, et al: Agreement across 10 artificial intelligence models in assessing HER2 in breast cancer whole slide images: Findings from the friends of cancer research digital PATH Project 2024. <https://friendsofcancerresearch.org/wp-content/uploads/SABCS-Poster-Digital-PATH-Project-Findings.pdf>
57. Brattoli B, Mostafavi M, Lee T, et al: A universal immunohistochemistry analyzer for generalizing AI-driven assessment of immunohistochemistry across immunostains and cancer types. *NPJ Precis Oncol* 8:277, 2024
58. Kapil A, Spitzmüller A, Brieu N, et al: HER2 quantitative continuous scoring for accurate patient selection in HER2 negative trastuzumab deruxtecan treated breast cancer. *Sci Rep* 14:12129, 2024
59. Garassino MCSJ, Paz-Ares L, et al: Normalized membrane ratio of TROP2 by quantitative continuous scoring is predictive of clinical outcomes in TROPION-Lung01. *J Thoracic Oncology* 19:S2-S3, 2024. 2024 IASLC World Conference on Lung Cancer
60. Renchou IP, Gwyther BM, Georgiakis ECT, et al: Spatial immune profiling of the colorectal tumor microenvironment predicts good outcome in stage II patients. *NPJ Digit Med* 3:71, 2020
61. Levy JJ, Zavras JP, Veziroglu JM, et al: Identification of spatial proteomic signatures of colon tumor metastasis: A digital spatial profiling approach. *Am J Pathol* 193:778-795, 2023
62. Fatemi M, Feng E, Sharma C, et al: Inferring spatial transcriptomics markers from whole slide images to characterize metastasis-related spatial heterogeneity of colorectal tumors: A pilot study. *J Pathol Inform* 14:100308, 2023
63. Sorin M, Rezaeian M, Karimi E, et al: Single-cell spatial landscapes of the lung tumour immune microenvironment. *Nature* 614:548-554, 2023
64. Lermi NO, Ayala MM, Ruiz SH, et al: Comparison of imaging-based single-cell resolution spatial transcriptomics profiling platforms using formalin-fixed, paraffin-embedded tumor samples. *bioRxiv* 10.1101/2024.12.13.628390 [pub ahead of print on December 17, 2024]
65. Walton NA, Nagarajan R, Wang C, et al: Enabling the clinical application of artificial intelligence in genomics: A perspective of the AMIA genomics and translational bioinformatics workgroup. *J Am Med Inform Assoc* 31:536-541, 2024
66. Hamamoto R, Koyama T, Kouno N, et al: Introducing AI to the molecular tumor board: One direction toward the establishment of precision medicine using large-scale cancer clinical and biological information. *Exp Hematol Oncol* 11:82, 2022
67. Asada K, Kaneko S, Takasawa K, et al: Integrated analysis of whole genome and epigenome data using machine learning technology: Toward the establishment of precision oncology. *Front Oncol* 11:666937, 2021
68. Dankwa-Mullan I: Health equity and ethical considerations in using artificial intelligence in public health and medicine. *Prev Chronic Dis* 21:E64, 2024
69. Tasci E, Zhuge Y, Camphausen K, et al: Bias and class imbalance in oncologic data-towards inclusive and transferrable AI in large scale oncology data sets. *Cancers (Basel)* 14:2897, 2022
70. Dankwa-Mullan I, Weeraratne D: Artificial intelligence and machine learning technologies in cancer care: Addressing disparities, bias, and data diversity. *Cancer Discov* 12:1423-1427, 2022
71. Frasca M, La Torre D, Pravettoni G, et al: Explainable and interpretable artificial intelligence in medicine: A systematic bibliometric review. *Discover Artif Intelligence* 4:15, 2024
72. The World Health Organization: Ethics and governance of artificial intelligence for health: Guidance on large multi-modal models 2024. <https://www.who.int/publications/i/item/9789240084759>
73. American Medical Informatics Association: Working Groups 2025. <https://amia.org/communities/working-groups>
74. Coalition for Health AI: Chai Assurance Standards Guide 2024. https://chai.org/wp-content/uploads/2024/06/CHAI_AssuranceGuide_062624.pdf
75. Richardson S, Lawrence K, Schoenthaler AM, et al: A framework for digital health equity. *NPJ Digit Med* 5:119, 2022
76. American Society of Clinical Oncology (ASCO): Principles for the Responsible Use of Artificial Intelligence in Oncology 2024. <https://www.asco.org/news-initiatives/policy-news-analysis/asco-six-guiding-principles-ai-oncology>
77. U.S. Food & Drug Administration: Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products: Discussion Paper and Request for Feedback 2025. <https://www.fda.gov/media/167973/download>
78. Center for Veterinary Medicine, Office of Inspections and Investigations, Oncology Center of Excellence, et al: Considerations for the use of artificial intelligence to support regulatory decision-making for drug and biological products: *Draft Guidance for Industry and other interested parties* 2025. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-artificial-intelligence-support-regulatory-decision-making-drug-and-biological>
79. Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research: Artificial intelligence-enabled device software functions: Lifecycle management and marketing submission recommendations. *Draft Guidance Industry Food Drug Adm Staff*, 2025. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/artificial-intelligence-enabled-device-software-functions-lifecycle-management-and-marketing>
80. Liu Q, Huang R, Hsieh J, et al: Landscape analysis of the application of artificial intelligence and machine learning in regulatory submissions for drug development from 2016 to 2021. *Clin Pharmacol Ther* 113:771-774, 2023
81. U.S. Food & Drug Administration: Artificial intelligence and machine learning (AI/ML)-Enabled medical devices 2024. <https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-ai-ml-enabled-medical-devices>
82. European Medicines Agency: Multidisciplinary: Artificial intelligence (AI). https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-guidelines/multidisciplinary-guidelines/multidisciplinary-artificial-intelligence-ai?utm_source=chatgpt.com
83. The Medicines and Healthcare products Regulatory Agency: Guidance: Software and artificial intelligence (AI) as a medical device. https://www.gov.uk/government/publications/software-and-artificial-intelligence-ai-as-a-medical-device/software-and-artificial-intelligence-ai-as-a-medical-device?utm_source=chatgpt.com
84. Research FoC: Considerations for developing reference data sets for digital pathology biomarkers: Friends of cancer research discussion document, 2025. <https://friendsofcancerresearch.org/wp-content/uploads/Considerations-for-Developing-Reference-Data-Sets-for-Digital-Pathology-Biomarkers.pdf>
85. Good machine learning practice for medical device development: Guiding principles. <https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles>
86. Chen Y, Esmailzadeh P: Generative AI in medical practice: In-depth exploration of privacy and security challenges. *J Med Internet Res* 26:e53008, 2024
87. Shreve JT, Khanani SA, Haddad TC: Artificial intelligence in oncology: Current capabilities, future opportunities, and ethical considerations. *Am Soc Clin Oncol Educ Book* 42:1-10, 2022
88. Abbasi AB, Layden J, Gordon W, et al: A unified approach to health data exchange: A report from the US DHHS. *JAMA* 333:1074-1079, 2025
89. Mirchev M, Mircheva I, Kerekovska A, et al: The academic viewpoint on patient data ownership in the context of big data: Scoping review. *J Med Internet Res* 22:e22214, 2020
90. Duggan MJ, Gervase J, Schoenbaum A, et al: Clinician experiences with ambient scribe technology to assist with documentation burden and efficiency. *JAMA Netw Open* 8:e2460637, 2025

Artificial Intelligence in the Clinic: Creating Harmony or Just Adding Noise?

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OVERVIEW

Although still limited, the integration of artificial intelligence (AI) in health care has rapidly expanded in the past few years, especially in oncology clinics. In this article, AI refers to the development and implementation of computer systems capable of performing tasks that typically require human intelligence, such as language understanding, learning, and reasoning. AI technology is currently being used as *ambient listening technology* (AI-driven systems that passively capture verbal interactions between patients and health care providers), *patient messaging chatbots* (AI-enabled conversational agents designed to interact with patients by text or voice platforms), and as tools for inbox management and patient care delivery. However, the question remains: Is AI truly fostering harmony in health care, or just adding noise to an already complex system? Although the current applications of this technology have shown promising results in affecting routine care provided by physicians, this article will focus on AI's broader impact on the health care system—highlighting how ambient listening technology can improve the clinical experience for both patients and physicians, whether AI can reduce physician burnout through minimizing *in-basket workload* (the volume of messages that clinicians must manage within the electronic health record system), and AI's usage as a diagnostic tool. Key concerns addressed in this article include the potential pitfalls associated with AI integration, such as the need for proper clinician training to optimize AI algorithms while ensuring patient safety. The ambiguities surrounding the disclosure of AI in health care and the lack of a legal framework also raise significant concerns regarding patient autonomy, data privacy, trust, and beneficence. Future directions of AI in addressing these challenges are explored, alongside its potential integration into overburdened hospitals, underserved communities, telemedicine, and rural health care settings.

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AI IN AMBIENT LISTENING AND PHYSICIAN-PATIENT INTERACTIONS

One of the key applications of artificial intelligence (AI) in health care is the use of ambient listening technology through AI voice assistants and natural language processors, such as Abridge AI and Nuance Dragon Ambient Experience (DAX).¹ These platforms blend voice-to-text technology to document in-person patient visits and telehealth dialogues within seconds. When comparing the use of AI ambient listening to standard electronic health record (EHR) practices by clinicians in outpatient settings, a multiphase study using simulated interactions between physicians and actors found significantly improved documentation quality with AI and a 26.3% reduction in consultation time.² The multidisciplinary study included clinicians and patient-actors in oncology, cardiology, pulmonology, urology, dermatology, and occupational/language therapy.² Improved documentation quality was also found in other studies that assessed the accuracy and Abridge AI integration with Epic EHR across 35 urology providers in the United States.³ This digital scribe

technology is now considered an effective tool to aid in reducing physician burnout, as physicians continue to report increased frustration during interactions with their EHR.⁴ However, findings regarding AI's impact on patient-physician relationships are mixed. Some studies report improved focus and patient satisfaction, while others show no significant difference in the quality of care. In a prospective observational study assessing patient satisfaction with and without DAX, 288 patients participated in an open-label arm and 304 were enrolled in a masked-phase.⁵ In the open-label arm, patients were made aware that DAX was used to document their visit, and patient satisfaction was evaluated through a Patient-Doctor Relationship Questionnaire-9 (PDRQ-9) scale. The open-label phase arm of the study reported patients felt the provider was more focused on them, spent less time typing, and indicated a more personable encounter.⁵ However, in the masked phase of the study where patients were unaware that DAX was used during their visit, no significant difference was seen in the total patient satisfaction as assessed by the PDRQ-9 scale.⁵ These results may indicate patient expectancy bias in the utilization of ambient

PRACTICAL APPLICATIONS

- Enhancing physician-patient interactions: artificial intelligence (AI) ambient listening technologies, such as Abridge AI and Dragon Ambient Experience, have the ability to assist physicians by transcribing and summarizing patient conversations. This technology allows physicians to remain more focused during patient visits, fostering a more personable experience, while reducing clinician mental fatigue.
- Reducing administrative burden: AI chatbots can be used to address patient queries, set an algorithm to prioritize more pertinent messages over others, and provide educational material to patients. Integrating this technology in health care settings has the potential to ease physician in-basket workload and automate routine administrative tasks.
- Supporting diagnostics and decision making: AI assistance in diagnostic data, such as medical imaging, has shown promise in improving early detection and accurate diagnosis of diseases such as breast cancer and tuberculosis. When used properly as a support tool, physicians can better tailor treatment plans to each patient's needs and provide a wider variety of patient support resources.

listening technologies but do not negate the potential benefit of this tool even if the perceived benefit of AI usage is from the bias alone. These findings can be used to improve patient follow-up, engagement, and encourage better compliance, but should be approached with caution to avoid ethical dilemmas.

Various forms of AI have been piloted in many different medical specialties. Oncologists have begun to integrate AI algorithms to synthesize complex data sets to aid in treatment planning and improve cancer care.⁶ AI processing patient imaging, risk factors, tumor genomic data analysis, and detection ability has been shown to produce results more accurately and promptly than humans.⁶ Cardiologists have begun to integrate AI-enhanced ECGs (AI-ECG) into their clinics as a tool for preventative medicine. AI-ECG algorithm predicts chronological age and compares it with the true age of the patient to predict long-term survival.⁷ These data can be used as a quantifiable marker of health and a reinforcement tool for positive lifestyle changes and patient education. Haberle et al⁸ described how general outpatient providers in 12 different specialties have integrated DAX and reported improved provider engagement without affecting patient safety. As shown by oncologists using AI for complex data sets, cardiologists integrating AI-ECGs into screening visits, and outpatient providers' use of DAX to improve

provider engagement, AI integration in health care has rapidly become multidisciplinary and continues to aid physicians in general and specialized care.

AI IN REDUCING PHYSICIAN BURNOUT AND IMPROVING WORKFLOW

Physician's extensive hours spent on EHRs and evidence of poor EHR usability are believed to have contributed to the rise in physician burnout and reduced patient interaction time.⁹ Because of the rapid computerization of the health care system, the implementation of EHRs was prematurely catalyzed by the federal government to improve efficiency, reduce physician workload, and improve health care quality. However, a 2017–2018 cross-sectional survey from US physicians across all specialties graded the current usability of EHR systems as an F by physician users and observed a significant increase in the odds of burnout.⁹ This standard metric for technology usability is much lower than expected in the health care field, and integrating new AI technology has shown to be a potential remedy to this issue.

Implementing AI tools to streamline EHR documentation and reduce in-basket messages has been proposed as a solution to optimize technology usability. Generative artificial intelligence (GenAI) chatbots have been aiding health care professionals in drafting replies to patient messages, transcribing telehealth visits, and creating patient education material.^{10,11} A cross-sectional study of 16 primary care physicians' opinions on GenAI responses to patient queries showed that although 30.3% GenAI responses were more often irrelevant, they were also more personable and empathetic responses than those of health care providers.¹⁰ As observed in the study, health care provider responses were more frequently incomplete and perceived as unresponsive than those of GenAI.¹⁰ Challenges that arose with GenAI were lengthy responses that could be difficult to interpret for patients who are non-native English speakers.¹⁰ GenAI also had trouble interpreting questions regarding laboratory results. Despite these drawbacks, EHR-integrated GenAI chatbots show the potential to enhance patient-physician relationships and communication by creating a more individualized experience for each patient.

Several institutions, such as Stanford Healthcare and Epic Systems Corporation, have engaged in EHR optimization approaches that use AI to reroute certain in-basket messages to reduce physician burnout. From July to August 2023, Stanford Healthcare routed select patient messages to Epic Systems to be categorized by GPT-3.5 Turbo and generate a drafted reply by GPT-4.¹² Incoming patient messages were divided into four categories: general, results, medications, and paperwork.¹² From these categories, a prompt was autopopulated to include the patient's message, demographics/medical history (name, age, allergies, etc), and a note of their last visit.¹² Presurveys and postsurveys were given to 162 clinicians to assess EHR burden, including cognitive task load, burnout, work exhaustion, satisfaction, and usability.¹² Out of

162 clinicians included in the study, 73 completed both surveys. The mean utilization rate of AI-drafted replies was 20%, with the highest utilization in primary care at 44%. There was no significant change in time spent per clinician on actions; however, statistically significant reductions in physician task load and work exhaustion scores were observed.¹² Clinician expectations for quality, utility, and time for AI-generated drafts were also met or exceeded postpilot study.¹² Although the adoption of AI-generated replies remains in its preliminary stages in clinical practice, these results suggest growing applicability in streamlining administrative health care tasks, reducing physician burnout, and improving workflow.

Similar models have also been proposed with the use of AI-enabled chatbots such as ChatGPT. ChatGPT's ability to communicate with patients in different languages and provide real-time clinical knowledge has been proposed as a leading tool for patient queries.¹³ AI-enabled chatbots can organize messages by priority, improve patient understanding, and therefore, decrease the in-basket load on physicians.¹³ Because of their broader accessibility for patients and physicians, the integration of AI chatbots to relieve the in-basket workload has the potential for wider implementation across institutions and hospitals. However, the integration of AI-enabled chatbots must be approached with caution. Machine learning models continue to be susceptible to error propagation and context-specific inaccuracies, such as diseases with nonspecific symptoms, that may lead to heightened clinical risk.¹³ Proper oversight is necessary to minimize adverse outcomes and maintain trust in automated health care tools such as AI-enabled chatbots.

A notable concern many institutions face with integrating AI is the cost of this tool. Epic Systems has released a statement addressing this concern, indicating that they plan to transition to a more cost-effective version of GPT-4 soon, reducing the cost of AI-integrated Epic EHR by 50%.¹⁴ Epic Systems is now collaborating with Cosmos AI, a database that combines billions of clinical data points from Epic EHR and provides a medical model for differential diagnoses and treatment plans.^{14,15} These results can be presented to clinicians and used to further their decision making, enhancing patient care while preserving cost-efficiency.

Oncology clinics have started to use AI chatbots beyond the scope of answering patient queries and have begun to integrate this technology into a diagnostic, treatment, and monitoring tool.¹⁶ Using AI chatbots in scenarios where an in-person visit is not necessary or as an adjunct to telemedicine visits has the potential to advance both patient and physician convenience while ensuring quality care. This form of digital health can suggest therapies specific to the nuances of each patient case and detect biomarkers vital for preventative cancer care.¹⁶ In a one-year prospective study on conversations between patients with breast cancer and chatbots, an AI chatbot, Vik, was used as a prescription reminder.¹⁷ Out of 4,737 patients included in the study, the average medication adherence rate was calculated over

4 weeks and it was found that the more patients used the AI chatbot, the more adherent they were to their medications.¹⁷ 88% of patients reported AI chatbot as a positive support tool in their breast cancer management.¹⁷ The integration of AI chatbots to reinforce medication adherence and other pertinent care could be used in multiple specialties to advance medicine and serve as a solution to a challenge physicians have faced for decades.

Although patients reported more personable and empathetic responses by AI chatbots, a significant barrier to patient trust is the potential lack of transparency with the utilization of AI in health care settings.¹⁸ The lack of knowledge about how AI algorithms reach an outcome has even led to mistrust among physicians regarding the usage of such tools in their practice and questions about the ethics of expecting patients to trust technology that even providers do not fully understand. A proposed solution is to only integrate simple AI algorithms that physicians can easily explain to their patients, such as risk assessment and medication reminders, and disregard its utility as a diagnostic tool.¹⁸ Although this appears to be the simplest solution, the unparalleled nature of AI systems to create and readjust their hypotheses is what makes AI a novel tool for medicine.¹⁸ This mistrust is a substantial issue that needs to be addressed by experts and future legislation on acceptable uses for AI in health care that protects and assures both providers and patients.

AI IN IMPROVING DIAGNOSTICS

Sophisticated large language models, such as ChatGPT, have been integrated into health care as a diagnostic tool in imaging, creating discharge summaries, operative reports, and medical documentation. Pilot studies suggest that despite ChatGPT's inaccuracies, it outperforms surgeons in thoroughness, precision, and quality of performing informed consent.¹¹ Health care record systems, such as Oracle Cerner's, now feature an automated note-taking assistant as standard protocol for patient visits.¹¹ However, without quality control regulations, the potential benefits of this tool to aid physicians could be accompanied by significant consequences. To reduce the possibility of missing critical nuances in patient diagnoses, regular assessment of AI tools and the creation of an information technology (IT) sector specific to AI technology is recommended.¹¹

The use of AI in analyzing complex medical imaging and data sets shows promise in early breast cancer detection. In a recent study conducted by McKinney et al,¹⁹ a large data set from US clinics showed a reduction of false positives by 5.7% and false negatives by 9.4% when using AI for breast cancer screening. Deep learning in AI algorithms allows for layers of networks that analyze specific features such as lines, texture, shape, and depth of lesions.²⁰ This network mimics the human brain's ability to recognize patterns and radiologists report improved diagnostic accuracy, time with patients, and productivity.²⁰ To improve workflow, AI natural learning processors can be trained to serve as a second opinion to

radiologists, reducing the second reader workload by 88%.^{19,20} These deep learning algorithms, such as convolutional neural networks, allow for automatic feature extraction and enhanced risk stratification for patients with cancer by identifying clinical features from radiographic images and predicting tumor recurrence or histologic subtypes.²⁰ In dermatology, AI is particularly effective in detecting melanoma, basal cell carcinoma, and squamous cell carcinoma by detecting microvariations in skin lesions that may be overlooked by the human eye.²⁰ Integrating AI as an imaging tool could help physicians recognize errors before presenting treatment options to patients and avoid hurdles that come alongside misdiagnosis or late detection.

Novel AI technology is also used as a diagnostic tool for tuberculosis (TB) detection. Current TB testing includes expensive and inefficient blood smears and/or sputum testing.²¹ In 2011, the World Health Organization issued a warning against the unreliable nature of these tests, but AI tools, such as Artificial Neural Network (ANN), may improve their dependability. TB detection reliability and accuracy were analyzed in 115 affected blood samples and 60 normal samples, and ANN was found to be particularly useful in the detection of multidrug-resistant TB.²¹ Upcoming research is focusing on the utility of specific biomarker detection with AI to further aid in targeted TB therapy and diagnosis.

However, AI algorithms struggle with suboptimal data inputs, atypical patterns, and rare lesions on imaging. These flaws serve as significant concerns to providers who may commonly face variable image and data quality in their practice. The use of reliable features is vital to the accuracy of AI detection of a lesion or diagnosis.²² However, radiomics allows for the use of whole data assessment and the creation of AI models on atypical features.²² Using strict computational parameters for feature detection can help circumvent the issue around accurate AI detection. Another major concern with machine learning is the lack of interpretability of data by physicians and patients. Input images are now including activation mapping by AI algorithms, showing the site of lesions, and plotting them on easily interpreted graphs for better physician and patient understanding.²²

PITFALLS OF AI IN THE CLINIC AND ETHICAL CONCERNS

Integrating AI into clinical settings, particularly to mitigate alarm fatigue, introduces critical challenges that may limit its intended effectiveness. AI algorithms often rely on data input and parameters set by users to function correctly. The effectiveness of AI-driven solutions in health care significantly depends on how well clinicians interact with and configure the systems designed to support them. In the case of alarm management systems, an AI algorithm would rely on preset parameters or predefined thresholds to filter and prioritize alarms.²³ However, if clinicians are not adequately trained in customizing these parameters to adapt them to the specific needs of individual patients, an AI system may fail to function as intended.²³ This could lead to scenarios in

which critical alarms are inadvertently filtered out or non-actionable alarms persist, undermining the purpose of AI integration.

Ambiguity around the disclosure of AI in health care and the lack of a legal framework also pose substantial concerns. According to a 2010–2020 systematic review of the ethical concerns related to AI usage in health care, 12 major ethical concerns were highlighted.²⁴ The most pertinent concerns to be considered are patient autonomy, data privacy, trust, and beneficence. Nine studies in a systematic review compared machine learning–based decisions to shared decision making between patients and doctors and found that AI algorithms enforced a paternalistic model ranking treatment options on the basis of value instead of patient preferences.²⁴ The presumption that all factors relating to the patient were considered by AI, when in fact they were not, could unjustly influence patient decision making and undermine patient autonomy. When approaching data privacy, 20 studies in the systematic review were identified to address issues with data usage, ownership, and custodianship.²⁴ Major data breaches included the use of sensitive information without the patient's awareness and the misuse of this information for financial benefit. This could make vulnerable populations increasingly susceptible to data privacy violations as hospitals could use information collected on them by AI for medical purposes without their knowledge.^{24,25} Currently, the governance of AI in health care remains under the general guidelines of Health Insurance Portability and Accountability Act (HIPAA), with no specific regulations on the nuances of AI usage.²⁴ This lack of legislation overlaps with patients' mistrust of the integration of AI, as there is a risk that collected data could be used outside of its intended purposes. To resolve this issue of trust, the literature suggests informing patients on how their data are shared and implementing robust encryption software programs and continuous monitoring to protect sensitive patient information.²⁴ Eleven studies in the systematic review discussed the issue of beneficence when implementing AI as a diagnostic tool.^{24,26} The possibility of AI missing signs of serious illness because of bias in its training data could deceive patients and potentiate harm. Before completely integrating AI into health care systems, it is crucial to prioritize the development of AI software programs that can be coached and trained to enhance beneficence.

Multidisciplinary governance committees, including IT, clinical, and operational leaders, should be instituted to oversee AI tool implementation.²⁷ Like how large hospitals construct additional health care roles to optimize workload, AI integration into health care systems will require a team of individuals to oversee and correct errors made by this tool. Allocating a specific committee for this task would further clarify liability for AI-assisted tasks. This committee would set optimization protocols, quality control of data, and product monitoring on the basis of HIPAA regulations.²⁸ This proposed solution to the lack of governance of AI shows promise to reduce mistrust and protect patient privacy.

FUTURE DIRECTIONS

Advancements in AI technology and its integration into health care settings allow for the exploration of future opportunities to improve patient care, clinical workflows, address challenges, and continuously reevaluate. Overburdened hospitals and underserved communities are at the forefront of future AI integration in medicine. AI-powered decision systems can be leveraged to enhance health care equity by incorporating them into telemedicine visits and address populations that face disproportionate barriers to health care.²⁹ These barriers can include financial constraints, cultural biases, literacy, and insurance coverage. In rural health care settings, AI-support systems could be monumental in expanding access to care and specialty services.²⁹ AI can also be used to tackle language barriers that worsen health disparities by using natural language processor algorithms to simplify medical jargon or rapidly translate it into multiple languages.²⁹

The progression of AI technology has attracted interest in its uses in rural eye care and routine diabetic retinopathy screenings. AI holds promise in image-driven specialties such as ophthalmology, which has a greater population need than available human resources.³⁰ Increased prevalence of diabetic retinopathy has become a growing burden on ophthalmologists and AI could address these concerns by expanding virtual access to care in high-risk remote populations.

A similar AI telehealth model is being proposed for integration into cardio-oncology clinics in urban and rural areas worldwide to combat data indicating that patients who live farther from treating hospitals have a worse prognosis.³¹ For patients in rural areas with less access to laboratories, AI-based blood diagnostics analyzers can be used to detect predictive biomarkers for targeted cancer therapy treatment.³¹ The future use of this technology could improve the efficiency of clinicians and increase patient convenience.

Continued development of AI tools is necessary to address the limitations of AI use in medicine. It is imperative that strategies are developed to help mitigate the negative impacts of AI, such as information overload, data quality requirements, and transparency of AI usage. Regular assessment of AI tools in practice must be conducted and feedback from patients and clinicians should be given consideration to ensure maximal benefit without unintended harm.

CONCLUSION

AI holds significant potential to improve the clinical experience for patients and physicians, from ambient listening technology supporting physician-patient interactions to AI-enabled chatbots reducing physician in-basket workload. Ambient listening technologies, such as Abridge AI and DAX,

have shown improved documentation quality, facilitated more personable patient encounters, and decreased mental fatigue among physicians, although the impact on patient satisfaction remains mixed. These AI tools have shown to be an asset in alleviating the administrative burden many physicians carry, significantly reducing physician burnout. The use of AI chatbots and GenAI algorithms presents a novel approach to answering patient queries, improving communication, prioritizing patient messages, and enhancing patient education. AI also shows promise as a diagnostic tool, especially in analyzing complex imaging and early disease detection in breast cancer and TB.

However, the pitfalls of AI remain significant. Information overload, mediocre performance with analyzing complex examinations (eg, physical examinations, laboratory results, etc), and ethical and legal ambiguity around disclosure of AI use all pose a threat to the successful integration of this technology in the future. Ethical concerns related to patient autonomy, data privacy, trust, and beneficence must be addressed by AI algorithm developers and legislators, and include regulations outside of the HIPAA to ensure patient safety and confidence are made a priority. Future developments of AI suggest its integration into overburdened hospitals, underserved communities, telemedicine, and rural health care settings, further enhancing access to care and tackling health care disparities. This is particularly promising in image-driven specialties, such as ophthalmology, and could reshape how patients perceive our health care system moving forward.

As AI adoption becomes more widespread, health care facilities can consider explaining the use of this technology to patients as a beneficial augmentation of the high-quality care their clinicians provide. This practice would be explained to patients as the institutional standard, as they would be automatically enrolled into these services with the option to opt out at any time. This approach addresses the growing concern among physicians and patients about the transparency of AI use in medicine and reinforces that patient autonomy remains a key concern. For a smooth transition, both parties must trust in the available technology and be knowledgeable about its mechanism to use it properly.

Balance in AI's utility as a tool is most important to ensure patient integrity and safety standards are upheld. Currently, AI's usage is limited to serving as a digital assistant or second opinion to physicians, but this may drastically shift in the next decade. Limiting AI's usage to a supportive tool in health care, assisting physicians with complex tasks, and reducing workload ensures human judgment and expertise remain the driving force in patient care. However, the question remains: how can we ensure patient confidence in care while still improving efficiency and leveraging AI technology?

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REFERENCES

- Lungren MP, Fishman EK, Chu LC, et al: More is different: Large language models in health care. *J Am Coll Radiol* 21:1151-1154, 2024
- Balloch J, Sridharan S, Oldham G, et al: Use of an ambient artificial intelligence tool to improve quality of clinical documentation. *Future Healthc J* 11:100157, 2024
- Dowling RA: Ambient clinical documentation shows promise for physicians: Technology may save health care professionals' time and help reduce burnout. *Urol Times* 51:34-36, 2023
- Ghatnekar S, Faletsky A, Nambudiri VE: Digital scribe utility and barriers to implementation in clinical practice: A scoping review. *Health Technol* 11:803-809, 2021
- Owens LM, Wilda JJ, Grifka R, et al: Effect of ambient voice technology, natural language processing, and artificial intelligence on the patient-physician relationship. *Appl Clin Inform* 15:660-667, 2024
- Chua IS, Gaziel-Yablowitz M, Korach ZT, et al: Artificial intelligence in oncology: Path to implementation. *Cancer Med* 10:4138-4149, 2021
- Harmon DM, Lopez-Jimenez F, Friedman PA: Introducing artificial intelligence into the preventive medicine visit. *Mayo Clinic Proc* 97:1575-1577, 2022
- Haberle T, Cleveland C, Snow GL, et al: The impact of nuance DAX ambient listening AI documentation: A cohort study. *J Am Med Inform Assoc* 31:975-979, 2024
- Melnick ER, Dyrbye LN, Sinsky CA, et al: The association between perceived electronic health record usability and professional burnout among US physicians. *Mayo Clinic Proc* 95:476-487, 2020
- Small WR, Wiesenfeld B, Brandfield-Harvey B, et al: Large language model-based responses to patients' in-basket messages. *JAMA Netw Open* 7:e2422399, 2024
- Miao J, Thongprayoon C, Cheungpasitporn W: Should artificial intelligence be used for physician documentation to reduce burnout? *Kidney360* 5:765-767, 2024
- Garcia P, Ma SP, Shah S, et al: Artificial intelligence-generated draft replies to patient inbox messages. *JAMA Netw Open* 7:e243201, 2024
- Matulis J, McCoy R: Relief in sight? Chatbots, in-baskets, and the overwhelmed primary care clinician. *J Gen Intern Med* 38:2808-2815, 2023
- McGinial S: Epic's Approach to AI with Sean McGinial, Director of AI at Epic, in Lynn J (ed): *Healthcare IT Today Interviews Podcast*, 2024
- Yale School of Medicine: Cosmos. 2024. <https://medicine.yale.edu/ybic/data-resources-services/cosmos/#:~:text=The%20Cosmos%20data%20set%20combines,to%20the%20centralized%20Cosmos%20database>
- Cohen AB, Schwamm LH: Digital health for oncological care. *Cancer J* 30:34-39, 2024
- Chaix B, Bibault J-E, Pienkowski A, et al: When chatbots meet patients: One-year prospective study of conversations between patients with breast cancer and a chatbot. *JMIR Cancer* 5:e12856, 2019
- Feldman RC, Aldana E, Stein K: Artificial intelligence in the health care space: How we can trust what we cannot know. *Stanford Law Policy Rev* 30:407, 2019
- McKinney SM, Sieniek M, Godbole V, et al: International evaluation of an AI system for breast cancer screening. *Nature* 577:89-94, 2020
- Goyal S: An overview of current trends, techniques, prospects, and pitfalls of artificial intelligence in breast imaging. *Rep Med Imaging* 14:15-25, 2021
- Dande P, Samant P: Acquaintance to artificial neural networks and use of artificial intelligence as a diagnostic tool for tuberculosis: A review. *Tuberculosis* 108:1-9, 2018
- Koçak B: Key concepts, common pitfalls, and best practices in artificial intelligence and machine learning: Focus on radiomics. *Diagn Interv Radiol* 28:450-462, 2022
- Sowan AK, Gomez TM, Tariela AF, et al: Changes in default alarm settings and standard in-service are insufficient to improve alarm fatigue in an intensive care unit: A pilot project. *JMIR Hum Factors* 3:e1, 2016
- Li F, Ruijs N, Lu Y: Ethics & AI: A systematic review on ethical concerns and related strategies for designing with AI in healthcare. *AI* 4:28-53, 2023
- Yadav N, Pandey S, Gupta A, et al: Data privacy in healthcare: In the era of artificial intelligence. *Indian Dermatol Online J* 14:788-792, 2023
- Baig MAA: Navigating biomedical ethical challenges of artificial intelligence in healthcare. *IJLAI Trans Sci Eng* 2:29-35, 2024
- Shah T, Kitts AB, Gold JA, et al: Electronic health record optimization and clinician well-being: A potential roadmap toward action. *NAM Perspect* 2020:29-35, 2020
- Ho CWL, Soon D, Caals K, et al: Governance of automated image analysis and artificial intelligence analytics in healthcare. *Clin Radiol* 74:329-337, 2019
- Molli VLP: Enhancing healthcare equity through AI-powered decision support systems: Addressing disparities in access and treatment outcomes. *Int J Sustain Develop* 3:1-12, 2024
- Chia MA, Turner AW: Benefits of integrating telemedicine and artificial intelligence into outreach eye care: Stepwise approach and future directions. *Front Med* 9:835804, 2022
- Kappel C, Rushton-Marovac M, Leong D, et al: Pursuing connectivity in cardio-oncology care—The future of telemedicine and artificial intelligence in providing equity and access to rural communities. *Front Cardiovasc Med* 9:927769, 2022

Multicancer Early Detection Tests at a Crossroads: Commercial Availability Ahead of Definitive Evidence

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OVERVIEW

Multicancer early detection tests (MCEDs), sometimes referred to as liquid biopsies, are tests that can screen for multiple cancers by analyzing blood, urine, and other bodily fluids for biomarkers released by cancer cells. These tests have the potential to change the cancer screening paradigm if they are shown to reduce cancer mortality. However, it is not yet known whether MCEDs reduce mortality. Randomized controlled trials, the gold standard for evaluating cancer screening programs, are currently evaluating the effectiveness of MCEDs. However, because cancer-specific and all-cause mortality are end points that can take years to reach, trials are being designed with surrogate end points such as stage of disease at detection. However, the correlation between cancer stage and survival appears to vary by cancer type, and many have argued that trials must also continue to follow for the gold standard of mortality end points until these surrogate end points are appropriately validated. The widespread use of MCEDs before conclusive evidence supporting their use has the potential to cause harm to patients, could widen health inequities, and further drive health care costs. Consequently, providers should engage in shared decision making regarding MCED tests with patients who inquire about MCEDs emphasizing that MCEDs should be additive to, not replacements for, the currently recommended cancer screening tests.

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INTRODUCTION

Multicancer early detection tests (MCEDs), sometimes referred to as liquid biopsies, are tests that can screen for multiple cancers by analyzing blood, urine, and other bodily fluids for biomarkers released by cancer cells. These biomarkers or analytes can be circulating tumor DNA, which can be analyzed for DNA methylation or fragmentation, RNA sequences, and proteins. Machine learning algorithms are trained to analyze the tumor biomarker data to identify the likely tissue of origin (TOO) or cancer signal of origin (CSO). If cancer is detected by an MCED test, additional diagnostic cancer-specific testing guided by the TOO or CSO is needed to confirm the cancer if it is present. However, the most appropriate diagnostic pathways after a positive MCED test have yet to be determined and, depending on the TOO or CSO, may require additional imaging such as computed tomography (CT) or positron emission tomography-CT and/or procedures and biopsy.

It is not yet known whether MCEDs reduce mortality. The gold standard for evaluating a cancer screening program is a randomized controlled trial (RCT) using cancer-specific and all-cause mortality as an end point. However, RCTs are associated with very high costs and can take years to decades to see results if at all. Therefore, MCED trials are being designed with alternative end points, and there is debate

surrounding the best end points, which we discuss in this article.

Currently, to our knowledge, no MCED has received approval by the US Food and Drug Administration (FDA). One MCED, Galleri, is now on the market and many more are expected to become commercially available through the Clinical Laboratory Improvement Act (CLIA). Under this act, the FDA considers diagnostic accuracy and not clinical outcomes when evaluating tests. Thus, MCEDs may become more widely available before we have the results of RCTs that will determine the effectiveness and safety of MCEDs. Although RCTs of MCEDs are ongoing and there are currently insufficient data from RCTs to recommend MCEDs, they could potentially augment the available cancer screening tests and identify some of the cancers for which we currently do not have screenings.

Cancers without a screening test account for almost half of the cancer diagnoses and 57% of the cancer deaths in the United States.¹ These cancers tend to be diagnosed at late stages and are associated with poorer prognosis and higher treatment costs. Thus, there is great potential for MCEDs to have significant clinical and economic impact. Because results from RCTs are typically a prerequisite for insurance coverage of cancer screening tests, most insurers currently do not cover MCEDs, although a few payers provide coverage

PRACTICAL APPLICATIONS

- Randomized controlled trials are currently being designed and some are underway to evaluate the effectiveness of multicancer early detection tests (MCEDs) using surrogate end points such as stage of disease.
- The correlation between stage of disease and survival may vary for different cancers, and many have argued that trials must continue to reach the mortality gold standard end points.
- Although the US Food and Drug Administration has not approved the use of any MCED for the screening of multiple cancers, the first MCED, Galleri (Grail, Menlo Park), is commercially available and thus, patients have begun to inquire about MCEDs.
- If survival data favor the use of MCEDs for cancer screening, these tests could be paradigm-changing. However, the widespread use of MCEDs before conclusive evidence supporting their use has the potential to cause harm to patients, could widen health inequities, and further drive health care costs.
- Clinicians are not obligated to initiate discussions about MCEDs until more is known about the effectiveness of MCEDs. If patients inquire about MCEDs, providers should engage in shared decision making emphasizing that MCEDs should be additive to, not replacements for, currently recommended cancer screening tests.

of MCEDs to their members.² Thus, the tests—that require a clinician order—are accessible to those who are willing to pay out-of-pocket.

Given the attention to MCEDs in the lay press and on social media, individuals have begun to ask their providers about Galleri and other MCEDs. To address the growing interest in MCEDs by the general population and uncertainty about their clinical value, this review focuses on the developing research on MCEDs to outline the outcomes that will support their widespread adoption, the potential impact of MCEDs on population health and value, and provides clinicians with the information to engage in shared decision making (SDM) to discuss MCEDs with patients who inquire about them.³

MULTICANCER EARLY DETECTION RESEARCH: WHICH END POINTS WILL JUSTIFY WIDESPREAD ADOPTION?

MCEDs hold the promise of screening for multiple cancers with a blood test that can be obtained easily and in

conjunction with other routine blood tests. The promise is tremendous for scaling screening measures with the potential to reach populations who currently struggle with access to health care, while potentially decreasing more invasive, costly, and uncomfortable procedures. Several of the tests currently in development screen for multiple cancers, including cancers with approved cancer screenings. Unfortunately, approximately 70% of cancers do not have US Preventive Services Task Force (USPSTF) evidence-based recommended screening guidelines and are found only when symptomatic.⁴

Current screening recommendations are based often on large, randomized trials that take years to decades for outcome data to mature. However, as technology is evolving quickly, balancing access with evidence of improved outcomes is becoming increasingly challenging. Therefore, identifying important end points that justify adoption must be considered when planning for the development of these strategies.

MCED Clinical Trial End Points

There has been a lot of debate surrounding the best end points for MCEDs and other screening tests. The gold standard would be all-cause mortality or cancer-specific mortality. The concern is the cost of these trials, the size, and then the length of time, over years to decades, to see results if at all. These end points would decrease lead-time bias of knowing about a disease sooner, but not affecting survival.⁵

Several surrogate end points have been proposed and recognized by guidelines such as the USPSTF.⁶ One of these end points has been shifting diagnoses to earlier stages. Earlier-stage cancers are assumed to be associated with improved survival and with the potential of decreased interventions such as the extent of surgery, radiation, and/or chemotherapy to gain survival benefits.^{7,8} However, the correlation between cancer stage and survival appears to vary by cancer type.^{9,10} It is uncertain in the case of MCED test-identified cancers if identifying cancers at an earlier stage will lead to reduced mortality. Other than shifting stage, identifying other validated surrogate end points remains challenging.⁵ Surrogate end points are not new to cancer trials and have been used for FDA approvals and include end points such as pathologic complete response for neoadjuvant therapeutic interventions in breast cancer.¹¹ Table 1 highlights several cancers with screenings that are currently recommended by the USPSTF recommendations and the level of evidence and trial end points that lead to these recommendations. In addition to survival end points, a surrogate end point was used, for example, with colorectal cancer screening. However, fecal testing was able to be compared, in that case, to what was already established as a screening intervention (colonoscopy) that had already been validated as a screening test.⁵ Although this surrogate may be considered, many have argued that trials must also continue to follow for the gold

TABLE 1. Selected Cancer Screenings Recommended by the USPSTF

Topic	Year	Screenings	Level of Evidence/ Recommendation
Breast cancer	2024	Mammograms every other year age 40-74 years (B) Dense breasts and disparities (I)	B, I Breast cancer–specific mortality, all-cause mortality, stage, false positive/biopsy, overdetected
Skin cancer	2023	Skin examinations	I MSM, all-cause mortality and stage
CRC	2021	Screening (multiple methods) all adults age 50-74 years (A); 45- 49 years (B); 76-85 years (C)	A, B, C CRC incidence, CRC-specific mortality
Lung cancer	2021	Low-dose CT age 50-80 years with 20 pack-year history, who smoke or quit within the past 15 years	B Lung cancer–specific mortality, all-cause mortality
Pancreatic cancer	2019	Recommends against	D Morbidity, all-cause mortality
Cervical cancer	2018	Cervical cytology every 3 years age 21-29 years; 30-65 years or every 5 with HPV testing alone or every 5 with co-testing (A) <21 years or > 65 years or after hysterectomy (D) ^a	A, D Stage, colposcopy rates
Prostate cancer	2018	Age 55-69 years —PSA (C), >70 years (D) ^a	C, D Prostate cancer–specific mortality, all-cause mortality, treatment benefit and harms

NOTE. A = substantial benefit; B = moderate benefit; C = offer on the basis of individual circumstances; D = discourage use; I = insufficient evidence (can be lacking, or poor quality, uncertainty of benefits and harms). USPSTF online March 6, 2025.

Abbreviations: CRC, colorectal cancer; CT, computed tomography; HPV, human papillomavirus; MSM, melanoma-specific mortality; PSA, prostate-specific antigen; USPSTF, US Preventive Services Task Force.

^aBeing updated.

standard of mortality end points until these surrogate end points are appropriately validated.^{12,13}

The State of Current MCED Tests

Although the potential of these tests does have promise, no MCED test is currently approved by the FDA nor Centers for Medicare & Medicaid Services for reimbursement. Only one test, Galleri, is commercially available through a CLIA-waiver. Although multiple ongoing large trials are investigating various MCEDs and methodologies, the trials to date have mostly reported on establishing and improving the test performance on diagnosing a cancer at a single time point, not yet whether the test influences outcomes.^{14,15} There is concern that despite the test, cancers such as breast and prostate are being test identified at mostly advanced stages and overall, a very low identification of stage I disease. Is the shedding of tumor DNA and evaluation of methylation patterns picking up on those cancers with early metastatic potential and a more aggressive clinical course?¹² The National Health Service (NHS)-Galleri study is a large, population-based study of 140,000 participants. The primary end point is a surrogate end point of incidence of stage III and IV cancers.¹⁶ However, the preplanned analysis of the first year of three planned yearly rounds of screening did not

trigger the NHS to move forward with a previously planned large-scale adoption of the test.¹³ In the PATHFINDER study, only 1.4% of the tests identified a CSO, and of those, there was a 62% false-positive rate.¹⁵ In addition to patients without a known cancer or symptoms, there may also be an evolving role for symptomatic undiagnosed patients to point toward a cancer and site of origin.¹⁷ The optimal workup for a positive test as well as who to test, when, and how often also remain under investigation.

Although there is expectation that with increasing numbers, the algorithm will improve, understanding effect on survival and/or other outcomes improving life for patients such as cost and morbidity should be identified. This determination of MCED clinical utility is especially important, given the estimated projected five-fold growth of the MCED market from \$4 billion (USD) in 2022 to \$18 billion (USD) in 2032 should these tests become widely available.¹⁸

Deverka et al¹⁹ articulate the significant evidentiary requirements for manufacturers and the complex challenges faced by payers as they deliberate a coverage determination for these novel precision techniques that screen for multiple cancers simultaneously. They must balance the many years it will take for trials enrolling tens of thousands of randomly

assigned patients to demonstrate a net survival benefit of adding MCEDs to standard screening against the potential harms of delaying their use—for example, lives lost due to cancer. In the interim, the potential use of intermediate end points to assess tests' net survival benefit should be explored to guide decision making.

UNINTENDED CONSEQUENCES OF MULTICANCER EARLY DETECTION: THE POPULATION HEALTH AND VALUE PERSPECTIVE

The Emergence of MCED Tests Should Not Be a Substitute for Promoting Recommended Cancer Screenings

Current MCED tests are additive to, not replacements for, current cancer screening tests. Although a more convenient blood-based screening test may prompt more patients to undergo cancer screening, it may also result in the misconception that patients have been adequately screened with only a MCED test. To mitigate this unwanted consequence, implementation programs for MCED testing should be designed to complement efforts to increase recommended cancer screenings, using MCED as a teachable moment.

Access to Follow-Up Care

If an initial MCED test demonstrates a marker for potential cancer diagnosis, patients may face substantial out-of-pocket expenses for necessary follow-up diagnostic services. Constrained access to clinically indicated follow-up testing is not unique to MCEDs. Financial barriers apply to almost all cancer screenings since an abnormal result from an initial test screen such as a screening mammogram for breast cancer or low-dose CT scan to screen for lung cancer typically leads to a recommended sequence of clinical interventions to determine whether a definitive diagnosis of cancer can be established (screening is an exception as federal regulations require that a colonoscopy following a positive initial non-invasive screening test be covered without consumer cost sharing). Because certain demographic patient groups at high risk for cancer may have difficulty paying substantial out-of-pocket costs for essential care, generous payer coverage for the follow-up diagnostic testing is needed to avoid exacerbating disparities in cancer screening and early cancer diagnoses.

Health Equity Issues May Be Both Improved and Exacerbated by MCED Screening, So Structural Barriers Must Be Explicitly Addressed by MCED Implementation Programs

Access to MCEDs provides additional opportunities to enhance equity. The convenience associated with a single blood test to screen for multiple cancers may lead to a reduction in disparities because of the proposed ability to detect more aggressive tumors that disproportionately affect minority patients. Moreover, although the impact of the availability of

MCEDs on recommended cancer screening rates is unknown, there is potential that the increased convenience of a MCED blood test can lead to a teachable moment in which eligible individuals, not yet up to date on recommended screenings, increase their use. Conversely, it is also possible that overall, recommended screening rates might decline, as some people may feel reassurance that a MCED is enough. This could happen despite manufacturers' strong emphasis that MCEDs are to be used in conjunction with, and not as a substitute for, recommended screenings. Clinicians, researchers, and policymakers must closely follow this interaction between MCED availability and recommended screening rates as the use of MCEDs evolves in various patient groups.

MCED tests may mitigate disparities in cancer screening if access to care and other cancer screenings are enhanced. Studies have shown high enthusiasm for MCED testing across populations, in part because of the simplicity of a blood test.²⁰ This may be particularly relevant in underserved populations. For example, Alaska Native persons cited travel as a major barrier to undergoing colonoscopy; those who were previously unscreened were more likely to state a preference for a multitarget stool DNA test.²¹

Disparities could also worsen if MCED tests continue to be available only through certain health plans or for a substantial out-of-pocket cost. Additionally, because follow-up diagnostic testing may involve advanced imaging, procedures, referrals to specialists, and lead to substantial out-of-pocket costs, patients in rural and safety-net settings may have difficulty accessing affordable follow-up care without investments in health care infrastructure and addressing workforce shortages.²² Researchers, health care systems, and policymakers should continuously evaluate and work to ensure appropriate access, use, and affordability of both MCED tests and follow-up testing to maximize their impact on improving health equity.

Payer Coverage Issues Need to Be Examined Even Before Complete Evidence Is Available

The coverage of MCED tests need to be examined and addressed proactively, since coverage decisions can affect access and primary care clinicians may be reluctant to offer testing without assurance of coverage. Coverage of MCED testing is complex because the tests are not FDA-approved, MCED test characteristics vary by cancer type and stage, follow-up diagnostic testing may be extensive and rigorous, prospective trials looking at mortality are not yet available, and cost-effectiveness has yet to be determined.¹⁹ Rapid diffusion of new technologies have contributed to rising health care costs, particularly if dissemination occurs before proof of superiority has been demonstrated (eg, laparoscopic cholecystectomy). One option for payers is to use coverage with evidence development and pay for testing only when rigorous data collection will add to and solidify the evidence base (eg, Medicare's coverage of the Alzheimer's treatment aducanumab).²³

TABLE 2. Three-Talk Model Approach for Discussing MCEDs With Patients

Patient Questions	Answers and Relevant Information
Choice or team talk	
What is an MCED test?	An MCED test looks for multiple cancers at once, including cancers that we currently do not have other tests or screenings for MCEDs are offered to people who have no signs or symptoms of cancer Those without symptoms have approximately a 1% chance (1 in 100) of the test being positive and among those with a positive test, about 4 of 10 will be found to have cancer upon further diagnostic testing ¹⁵ This test does not diagnose cancer. If the test is positive, further testing is required to determine whether cancer is present, and where it may be located. Follow-up tests may include scans and biopsies There are no established guidelines for the most appropriate diagnostic tests after a positive MCED test result
What do MCED tests detect?	MCED tests detect DNA or other cancer cell components shed into the blood
What MCED tests are available?	Currently, there is only one MCED blood test available: The Galleri test (GRAIL, Menlo Park, CA)
Who is eligible for MCED testing?	The GRAIL Galleri test is available by prescription for patients age 50 years or older as an addition to and not in place of guideline-recommended cancer screening tests. However, more research is needed to determine the recommended starting and stopping ages and frequency of testing If you chose to have an MCED test, you should be willing to have follow-up testing and treatment if you receive a positive result
How much does the test cost?	The GRAIL Galleri test is listed at \$949 (USD). It is not covered by most insurers and typically must be paid out-of-pocket You may be able to use your flexible spending account, use your health savings account, or inquire about a patient assistance or payment plan to cover the cost Additional costs may arise from follow-up tests if the MCED result is positive
How long do the results take?	Galleri test results are typically available about 2 weeks after the lab receives the sample
How often do I get the test?	Currently, GRAIL recommends testing annually with Galleri as an addition to and not in place of guideline-recommended tests. However, the optimal testing frequency is still unknown
Option talk	
What are the potential benefits of MCED testing?	MCED tests may detect cancers that currently have no screening options. The Galleri test claims to be able to detect more than 50 cancers
What are the potential limitations, harms, or uncertainties of MCED testing?	We do not yet know whether MCED tests extend your life or improve quality of life The Galleri test does not detect all cancers, nor does it detect all cancers equally well. The ability to detect a cancer is dependent on the type of cancer MCEDs identify some cancers at an earlier, possibly more treatable stage and other cancers will be detected at a later stage, when treatment may be less effective. MCEDs appear to be able to better detect later-stage cancers than early-stage cancers A false negative is when cancer is present and it is missed by the test. The false-negative rate of Galleri is low and estimated to be 0.5% (1 in 200). A false-negative result should not replace the need for continued, regular, guideline-recommended cancer screenings ¹⁵ Among those with a positive test, 4 of 10 will be found to have cancer upon further diagnostic testing ¹⁵ Those with a positive test but no cancer found upon further testing may represent false positives. Those individuals will need to be watched carefully, including by repeating the Galleri test in short interval of time (eg, 3-6 months) to be certain that a small cancer was not missed by the initial diagnostic testing and for symptoms that might represent cancer The risk for false positives is 0.5% (1 in 200) and lower with MCED tests than with any other currently recommended screening tests. ¹⁵ False positives can lead to unnecessary tests and procedures, costs, and anxiety A positive result, whether true positive or false positive, may cause anxiety and distress The appropriate process for evaluating a positive test is still uncertain Follow-up invasive procedures, biopsies, or surgeries after a positive MCED result may cause harm Overdiagnosis can occur when an MCED test detects cancer that would not have caused symptoms or affected your health. This can lead to unnecessary procedures Overtreatment is related to overdiagnosis and occurs when excessive or unnecessary care is provided. This may expose you to avoidable procedures, treatments or therapies, side effects, and complications Incidental findings are abnormalities unrelated to cancer that may be discovered during follow-up testing. These findings may require follow-up testing of their own and possible treatment, involving additional time, effort, risks, side effects, and costs
How likely am I to experience those harms?	With the Galleri test, the risk of a false positive is 0.5% (1 in 200) and false negative is 0.5% (1 in 200) ¹⁵ The exact rates of overdiagnosis, overtreatment, and incidental findings related to MCED testing are not yet known
How accurate is an MCED test at predicting where the cancer is originating?	The Galleri test can identify the origin of cancer (aka tissue of origin or cancer signal of origin) with approximately 90% accuracy ²⁴

(continued on following page)

TABLE 2. Three-Talk Model Approach for Discussing MCEDs With Patients (continued)

Patient Questions	Answers and Relevant Information
What might a positive MCED result mean?	A positive MCED result may indicate detection of DNA or other components shed by cancer cells. Further testing is required to confirm a cancer diagnosis Among individuals with cancer, the Galleri test can correctly identify 43% of them. Thus, about 4 of 10 individuals with a cancer signal detected will be found to have cancer upon further testing ¹⁵ MCEDs do not measure inherited genetic risk of having cancer in the future. Genetic risk can only be measured by testing the DNA in your genes (known as genetic testing). Examples of genetic tests are the test for <i>BRCA 1</i> and 2. MCEDs do not test your genes. Instead, they test for DNA shed by tumor cells
What might a negative MCED result mean?	A negative Galleri result indicates there is a very low chance (about 1 in 100) of having cancer at the time of testing, but it does not eliminate the need for regular screenings or attention to new symptoms ¹⁵
What could happen if I do not have the test?	Choosing to not have the test is reasonable as we do not have all the evidence to recommend MCED testing. However, you should complete all the cancer screening tests that are recommended for you. These tests have been shown to detect cancers early when they are most treatable
Decision talk	
How to decide?	MCED tests are not a recommended part of your routine cancer screenings at this time MCEDs are not a replacement for guideline-recommended cancer screening tests. You should complete all the available recommended cancer screening tests for someone of your age, sex, family history, and health profile If you are unsure about getting tested, it may be best to wait. We can always revisit your decision as more information becomes available Another alternative is to consider participating in an MCED clinical trial that is helping to answer some of the uncertainties about MCEDs. You can learn more about MCED clinical trials at ClinicalTrials.gov Additional resources are available to help you make an informed decision about whether to consider an MCED test. We can refer you to them I will continue to be available to answer questions and provide you with support and guidance

Abbreviation: MCED, multicancer early detection test; USD, US dollars.

WHAT SHOULD YOU SAY WHEN YOUR PATIENT ASKS FOR THE TEST?

The Challenges of Ordering MCEDs in Practice

The American Cancer Society has issued guidance for primary care clinicians discussions about MCEDs and the guidance states that clinicians are not obligated to initiate discussions about MCEDs until more is known about their effectiveness.²⁴ However, given the growing interest in MCEDs, patients may ask about the tests. Before testing, clinicians need to be prepared to clearly communicate the uncertain clinical benefits and potential (including financial) risks of MCED tests. Clinicians should also be prepared with the guidance on managing MCED results, particularly positive tests, which can be particularly challenging, given the lack of clinical practice guidelines for managing positive MCED tests. This may lead to many ordering primary care clinicians needing to consult with oncologists.

Shared Decision-Making Approach to MCEDs

The majority of patients who ask about MCEDs will require education and a discussion to make informed decisions. The lack of clinical practice guidelines and the uncertainty surrounding MCEDs make discussions about MCEDs between clinicians and patients well suited for SDM. SDM is a collaborative discussion that considers the clinical evidence, patient's personal values, preferences, and circumstances to review the benefits and harms of options and identify the best course of action. Several frameworks exist for SDM. One commonly used framework for SDM is the three-talk model:

choice, option, and decision talk.²⁵ In choice talk, also known as team talk, the clinician describes the choices. In the option talk, the clinician compares and provides detailed information about the options. The option talk may involve the use of decision support tools or aids if these are available. In decision talk, the clinician and the patient consider the patient's goals and preferences and decide on best course of action. Selby et al²⁶ and Hoffman et al²⁴ have outlined the MCED core concepts using the three-talk model for SDM for primary care physicians. In this article, we adapt the three-talk model to an MCED discussion with patients.

Using the three-talk model as an approach for SDM for discussing MCEDs, [Table 2](#) shows some key questions and potential responses that providers might use for education and SDM. Choice talk provides basic education about MCEDs, what the tests detect, who is eligible, which test is available, and its cost. Option talk education centers around the option of testing including the potential benefits, harms, likelihood of harm, interpretation of test results and test uncertainties as well as the option of not testing. Decision talk centers around helping patients decide and recognizes that, given the many uncertainties, even after participating in a SDM discussion, some patients may still not feel ready to make a decision about whether or not to have an MCED test. They may require time to process the information and/or to discuss it with family or other members of their networks. Clinicians can acknowledge that the decision to have an MCED is not straightforward, given that we still lack important information about the effectiveness of MCEDs, provide support by continuing to answer questions as they arise, and direct them to resources for further education.

Greene and Vassy²⁷ provide a comprehensive review of patient educational materials on MCED tests, which can further aid in patient understanding and decision making.

CONCLUSION

MCED tests hold tremendous promise for improving cancer screening, addressing health inequities, and ultimately

decreasing cancer mortality. However, until an evidence base is compiled, clinicians (at the individual patient level) and policymakers (at the population health level) must act responsibly to weigh potential benefits and harms. As MCED tests disseminate, we should draw on lessons—both positive and negative—from experiences with other unproven innovations to ensure implementation is safe, equitable, and adapted to the evolving evidence base.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Guerra CE, Sharma PV, Castillo BS: Multi-cancer early detection: The new frontier in cancer early detection. *Annu Rev Med* 75:67-81, 2024
- GRAIL: Grail—Partnerships. 2025. <https://grail.com/our-partners/>
- Lin GA, Phillips KA, Fendrick AM: Reading the crystal ball: Primary care implications while awaiting outcomes for multi-cancer early detection tests. *Healthc (Amst)* 11:100705, 2023
- Vittone J, Gill D, Goldsmith A, et al: A multi-cancer early detection blood test using machine learning detects early-stage cancers lacking USPSTF-recommended screening. *NPJ Precis Oncol* 8:91, 2024
- Webb AB, Berg CD, Castle PE, et al: Considerations for using potential surrogate endpoints in cancer screening trials. *Lancet Oncol* 25:e183-e192, 2024
- United States Preventive Services Task Force: Home. 2025. www.uspreventiveservicestaskforce.org/uspstf/home
- Callister MEJ, Crosbie EJ, Crosbie PAJ, et al: Evaluating multi-cancer early detection tests: An argument for the outcome of recurrence-updated stage. *Br J Cancer* 129:1209-1211, 2023
- Hubbell E, Clarke CA, Aravanis AM, et al: Modeled reductions in late-stage cancer with a multi-cancer early detection test. *Cancer Epidemiol Biomarkers Prev* 30:460-468, 2021
- Feng X, Zahed H, Onwuka J, et al: Cancer stage compared with mortality as end points in randomized clinical trials of cancer screening: A systematic review and meta-analysis. *Jama* 331:1910-1917, 2024
- Owens L, Gulati R, Etzioni R: Stage shift as an endpoint in cancer screening trials: Implications for evaluating multicancer early detection tests. *Cancer Epidemiol Biomarkers Prev* 31:1298-1304, 2022
- Litton JK, Regan MM, Pusztai L, et al: Standardized definitions for efficacy end points in neoadjuvant breast cancer clinical trials: NeoSTEEP. *J Clin Oncol* 41:4433-4442, 2023
- Robbins HA: Multicancer early detection tests—Keeping a high bar for evidence of benefit. *N Engl J Med* 391:292-294, 2024
- McCartney M, Cohen D: Galleri promises to detect multiple cancers-but new evidence casts doubt on this much hyped blood test. *BMJ* 386:q1706, 2024
- Klein EA, Richards D, Cohn A, et al: Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol* 32:1167-1177, 2021
- Schrag D, Beer TM, McDonnell CH 3rd, et al: Blood-based tests for multicancer early detection (PATHFINDER): A prospective cohort study. *Lancet* 402:1251-1260, 2023
- Neal RD, Johnson P, Clarke CA, et al: Cell-free DNA-based multi-cancer early detection test in an asymptomatic screening population (NHS-Galleri): Design of a pragmatic, prospective randomised controlled trial. *Cancers (Basel)* 14:4818, 2022

17. Nicholson BD, Oke J, Virdee PS, et al: Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPPLIFY): A large-scale, observational cohort study. *Lancet Oncol* 24:733-743, 2023
 18. Miller SJ, Sly JR, Rolfo C, et al: Multi-cancer early detection (MCED) tests: Prioritizing equity from bench to bedside. *Health Aff Sch* 2:qxae039, 2024
 19. Deverka PA, Douglas MP, Phillips KA: Multicancer screening tests: Anticipating and addressing considerations for payer coverage and patient access. *Health Aff (Millwood)* 41:383-389, 2022
 20. Gelhorn H, Ross MM, Kansal AR, et al: Patient preferences for multi-cancer early detection (MCED) screening tests. *Patient* 16:43-56, 2023
 21. Redwood DG, Blake ID, Provost EM, et al: Alaska native patient and provider perspectives on the multitarget stool DNA test compared with colonoscopy for colorectal cancer screening. *J Prim Care Community Health* 10:2150132719884295, 2019
 22. Stimpson JP, Pagán JA, Chen LW: Reducing racial and ethnic disparities in colorectal cancer screening is likely to require more than access to care. *Health Aff (Millwood)* 31:2747-2754, 2012
 23. Phillips KA: CMS coverage with evidence development-challenges and opportunities for improvement. *JAMA Health Forum* 3:e223061, 2022
 24. Hoffman RM, Wolf AMD, Raoof S, et al: Multicancer early detection testing: Guidance for primary care discussions with patients. *Cancer* 131:e35823, 2025
 25. Elwyn G, Frosch D, Thomson R, et al: Shared decision making: A model for clinical practice. *J Gen Intern Med* 27:1361-1367, 2012
 26. Selby K, Elwyn G, Volk RJ: Multi-cancer early detection tests, primary care, and shared decision making. *Ann Intern Med* 176:718-720, 2023
 27. Greene MP, Vassy JL: Helping patients understand multi-cancer early detection tests: A scoping review. *Per Med* 21:131-137, 2024
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Survivorship Care for People Affected by Advanced or Metastatic Cancer: Building on the Recent Multinational Association of Supportive Care in Cancer-ASCO Standards and Practice Recommendations

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OVERVIEW

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Although there is a growing number of people living with advanced or metastatic cancer, primarily because of more effective treatment regimens, there are limited estimates of the actual number of people living with advanced or metastatic cancer. Many people will have treatable but not curable cancers, may have survival measured in years, and may have periods on and off therapy. People with advanced or metastatic disease, as well as their families and caregivers, may experience significant unmet needs, overlapping yet distinct to those with potentially curable cancer. Recently, the Multinational Association of Supportive Care in Cancer and ASCO developed standards and practice recommendations relevant to the delivery of quality survivorship care for people living with advanced or metastatic cancer. The recommendations included seven domains: (1) person-centered care; (2) coordinated and integrated care; (3) evidence-based and comprehensive care; (4) evaluated and communicated care; (5) accessible and equitable care; (6) sustainable and resourced care; and (7) research and data-driven care. Immediate priorities to improve clinical care include focusing on (1) discussions regarding prognosis and goals of care; (2) routinely assessing physical, psychological, and social unmet needs with referral to appropriate supportive care services; and (3) creating blended models of care, incorporating elements of palliative care and survivorship services. Additional areas for focus include (1) advocacy and policy; (2) system design and health care delivery; (3) defining, measuring, and managing quality; (4) addressing inequity; and (5) research specifically focused on these cancer populations.

INTRODUCTION

The Office of Cancer Survivorship at the US National Cancer Institute notes that an individual is considered a cancer survivor from the time of diagnosis through the balance of life. There are many types of survivors, including those living with cancer and those free of cancer.^{1,2} Also, noting [t]here is no one face or kind of cancer survivor. Some have been treated for cancer and remain cancer-free, while others continue to live with cancer. The experiences and goals of care for each cancer survivor are unique and dynamic. The figure below depicts one way to think about the different types of cancer survivors, including those diagnosed with early-stage cancer or advanced cancer and those who are diagnosed with or progress to end-stage cancers (Fig 1).^{1,2}

Novel and increasingly effective therapies as well as the early detection of cancers through population-based screening programs have transformed cancer from a disease that was largely incurable to one from which millions of people have

survived. In the United States, 5-year survival from cancer is now 72% and there are an estimated 18 million cancer survivors.^{3,4} As cancer survival has increased, the focus of cancer research and care has expanded from being concerned primarily with keeping people alive to focusing attention on the experience of survival and how well patients live after diagnosis. Cancer survivorship, starting at diagnosis through the end of life, is now an accepted and important part of the cancer research and care continuum.^{1,2}

As the field of cancer survivorship has matured, the heterogeneity of cancer survivors and their unique survivorship needs have emerged and are being increasingly recognized.^{5,6} In addition, the frequent operationalization of cancer survivor to include only those who are in the post-treatment phase is being challenged.⁷⁻⁹ As part of this process, attention is focused on defining and categorizing the diversity of cancer survivors to better understand and address the unique challenges survivors face at different stages of the cancer survivorship trajectory.^{5-7,9} Instead of viewing cancer survivors

PRACTICAL APPLICATIONS

- The prevalence of people living with advanced or metastatic disease is uncertain, but these data are critical for health service planning and research.
- Unmet needs of people affected by advanced or metastatic disease are considerable. They overlap with but are distinct from those with early-stage, potentially curable cancers.
- The Multinational Association of Supportive Care in Cancer and ASCO have developed standards and practice recommendations relevant to best-practice survivorship care of people affected by advanced or metastatic cancer. These resources are available in multiple languages.
- Recommendations to improve the clinical care of people with advanced or metastatic cancer are provided.
- Other areas for focus include advocacy and policy development, health system planning, and greater focus on quality, equity, and research.

collectively as a homogeneous group, various survivorship categories have been proposed, including Mullan's seasons of survivorship (acute, extended, and permanent survival),¹⁰ Surbone's stage-based categories (acute, chronic, long-term, and cured)⁶ and Mollica's goals of care categories (curative intent, intent to prolong life, and end-of-life).⁹

An important and emerging cancer survivorship population are those living with advanced or metastatic cancer (ie, solid

or hematologic malignancies that are treatable but predominantly not curable).^{2,7,8,11} Indeed, one of the authors of this article (A.L.S.) is living with metastatic cancer and expands on her own story in [Box 1](#).

Although cure remains unlikely, novel therapies are extending survival. With gains in survival and improvements in prognosis, goals of care have shifted from palliative and end-of-life care to living well in the extra years afforded by these treatments.^{2,7,12} However, our current survivorship care systems are not designed to provide optimal care for people affected by advanced or metastatic cancers.^{2,7} There are several reasons for this. Our survivorship care systems, including models of care, guidelines, interventions, and services, require evidence, of which relatively little exists specific to the advanced or metastatic survivorship populations.^{2,7,9} To a certain extent, these evidence gaps are understandable, given the emerging nature of these groups.

A fundamental issue is the invisibility of these populations to researchers, funders, and policymakers, due at least partly to lack of data. Reporting on the number of people living with an advanced or metastatic diagnosis has been challenging as most cancer registries do not routinely collect recurrence and restaging data beyond recently introduced recurrence-progression-transformation data in some European countries via the European Network of Cancer Registries.^{13,14} Although the recent Lancet Breast Cancer Commission recognized this issue and urgently called for the collection of staging and recurrence data within all population-based cancer registries, such changes will take time and require significant improvements in cancer registry funding, technology, and infrastructure.¹⁵ In the meantime, estimates of metastatic and advanced cancer prevalence have been made through modeling using the mortality and incidence analysis model¹⁶⁻¹⁸ and through record linkage studies.¹¹ In the United States, substantial increases have been reported in

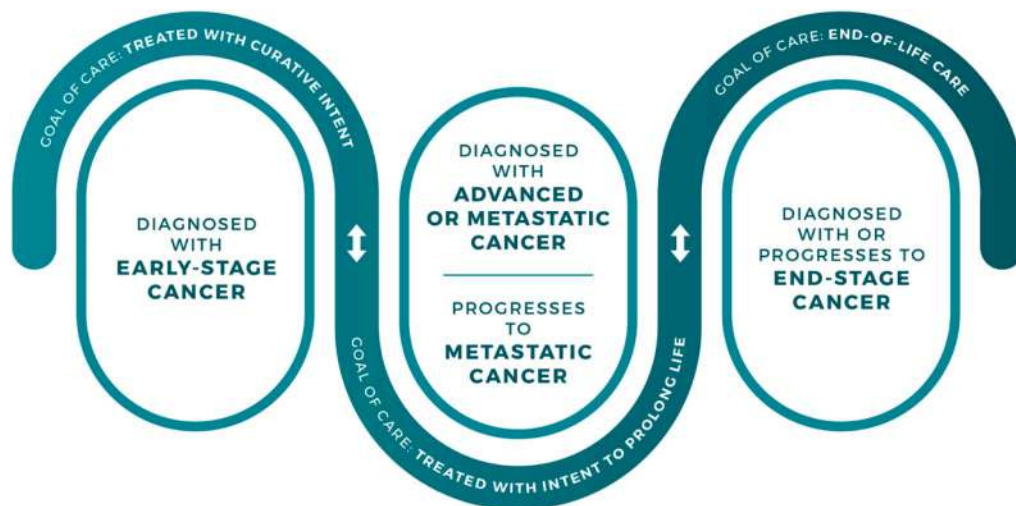


FIG 1. Phases of cancer survivorship: a graphic created by the National Cancer Institute.¹

BOX 1. The Lived Experience of a Metastatic Breast Cancer Survivor—A.L.S.

Being diagnosed with de novo stage IV metastatic breast cancer at age 49 years was devastating. No family history, no warning signs, a healthy active lifestyle. My three girls were age 9, 12, and 14 years. I was within weeks of submitting my PhD and had just started lecturing with the Master of Public Health program at the University of Sydney. Nothing can prepare you for news like this, for grappling with losing your taken-for-granted future, with the realization you are unlikely to see your children finish school, go to university, find partners, and have children.

Among the terror and disbelief surrounding that initial diagnosis, I drew comfort from the knowledge that if you are going to get cancer, then breast cancer is surely the one to get. Fantastic supportive care, well funded, and an enviable community of people with lived experience with whom to connect and learn.

The reality was vastly different. There was an unfathomable disconnect between what my oncologist was telling me and what I experienced on leaving her office. Although she reassured me treatment advances meant I might live for years and that metastatic breast cancer is increasingly treated as a chronic disease, most of the cancer supportive care services I tried to access did not want to know me, did not understand my needs, and could not provide the support I needed. I felt invisible, because, essentially, I was. With no collection of recurrence data, it is impossible to count how many people are living with metastatic breast cancer, or indeed any advanced or metastatic cancer. In the absence of epidemiologic prevalence data, many cancer support services have failed to recognize and respond to the changing cancer survivorship paradigms. No longer can we classify patients with cancer into those who will survive and those who will die. Instead, there are an increasing number of us who will not be cured, but who are not yet actively dying.

Our needs are complex and diverse. Although there is overlap with mainstream survivorship needs, there are also critical differences. Fear of cancer recurrence (or more aptly fear of progression) is not a might happen, but a will happen. Death is a reality not a possibility and existential distress unavoidable. As is the gradual (or not so gradual) functional decline, as our side effect and disease burden increases. For example, now that I'm grappling with extensive and at times debilitating side effects from (my highly effective) antibody-drug conjugate treatment, I look back fondly on my first line of treatment and the excellent quality of life I had. Likewise, financial toxicity never goes away but becomes more distressing: should (can?) I continue to work? But if I don't, I'll need to rely on my savings, and my superannuation/pension will be diminished, and what if I live longer than anticipated? Do I need to keep some savings in case there is a drug I need to access that is not funded by the government? Or for a clinical trial that I might need to travel to access? Or do I instead focus on using my time and money on making memories with my family and friends?

I've personally experienced 9 years of 3-weekly intravenous treatment cycles (150+ cycles). Bloods every 3 weeks, oncologist every 3 weeks, scans every 9 weeks, and echocardiograms every 3 months. Plus an ever-changing lineup of allied health care professionals for my most pressing side effects. Living with an advanced or metastatic cancer diagnosis is expensive, time-consuming, exhausting, and never-ending.

RECOMMENDATIONS

Urgent system-level changes are required if we are to support the growing number of people living long-term with an incurable advanced or metastatic cancer diagnosis. In particular:

1. The recognition that people with advanced or metastatic cancer are a distinct subpopulation with unique supportive care needs and that they should be prioritized within state and national cancer plans.
2. Data regarding the number of people living with advanced and metastatic disease are needed to support health service planning.
3. The identification of structural barriers to equitable access to survivorship care for people with advanced or metastatic cancer.
4. Building capacity, knowledge, and understanding (at the system level) among our cancer organizations and health care professionals about who we are and what our needs are.
5. The development of new models of care that blend elements of survivorship and palliative care; this will require research and funding targeted specifically at those with advanced or metastatic cancer to develop the evidence base to inform these new models of care.

The newly developed Multinational Association of Supportive Care in Cancer-ASCO care standards and practice recommendations are likely to play a critical role in driving equitable access to care and the development of national and local models of care for people with advanced or metastatic cancer.

the number of survivors with metastatic cancer for the six most common cancers (breast, prostate, bladder, lung, melanoma, and colorectal) between 1990 and 2018 (estimate for 2018, $n = 623,405$; projection for 2025, $n = 693,452$).¹⁷ In the United Kingdom, linkage of existing health record data led to an estimate of 162,561 people living with treatable but not curable cancer (a cancer that is highly unlikely to be eradicated and that, in the absence of other more imminent causes of death, is highly likely to lead to death).¹¹ An advantage of algorithmic approaches using linked health record data sets over modeling is that this can potentially provide comprehensive demographic and clinical characteristics of the advanced or metastatic cancer populations.

A closely related research issue is the inability to identify people with stage IV or recurrent/relapsed disease within many large health-related and cancer-specific databases and national cross-sectional surveys of cancer survivors.^{2,19} Without this information, it is challenging for researchers to identify those living with advanced or metastatic cancer for epidemiologic research into factors associated with longer-term survival or quality of life after an advanced or metastatic diagnosis.

SUPPORTIVE CARE NEEDS OF PEOPLE AFFECTED BY ADVANCED OR METASTATIC CANCER

People affected by advanced or metastatic cancer often have complex and diverse care needs. These needs are often reported in the context of inconsistent and unreliable health systems and challenges navigating unpredictable disease and treatment trajectories.²⁰ Consequently, people affected by advanced or metastatic cancer often report significant unmet care needs²¹ including access to financial support; receiving timely and necessary health information; engaging

with complex health systems and health care teams; uncertainty, fear, and other psychological concerns; and pain, physical deterioration, fatigue, and other physical concerns (Fig 2).²¹

Domains of unmet care needs transcend the disease trajectory (ie, early-stage with curative intent; advanced-stage with treatment-intent; and end-stage with palliative-intent); however, it is the underlying experiences within these domains that differ in their characteristics (ie, nature, frequency, and intensity of their presentation) along with different causal or contributing factors that are unique for people affected by advanced or metastatic cancer.²¹ For example, these individuals require more frequent and prolonged interactions with the health system^{22,23}; have greater challenges obtaining health, life, and travel insurance^{24,25}; encounter barriers accessing disability support; experience discrimination and stigma relating to maintaining or returning to work living with, or caring for someone with, a life-limiting illness^{26,27}; confront the reality of living life while also preparing for death (walking two roads)²⁸; traverse the requirements of cancer treatment together with the needs of survivorship and palliative care systems; experience complex toxicity profiles ranging from cumulative low-grade to sudden high-grade toxicities; receive multimodal and sequential treatment regimens; and consequently must manage intense psychological and existential burdens²⁹ such as a fear of cancer progression, uncertainty about prognosis, legacy building, worry for family and friends,³⁰ and compassion fatigue experienced by caregivers.³¹ Inevitably, the scale and magnitude of unmet needs in these populations will vary worldwide across various health care systems and resource settings, and are products of individual-level and system-level barriers and enablers.^{32,33} Accordingly, there is a clear need for standardized approaches to survivorship care

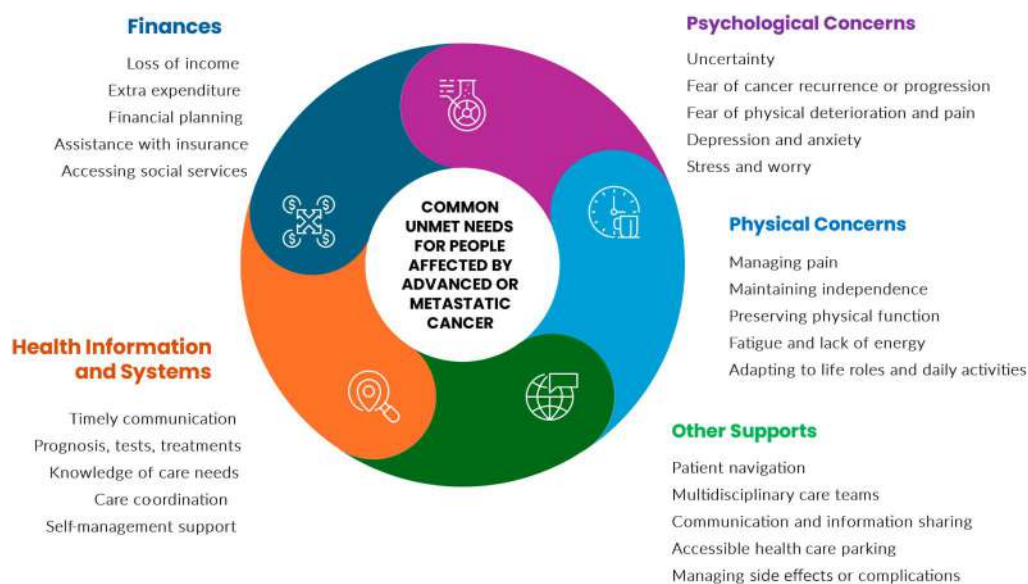


FIG 2. Common unmet needs for people affected by advanced or metastatic cancer.²¹

for people affected by advanced or metastatic cancer that promote quality and consistency of care, as well as an expected standard of care worldwide.⁷

MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER-ASCO STANDARDS AND PRACTICE RECOMMENDATIONS

Recognizing current survivorship care models are not designed nor well prepared to provide quality survivorship care for people affected by advanced or metastatic cancers, the Multinational Association of Supportive Care in Cancer (MASCC) and ASCO developed a set of international survivorship care standards with underlying objectives each supported by a series of practice recommendations for the provision of quality survivorship care for people affected by advanced or metastatic cancer.^{34,35} These standards were designed to support the optimization of care experiences and health outcomes by providing practice recommendations within each standard to be adopted by a variety of stakeholders (ie, cancer survivors, caregivers, health professionals, health care leaders and administrators, policy-makers, health ministries, and governments worldwide) that inform best-practice clinical care, and advance research, policy, and advocacy around cancer survivorship for those with advanced or metastatic cancer.

To ensure broad representativeness, appropriateness, applicability, and suitability, the MASCC-ASCO standards and practice recommendations were iteratively developed through a staged process, including (1) a systematic review involving 81 studies reporting unmet supportive care needs of people affected by advanced or metastatic cancer²¹; and (2) a scoping review of 17 cancer survivorship, supportive care, and palliative care frameworks and guidelines^{34,35}; that

informed idea generation for (3) an international modified Delphi consensus process to establish consensus among 77 experts (>10% were people with lived experience) across 33 countries (33% were low- to middle-resource countries). This process resulted in the development of seven care standards and objectives underpinned by 45 practice recommendations required to achieve them.^{34,35} These are available in 14 languages. Collectively, the standards represent core principles of quality health care, providing headline and easy-to-remember domains of care that guide routine care provision. Each care standard was contextualized to the advanced or metastatic cancer setting through its defined objective and descriptive line-item practice recommendations, which serve to provide vision, purpose, and instruction to stakeholders who oversee, resource, provide, or receive survivorship care (Fig 3).

Person-centered care recognizes people affected by advanced or metastatic cancer as individuals with agency and partners in cancer care who are embedded within trusted health systems that respond to their unique needs. Practice recommendations to achieve this includes routine screening for supportive care and unmet care needs; survivorship care planning; person-reported outcome and experience measures; self-management strategies and support; recognizing personal agency and shared decision making; and evaluation of financial needs with appropriate supports. *Coordinated and integrated care* focuses on the continuity of care, coordination of care, and integration of health services across survivorship and palliative care phases. Practice recommendations include patient navigation; early referral to multidisciplinary and interprofessional supportive care services; team-care arrangements; timely referral to specialist palliative care if indicated; models of care suitable to the needs and preferences of people affected by advanced or

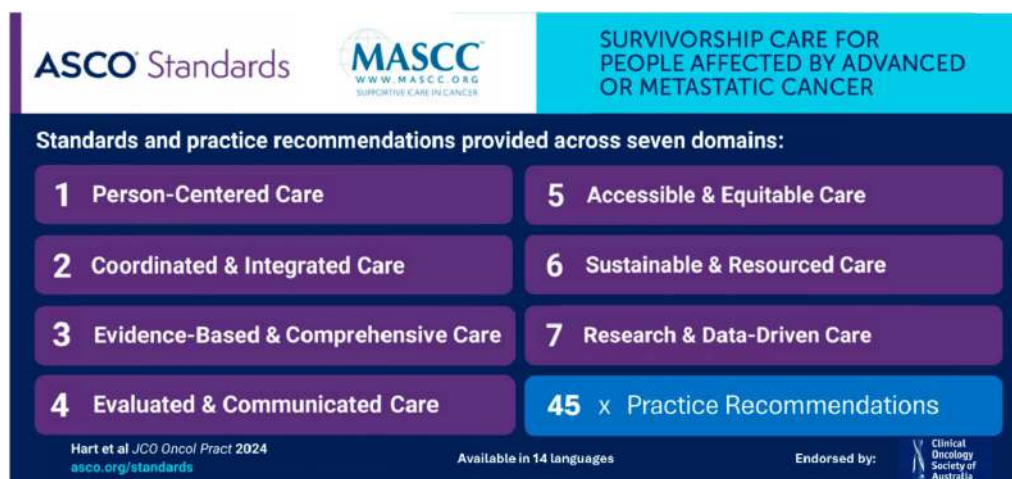


FIG 3. Graphical summary of the seven standards^{34,35} by MASCC and ASCO, and endorsed by the Clinical Oncology Society of Australia, available in 14 languages. Standards and objectives are underpinned by 45 practice recommendations, and accompanied by tools and resources online at ASCO.³⁶ MASCC, Multinational Association of Supportive Care in Cancer.

metastatic cancer; care plans to facilitate transition of care where required; and models of peer-support via community and support groups. *Evidence-based and comprehensive care* promotes up-to-date evidence-based clinical best practice embedded in comprehensive supportive care systems informed by professional development and education. Practice recommendations to achieve this include use of evidence-informed supportive care interventions supported by high-quality research; multidisciplinary and interprofessional supportive care practices; education and professional development of health professionals; and the inclusion of lived experience of people affected by cancer into education materials.

Evaluated and communicated care focuses on systematic monitoring of supportive care needs underpinned by timely and effective multilateral communication. Practice recommendations to achieve this include repeat assessments of supportive care interventions with referrals; clear and timely communication processes between health care professionals, providers, and people affected by cancer; routine objective and subjective evaluations of supportive care needs, outcomes, and experiences; secure medical records accessible on demand by health professionals; and care settings that routinely engage in service evaluation and quality improvement activities. *Accessible and equitable care* requires models of care that purposefully ensure quality of care does not vary because of personal, cultural, or religious factors. Practice recommendations include delivery of consistent high-quality supportive care regardless of personal factors while respecting cultural and spiritual needs; care models and modalities that optimize accessibility and safety (eg, virtual care); inclusive and innovative supportive care that eliminates disparities; and facilitation of access to financial and legal assistance to guide financial literacy. *Sustainable and resourced care* ensures that models of survivorship care are sustainably designed to deliver value-based quality care in a cost-effective and clinically meaningful way. Practice recommendations to achieve this include stepped care approaches matching intensity and acuity of care needs to the level of care required; properly resourced care settings; routine evaluation of supportive care services at all organizational levels; care settings with leadership that value and invest in supportive care; delivery of resource-stratified care; and access to care models that are clinically and cost-effective supported by adequate financial investment. *Research and data-driven care* promotes quality and efficiency in survivorship care through well-designed, properly funded research within established systems for data capture and information sharing. Practice recommendations to achieve this include involving people affected by advanced or metastatic cancer in codesign, participation, and transition from clinical trials addressing survivorship care; information and support to access all available clinical trials; evaluation using cross-cultural standardized tools; global data capture and storage harmonization; routine capture of experience, treatment, and outcome data; realized benefits of research into survivorship care; and the storage of

deidentified data into data repositories to facilitate future research and health service evaluations.

IMPLEMENTING THE SURVIVORSHIP CARE STANDARDS AND PRACTICE RECOMMENDATIONS

The MASCC-ASCO standards and practice recommendations were explicitly developed for implementation in low-, middle-, and high-resource countries, acknowledging that resourcing, capacity, and capability differ greatly, worldwide.^{32,33} In particular, the intent of this product is to set a consistent standard of care to aspire toward, as it is recognized that very few, if any, hospitals or health care providers worldwide would be currently achieving or able to achieve all practice recommendations within all standards of care. Instead, this product can be used to perform an assessment of quality care provision within the context of each stakeholder (Fig 4). The standards and practice recommendations are a first step toward improving survivorship care for people affected by advanced or metastatic cancer and set the foundation for future work. At the individual level, the product supports health care professionals to identify the quality of survivorship care they are currently providing and identify which areas of practice they can adopt today, which areas of practice they can reasonably adopt in the future, and areas of practice that require some level of investment (training, education, time, and financial) to further improve quality care provision in the long term. Similarly, the standards and recommendations support people affected by advanced or metastatic cancer by enabling them to better understand what quality survivorship care looks like, improving their health literacy, and facilitating self-advocacy efforts for their own care needs.

At the system level, the MASCC-ASCO product enforces the notion that quality provision of survivorship care requires a whole-of-system care approach involving transdisciplinary care models that are not reliant on a single health care profession or professional within a given service. Of particular importance is the recognition that many tasks can be performed by multiple health care professionals, permitting flexibility across different resource settings. For example, high-resource countries and communities may have larger workforces with narrower scopes of accreditation across various professions to perform clearly defined tasks within a tightly regulated scope of practice. By contrast, low- and middle-resource countries and communities may have limited budgets with smaller workforces performing broader tasks as generalists to meet the needs of people affected by advanced or metastatic cancer. Accordingly, the MASCC-ASCO standards and practice recommendations afford health care settings the flexibility to self-assess and select the most appropriate care models and operational structure on the basis of local workforce availability and infrastructure. Beyond this, health care leaders and administrators, policy-makers, health ministries, and other government agencies can use the standards and practice recommendations to guide health service planning, by understanding what areas of resourcing and investment can be targeted for short-,



FIG 4. Potential uses of the standards and practice recommendations by various stakeholders.

middle-, and long-term strategic benefit and health care improvements, including the ability to identify which professions to establish, develop, or expand to enhance system capability and capacity.

CHANGING THE SURVIVORSHIP PARADIGM FOR PEOPLE AFFECTED BY ADVANCED OR METASTATIC CANCER IN CLINICAL SETTINGS

To address the care complexities of individuals affected by advanced or metastatic cancer, it is essential to adapt the survivorship care model and its areas of focus.⁷ Here, we suggest recommendations that can be pursued in clinical practice, almost immediately.

Regular Discussions Regarding Prognosis and Goals of Care

MASCC-ASCO standard 1 (person-centered care) emphasizes the importance of providing clear, timely prognostic information so that people's goals of care, life goals and personal agency (is) respected and supported through shared decision making throughout their disease trajectory.^{34,35,37,38} Communicating about prognosis with primary care professionals is also critical to inform appropriate non-cancer-related care (such as screening for other cancers, management of chronic medical conditions, and health promotion), and is reflected in the MASCC-ASCO recommendation 4.2 (clear and timely communication processes, adopted by and between their health care providers).^{34,35} Other health care professionals, such as medical specialists and rehabilitation clinicians, would also benefit from understanding prognostic information. If a person's prognosis is deemed poor, early involvement of palliative care or end-of-life clinicians would be appropriate.

Guidelines and tools have been developed to assist clinicians with prognostication, although the extent to which they are

used in clinical practice is not clear.^{39,40} It is also important to acknowledge that tools previously developed on the basis of outdated historical registry and treatment data may no longer be correct, particularly for those living with advanced or metastatic cancer. Further work is required to improve prognostic estimates for people with advanced or metastatic cancer, as well as health care professional education to improve prognostic discussions. As people are living longer with advanced and metastatic cancer, it will also be important to evaluate and communicate the potential role and benefit of surveillance for prior cancers that have been previously treated, chronic disease management (eg, control of diabetes, obesity, etc), screening for other cancers (eg, mammography for women living with advanced melanoma), and other domains of cancer survivorship care.

Assess Physical and Psychological Unmet Needs and Refer to Appropriate Supportive Care Services

MASCC-ASCO standard 1 (person-centered care) highlights the importance of incorporating regular, proactive screening for physical and psychosocial needs, ideally using validated patient-reported outcomes (PROs) and measures. The use of PROs in routine cancer care is recommended internationally and its use is increasing.⁴¹ However, in people with advanced or metastatic cancer, specific challenges may arise. For example, patient-reported symptoms may be due to cancer, its treatment, or an unrelated medical condition, and a broad view of potential etiologies should be retained.

Screening for physical and psychosocial needs should trigger a review with an appropriate health care professional to address these needs.^{34,35,42,43} This can also facilitate triaging and referral to appropriate services, so that those with the greatest level of unmet need might access services delivered by specialist cancer centers, while those with less complex needs might be able to be referred to nongovernment organizations or community groups.⁴⁴ Services and resources

should be tailored to the unique requirements of these populations to ensure they are affordable, acceptable, available, and appropriate.^{34,35} Where possible, self-management should be encouraged with consideration of the person's health literacy.⁴⁵ This may incorporate an element of peer support.^{34,35,46} A tailored approach assessing self-management capabilities, attitudes, and preferences is warranted.

Create Blended Models of Care, Incorporating Elements of Palliative Care and Survivorship Services

Novel models of care for people living with advanced or metastatic cancer should incorporate elements of both palliative care and survivorship care. Although both disciplines emphasize person-centered care and promote shared decision making, palliative care focuses on addressing acute physical and emotional needs, prognostic discussions, and addressing spiritual and existential concerns. By contrast, the strengths of survivorship care include addressing longer-term physical and psychosocial challenges, managing comorbidities, and a focus on surveillance for new malignancies.⁴⁷⁻⁴⁹ Early access to palliative care is an essential component of comprehensive cancer care for many people living with advanced or metastatic cancer.⁵⁰ However, it is important to recognize that palliative care services may not meet the needs of those living with advanced or metastatic cancer, for example, those who may be experiencing and/or need monitoring for potential late and long-term effects from previous treatments. Furthermore, people living with advanced or metastatic cancer may have had previous cancers that may still require surveillance.

Finally, current models of palliative, supportive, and survivorship care are not uniformly defined and organized within health care systems. Although some survivorship programs may offer services to those with advanced or metastatic cancer, others are specifically targeting those with early-stage or treatable cancers (Box 1). Although some palliative care programs offer supportive care, others focus mainly on end of life. This lack of standardization further leads to confusion for clinicians, patients, and their caregivers. Although standardization across health care systems may not be possible, programs should clearly define their services and work across silos to provide the needed services for those living with advanced or metastatic cancers.

New models should prioritize equitable access to tailored services designed to address the unique needs of individuals with advanced or metastatic cancer and their caregivers. The importance of accessible, equitable models of survivorship care is emphasized in the MASCC-ASCO standard 5 (accessible and equitable care).^{34,35} Examples include specialized survivorship nurses for those with advanced or metastatic cancer^{51,52} and peer support programs,⁴⁶ which aligns with MASCC-ASCO recommendation 2.7 (offer models of peer support through support groups and other community-led organizations).

SYSTEM CONSIDERATIONS IN ADVANCED OR METASTATIC CANCER SURVIVORSHIP

The 2006⁵³ and 2013⁵⁴ Institute of Medicine (IOM) recommendations on survivorship care provide a robust framework for considering priorities for clinical care, policy, and research in metastatic survivorship.⁷ Although these reports did not specifically address people living with advanced or metastatic cancer, both reports provide broad recommendations for how to improve survivorship care.

Advocacy and Policy

The 2006 IOM report emphasized raising awareness of cancer survivorship as a public health issue. However, most cancer plans lack specific objectives regarding advanced and metastatic cancers. At the community level, collaboration between cancer centers, academic institutions, and community organizations can increase awareness of therapeutic advances, treatment toxicities, employment and financial challenges, and care models. Policymakers should incorporate metastatic survivorship into cancer plans and implement measures to address the vocational, rehabilitative, and financial needs of these patients.

System Capacity and Health Care Delivery

The IOM reports emphasized building health care providers' skills and knowledge about treatment advances and toxicities. Professional cancer organizations such as ASCO and the European Society for Medical Oncology should incorporate metastatic survivorship into professional development curricula.⁵⁵ At a system level, MASCC-ASCO standard 6 focuses on building capacity for delivering metastatic survivorship care through leadership that value(s), support(s), facilitate(s), and invest(s) in supportive care (6.3) and adequate financial investment (6.6).^{34,35}

Developing learning health care systems can enhance real-time data analysis and enable consistent collection of PROs and experiences,⁵⁴ improving symptom management and survivorship care. This will provide much needed data regarding the prevalence, frequency, and trajectory of symptoms and unmet care needs, directing symptom science research, and guiding management of chronic treatment-related toxicities.^{7,56}

Defining, Measuring, and Managing Quality

Quality care metrics for metastatic survivorship care require input from diverse stakeholders, including people with direct lived experience, caregivers, providers, and policymakers. Collaborative efforts, such as the MASCC-ASCO standards and practice recommendations, are critical to establishing global standards. Integrating these metrics into clinical practice guidelines will promote consistent adoption of best

practice. The MASCC-ASCO recommendations 4.5 and 6.3 emphasize the importance of embedding routine evaluation and quality improvement activities into services for people living with advanced or metastatic cancer.^{34,35}

Addressing Inequity

Equitable access to survivorship care is a central theme of both of the IOM reports,^{53,54} the 2020 ASCO report on cancer disparities and health equity,⁵⁷ and MASCC-ASCO recommendation 5 (accessible and equitable care). Addressing disparities in access, clinical trial participation, identification and management of structural barriers, and promotion of awareness and action regarding disparities should also be applied to the care of those with advanced or metastatic cancer. Although there are a number of factors associated with inequity in cancer outcomes and care (eg, geography, ethnicity, and health literacy^{58,59}), financial toxicity is a particular challenge for those with advanced or metastatic cancer, as ongoing treatment disrupts employment and increases financial strain.^{2,21} Specific measures to address financial toxicity are noted in MASCC-ASCO recommendation 5.7, including providing access to financial navigators or social workers to access financial assistance and provide guidance in financial literacy.⁶⁰ Policies to improve insurance and disability support are necessary to meet the needs of a population living longer with metastatic disease and accumulating functional limitations.⁶¹

Research

Advanced or metastatic cancer survivorship research is essential to address the evolving needs of this population^{2,56,62} and is specifically addressed in MASCC-ASCO standard 7 (research and data-driven care),^{34,35} with numerous areas of research identified in Table 1. To further bridge this gap, MASCC is currently conducting a global Delphi consensus process to establish research priorities (building on Mollica and colleagues' areas of research needs^{2,9}) with an intent to stratify priorities by low-, middle-, and high-resource countries and communities that may prioritize survivorship care needs differently. It is anticipated that this work, together with the MASCC-ASCO standards and practice recommendations, will highlight the importance of uniquely and systematically addressing the needs of people affected by advanced or metastatic cancer.

Critically, researchers need to be supported and encouraged to recruit those with an advanced or metastatic diagnosis to interventional research studies to understand whether symptom management and health behavior modification interventions designed for cancer survivors in general are effective for those with advanced or metastatic cancer or whether they need to be adapted. In addition, the involvement of people with lived experience (cancer survivors and caregivers) is vital for identifying survivorship needs, developing innovative care models, and supporting caregivers,²¹ and MASCC-ASCO standard 7 specifically calls for

TABLE 1. Identified Key Research Areas for People With Advanced or Metastatic Cancers (adapted from Mollica et al²⁹)

Research Priority	Examples
Epidemiology	Identifying new methods of using existing data sources, such as cancer registries, to better estimate the number of people living with metastatic disease; developing novel methods for capturing, monitoring, and managing symptoms; and integrating clinical, genomic, and lifestyle factors with outcomes in this group of cancer survivors
Symptom management	Identifying those with the greatest symptom burden, describing factors that contribute to symptom burden, and understanding mechanisms of symptoms including those associated with novel therapies
Psychosocial aspects	Describing psychosocial needs, creating survivor- and caregiver-centric models of holistic care, and developing interventions to improve coping and address psychosocial/existential needs
Health care delivery	Describing care patterns and unmet caregiver needs across the disease trajectory, identifying and addressing provider barriers to delivering quality survivorship care, and developing and testing innovative models of care
Health behaviors	Identifying existing sources of data on health behavior in this patient group, determining whether interventions for health behaviors in other cancer survivor populations can be adapted for this patient group, and assessing patient and provider preferences on having health behavior discussion with this group of cancer survivors
Targeted grant funding	Need for advanced and metastatic cancer studies examining symptom trajectories, innovative models of care, the impact of newer therapies on survivor needs, financial hardship, and caregiver support

their involvement in codesign of research and as participants in studies focused on addressing cancer care. Additionally, clinical trials should promote equitable participation, including among underrepresented groups,^{21,57,59,63} to enhance data diversity and relevance. Special focus should be paid to aging populations⁵⁴ and culturally and linguistically diverse groups, such as Asian patients with metastatic epidermal growth factor receptor-mutant non-small cell lung cancer,^{64,65} to improve outcomes across various groups.

CONCLUSION

There is a growing, though poorly quantified number of people living with advanced or metastatic cancer. People with advanced or metastatic disease, as well as their families and caregivers, may experience significant unmet needs, overlapping yet distinct to those with potentially curable

cancer. MASCC and ASCO have developed standards and practice recommendations relevant to the delivery of quality survivorship care for people living with advanced or metastatic cancer, which can be used to assess current care and guide future plans. We have suggested areas for immediate clinical priority, as well as focus areas relating to advocacy and policy, system delivery, and research.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- National Cancer Institute. <https://cancercontrol.cancer.gov/ocs/definitions>
- Mollica MA, Smith AW, Tonorez E, et al: Survivorship for individuals living with advanced and metastatic cancers: National Cancer Institute meeting report. *J Natl Cancer Inst* 114:489-495, 2022
- Miller KD, Nogueira L, Devasia T, et al: Cancer treatment and survivorship statistics, 2022. *CA Cancer J Clin* 72:409-436, 2022
- Tonorez E, Devasia T, Mariotto AB, et al: Prevalence of cancer survivors in the United States. *J Natl Cancer Inst* 116:1784-1790, 2024
- Miller KD, Pandey M, Jain R, et al: Cancer survivorship and models of survivorship care: A review. *Am J Clin Oncol* 38:627-633, 2015
- Surbone A, Tralongo P: Categorization of cancer survivors: Why we need it. *J Clin Oncol* 34:3372-3374, 2016
- Lai-Kwon J, Heynemann S, Hart NH, et al: Evolving landscape of metastatic cancer survivorship: Reconsidering clinical care, policy, and research priorities for the modern era. *J Clin Oncol* 41:3304-3310, 2023
- Langbaum T, Smith TJ: Time to study metastatic-cancer survivorship. *N Engl J Med* 380:1300-1302, 2019
- Mollica MA, Tesaro G, Tonorez ES, et al: Current state of funded National Institutes of Health grants focused on individuals living with advanced and metastatic cancers: A portfolio analysis. *J Cancer Surviv* 15:370-374, 2021
- Mullan F: Seasons of survival: Reflections of a physician with cancer. *N Engl J Med* 313:270-273, 1985
- White R, Stanley F, Than J, et al: Treatable but not curable cancer in England: A retrospective cohort study using cancer registry data and linked data sets. *BMJ Open* 11:e040808, 2021
- Nekhlyudov L, Mollica MA, Jacobsen PB, et al: Developing a quality of cancer survivorship care framework: Implications for clinical care, research, and policy. *J Natl Cancer Inst* 111:1120-1130, 2019
- Morgan E, O'Neill C, Bardot A, et al: Collecting long-term outcomes in population-based cancer registry data: The case of breast cancer recurrence. *JCO Glob Oncol* 10:1200/GO-24-00249
- European Network of Cancer Registries: ENCR recommendations: Recording recurrence, progression and transformation episodes, 2025. https://www.enrcr.eu/sites/default/files/Recommendations/ENCR_Recording-Recurrence-Progression-Transformation_EN_Feb2025.pdf
- Coles CE, Earl H, Anderson BO, et al: The Lancet Breast Cancer Commission. *Lancet* 403:1895-1950, 2024
- Clements MS, Roder DM, Yu XQ, et al: Estimating prevalence of distant metastatic breast cancer: A means of filling a data gap. *Cancer Causes Control* 23:1625-1634, 2012
- Galluccio L, Devasia TP, Tonorez E, et al: Estimation of the number of individuals living with metastatic cancer in the United States. *J Natl Cancer Inst* 114:1476-1483, 2022
- Gogate A, Wheeler SB, Reeder-Hayes KE, et al: Projecting the prevalence and costs of metastatic breast cancer from 2015 through 2030. *JNCI Cancer Spectr* 5:pkab063, 2021
- Doose M, Mollica MA, Attai DJ, et al: Identifying and describing cancer survivors: Implications for cancer survivorship research and clinical care. *Cancer* 128:383-390, 2022
- Rimmer B, Crowe L, Todd A, et al: Assessing unmet needs in advanced cancer patients: A systematic review of the development, content, and quality of available instruments. *J Cancer Surviv* 16:960-975, 2022
- Hart NH, Crawford-Williams F, Crichton M, et al: Unmet supportive care needs of people with advanced cancer and their caregivers: A systematic scoping review. *Crit Rev Oncol Hematol* 176:103728, 2022
- Brooks GA, Cronin AM, Uno H, et al: Intensity of medical interventions between diagnosis and death in patients with advanced lung and colorectal cancer: A CanCORS analysis. *J Palliat Med* 19:42-50, 2016
- Luta X, Diemberger K, Bowden J, et al: Intensity of care in cancer patients in the last year of life: A retrospective data linkage study. *Br J Cancer* 127:712-719, 2022
- Lim JHC, Keenan C, Flaherty GT: All my life to live: Travel health benefits and risks for cancer survivors. *J Travel Med* 29:taac069, 2022
- Rotter J, Spencer JC, Wheeler SB: Financial toxicity in advanced and metastatic cancer: Overburdened and underprepared. *JCO Oncol Pract* 15:e300-e307, 2019
- Beerd DCE, Zegers AD, van Andel ES, et al: Experiences and perspectives of patients with advanced cancer regarding work resumption and work retention: A qualitative interview study. *Support Care Cancer* 30:9713-9721, 2022
- Tevaarwerk AJ, Lee JW, Terhaar A, et al: Working after a metastatic cancer diagnosis: Factors affecting employment in the metastatic setting from ECOG-ACRIN's Symptom Outcomes and Practice Patterns study. *Cancer* 122:438-446, 2016

28. Arantzamendi M, García-Rueda N, Carvajal A, et al: People with advanced cancer: The process of living well with awareness of dying. *Qual Health Res* 30:1143-1155, 2020
29. Wang Z, Xu D, Yu S, et al: Effectiveness of meaning-centered interventions on existential distress and mental health outcomes in cancer survivors and their family caregivers: A systematic review and meta-analysis of randomized controlled trials. *Worldviews Evid Based Nurs* 22:e12752, 2025
30. Rodríguez-González A, Velasco-Durantez V, Martín-Abreu C, et al: Fatigue, emotional distress, and illness uncertainty in patients with metastatic cancer: Results from the prospective NEOETIC_SEOM study. *Curr Oncol* 29:9722-9732, 2022
31. Orbay I, Baydur H, Uçan G: Compassion fatigue in informal caregivers of children with cancer; a section from Turkey. *Soc Work Public Health* 37:729-743, 2022
32. Hart NH, Stout NL, Haywood D, et al: World Health Organization package of interventions for rehabilitation for cancer: A MASCC-endorsed resource for global action to address unmet rehabilitation needs of people affected by cancer. *Support Care Cancer* 32:417, 2024
33. Signorelli C, Hart NH, Mullen L, et al: Aligning the World Health Organization's (WHO) package of interventions for rehabilitation for cancer with the mission of the International Psycho-Oncology Society's: Promoting psychosocial care for all people affected by cancer. *J Psychosoc Oncol Res Pract* 6:144, 2024
34. Hart NH, Nekhlyudov L, Smith TJ, et al: Survivorship care for people affected by advanced or metastatic cancer: MASCC-ASCO standards and practice recommendations. *JCO Oncol Pract* 20:1160-1172, 2024
35. Hart NH, Nekhlyudov L, Smith TJ, et al: Survivorship care for people affected by advanced or metastatic cancer: MASCC-ASCO standards and practice recommendations. *Support Care Cancer* 32:313, 2024
36. American Society of Clinical Oncology: Survivorship Care for People Affected by Advanced or Metastatic Cancer Standards. 2024. <https://asco.org/practice-patients/cancer-care-standards/survivorship-care-people-affected-advanced-or-metastatic>
37. Moth EB, Stockler MR, Kiely BE: Estimating prognosis in advanced cancer: Time to embrace uncertainty. *J Geriatr Oncol* 13:389-390, 2022
38. Vasista A, Stockler MR, Martin A, et al: Communicating prognostic information: What do oncologists think patients with incurable cancer should be told? *Intern Med J* 50:1492-1499, 2020
39. Clayton JM, Hancock KM, Butow PN, et al: Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers. *Med J Aust* 186:S77-S105, 2007
40. Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. *J Clin Oncol* 35:3618-3632, 2017
41. Di Maio M, Basch E, Denis F, et al: The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO Clinical Practice Guideline. *Ann Oncol* 33:878-892, 2022
42. Le Bouillier C, Jeyasingh-Jacob J, Jones L, et al: Improving personalised care and support planning for people living with treatable-but-not-curable cancer. *BMJ Open Qual* 12:e002322, 2023
43. Presley CJ, Arrato NA, Shields PG, et al: Functional trajectories and resilience among adults with advanced lung cancer. *JTO Clin Res Rep* 3:100334, 2022
44. Brick RS, Gallicchio L, Mollica MA, et al: Survivorship concerns among individuals diagnosed with metastatic cancer: Findings from the Cancer Experience Registry. *J Cancer Surviv* 10.1007/s11764-024-01573-8 [epub ahead of print on April 9, 2024]
45. Howell D, Mayer DK, Fielding R, et al: Management of cancer and health after the clinic visit: A call to action for self-management in cancer care. *J Natl Cancer Inst* 113:523-531, 2021
46. Li Z, Laginha KJ, Boyle F, et al: Professionally led support groups for people living with advanced or metastatic cancer: A systematic scoping review of effectiveness and factors critical to implementation success within real-world healthcare and community settings. *J Cancer Surviv* 10.1007/s11764-023-01515-w [epub ahead of print on January 8, 2024]
47. Geerse OP, Lakin JR, Berendsen AJ, et al: Cancer survivorship and palliative care: Shared progress, challenges, and opportunities. *Cancer* 124:4435-4441, 2018
48. Sedhom R, Bates-Pappas GE, Feldman J, et al: Tumor is not the only target: Ensuring equitable person-centered supportive care in the era of precision medicine. *Am Soc Clin Oncol Educ Book* 44:e434026, 2024
49. Stegmann ME, Geerse OP, van Zuylen L, et al: Improving care for patients living with prolonged incurable cancer. *Cancers* 13:2555, 2021
50. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 35:96-112, 2017
51. Lai-Woon J, Kelly B, Lane S, et al: Feasibility, acceptability, and utility of a nurse-led survivorship program for people with metastatic melanoma (MELCARE). *Support Care Cancer* 30:9587-9596, 2022
52. Warren M, Mackie D, Leary A: The complexity of non face-to-face work with patients affected by metastatic breast cancer and their carers. The 'hidden consultations' of the clinical nurse specialist. *Eur J Oncol Nurs* 16:460-464, 2012
53. National Research Council: From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC, The National Academies Press, 2006
54. Committee on Improving the Quality of Cancer Care: Addressing the Challenges of an Aging Population; Board on Health Care Services; Institute of Medicine, et al (eds): Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis. Washington, DC, National Academies Press, 2013
55. Shapiro CL, Jacobsen PB, Henderson T, et al: ReCAP: ASCO core curriculum for cancer survivorship education. *JCO Oncol Pract* 12:145, e108-e117, 2016
56. Smith AL, Hart NH, Jefford M, et al: Survivorship research for people with metastatic or advanced cancer: A time for action. *Asia Pac J Oncol Nurs* 9:185-186, 2022
57. Patel MI, Lopez AM, Blackstock W, et al: Cancer disparities and health equity: A policy statement from the American Society of Clinical Oncology. *J Clin Oncol* 38:3439-3448, 2020
58. Aranda S, Jefford M: Social inequity and cancer. *Asia Pac J Oncol Nurs* 10:100178, 2023
59. Islami F, Baeker Bispo J, Lee H, et al: American Cancer Society's report on the status of cancer disparities in the United States, 2023. *CA Cancer J Clin* 74:136-166, 2024
60. Chan RJ, Milch VE, Crawford-Williams F, et al: Patient navigation across the cancer care continuum: An overview of systematic reviews and emerging literature. *CA Cancer J Clin* 73:565-589, 2023
61. Nekhlyudov L, Campbell GB, Schmitz KH, et al: Cancer-related impairments and functional limitations among long-term cancer survivors: Gaps and opportunities for clinical practice. *Cancer* 128:222-229, 2022
62. Crawford-Williams F, Koczwara B, Chan RJ, et al: Defining research and infrastructure priorities for cancer survivorship in Australia: A modified Delphi study. *Support Care Cancer* 30:3805-3815, 2022
63. Pierce L: ASCO's commitment to addressing equity, diversity, and inclusion of Black cancer patients and survivors. *JCO Oncol Pract* 17:255-257, 2021
64. Kawaguchi T, Matsumura A, Fukai S, et al: Japanese ethnicity compared with Caucasian ethnicity and never-smoking status are independent favorable prognostic factors for overall survival in non-small cell lung cancer: A collaborative epidemiologic study of the National Hospital Organization Study Group for Lung Cancer (NHSGLC) in Japan and a Southern California Regional Cancer Registry databases. *J Thorac Oncol* 5:1001-1010, 2010
65. Ou SH, Zogas A, Zell JA: Asian ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. *J Thorac Oncol* 4:1083-1093, 2009

Incorporating Targeted Therapy Into Neuro-Oncology Practice

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OVERVIEW

The integration of targeted therapies into neuro-oncology is revolutionizing the management of primary CNS malignancies. Advances in sequencing technologies and the incorporation of molecular alterations into CNS tumor classification have led to more precise tumor prognosis and enabled the identification of actionable oncogenic drivers. However, challenges such as drug delivery, tumor and microenvironment heterogeneity, and limitations of preclinical models complicate the selection of effective therapies. This review presents a comprehensive framework for optimizing drug selection in neuro-oncology. We discuss strategies to enhance drug development and improve clinical trial success, including window-of-opportunity trials and advanced imaging techniques. Additionally, we highlight recent advances in the treatment of isocitrate dehydrogenase-mutant gliomas, focusing on the INDIGO study and its role in the regulatory approval of vorasidenib. The review also examines the use of MAPK inhibitors, from BRAF inhibitors to PAN-RAF inhibitors, in both pediatric and adult patients, as well as novel investigational agents. Finally, we explore emerging targeted therapies for rarer oncogenic drivers, such as FGFR and NTRK alterations, emphasizing the need for CNS-specific drug development strategies.

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INTRODUCTION

The management of CNS malignancies remains a significant challenge due, in part, to intertumoral, intratumoral, and microenvironmental heterogeneity, limited availability of preclinical models, and the complexities of CNS drug delivery. Additional limitations in clinical trial design include difficulties in powering trials for regulatory approval when patient populations are small, the absence of standard-of-care treatment for randomization in certain rare tumors, and the inclusion of both primary and secondary CNS tumors in basket studies. However, recent advances in next-generation sequencing technologies are reshaping CNS tumor classification. These technologies, along with various computational tools, have not only facilitated the identification of several potentially actionable oncogenic driver mutations but also spurred the development of targeted therapies aimed at these alterations. This manuscript outlines systematic approaches for optimizing drug selection in the treatment of CNS malignancies. It offers a practical overview of integrating targeted therapies into neuro-oncology practice, highlighting both currently approved treatments and strategies under investigation.¹⁻⁴

LIMITATIONS TO SELECTION OF CNS-ACTIVE DRUGS

Biological Barriers to CNS Drug Delivery

CNS drug delivery is challenged by unique biological barriers, including the blood-brain barrier (BBB), tumor and microenvironment heterogeneity, and limitations of preclinical models. The BBB, formed by endothelial cells and astrocytic endfeet connected by tight junctions, prevents over 95% of drugs from reaching the brain parenchyma.⁵⁻⁷ By contrast, the cerebrospinal fluid (CSF) barrier is formed by fenestrated capillaries embedded in connective tissue stroma and surrounded by secretory epithelium, and enables selective nutrient and drug movement into the CSF (Fig 1).⁵ Because of their vastly different permeability profiles, pharmacokinetics (PK) measurements in brain parenchyma and CSF are not interchangeable. For instance, isocitrate dehydrogenase (IDH) inhibitor vorasidenib could be erroneously deemed a poor CNS drug candidate based solely on its CSF concentrations, which are approximately 200-fold lower than in the brain parenchyma.⁸

CNS PK are further complicated by the brain-tumor barrier, which disrupts the BBB and exhibits heterogeneous

PRACTICAL APPLICATIONS

- Next-generation sequencing, along with computational tools, has led to more accurate classification of CNS tumors and the identification of several potentially actionable oncogenic alterations.
- CNS drug delivery remains a significant challenge in neuro-oncology, primarily because of the blood-brain barrier, tumor and microenvironmental heterogeneity, and limitations of preclinical models.
- Vorasidenib should be considered after biopsy or resection in patients with WHO grade 2 *IDH* glioma who are not in immediate need for radiotherapy and/or chemotherapy.
- The efficacy of vorasidenib in higher-grade gliomas, its role in maintenance therapy, potential in combination with chemotherapy, and long-term outcomes remain unknown.
- Targeted therapies may offer an effective and durable therapeutic option in highly selected glioma patients with druggable molecular alterations (BRAF and NTRK).

permeability because of efflux pump upregulation, astrocyte reprogramming, and leaky capillaries.⁹ Because BBB breakdown enhances gadolinium contrast on magnetic resonance imaging (MRI), measuring tumor drug concentrations only in contrast-enhancing regions can severely overestimate drug BBB permeability. By contrast, tumor regions that are less accessible to locoregional therapies often have intact BBB and therefore lower drug levels.^{10,11}

Furthermore, these tumors present high intratumoral and intertumoral heterogeneity in neoplastic and nonneoplastic compartments, low lymphocyte infiltration, and a high abundance of myeloid subsets, which together create a highly protumorigenic immunosuppressive microenvironment. Additionally, these compartments exhibit dynamic changes with tumor progression and therapeutic interventions.¹²

Limitations of Preclinical PK Models

Preclinical models often fail to recapitulate the composition of the human brain. The mouse brain has over 25,000 times less white matter than the human brain, with a disproportionately lower white-to-gray-matter ratio (8:92 in mice v 45:55 in humans; Fig 1).¹³ Most drugs administered through the bloodstream have drastically lower levels in the physiologically less perfused white matter relative to the gray

matter.^{14–17} As a result, murine models tend to overestimate brain drug penetration.

Orthotopic xenograft models also tend to artificially perturb the BBB and fail to replicate the infiltrative growth patterns of gliomas, while traditional glioma cell lines may lose genotypic fidelity to the source tumor, reducing their clinical relevance.^{18–20} IDH-mutated (IDHm) glioma cell lines are particularly difficult to culture, making these models limited in availability and reliability.²¹ CNS metastasis models are less affected by these limitations since their hematogenous spread can be replicated through intracardiac or intracarotid injection. These models also tend to be well demarcated and retain driver mutations much more similarly to their real-world counterparts yet remain underutilized.^{22–24}

Overall, these nuances underscore the critical need for a paradigm shift toward integrating in vivo human data and developing noninvasive PK tools to enhance drug selection for CNS oncology trials and ultimately for personalized medicine.

A SYSTEMATIC APPROACH TO PREDICT CNS DRUG ACTIVITY AND ITS PRACTICAL APPLICATION

In 2020, the Adult Brain Tumor Consortium (ABTC) established baseline criteria for drugs to be considered suitable for efficacy trials.²⁵ According to these, drugs that work through direct drug-tumor interaction must accumulate at therapeutic concentrations within the target tumor volume. As most primary brain tumors, and even micrometastatic systemic cancers, invade areas in the brain with partially, or fully intact BBB, assessing drug penetration beyond contrast-enhancing regions is crucial. Therefore, three key PK parameters should be considered when evaluating a drug's potential CNS activity:

1. Effective concentration (eg, IC₅₀, IC₉₀, etc) against the target cancer type
2. Maximum plasma concentration (C_{max}) at the maximum tolerated dose (MTD) in humans
3. Drug concentration in non-contrast-enhancing brain regions in humans measured directly or indirectly.

A 2022 analysis of genotypically targeted drugs against glioblastoma found that CNS drug selection is based on incomplete data.²⁶ Only one drug (ribociclib) had all three required parameters, including measurements from non-enhancing tumor regions in humans. Expanding the data set to include PK information from contrast-enhancing tumor in humans increased data completeness to 11% (six drugs). When animal brain PK data were included, this rose to 33%. However, the majority of drugs did meet two of the three criteria, allowing the least-promising candidates for CNS use to be eliminated.

To address missing information, the following inference strategies can be applied:

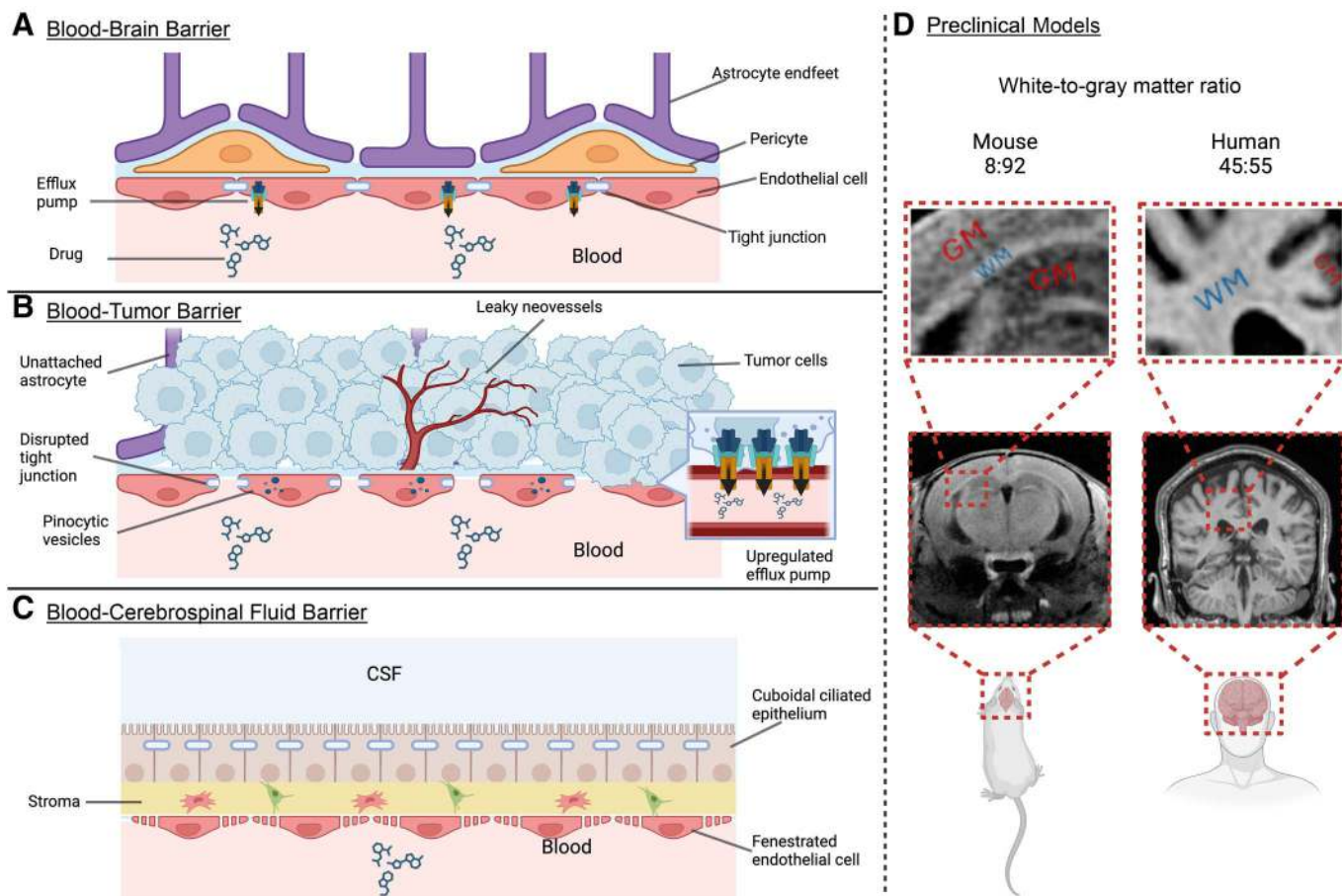


FIG 1. Limitations to selection of CNS-active drugs. (A) Normal blood-brain barrier with tight junctions, pericyte cells, astrocyte endfeet, and efflux pumps prevents over 95% of drugs reaching brain parenchyma. (B) Blood-tumor barrier with disrupted tight junctions, pinocytotic vesicles, upregulated efflux pump, leaky neovessels, and unattached astrocyte endfeet. (C) Blood-cerebrospinal fluid-barrier with fenestrated endothelial cell, stroma, and cuboidal ciliated epithelium. (D) Preclinical models overestimate brain drug penetration because of a lower white-to-gray matter ratio in mice compared to humans. CSF, cerebrospinal fluid; GM, gray matter; WM, white matter.

1. If IC_{50} for the target cancer and the human plasma C_{max} are known, the required brain-to-plasma ratio can be estimated.
2. If brain drug concentration is known at MTD, it defines the upper limit of IC_{50} threshold for efficacy for the target tissue.
3. If IC_{50} for the target cancer and animal brain-to-plasma concentrations are known, but human PK data are missing, blood measurements in early-phase trials can determine whether therapeutic brain levels are feasible.

For instance, if a drug's plasma C_{max} is tenfold lower than the IC_{50} , it would need to accumulate over tenfold higher in the brain than in plasma—an unlikely scenario. However, highly potent drugs (eg, IC_{50} in the nanomolar range) may remain effective despite low CNS penetration.^{26,27} A real-world example is tovorafenib, which demonstrated an IC_{50} of approximately 0.5 μM in *NF1* and *BRAF* mutated glioma cell lines,²⁸ and a 24% plasma-to-brain ratio in normal mouse brain.²⁹ Its human plasma C_{max} of 13.6 μM far exceeds the levels necessary for therapeutic brain levels, thus predicting clinical efficacy as shown in the FIREFLY-1 trial for pediatric low-grade *BRAF*-mutated glioma.^{30,31}

FUTURE METHODS TO GENERATE DATA TO ENHANCE CNS-ACTIVE DRUG SELECTION

Expanding Publicly Accessible PK and PD Data

There is an urgent need to expand publicly available data sets on IC_{50} , and human PK and pharmacodynamics (PD). Pharmacogenomic tools such as CellMiner NCI-60^{32,33} and the Genomics of Drug Sensitivity in Cancer tool^{34,35} provide valuable IC_{50} data but require expansion. High-throughput screening platforms using 3D chip-based models could significantly accelerate data acquisition.³⁶ High-throughput screening can also be applied to test drug synergy.³⁷

Integrating PK/PD Data Into Early-Phase Clinical Trials

Tissue-based assessments in early-phase clinical trials can bridge critical gaps in human brain PK/PD data. Window-of-opportunity trials (WoO), in which patients receive therapeutic drug doses before surgical intervention, allow for ex vivo PK/PD analysis.³⁸ Examples include microdialysis studies measuring unbound drug in vivo, showing at least

5-fold lower drug concentration in nonenhancing, compared with contrast-enhancing brain tumor regions for multiple drugs.^{10,11} Overall WoO studies represent the most accurate method for establishing human PK/PD profiles, but their invasiveness, high costs, and the need for specialized expertise limit their broader implementation.

Advancing Noninvasive PK Imaging

Noninvasive imaging offers an alternative to some surgical studies, enabling drug biodistribution analysis in vivo. Positron emission tomography (PET) is the most sensitive PK imaging modality, capable of picomolar-level drug quantification.³⁹ PET is often used to guide the selection of CNS-active agents, such as osimertinib from a cohort of EGFR inhibitors on the basis of its superior brain penetration.⁴⁰ However, PET requires radiolabeling, which can alter PK, is costly, and entails regulatory hurdles for investigational new drug approval, making it most viable when integrated early on from preclinical drug development.^{39,41}

Alternatively, MRI-based techniques allow drug detection without chemical modification, eliminating the regulatory and financial barriers but at the cost of sensitivity and often specificity. MR spectroscopy (MRS) directly detects drugs or metabolites with unique spectral profiles when present at millimolar concentrations.⁴²⁻⁴⁶ Chemical exchange saturation transfer (CEST) MRI amplifies sensitivity by targeting the exchangeable protons of the target compound, allowing submillimolar in vivo detection of chemotherapeutics, such as methotrexate or gemcitabine, and can be used to detect colocalized substances such as albumin as used in nab-paclitaxel.^{47,48}

PD-Based Imaging for Drug Selection

PD imaging can track tumor response through on-target or off-target effects providing indirect PK insights as well. Ideal PD markers should respond within hours after administration, correlate with both tumor and target tissue, and be reproducible. Examples include changes in tracer uptake in response to a drug targeting a metabolic modulator pathway as seen in [¹⁸F] fluorodeoxyglucose (FDG) uptake reduction mammalian target of rapamycin (mTOR) inhibition,^{49,50} or amino acid (FET) uptake reduction in IDHm inhibitor therapy.⁵¹ MRS can determine PK/PD when the drug-induced metabolite both in tumor (eg, lactate) and in normal brain (eg, glutamate) as seen with dichloroacetate.⁵² MRS can also detect IDHm inhibitor-induced reduction in R(-)-2-hydroxyglutarate (2HG) levels many months before changes in growth trajectories.^{46,53} CEST MRI can detect pH changes and thus predict responses to drugs that modulate acidity such as HIF2- α inhibitors.⁵⁴ Finally, multiparametric approaches, combining PET, diffusion MRI, and CEST MRI, have been used to track antitumor responses, as seen with the PI3K/mTOR1/2 inhibitor paxalisib (GDC-0084).⁵⁰ These biomarkers could aid in patient enrichment strategies for clinical trials, identifying responders early.

Enhancing Sensitivity for Early Efficacy Signals

PD sensitivity can be improved by comparing pretreatment and on-treatment growth rates. This allows patients to serve as their own controls and thus reduces the sample size required to detect early efficacy signals.^{53,55,56}

TARGETED THERAPY FOR PATIENTS WITH IDH-MUTANT GLIOMA

Vorasidenib Drug Development

IDHm gliomas are diffusely infiltrating primary brain tumors characterized by somatic mutations in the *IDH1* or *IDH2* genes. Despite the standard treatment approach, which includes surgery, radiation therapy, and chemotherapy—each associated with short-term and long-term toxicities—these tumors inevitably recur.⁵⁷

Mutations in the *IDH* genes are early events in glioma-genesis, leading to the loss of the normal enzyme's ability to catalyze the conversion of isocitrate to α -ketoglutarate (α -KG). These mutations also confer a gain of function, enabling the nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)-dependent reduction of α -KG to 2HG. The resulting loss of NADPH and α -KG, coupled with the accumulation of the oncometabolite 2HG, drives a variety of oncogenic processes in glioma.⁵⁸⁻⁶⁰ As a result, targeting 2HG depletion by directly inhibiting the mutant IDH enzyme has become a highly promising therapeutic strategy.⁶¹

mIDH inhibitors are FDA-approved for various indications and have been studied for glioma treatment. Ivosidenib and olutasidenib are approved for relapsed or refractory (RR) AML with *IDH1* mutations, while enasidenib is approved for RR AML with *IDH2* mutations. Additionally, ivosidenib is approved for newly diagnosed *IDH1*-mutant AML in patients ineligible for intensive chemotherapy, as well as for unresectable, locally advanced, or metastatic *IDH1*-mutant cholangiocarcinoma.

Vorasidenib, a brain-penetrant, dual mIDH inhibitor, demonstrated good tolerability in a phase I dose-escalation study involving 52 patients with recurrent glioma. Dose-limiting toxicities, including elevated transaminase levels, were observed at doses ≥ 100 mg but were reversible. Vorasidenib demonstrated preliminary antitumor activity in these patients. The protocol-defined objective response rate (ORR) in the nonenhancing glioma patients was 18%, including one partial response and three minor responses, with a median progression-free survival (PFS) of 36.8 months (95% CI, 11.2 to 40.8). By contrast, patients with enhancing glioma had a median PFS of 3.6 months (95% CI, 1.8 to 6.5) with no confirmed radiographic responses.⁶² A summary of published studies including targeted therapies in gliomas is provided in [Table 1](#).

To evaluate the biological potential and identify the optimal IDH inhibitor and dose for a phase III study, a perioperative phase I trial was conducted with vorasidenib (10 or 50 mg once daily) and ivosidenib (500 mg once daily or 250 mg twice daily) in 49 patients with recurrent IDH-mutant gliomas requiring tumor resection. The primary end point was the concentration of 2HG in resected tumors. A remarkable reduction of over 90% in 2HG levels was observed in patients treated daily doses of vorasidenib 50 mg and ivosidenib 500 mg, while the effect was less pronounced at lower doses of vorasidenib and ivosidenib 250 mg twice daily. Given its demonstrated brain penetrance and more consistent 2HG suppression, vorasidenib was selected to be tested in the phase III INDIGO trial.⁶³

In INDIGO, a double-blind, phase III trial, patients with nonenhancing grade 2 mIDH glioma who had undergone no previous treatment other than surgery were randomly assigned to oral vorasidenib (40 mg once daily, n = 168) or matched placebo (n = 163). At a median follow-up of 14.2 months, 226 patients (68.3%) continued to receive vorasidenib or placebo. PFS, the primary end point, was significantly improved in the vorasidenib group compared with the placebo group (median PFS, 27.7 months v 11.1 months; hazard ratio [HR] for disease progression or death, 0.39; [95% CI, 0.27 to 0.56; $P < .001$]). At the time of progression, patients had the option to cross over to the experimental arm, which may preclude the analysis of survival benefit. In patients with pretreatment/on-treatment scans available (n = 123), vorasidenib reduced tumor growth rate (pretreatment: 13.2% [95% CI, 10.3 to 16.3] v on-treatment -3.3% [95% CI, -5.2 to -1.2]), while no significant change was observed with placebo (pretreatment: 18.3% [95% CI, 15.0 to 21.7] v on-treatment 12.2% [95% CI, 9.5 to 14.9]; difference of slopes changes 11.0 [95% CI, 4.5 to 17.8]; $P < .001$).⁶⁴ There was no difference in health-related quality of life between the two groups, and no notable changes in neurocognitive function were observed (median follow-up was 14.2 months). No significant difference in seizure frequency or severity was seen at 14.2 months.⁷⁵ More mature data reveal an increase in seizure frequency in the placebo group, likely indicative of tumor growth.⁷⁶

Vorasidenib in Clinical Practice

Indications—What Do We Know and What We Do Not Know

The results of the INDIGO study are exciting, and, probably, one of the most promising results we have seen in glioma trials in recent years. How should we translate the results from this selected study population into daily clinical practice? How do we select patients who will benefit from vorasidenib without jeopardizing survival?

Translated from the INDIGO study, it is clear that patients with predominantly non-contrast-enhancing grade 2 mIDH glioma, who have undergone resection or biopsy 1–5 years

before the start of vorasidenib and provided there is no immediate need for treatment with radiotherapy (RT) and/or chemotherapy, have a prolonged PFS with vorasidenib compared with placebo. Both mIDH astrocytoma and oligodendroglioma benefit, with HR for PFS of 0.47 (95% CI, 0.29 to 0.75) and 0.32 (95% CI, 0.18 to 0.57), respectively.⁶⁴

One important unanswered question is whether the benefit of PFS applies only to grade 2 tumors or if patients with grade 3 gliomas also benefit from treatment with vorasidenib. The histologic criteria for grading are subjective, resulting in high interobserver variability.⁷⁷ Furthermore, there is significant spatial and temporal heterogeneity in the tumors, and no significant differences in survival outcome are found in grade 2 versus grade 3 tumors after treatment with RT and chemotherapy.^{78–80} Recent work by Elia et al⁸¹ showed that in a highly selected group of grade 3 gliomas, a watch-and-wait policy after radical resection appears to be feasible. All in all, grade most likely is a biological continuum rather than a black and white difference between grade 2 and 3. If so, some patients with grade 3 nonenhancing gliomas might also benefit from vorasidenib.⁸²

Many other questions remain unanswered: are there selected groups of patients with enhancing tumors who could still benefit from vorasidenib? What is the right timing for treatment with vorasidenib? The INDIGO study is limited to the 1–5 years' interval after surgery for initiating treatment, in patients with measurable residual disease. What should be done for patients without measurable residual disease after surgery? Is there a role for a neoadjuvant setting, are combinations with RT and/or chemotherapy possible, and is there a role for maintenance therapy after RT and/or chemotherapy? Some of these questions will hopefully be answered in planned trials, yet-to-be-planned trials, or (inter) national registries (Table 2).⁸³

Practical Management

The recommended dose of vorasidenib is 40 mg once daily. Available pills are 40 mg or 10 mg to allow for dose reductions. The most common side effects of vorasidenib are elevated liver enzymes, headache, fatigue, and gastrointestinal complaints. Elevated liver enzymes have the most practical implications. In INDIGO, 29.9% of patients in the vorasidenib arm had their treatment temporarily interrupted and 10.8% required a dose reduction; in 3.6%, it was permanently discontinued. In daily practice, this means frequent monitoring of liver enzymes is required: current recommendations are every 2 weeks for the first 2 months, and then once per month as long as the patient is on vorasidenib. It is key to educate the patients and caregivers regarding commonly used hepatotoxic drugs such as acetaminophen and healthy dietary habits. There are limited data on vorasidenib use during pregnancy or lactation, and animal data suggest teratogenicity. Adequate birth control is advised for both female and male patients while on treatment, and breastfeeding should be avoided. For imaging

TABLE 1. Overview of Targeted Therapy Clinical Trials in Gliomas: Published Data

Drug and Trial	Design (phase, patients)	Outcomes	Toxicities ≥Grade 3
IDH inhibitors			
Vorasidenib ⁶² NCT02481154	I, F-I-H N = 52 <i>IDH1/2</i> gliomas	ORR Nonenhancing glioma: 18% Enhancing glioma: 0% PFS: 7.5 months	ALT increase: 5% AST increase: 3% Fatigue: 2% Nausea: 2%
Vorasidenib and ivosidenib ⁶³ NCT03343197	I, perioperative N = 24 surgical candidate grade 2/3 <i>IDH1</i> -R132H CNS tumors	[2-HG] reduction Vorasidenib 50 mg: 92.6% Ivosidenib 500 mg: 91.1% ORR Vorasidenib 50 mg: 42.9% Ivosidenib 500 mg: 35.7%	Vorasidenib 50 mg ALT increase: 7% HypoPhos: 7% Ivosidenib 500 mg HypoNa: 6%
INDIGO trial Vorasidenib ⁶⁴ NCT04164901	III N = 331 residual/recurrent grade 2 <i>IDH</i> glioma	PFS: 27.7 months vorasidenib v 11.1 months placebo HR, 0.39 (95% CI, 0.27 to 0.56; $P < .001$) TTNI: NR vorasidenib vs 17.8 months placebo HR, 0.26 (95% CI, 0.15 to 0.43; $P < .001$)	ALT increase: 9% AST increase: 4% GGT increase: 3% Fatigue: 0.6%
Olutasidenib ⁶⁵ NCT03684811	Ib/II N = 26 relapsed <i>IDH1</i> -R132 glioma	ORR 8%	ALT increase: 12% AST increase: 12% HypoPhos: 4% Nausea: 4%
Ivosidenib ⁶⁶ NCT02073994	I N = 66 relapsed <i>IDH1</i> glioma	ORR Nonenhancing glioma: 4% Enhancing glioma: 0%	HypoPhos: 3%
Safusidenib ⁶⁷ NCT04458272	I, F-I-H N = 47 relapsed <i>IDH1</i> -R132 glioma	ORR Nonenhancing glioma: 33% Enhancing glioma: 17% PFS Nonenhancing glioma: NR Enhancing glioma: 10.4 weeks	ANC decrease: 12.8% ALT increase: 6.4% AST increase: 4.3% HypoPhos: 4% Diarrhea: 4%
BAY1436032 ⁶⁸ NCT02746081	I, F-I-H n = 45 <i>IDH1</i> -R132 glioma (39 LGG, 16 grade 4 astrocytoma)	ORR LGG: 11% Grade 4 astrocytoma: 0%	ALT increase: 4% Lipase increase: 2% Nausea: 2%
LY3410738 ⁶⁷ NCT04521686	I, F-I-H n = 27 <i>IDH1</i> gliomas	ORR Enhancing glioma: 13%	Anemia: 3% HypoNa: 3% Cholangitis 3%
MAPK inhibitors			
ROAR trial Dabrafenib-trametinib ⁶⁸ NCT02034110	II n = 58 BRAF V600E gliomas (45 HGG, 13 LGG)	ORR LGG: 54% HGG: 33% PFS LGG: NR HGG: 3.8 months	Fatigue: 9% ANC decrease: 9% Neutropenia: 5% AST increase: 3% Pyrexia: 2% ALT increase: 2%
Dabrafenib-trametinib ⁶⁹ NCT02684058	II randomized v SOC chemotherapy N = 110 BRAF V600 pediatric LGG	ORR: 47% dabrafenib/trametinib v 11% SOC chemotherapy RR, 4.31 (95% CI, 1.7 to 11.2; $P < .001$) PFS: 20.1 months dabrafenib/trametinib v 7.4% SOC chemotherapy HR, 0.31 (95% CI, 0.17 to 0.55; $P < .001$)	Neutropenia: 10% Pyrexia: 8% Increase weight: 7% ALT increase: 5% ANC decrease: 5% AST increase: 3%
FIREFLY-1 trial Tovorafenib ³⁰ NCT04775485	II N = 137 BRAF altered pediatric LGG (101 KIAA1549:BRAF fusion, 22 BRAF V600E)	ORR BRAF fusion: 69% BRAF mutation: 50% Previous MAPKi: 71% MAPKi naïve: 61%	CPK increase: 12% Anemia: 10% Rash: 8% Decreased growth velocity: 5% ALT increase: 5% AST increase: 3%
Other			
RAGNAR trial Erdafitinib ⁷⁰ NCT04083976	II n = 37 mFGFR gliomas (30 HGG, 7 LGG)	ORR LGG: 29% HGG: 10%	Stomatitis: 12% Anemia: (8%) Hand-foot syndrome: 6% HyperPhos: 5% ALT increase: 5% HypoNa: 4% Onycholysis: 3%

(continued on following page)

TABLE 1. Overview of Targeted Therapy Clinical Trials in Gliomas: Published Data (continued)

Drug and Trial	Design (phase, patients)	Outcomes	Toxicities ≥Grade 3
TARGET trial Fexagratinib ⁷¹ NCT02824133	I/II N = 12 FGFR-TACC fusion positive relapse HGG	PFS 6 months: 25% (95% CI, 5 to 57) PFS: 1.4 months (95% CI, 9 to 67) ORR: 8% (1 partial response)	Stomatitis: 8% ALT increase: 8% Hyperglycemia: 8% Lymphopenia: 8%
SCOUT and NAVIGATE trial Larotrectinib ⁷² NCT02637687, NCT02576431	I/II pooled analysis n = 33 NTRK fusion-positive CNS tumors (26 < 18 years)	ORR <18 years: 38% >18 years: 0% PFS 18.3 months (95% CI, 6.7 to NE)	Dysphagia: 6% Memory impairment: 6% Vomiting: 3% ANC decrease: 3% Irritability: 3%
STARTRK-NG Entrectinib ⁷³ NCT02650401	I/II n = 16 NTRK fusion-positive CNS tumors <22 years	ORR 50%	Weight gain: 16% ANC decrease: 16% Neutropenia: 7% ALT increase: 4%
Everolimus ⁷⁴ NCT00411619	I/II N = 28 definitive TSC and growing SEGA	Reduction of tumor volume at 6 months ≥30%: 75% ≥50%: 32% DOR 67.8 months (4.7-83.2)	Stomatitis: 4% Sinusitis: 4% WBC decrease: 4%

Abbreviations: [2-HG] = 2-hydroxyglutarate concentration; ANC, absolute neutrophil count; CPK, creatine phosphokinase; DOR, duration of response; F-I-H, first-in-human; GGT, gamma-glutamyl transferase; HGG, high-grade glioma; HR, hazard ratio; IDH, isocitrate dehydrogenase; LGG, low-grade glioma; MAPKi, MAPK inhibitor; mFGFR, mutant FGFR; mIDH, mutant IDH; NE, not estimable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; RR, risk ratio; SEGA, subependymal giant cell astrocytoma; SOC, standard-of-care; TSC, tuberous sclerosis complex; TTNi, time to next intervention.

follow-up, a MRI brain with gadolinium sequences is recommended every 3 months for the first 3 years, and thereafter at least every 6 months.^{84,85}

Other IDH Inhibitors

Although ivosidenib exhibits relatively low brain penetration in preclinical models, potentially limiting its efficacy for IDH-mutant glioma, ivosidenib is very potent, with an IC₅₀ measured below 10 nM and it has been shown to reduce intratumoral 2HG levels by more than 90%.⁶³ In a phase I trial that included 66 patients with recurrent IDH1-mutant gliomas, ivosidenib 500 mg once per day demonstrated good tolerability. Antitumor activity in 31 enhancing tumors resulted in no complete or partial responses and 45% stable disease. In nonenhancing tumors (n = 35), there was one partial response (4%) and 85% stable disease.⁶⁶ In a cohort of 30 patients with IDH-mutant glioma (n = 21 grade 2), off-label use of ivosidenib demonstrated good tolerability. Antitumor activity in 22 nonenhancing tumors resulted in 12 stable diseases, five minor responses, and three partial responses. Seizure frequency was stable or improved in most patients.⁸⁶

In an early-phase study of recurrent or progressive IDH1m gliomas, olutasidenib 150 mg twice daily, a brain-penetrant selective inhibitor of mIDH1 demonstrated a disease control rate (ORR plus stable disease) of 48% with responses in enhancing gliomas.⁶⁵ Furthermore, investigational agents such as safusidenib, BAY1436032, and LY3410738 have shown objective responses in early-phase clinical trials

involving patients with enhancing and/or nonenhancing IDH-mutant gliomas.^{67,87,88}

As expected with the use of these epigenetic drugs, reduction in tumor growth rates and volume reductions may be observed many months after treatment initiation.^{53,89}

EMERGING THERAPEUTICS FOR RARE ONCOGENIC DRIVERS

RAS-RAF-MEK-ERK Pathway

Alterations in the RAS-RAF-MEK-ERK signaling pathway are among the most common oncogenic events in cancer. BRAF is a serine/threonine kinase that, in its nonmutant state, is activated by RAS, triggering BRAF homodimerization or heterodimerization. This activation leads to downstream signaling through MEK and ERK, resulting in the activation of nuclear transcription factors responsible for cell proliferation.⁹⁰ BRAF alterations can be categorized into three functional classes. Class I mutations, which include the BRAF V600 mutations, are characterized by RAS-independent monomer signaling and account for over 90% of BRAF alterations in cancer (Fig 2).⁹¹ The prevalence of the V600E mutation varies across CNS tumors, being present in 60% of pleomorphic xanthoastrocytomas, 40% of gangliogliomas, 2% of adult low-grade gliomas (LGG), and 1%-2% of glioblastomas.^{92,93} By contrast, Class II mutations rely on RAS-independent dimerization for signaling and encompass a variety of mutations and fusions, such as the BRAF:KIAA1549 fusion, which is found in up to 70% of

TABLE 2. Ongoing Molecularly Targeted Therapy Trials in Gliomas

Trial Name and NCT Number	Treatment	Patient Population	Design (phase and comparator)
IDH inhibitors			
ViCToRy NCT05609994	Vorasidenib + PEPIDH1M vaccine	Adult patients with recurrent mIDH1 LGG	I
NCT06478212	Vorasidenib + temozolomide	Age ≥12 years with mIDH1/2 gliomas	Ib/II
NCT05484622	Vorasidenib + pembrolizumab	Adult patients with recurrent or progressive mIDH1 grade 2/3 gliomas	I
VIGOR NCT06809322	Vorasidenib	Adult patients with mIDH1/2 grade 2/3 gliomas after first-line chemoradiation	III Placebo
NCT06161974	Olutasidenib + temozolomide	Age 12-39 years with mIDH1 HGG	I
NCT04521686	LY3410738 monotherapy and in combination with chemotherapy or durvalumab	Adult patients with relapsed mIDH1/2 gliomas	I
NCT02381886	IDH305	Adult patients with IDH1 R132 gliomas	I
NCT05577416	Safusidenib	Adult patients with mIDH1 LGG before surgery	I
NCT05303519	Safusidenib	Adult patients with recurrent mIDH1 grade 2/3 gliomas	II
NCT03030066	Safusidenib	Adult patients with recurrent IDH1 R132 gliomas	I Japan only
NCT04458272	Safusidenib	Treatment-naïve adult patients with IDH1 R132 grade 2 gliomas	II Japan only
MAPK inhibitors			
NCT06712875	Dabrafenib/trametinib + nivolumab Trametinib + nivolumab	Age ≤26 years with pediatric LGG/HGG KIAA1549:BRAF fusion or BRAF V600 pediatric LGG/HGG	II
NCT04201457	Dabrafenib/trametinib + hydroxychloroquine	Age ≤ 30 years with BRAF V600 LGG/HGG or BRAF duplication or fusion LGG	I/II
NCT03919071	Dabrafenib/trametinib	Age 3-25 years with mBRAF V600 HGG after chemoradiation	II
NCT03363217	Trametinib	Age ≤25 years with progressive LGG NF1, KIAA1549:BRAF fusion and MAPK/ERK activating mutation	II
NCT06666348	Mirdametininib + vinblastine	Age 2-25 years with pediatric LGG with KIAA1549:BRAF fusion or MAPK alterations other than BRAF V600E	I/II
VICTORY NCT06381570	Tovorafenib + vinblastine	Age ≤25 years with progressive BRAF/CRAF altered LGG	I
LOGGIC/FIREFLY-2 NCT05566795	Tovorafenib	Age ≤25 years with RAF activating alteration LGG	III SOC chemotherapy
FIRELIGHT-1 NCT04985604	Tovorafenib Tovorafenib + pimasertib	Age ≥12 years. Recurrent solid tumors with BRAF and MAPK alterations	I/II
NCT05503797	Plixorafenib (FORE8394)	Age ≥ 10 years with recurrent BRAF V600E gliomas	II
NCT04166409	Selumetinib	Age 2 to 21 years with BRAF V600E LGG	III Vincristine + Carboplatin
Perfume NCT06159478	Binimetinib	Age ≥12 years with recurrent BRAF rearranged LGG	II Japan only
NCT02285439	Binimetinib	Age ≤18 years with BRAF rearranged and other MAPK alterations LGG	I/II
NCT05804227	Ulixertinib	Age ≥18 years with mNF1 grade 1 to 3 glioma or grade 2/3 oligodendroglioma	I
Other			
NCT05859334	Erdaftinib	Age ≥18 years with progressive FGFR-TACC fusion-positive IDH-WT gliomas	II

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TABLE 2. Ongoing Molecularly Targeted Therapy Trials in Gliomas (continued)

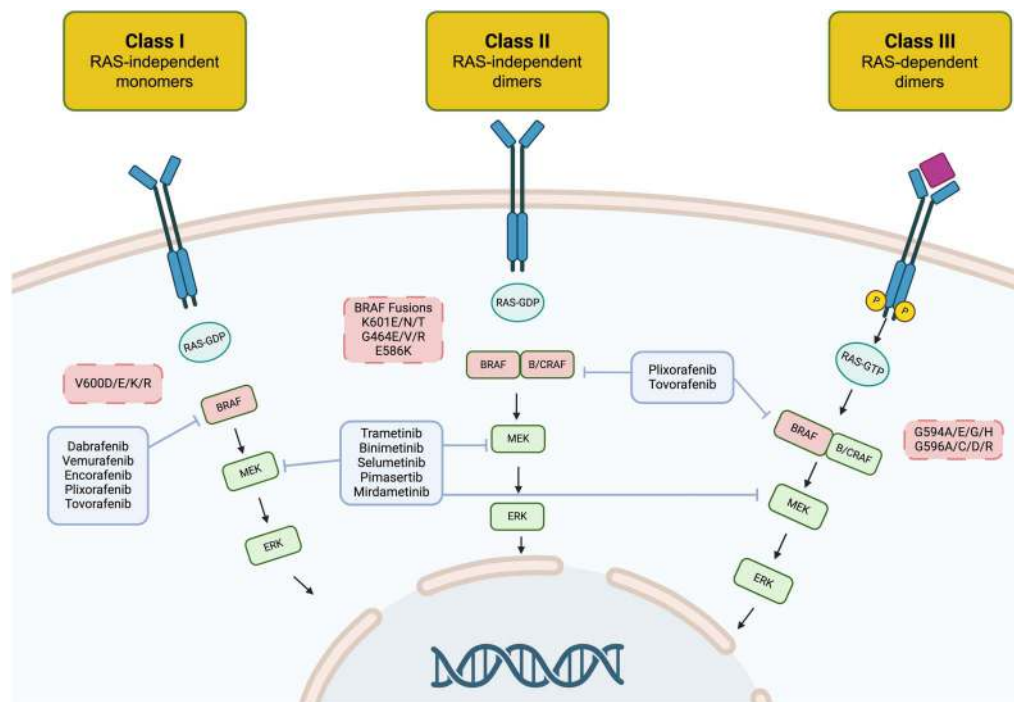
Trial Name and NCT Number	Treatment	Patient Population	Design (phase and comparator)
FIGHT-209 NCT05267106	Pemigatinib	Age ≥18 years with progressive FGFR 1-3 alterations gliomas	II
NCT04655404	Larotrectinib	Age ≤21 years with NTRK fusion HGG	I
NCT06558691	Entrectinib	Age <3 years with NTRK or ROS1 HGG	II

Abbreviations: HGG, high-grade gliomas; IDH, isocitrate dehydrogenase; LGG, low-grade gliomas; mBRAF, mutant BRAF; mIDH, mutant IDH; mNF1, mutant NF1; SOC, standard-of-care; WT, wild type.

pediatric pilocytic astrocytomas. The role of BRAF alterations as a predictive and prognostic biomarker in gliomas is still to be determined.⁹⁴⁻⁹⁶

Class I BRAF inhibitors, such as dabrafenib and vemurafenib, demonstrated unprecedented response rates in early clinical trials for BRAF V600-mutant melanoma.^{97,98} However, development of secondary cutaneous neoplasms was observed, attributed to the paradoxical activation of BRAF wild-type (WT) dimers and ERK signaling.⁹⁹ To mitigate this effect, combination therapy with MEK inhibitors, such as trametinib, was introduced, resulting in a decreased incidence of proliferating skin lesions and improved therapeutic efficacy.¹⁰⁰ Dabrafenib/trametinib combination received FDA approval as a tissue-agnostic treatment for advanced solid tumors harboring BRAF V600E mutation, including adult and pediatric LGG and high-grade gliomas (HGG) and for first-line treatment of patients with pediatric BRAF V600E LGG who require systemic therapy. Data to support its use in

primary CNS tumors come mainly from two studies. The phase II ROAR basket trial included adult patients with recurrent BRAF V600E mutant HGG and LGG. The ORR and median duration of response (DoR) were 33% (95% CI, 20 to 49) and 36.9 months (95% CI, 7.4 to 44.2) for the HGG cohort (n = 45), and 69% (95% CI, 39 to 91) with DoR not reached for the LGG cohort (n = 13), respectively.⁶⁸ The second study focused on pediatric LGG patients. In the first-line setting, a randomized phase II trial included 110 pediatric patients with diagnosis of BRAF V600x (96% V600E)-mutant LGG who were randomly assigned to dabrafenib/trametinib versus standard-of-care carboplatin plus vincristine. ORR for the dabrafenib/trametinib versus chemotherapy groups were 46% versus 11%, respectively, and median PFS was 20.1 months (95% CI, 12.8 to not evaluable) with dabrafenib/trametinib and 7.4 months (95% CI, 3.6 to 11.8) with chemotherapy (HR, 0.31 [95% CI, 0.17 to 0.55], *P* < .001). Most frequent tumor types were pilocytic astrocytoma (37%) and ganglioglioma (33%).⁶⁹ The safety profile observed in these

**FIG 2.** BRAF functional classes and their inhibitors.

trials was consistent with that reported in previous studies. The most common toxicities of grade 3 or higher included pyrexia, fatigue, and decreased neutrophil count. Permanent discontinuation because of adverse effects was below 10%.^{68,69} Additionally, a reduction in left ventricular ejection fraction of 10% or greater was observed in 6% of patients receiving the combination treatment, warranting periodic cardiac evaluation. Similarly, uveitis was reported in 2% of patients across the trials, requiring monitoring.¹⁰¹

Tovorafenib is a novel, CNS-penetrant, first-in-class, FDA-approved BRAF type II inhibitor, which targets both BRAF V600 mutations and BRAF fusions without paradoxical activation of the MAPK pathway. The phase II FIREFLY-1 trial evaluated tovorafenib monotherapy in children, adolescents, and young adults with refractory or relapsed BRAF-altered pediatric LGG or advanced solid tumors, including patients who had previously received treatment with BRAF or MEK inhibitors. The study included 137 patients, with most tumors harboring BRAF:K11A1549 fusions (74%) and BRAF V600E mutations (16%). ORR for tumors with BRAF fusions and BRAF mutations were 69% and 50%, respectively, with 17% complete responses in the entire cohort. Interestingly, ORR for previously treated patients with MAPK inhibitors was 71% compared with 61% for MAPK inhibitor-naïve patients. The most frequent treatment-related adverse events grade ≥ 3 were elevated creatine phosphokinase (12%), anemia (11%), and rash (8%). Other clinically significant adverse events included hair color changes (76%), which may have a notable psychosocial impact, particularly in younger patients, and decreased growth velocity (12%), with varying degrees of recovery after treatment discontinuation. Additionally, intratumoral hemorrhage was observed in 15 patients; however, the association between tovorafenib and tumor-related bleeding remains uncertain.³⁰ The main limitation of this study is the lack of randomization. However, this design illuminates some alternative trial designs that may support registration when the traditional approaches, such as large, randomized trials, are unfeasible.

The LOGGIC/FIREFLY-2 trial (ClinicalTrials.gov identifier: [NCT05566795](#)) is an ongoing study evaluating tovorafenib in comparison with chemotherapy in the first-line treatment of pediatric LGG. The FIRELIGHT-1 trial (ClinicalTrials.gov identifier: [NCT04985604](#)) focuses on patients with relapsed solid tumors, including CNS malignancies, harboring BRAF fusions or other MAPK pathway alterations. This trial includes two treatment arms: tovorafenib monotherapy and in combination with MEK inhibitor pimasertib. These ongoing and upcoming studies with tovorafenib will provide additional insights into the role of this drug in this heterogeneous population (Table 2).

Similarly, plixorafenib (FORE8349) is an experimental, oral, highly selective BRAF inhibitor that targets V600 and non-V600 alterations by disrupting BRAF monomers and BRAF-BRAF/BRAF-CRAF heterodimers without paradoxical

activation of the MAPK pathway.¹⁰² A phase I/IIa trial that included 113 patients with advanced solid tumors supported the CNS activity of plixorafenib, demonstrating an ORR of 66.7% (95% CI, 29.9 to 92.5) in nine patients with BRAF V600-mutant MAPK-naïve primary CNS tumors.¹⁰³ The most common adverse event was grade 1 to 2 liver function test changes. Interestingly, and most likely related to its novel mechanism of action, plixorafenib demonstrated a benign safety profile when compared with approved BRAF inhibitors, including no uveitis, retinal detachment, left ventricular ejection fraction or secondary skin cancers, and only grade 1 rash and pyrexia. This safety profile translates in better tolerability and decreases patient burden as serial dermatology and ophthalmology evaluations as well as echocardiograms are not required. These early-phase results led to the ongoing [NCT05503797](#) FORTE Phase II basket study, which enrolls patients age 10 years and older into four subprotocols, including advanced solid and CNS tumors with BRAF fusions and BRAF V600 mutant recurrent CNS tumors.

As BRAF alterations evolve as druggable biomarkers in CNS tumors, and novel and safer brain-penetrant inhibitors are developed, upcoming trials should address the best treatment sequence for patients with BRAF-altered CNS tumors,⁹⁶ especially for adult patients with HGG, in which first-line treatments have remained basically unchanged for over two decades.¹⁰⁴

NTRK

NTRK genes encode for a family of tropomyosin receptor kinase (TRK) proteins that, when activated, promote cell proliferation and survival.¹⁰⁵⁻¹⁰⁷ NTRK gene fusions result in a constitutively active protein and are found in about 1% of adult and 3%-5% of pediatric gliomas and in up to 40% of pediatric nonbrainstem HGG.^{108,109} NTRK mutations or amplification have been associated with a lack of response with some NTRK inhibitors. However, NTRK fusions have been associated with remarkable responses leading to regulatory approval. Larotrectinib is a selective inhibitor of TRK that has been approved as tumor-agnostic therapy for adult and pediatric patients whose tumors harbor a NTRK fusion and have no satisfactory alternative treatment on the basis of data from three single-arm clinical trials: LOXO-TRK-14001 (ClinicalTrials.gov identifier: [NCT02122913](#)), SCOUT (ClinicalTrials.gov identifier: [NCT02637687](#)), and NAVIGATE (ClinicalTrials.gov identifier: [NCT02576431](#)).¹¹⁰ Evidence of its utility in CNS primary tumors comes from a pooled analysis from early phase trials that included 33 patients, mostly pediatric (n = 26). ORR was 38% (95% CI, 16 to 49) for pediatric patients, with three (9%) complete responses and seven (21%) partial responses. Interestingly there were no responses in adult patients. Median PFS for the whole cohort was 18.3 months (95% CI, 6.7 to not estimable).⁷²

Entrectinib is another potent TRK inhibitor that was specifically designed to cross the BBB, with reported preclinical

brain/plasma concentrations ratio of 0.43.¹¹¹ Intracranial activity was confirmed in early-phase trial including patients with CNS metastases.¹¹² The STARTRK-NG phase I/II trial included 16 pediatric patients with primary brain tumors with NTRK ($n = 11$), ROS1 ($n = 4$), or ALK ($n = 1$) fusions, three patients in the NTRK group had a complete response, and two had a partial response.⁷³ Among them, a patient with epithelioid glioblastoma achieved a complete response and had DoR of 25 months. Interestingly, in the ROS1 fusion-positive subgroup, one patient with a H3 K27M diffuse midline glioma had a complete response with a DoR of 22 months and partial responses were seen in two participants.⁷³ So far, evidence for entrectinib in adult patients with CNS tumors comes from case reports.^{113,114} In concordance with physiologic function of TRK (A/B/C), NTRK inhibitors show a unique toxicity profile that includes weight gain, nociception and memory impairment, ataxia, as well as fatigue, hallucinations, and decreased neutrophil count.^{72,73,115}

Mammalian Target of Rapamycin

Subependymal giant cell astrocytoma (SEGA) is a rare type of circumscribed astrocytic glioma that seems to arise from the subependymal nodules in patients with tuberous sclerosis complex (TSC). TSC is an autosomal dominant genetic disorder that can affect multiple systems, caused by mutations in TSC1 or TSC2 genes.¹¹⁶ Approximately 10% of patients with TSC develop SEGA.¹¹⁷ As a result of these mutations, mTOR complex 1 is constitutively upregulated, leading to cell proliferation.¹¹⁸ A phase I to II study included 28 adult and pediatric patients with diagnosis of TSC and growth of SEGA, who were treated with the mTOR inhibitor, everolimus. A significant reduction in the tumor volume was seen at 6 months, with 21 (75%) patients having a reduction of $\geq 30\%$ and nine (32%) of $\geq 50\%$.⁷⁴ On the basis of the results of this study, everolimus obtained regulatory approval by FDA. These findings were confirmed by a long-term follow-up report of this study that showed a median duration of treatment of 67.8 months (4.7–83), and 52% and 61% volume reductions of ≥ 50 and $\geq 30\%$, respectively.¹¹⁹ Interestingly, no patient required surgery during the treatment period, and everolimus demonstrated to be a long-term safe medication.

FGFR

FGFR alterations, including mutations and fusions, contribute to cellular proliferation and tumorigenesis. FGFR1 mutations are predominantly observed in pediatric gliomas but can also be found in both LGG and HGG. By contrast, FGFR2 and FGFR3 alterations primarily occur as fusions, with FGFR3-TACC3 fusions being almost exclusively detected in adult HGG.¹²⁰ FGFR-TACC chromosomal translocations describe the fusions of tyrosine kinase coding domain of the FGFR gene to the coiled-coil domain of TACC. FGFR3-TACC3 (F3T3) is the most recurrent gene fusion in cancer and the most prevalent type of gene fusion in adult

glioma. Because of their histopathologic and molecular features, it has been suggested that F3T3 gliomas represent a unique entity among IDH WT gliomas. F3T3 gene fusion is present in 3%–6% of IDH WT gliomas and is an independent predictor of a favorable outcome in these tumors (independent of tumor grading).¹²¹ F3T3 fusion is a potent oncogene that confers sensitivity to FGFR inhibitors. Of note, the F3T3 fusion is retained in recurrent glioblastoma.^{121–124} Erdafitinib is a potent FGFR1–4 inhibitor approved for the treatment of FGFR-altered urothelial carcinoma. Clinical evidence regarding its activity in CNS tumors comes from the phase II RAGNAR trial that included 30 heavily pre-treated patients with HGG and 7 with LGG. To note, this trial allowed patients with a variety of alterations, including mutations and fusions. ORR for HGG and LGG was 10% and 29%, respectively, DOR was not reached. Interestingly, two patients from the HGG cohort, whose tumors had F3T3 fusion had partial responses and one of them had a 24-month ongoing partial response at data cutoff.⁷⁰ Tumor heterogeneity, especially in glioblastoma, has been one of the major causes, for which promising treatments fail to show significant benefits in clinical trials.⁷¹ Consequently, two ongoing phase II trials have been specifically designed to evaluate the efficacy of erdafitinib in glioma patients with FGFR alterations. NCT05859334 ETCTN 10559 is recruiting patients with recurrent IDH-wildtype gliomas with a F3T3 fusion to receive treatment with erdafitinib. Whereas FIGHT-209 (ClinicalTrials.gov identifier: NCT05267106) included patients with glioblastomas and other CNS tumors with FGFR 1–3 fusions or mutations.

CONCLUSION

A CNS-specific framework for drug selection is essential to improving clinical trial success in neuro-oncology. Inadequate preclinical models and a reliance on data from only contrast-enhancing tumor regions tend to overestimate drug penetration. Expanding human PK/PD data through WoO trials, microdialysis, and imaging advances will enable more accurate drug prioritization. In the interim, systematic data-driven screening can identify agents with low CNS activity early, preventing ineffective trials and streamlining drug development.

Tumor profiling is becoming an essential component of the diagnostic workup for patients with primary CNS tumors.¹²⁵ Consequently, assays with broad gene panels may identify targetable oncogenic drivers in these tumors. However, the prevalence of driver alterations proven to be actionable other than IDH is below 10% in gliomas,¹²⁶ the exception being BRAF alterations, with the BRAF-KIAA1549 fusion observed in up to 70% of pediatric pilocytic astrocytoma and the BRAF V600E mutation detected in approximately 60% of pleomorphic xanthoastrocytoma.^{127,128}

In addition to the fact that designing and executing registrational clinical trials for these rare tumors with oncogenic drivers poses significant challenges, the obstacle of BBB

permeability further complicates the treatment of CNS tumors. However, data from studies such as Indigo and FIREFLY demonstrated that these studies are feasible and can end on new treatment options for our patients. In neuro-oncology practice, advocating for tumor profiling is crucial,

as identifying these rare but targetable alterations can offer brain tumor patients more effective treatments with fewer side effects. Ongoing clinical trials will further clarify the role and best timing to incorporate these therapeutic strategies during the disease course.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc.

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REFERENCES

- Mandel JJ, Yust-Katz S, Patel AJ, et al: Inability of positive phase II clinical trials of investigational treatments to subsequently predict positive phase III clinical trials in glioblastoma. *Neuro Oncol* 20:113-122, 2018
- Bagley SJ, Kothari S, Rahman R, et al: Glioblastoma clinical trials: Current landscape and opportunities for improvement. *Clin Cancer Res* 28:594-602, 2022
- Patel RR, Verma V, Miller AB, et al: Exclusion of patients with brain metastases from cancer clinical trials. *Neuro Oncol* 22:577-579, 2020
- Tan AC, Boggs DH, Lee EQ, et al: Clinical trial eligibility criteria and recently approved cancer therapies for patients with brain metastases. *Front Oncol* 11:780379, 2021
- Xiang J, Hua Y, Xi G, et al: Mechanisms of cerebrospinal fluid and brain interstitial fluid production. *Neurobiol Dis* 183:106159, 2023
- Pardridge WM: Blood-brain barrier delivery. *Drug Discov Today* 12:54-61, 2007
- Alcaniz J, Winkler L, Dahlmann M, et al: Clinically relevant glioblastoma patient-derived xenograft models to guide drug development and identify molecular signatures. *Front Oncol* 13:1129627, 2023
- Konteatis Z, Artin E, Nicolay B, et al: Vorasidenib (AG-881): A first-in-class, brain-penetrant dual inhibitor of mutant IDH1 and 2 for treatment of glioma. *ACS Med Chem Lett* 11:101-107, 2020
- Arvanitis CD, Ferraro GB, Jain RK: The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. *Nat Rev Cancer* 20:26-41, 2020
- Blakeley JO, Olson J, Grossman SA, et al: Effect of blood brain barrier permeability in recurrent high grade gliomas on the intratumoral pharmacokinetics of methotrexate: A microdialysis study. *J Neurooncol* 91:51-58, 2009
- Lee EQ, Alexander BM, Romo CG, et al: Phase I study of adavosertib with radiation therapy and temozolomide in newly diagnosed glioblastoma and intratumoral drug levels in recurrent glioblastoma. *Clin Cancer Res* 31:983-992, 2025
- Read RD, Tapp ZM, Rajappa P, et al: Glioblastoma microenvironment-from biology to therapy. *Genes Dev* 38:360-379, 2024
- Mota B, Dos Santos SE, Ventura-Antunes L, et al: White matter volume and white/gray matter ratio in mammalian species as a consequence of the universal scaling of cortical folding. *Proc Natl Acad Sci U S A* 116:15253-15261, 2019
- Fagiolino P, Talevi A, Vázquez M, et al: Blood flow distribution and membrane transporters as determinant factors of tissue drug concentration, in Talevi A, Quiroga PA (eds): *ADME Processes in Pharmaceutical Sciences*, Cham, Switzerland, Springer, 2024, pp 459-488
- Thalman SW, Powell DK, Ubele M, et al: Brain-blood partition coefficient and cerebral blood flow in canines using calibrated short TR recovery (CaSTRR) correction method. *Front Neurosci* 13:1189, 2019
- Parkes LM, Rashid W, Chard DT, et al: Normal cerebral perfusion measurements using arterial spin labeling: Reproducibility, stability, and age and gender effects. *Magn Reson Med* 51:736-743, 2004
- Muer JD, Didier KD, Wannebo BM, et al: Sex differences in gray matter, white matter, and regional brain perfusion in young, healthy adults. *Am J Physiol Heart Circ Physiol* 327:H847-H858, 2024
- Chen P, Scarpelli ML, Healey DR, et al: MRI and amino acid PET detection of whole-brain tumor burden. *Front Oncol* 13:1248249, 2023
- Lee J, Kotliarova S, Kotliarov Y, et al: Tumor stem cells derived from glioblastomas cultured in bFGF and EGF more closely mirror the phenotype and genotype of primary tumors than do serum-cultured cell lines. *Cancer Cell* 9:391-403, 2006
- Allen M, Bjerke M, Edlund H, et al: Origin of the U87MG glioma cell line: Good news and bad news. *Sci Transl Med* 8:354re3, 2016
- Balvers RK, Kleijn A, Kloezeman JJ, et al: Serum-free culture success of glial tumors is related to specific molecular profiles and expression of extracellular matrix-associated gene modules. *Neuro Oncol* 15:1684-1695, 2013
- Liu Z, Dong S, Liu M, et al: Experimental models for cancer brain metastasis. *Cancer Pathog Ther* 2:15-23, 2024

23. Westphal M, Maire CL, Lamszus K: EGFR as a target for glioblastoma treatment: An unfulfilled promise. *CNS Drugs* 31:723-735, 2017
24. Colclough N, Chen K, Johnström P, et al: Preclinical comparison of the blood-brain barrier permeability of osimertinib with other EGFR TKIs. *Clin Cancer Res* 27:189-201, 2021
25. Grossman SA, Romo CG, Rudek MA, et al: Baseline requirements for novel agents being considered for phase II/III brain cancer efficacy trials: Conclusions from the Adult Brain Tumor Consortium's first workshop on CNS drug delivery. *Neuro Oncol* 22:1422-1424, 2020
26. Ghanem P, Fatteh M, Kamson DO, et al: Druggable genomic landscapes of high-grade gliomas. *Front Med* 10:1254955, 2023
27. Zhang W, Vaubel RA, Oh JH, et al: Delivery versus potency in treating brain tumors: BI-907828, a MDM2-p53 antagonist with limited BBB penetration but significant *in vivo* efficacy in glioblastoma. *Mol Cancer Ther* 23:47-55, 2024
28. Alaal LA, Yuan M, Eberhart C, et al: Abstract 3414: The pan-RAF inhibitor tovorafenib suppresses NF1-mutant glioma through upregulation of FOXO1 and triggering of oncogene-induced senescence. *Cancer Res* 83:3414, 2023 (suppl 7)
29. Sun Y, Alberta JA, Pilarz C, et al: A brain-penetrant RAF dimer antagonist for the noncanonical BRAF oncoprotein of pediatric low-grade astrocytomas. *Neuro Oncol* 19:774-785, 2017
30. Kilburn LB, Khuong-Quang DA, Hansford JR, et al: The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: The phase 2 FIREFLY-1 trial. *Nat Med* 30:207-217, 2024
31. Nysom K, Kilburn LB, Leary SES, et al: Radiographic and visual response to the type II RAF inhibitor tovorafenib in children with relapsed/refractory optic pathway glioma in the FIREFLY-1 trial. *Neuro Oncol* noae274, 2024
32. Reinhold WC, Sunshine M, Liu H, et al: CellMiner: A web-based suite of genomic and pharmacologic tools to explore transcript and drug patterns in the NCI-60 cell line set. *Cancer Res* 72:3499-3511, 2012
33. Reference deleted
34. Iorio F, Knijnenburg TA, Vis DJ, et al: A landscape of pharmacogenomic interactions in cancer. *Cell* 166:740-754, 2016
35. Yang W, Soares J, Grenier P, et al: Genomics of Drug Sensitivity in Cancer (GDSC): A resource for therapeutic biomarker discovery in cancer cells. *Nucleic Acids Res* 41:D955-D961, 2013
36. Lin GL, Wilson KM, Cerbelli M, et al: Therapeutic strategies for diffuse midline glioma from high-throughput combination drug screening. *Sci Transl Med* 11:eaaw0064, 2019
37. Lee DW, Choi YS, Seo YJ, et al: High-throughput screening (HTS) of anticancer drug efficacy on a micropillar/microwell chip platform. *Anal Chem* 86:535-542, 2014
38. Singh K, Hotchkiss KM, Parney IF, et al: Correcting the drug development paradigm for glioblastoma requires serial tissue sampling. *Nat Med* 29:2402-2405, 2023
39. Wagner C, Langer O: Approaches using molecular imaging technology—Use of PET in clinical microdose studies. *Adv Drug Deliv Rev* 63:539-546, 2011
40. Ballard P, Yates JWT, Yang Z, et al: Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. *Clin Cancer Res* 22:5130-5140, 2016
41. Burt T, Young G, Lee W, et al: Phase 0/microdosing approaches: Time for mainstream application in drug development? *Nat Rev Drug Discov* 19:801-818, 2020
42. Mendelson JH, Woods BT, Chiu TM, et al: *In vivo* proton magnetic resonance spectroscopy of alcohol in human brain. *Alcohol* 7:443-447, 1990
43. De La Fuente MI, Young RJ, Rubel J, et al: Integration of 2-hydroxyglutarate-proton magnetic resonance spectroscopy into clinical practice for disease monitoring in isocitrate dehydrogenase-mutant glioma. *Neuro Oncol* 18:283-290, 2016
44. Suh CH, Kim HS, Jung SC, et al: 2-Hydroxyglutarate MR spectroscopy for prediction of isocitrate dehydrogenase mutant glioma: A systemic review and meta-analysis using individual patient data. *Neuro Oncol* 20:1573-1583, 2018
45. Andronesi OC, Rapalino O, Gerstner E, et al: Detection of oncogenic IDH1 mutations using magnetic resonance spectroscopy of 2-hydroxyglutarate. *J Clin Invest* 123:3659-3663, 2013
46. Andronesi OC, Arrillaga-Romany IC, Ly KI, et al: Pharmacodynamics of mutant-IDH1 inhibitors in glioma patients probed by *in vivo* 3D MRS imaging of 2-hydroxyglutarate. *Nat Commun* 9:1474-1479, 2018
47. Schreck KC, Hsu FC, Berrington A, et al: Feasibility and biological activity of a ketogenic/intermittent-fasting diet in patients with glioma. *Neurology* 97:E953-E963, 2021
48. Li Y, Chen H, Xu J, et al: CEST theranostics: Label-free MR imaging of anticancer drugs. *Oncotarget* 7:6369-6378, 2016
49. Wen PY, Cloughesy TF, Olivero AG, et al: First-in-human phase I study to evaluate the brain-penetrant PI3K/mTOR inhibitor GDC-0084 in patients with progressive or recurrent high-grade glioma. *Clin Cancer Res* 26:1820-1828, 2020
50. Ellingson BM, Yao J, Raymond C, et al: Multiparametric MR-PET imaging predicts pharmacokinetics and clinical response to GDC-0084 in patients with recurrent high-grade glioma. *Clin Cancer Res* 26:3135-3144, 2020
51. Galldiks N, Werner JM, Stetter I, et al: Evaluation of early metabolic changes following vorasidenib using FET PET in patients with IDH-mutant gliomas. *Neurooncol Adv* 6:vdae210, 2024
52. Kamson DO, Chinnasamy V, Grossman SA, et al: *In-vivo* magnetic resonance spectroscopy of lactate as a non-invasive biomarker of dichloroacetate activity in cancer and non-cancer central nervous system disorders. *Front Oncol* 13:1077461, 2023
53. Kamson DO, Puri S, Sang Y, et al: Impact of frontline ivosidenib on volumetric growth patterns in isocitrate dehydrogenase-mutant astrocytic and oligodendroglial tumors. *Clin Cancer Res* 29:4863-4869, 2023
54. Strowd R, Ellingson B, Raymond C, et al: Activity of a first-in-class oral HIF2- α inhibitor, PT2385, in patients with first recurrence of glioblastoma. *J Neurooncol* 165:101-112, 2023
55. Ellingson BM, Gerstner ER, Lassman AB, et al: Hypothetical generalized framework for a new imaging endpoint of therapeutic activity in early phase clinical trials in brain tumors. *Neuro Oncol* 24:1219-1229, 2022
56. Graillon T, Sanson M, Campello C, et al: Everolimus and octreotide for patients with recurrent meningioma: Results from the phase II CEVOREM trial. *Clin Cancer Res* 26:552-557, 2020
57. van den Bent MJ, Geurts M, French PJ, et al: Primary brain tumours in adults. *Lancet* 402:1564-1579, 2023
58. Koivunen P, Lee S, Duncan CG, et al: Transformation by the (R)-enantiomer of 2-hydroxyglutarate linked to EGLN activation. *Nature* 2012 483:484-488
59. Noushmehr H, Weisenberger DJ, Diefes K, et al: Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell* 17:510-522, 2010
60. Turcan S, Rohle D, Goenka A, et al: IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature* 483:479-483, 2012
61. de la Fuente MI, Touat M, van den Bent MJ, et al: The role of vorasidenib in the treatment of isocitrate dehydrogenase-mutant glioma. *Neuro Oncol* noae259, 2024
62. Mellinghoff IK, Penas-Prado M, Peters KB, et al: Vorasidenib, a dual inhibitor of mutant IDH1/2, in recurrent or progressive glioma; results of a first-in-human phase I trial. *Clin Cancer Res* 27:4491-4499, 2021
63. Mellinghoff IK, Lu M, Wen PY, et al: Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: A randomized, perioperative phase 1 trial. *Nat Med* 29:615-622, 2023
64. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al: Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N Engl J Med* 389:589-601, 2023
65. de la Fuente MI, Colman H, Rosenthal M, et al: Olutasidenib (FT-2102) in patients with relapsed or refractory IDH1-mutant glioma: A multicenter, open-label, phase Ib/II trial. *Neuro Oncol* 25:146-156, 2023
66. Mellinghoff IK, Ellingson BM, Touat M, et al: Ivosidenib in isocitrate dehydrogenase 1-mutated advanced glioma. *J Clin Oncol* 38:3398-3406, 2020
67. Natsume A, Arakawa Y, Narita Y, et al: The first-in-human phase I study of a brain-penetrant mutant IDH1 inhibitor DS-1001 in patients with recurrent or progressive IDH1-mutant gliomas. *Neuro Oncol* 25:326-336, 2023
68. Wen PY, Stein A, van den Bent M, et al: Dabrafenib plus trametinib in patients with BRAFV600E-mutant low-grade and high-grade glioma (ROAR): A multicentre, open-label, single-arm, phase 2, basket trial. *Lancet Oncol* 23:53-64, 2022
69. Bouffet E, Hansford JR, Garré ML, et al: Dabrafenib plus trametinib in pediatric glioma with BRAF V600 mutations. *N Engl J Med* 389:1108-1120, 2023
70. Pant S, Schuler M, Iyer G, et al: Erdafitinib in patients with advanced solid tumours with FGFR alterations (RAGNAR): An international, single-arm, phase 2 study. *Lancet Oncol* 24:925-935, 2023
71. Picca A, Di Stefano AL, Savatovsky J, et al: Target: A phase I/II open-label multicenter study to assess safety and efficacy of hexagratinib in patients with relapsed/refractory FGFR fusion-positive glioma. *Neurooncol Adv* 6:vdae068, 2024
72. Doz F, van Tilburg CM, Georger B, et al: Efficacy and safety of larotrectinib in TRK fusion-positive primary central nervous system tumors. *Neuro Oncol* 24:997-1007, 2022
73. Desai AV, Robinson GW, Gauvain K, et al: Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG). *Neuro Oncol* 24:1776-1789, 2022
74. Krueger DA, Care MM, Holland K, et al: Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N Engl J Med* 363:1801-1811, 2010
75. Peters K, Mellinghoff I, van den Bent M, et al: QOL-26. A randomized, double-blind phase 3 study of vorasidenib vs placebo in patients with mutant IDH1/2/DIFFUSE glioma (INDIGO): Analysis of health-related quality of life, neurocognition and seizures. *Neuro Oncol* 25:v254-v255, 2023 (suppl 5)
76. Mellinghoff IK, van den Bent MJ, Touat M, et al: CTNI-53. A global, randomized, double-blinded, phase 3 study of vorasidenib versus placebo in patients with adult-type diffuse glioma with an IDH1/2 mutation (INDIGO): Updated efficacy results. *Neuro Oncol* 26:viii108-viii109, 2024 (suppl 8)
77. Van Den Bent MJ: Interobserver variation of the histopathological diagnosis in clinical trials on glioma: A clinician's perspective. *Acta Neuropathol* 120:297-304, 2010
78. Darlix A, Rigau V, Fraisse J, et al: Postoperative follow-up for selected diffuse low-grade gliomas with WHO grade III/IV foci. *Neurology* 94:E830-E841, 2020
79. von Deimling A, Ono T, Shirahata M, et al: Grading of diffuse astrocytic gliomas: A review of studies before and after the advent of IDH testing. *Semin Neurol* 38:19-23, 2018
80. van der Vaart T, Wijnenga MMJ, van Garderen K, et al: Differences in the prognostic role of age, extent of resection, and tumor grade between astrocytoma IDHmt and oligodendroglioma: A single-center cohort study. *Clin Cancer Res* 30:3837-3844, 2024

81. Elia A, Roux A, Trancart B, et al: Watch-and-wait approach versus adjuvant treatment after radical awake resection in selected adult-type grade 3 gliomas, isocitrate dehydrogenase mutant: A case-matched cohort. *Neurooncol Adv* 6:vdae189, 2024
82. Preusser M, Geurts M, Hainfellner JA, et al: What is an isocitrate dehydrogenase-mutated central nervous system World Health Organization grade 2 glioma, or who should receive vorasidenib? *Neuro Oncol* 25:1915-1917, 2023
83. Darlix A, Preusser M, Hervey-Jumper SL, et al: Who will benefit from vorasidenib? Review of data from the literature and open questions. *Neurooncol Pract* 12:i6-i18, 2025 (suppl 1)
84. Still MEH, Moor RSF, Ghiaseddin AP, et al: How do I prescribe and manage mIDH inhibitors in patients with IDH-mutant glioma? *Neurooncol Pract* 12:i19-i25, 2025 (suppl 1)
85. Patel MP, Serventi JN, Dunbar EM, et al: Vorasidenib: Patient and caregiver information sheet. *Neurooncol Pract* 12:i26-i28, 2025 (suppl 1)
86. Peters KB, Alford C, Heltemes A, et al: Use, access, and initial outcomes of off-label ivosidenib in patients with IDH1 mutant glioma. *Neurooncol Pract* 11:199-204, 2024
87. Rodon J, Goyal L, Mercade TM, et al: Abstract CT098: A first-in-human phase 1 study of LY3410738, a covalent inhibitor of mutant IDH, in advanced IDH-mutant cholangiocarcinoma and other solid tumors. *Cancer Res* 83:CT098, 2023 (suppl 8)
88. Wick A, Bahr O, Schuler M, et al: Phase I assessment of safety and therapeutic activity of BAY1436032 in patients with IDH1-mutant solid tumors. *Clin Cancer Res* 27:2723-2733, 2021
89. Wen P, Mellinghoff I, van den Bent M, et al: LTBK-06. Impact of vorasidenib treatment on mutant IDH1 or IDH2 diffuse glioma tumor growth rate: Results from the randomized, double-blind, phase 3 INDIGO study. *Neuro Oncol* 25:v310-v311, 2023 (suppl 5)
90. Chang F, Steelman LS, Lee JT, et al: Signal transduction mediated by the Ras/Raf/MEK/ERK pathway from cytokine receptors to transcription factors: Potential targeting for therapeutic intervention. *Leukemia* 17:1263-1293, 2003
91. Dankner M, Rose AAN, Rajkumar S, et al: Classifying BRAF alterations in cancer: New rational therapeutic strategies for actionable mutations. *Oncogene* 37:3183-3199, 2018
92. Andrews LJ, Thornton ZA, Saincher SS, et al: Prevalence of BRAF V600 in glioma and use of BRAF inhibitors in patients with BRAF V600 mutation-positive glioma: Systematic review. *Neuro Oncol* 24:528-540, 2022
93. Schindler G, Capper D, Meyer J, et al: Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol* 121:397-405, 2011
94. Vuong HG, Altibi AMA, Duong UNP, et al: BRAF mutation is associated with an improved survival in glioma-A systematic review and meta-analysis. *Mol Neurobiol* 55:3718-3724, 2018
95. Schreck KC, Langat P, Bhawe VM, et al: Integrated molecular and clinical analysis of BRAF-mutant glioma in adults. *NPJ Precis Oncol* 7:23-11, 2023
96. Blaquier JB, D'Angelo F, Tejera D, et al: Abstract 5137: BRAF mutations in primary central nervous system tumors. *Cancer Res* 84:5137, 2024 (suppl 6)
97. Falchook GS, Long GV, Kurzrock R, et al: Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: A phase 1 dose-escalation trial. *Lancet* 379:1893-1901, 2012
98. Flaherty KT, Puzanov I, Kim KB, et al: Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med* 363:809-819, 2010
99. Poulikakos PI, Zhang C, Bollag G, et al: RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. *Nature* 464:427-430, 2010
100. Flaherty KT, Infante JR, Daud A, et al: Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 367:1694-1703, 2012
101. Novartis Pharmaceuticals Corporation: Tafinlar (dabrafenib) [package insert]. 2025
102. Zhang C, Spevak W, Zhang Y, et al: RAF inhibitors that evade paradoxical MAPK pathway activation. *Nature* 526:583-586, 2015
103. De La Fuente MI, Rodon Ahnert J, Yaeger R, et al: Safety and efficacy of the novel BRAF inhibitor FORE8394 in patients with advanced solid and CNS tumors: Results from a phase 1/2a study. *J Clin Oncol* 41, 2023 (suppl 16; abstr 3006)
104. de la Fuente MI, Lassman AB: Pre-radiation targeted therapy for highly selected patients with newly diagnosed glioblastoma: New tricks for an old dog? *Neuro Oncol* noaf014, 2025
105. Thomas SM, DeMarco M, D'Arcangelo G, et al: Ras is essential for nerve growth factor- and phorbol ester-induced tyrosine phosphorylation of MAP kinases. *Cell* 68:1031-1040, 1992
106. Kao S, Jaiswal RK, Kolch W, et al: Identification of the mechanisms regulating the differential activation of the MAPK cascade by epidermal growth factor and nerve growth factor in PC12 cells. *J Biol Chem* 276:18169-18177, 2001
107. Holgado-Madruga M, Moscatello DK, Emlet DR, et al: Grb2-associated binder-1 mediates phosphatidylinositol 3-kinase activation and the promotion of cell survival by nerve growth factor. *Proc Natl Acad Sci USA* 94:12419-12424, 1997
108. Okamura R, Boichard A, Kato S, et al: Analysis of NTRK alterations in pan-cancer adult and pediatric malignancies: Implications for NTRK-targeted therapeutics. *JCO Precis Oncol* [10.1200/PO.18.00183](#)
109. Wu G, Diaz AK, Paugh BS, et al: The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. *Nat Genet* 46:444-450, 2014
110. Drilon A, Laetsch TW, Kummar S, et al: Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 378:731-739, 2018
111. Menichincheri M, Ardini E, Magnaghi P, et al: Discovery of entrectinib: A new 3-aminoindazole as a potent anaplastic lymphoma kinase (ALK), c-ros oncogene 1 kinase (ROS1), and pan-tropomyosin receptor kinases (Pan-TRKs) inhibitor. *J Med Chem* 59:3392-3408, 2016
112. Doebele RC, Drilon A, Paz-Ares L, et al: Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. *Lancet Oncol* 21: 271-282, 2020
113. Grogan PT, Deming DA, Helgager J, et al: Entrectinib demonstrates prolonged efficacy in an adult case of radiation-refractory NTRK fusion glioblastoma. *Neurooncol Adv* 4:vdae046, 2022
114. Cerretti G, Padovan M, Guerriero A, et al: Prolonged response to entrectinib in an adult patient with recurrent glioblastoma harboring a GOPC::ROS1 fusion. *Neurooncol Adv* 6:vdae077, 2024
115. Liu D, Flory J, Lin A, et al: Characterization of on-target adverse events caused by TRK inhibitor therapy. *Ann Oncol* 31:1207-1215, 2020
116. Crino PB, Nathanson KL, Henske EP: The tuberous sclerosis complex. *N Engl J Med* 355:1345-1356, 2006
117. Goh S, Butler W, Thiele EA: Subependymal giant cell tumors in tuberous sclerosis complex. *Neurology* 63:1457-1461, 2004
118. Chan JA, Zhang H, Roberts PS, et al: Pathogenesis of tuberous sclerosis subependymal giant cell astrocytomas: Biallelic inactivation of TSC1 or TSC2 leads to mTOR activation. *J Neuropathol Exp Neurol* 63:1236-1242, 2004
119. Franz DN, Agricola K, Mays M, et al: Everolimus for subependymal giant cell astrocytoma: 5-year final analysis. *Ann Neurol* 78:929-938, 2015
120. Morin E, Apfelbaum AA, Sturm D, et al: A diverse landscape of FGFR alterations and co-mutations defines novel therapeutic strategies in pediatric low-grade gliomas. *bioRxiv* 19: 2024.08.27.609922, 2024
121. Di Stefano AL, Picca A, Saragoussi E, et al: Clinical, molecular, and radiomic profile of gliomas with FGFR3-TACC3 fusions. *Neuro Oncol* 22:1614-1624, 2020
122. Singh D, Chan JM, Zoppoli P, et al: Transforming fusions of FGFR and TACC genes in human glioblastoma. *Science* 337:1231-1235, 2012
123. Yoshihara K, Wang Q, Torres-Garcia W, et al: The landscape and therapeutic relevance of cancer-associated transcript fusions. *Oncogene* 34:4845-4854, 2015
124. Lasorella A, Sanson M, Iavarone A: FGFR-TACC gene fusions in human glioma. *Neuro Oncol* 19:475-483, 2017
125. Louis DN, Perry A, Reifenberger G, et al: The 2016 World Health Organization classification of tumors of the central nervous system: A summary. *Acta Neuropathol* 131:803-820, 2016
126. Fougner V, Urup T, Poulsen HS, et al: Actionable alterations in glioblastoma: Insights from the implementation of genomic profiling as the standard of care from 2016 to 2023. *Neurooncol Pract* 12:34-44, 2025
127. Jones DTW, Kocalkowski S, Liu L, et al: Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. *Cancer Res* 68:8673-8677, 2008
128. Dias-Santagata D, Lam Q, Vernovsky K, et al: BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: Diagnostic and therapeutic implications. *PLoS One* 6:e17948, 2011

One Step Ahead: Preventing Tumor Adaptation to Immune Therapy

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OVERVIEW

Immune checkpoint inhibitors are cancer therapeutics that have shown remarkable success in extending lives in many cancers, including melanoma, MSI-high cancers, and other cancers. However, these therapeutics have not shown benefit for many patients with cancer, especially those with advanced cancer diagnoses. In addition, many patients develop resistance to these therapeutics and/or life-altering adverse events that can include cardiotoxicity, pneumonitis, thyroiditis, pancreatitis, and hepatitis. Extensive efforts to improve cancer care by uncovering mechanisms of resistance to immune therapy in solid tumors have led to identification of new sources of resistance and to the development of new approaches to activate or sustain antitumor immunity. Chronic stimulation of T cells by tumors and by checkpoint inhibitors can lead to a progressive state of T-cell exhaustion. Chronic T-cell activation by the tumor microenvironment (TME) or immune therapeutics can upregulate the expression and function of alternate checkpoints, including the T-cell protein LAG-3. Persistent interferon signaling in the TME can drive epigenetic changes in cancer cells that enable tumors to counter immune activation and disrupt tumor cell elimination. In addition, immune-suppressive macrophages can flood tumors in response to signals from dying tumor cells, further preventing effective immune responses. New clinical developments and/or approvals for therapies that target alternate immune checkpoints, such as the T-cell checkpoint LAG-3; myeloid cell proteins, such as the kinase phosphoinositide 3-kinase gamma isoform; and chronic interferon signaling, such as Jak 1 inhibitors, have been approved for cancer care or shown promise in recent clinical trials.

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INTRODUCTION

In 2018, the Nobel Prize for Medicine was awarded to James Allison and Tasuko Honjo for identification of novel strategies to promote antitumor immunity. These investigators made fundamental observations that proteins expressed on the surface of chronically stimulated T cells, PD-1 and CTLA-4, suppressed T-cell functions, thereby rendering T cells exhausted.¹⁻⁴ Antibody inhibitors of PD-1 and CTLA-4, nivolumab (nivo)/pembrolizumab and ipilimumab, respectively, have shown remarkable success as cancer therapeutics and are approved widely for treatment of patients with cancer.^{5,6} A 10-year study of patients with melanoma treated with nivo plus ipilimumab versus either antibody alone recently showed that 43% of dual antibody-treated patients with melanoma survived a median of 10 years.⁷ Additional inhibitory immune checkpoints LAG-3, TIGIT, TIM3, and GITR and activating checkpoints ICOS, 4-1BB, OX40, and CD40 have since been identified and therapeutically targeted.⁸ While showing remarkable success in Hodgkin's lymphoma, melanoma, microsatellite instability (MSI)-high cancers, and some other cancers, immune checkpoint blockade (ICB) therapeutics have not yet shown benefit for many patients with cancer, especially those with

advanced cancer diagnoses.⁹⁻¹¹ In addition, many patients eventually develop resistance to ICB and/or life-altering adverse events that can include cardiotoxicity, pneumonitis, thyroiditis, pancreatitis, and hepatitis.¹²

The development and commercialization of chimeric antigen receptor T (CAR-T) cells has also revolutionized cancer care. CAR-T cells are autologous T cells transduced to express engineered cell surface receptors for tumor cells with intracellular motifs designed to activate T-cell proliferation and cytotoxicity.¹³ CAR-T-cell therapy has achieved notable success in some hematologic cancers, including acute lymphoblastic leukemia, non-Hodgkin's lymphoma, and multiple myeloma. Although a revolutionary development, CAR-T-cell therapy has not yet achieved clinical approval for treatment of solid tumors.¹⁴ Lack of persistence or penetrance in the tumor microenvironment (TME) and toxicity are the main causes for failure of solid tumor CAR-T therapy.¹⁴ Improvements in CAR-T construction include enhancing the affinity of the tumor cell-targeting receptor, adding elements to improve trafficking to the TME, and adding signaling domains to maintain T-cell activation through autocrine IL12 expression.¹⁵ Combination of CAR-T therapy with other

PRACTICAL APPLICATIONS

- Immune checkpoint inhibitors have revolutionized cancer therapy.
- Resistance to immune checkpoint blockade (ICB) develops from upregulation of alternative checkpoints, myeloid cell recruitment, and tumor fibrosis.
- Myeloid cell–targeted therapies, including phosphoinositide 3-kinase gamma isoform inhibitors, show promise as immune therapeutics used in conjunction with T-cell–targeted therapeutics.
- LAG-3 is an exciting new target for ICB, with numerous clinical trials and alternative agents in clinical development.
- Jak1 inhibition restores responsiveness to checkpoint inhibitors in resistant tumors.

immune therapeutic approaches promises to sustain efficacy for the success of this novel therapeutic approach. Additional approaches to restore antitumor immunity include novel engineered bispecific antibodies (BsAbs) that bind to CD3 on T cells and a tumor cell–specific antigen BiTEs.¹⁶ Extensive efforts to uncover mechanisms of resistance to immune therapy in solid tumors have led to new clinical developments and/or approvals for therapies discussed in this article.

OVERVIEW OF MECHANISMS OF RESISTANCE TO IMMUNE THERAPY

Primary or acquired resistance to immune therapy can arise because of treatment selection pressures that lead to genetic changes in tumor cells; wound healing responses of the microenvironment to therapy-induced damage that can result in increased blood vessel development (angiogenesis), macrophage accumulation, and deposition of extracellular matrix that resembles granulomas; and upregulation of mechanisms in the immune system that prevent over-responsiveness to stimuli. Antigen presentation by tumor cell major histocompatibility complex (MHC) I is essential to enable T cells to target and kill tumor cells. A high tumor mutational burden, which can generate numerous neoantigens, has been associated with responsiveness to anti-PD-1 therapy.¹⁷ Heterozygosity of MHC I protein (MHC 1) loci is also associated with enhanced responsiveness to checkpoint inhibitors.¹⁸ Loss of antigen presentation in tumors caused by somatic loss of heterozygosity at MHC-I loci,¹⁹ loss of $\beta 2$ macroglobulin expression on tumor cells,²⁰ and loss of responsiveness to interferon gamma (IFN γ) because of inactivating or deletion mutations of *JAK1*, *JAK2*, or other

IFN γ response genes can promote resistance to therapy.²⁰ Therapeutic resistance can also occur by immunoediting, when activated T cells eliminate tumor cells bearing recognized neoantigens, leaving behind viable tumor cells that are no longer recognized by host T cells.²¹ In some tumors, persistent interferon production by immune cells and chronic interferon signaling in tumor cells lead to T-cell exhaustion and resistance to immune therapy.²² Inhibition of JAK1 signaling can prevent T-cell exhaustion and break resistance to checkpoint inhibitors in animal models of cancer.²³ Accordingly, the JAK1 inhibitor itacitinib promoted T-cell differentiation toward nonexhausted states when added to anti-PD-1 in patients with non–small cell lung cancer (NSCLC) who had previously shown resistance to anti-PD-1 therapy.²³ In addition, the Jak1/2 inhibitor ruxolitinib reduced neutrophil/lymphocyte ratios and immune-suppressive myeloid cell content and enhanced the efficacy of anti-PD-1 therapy in animal models of solid and hematologic tumors.²⁴ Ruxolitinib combined with nivolumab also improved response rates in patients with Hodgkin lymphoma who were previously refractory to anti-PD-1.²⁴ These paradoxical findings resemble those observed in studies of chronic viral infection; limited interferon signaling is required for effective immune responses, but chronic interferon signaling suppresses T-cell function because of upregulation of a host of immune-suppressive interferon–stimulated genes (ISGs), including immune checkpoints. Thus, mutations and changes in the TME that interfere with effective immune activation or persistent signaling from ineffective immune responses can each promote immunotherapy resistance.

Chronic T-cell activation by the TME or ICB therapy can upregulate the expression and function of a variety of immune checkpoint molecules, including PD-1, PD-L1, CTLA-4, LAG-3, TIM-3, TIGIT,²⁵ and others. Chronic stimulation of T cells leads to a progressive state of T-cell exhaustion.²⁶ Immune checkpoint inhibitors (ICIs) target coinhibitory molecules present on the surface of exhausted T cells, restoring T-cell function²⁷ and/or preventing the exhaustion of new T-cell clones that are recruited to the tumor.²⁸ The US Food and Drug Administration (FDA) has approved several ICIs, including monoclonal antibodies against PD-1 (nivo, pembrolizumab, and cemiplimab), CTLA-4 (ipilimumab), and LAG-3 (relatlimab), whereas additional inhibitors of TIM-3 and TIGIT are currently undergoing clinical trials (Table 1). Despite the notable clinical achievements with these inhibitors, some patients still do not exhibit a positive response, and others develop resistance mechanisms to even combinatorial ICIs.

Three key mechanisms may be most significant in generating resistance to targeted immune therapy: dysregulation of immune responses and chronic inflammatory signaling leading to expression of alternative immune checkpoints; immune-suppressive environments created by macrophages, neutrophils, or regulatory B cells^{53,54}; and a profibrotic microenvironment driven by TGF β

TABLE 1. Immune-Oncology Therapeutics

Therapeutic Name	Target	Commercial Name	Clinical Status	Indication	Reference
Ipilimumab	CTLA-4	Yervoy	Approved in 2011	MEL, NSCLC, RCC, others	4-7,29
Pembrolizumab	PD-1	Keytruda	Approved in 2014	MEL, NSCLC, others	30
Nivolumab	PD-1	Opdivo	Approved in 2014	MEL, NSCLC, others	6,7,29
Cemiplimab	PD-1	Libtayo	Approved in 2018	cSCC, BCC, NSCLC	30
Dostarlimab	PD-1	Jemperli	Approved in 2021	EC	30
Atezolizumab	PD-L1	Tecentriq	Approved in 2016	TCC, NSCLC, SCLC, others	30
Durvalumab	PD-L1	Imfinzi	Approved in 2017	MCC, TCC, RCC	30
Avelumab	PD-L1	Bavencio	Approved in 2017	MCC, TCC, RCC	30
Relatlimab	LAG-3	Opdualag (relatlimab + nivo)	Approved in 2022	MEL	31-35
Fianlimab	LAG-3	NA	Phase III (NCT05352672)	MEL	36
FS118	LAG-3/PD-L1 tetravalent	NA	Phase I/II (NCT03440437)	Advanced malignancies	37
Tebotelimab	LAG-3/PD-1 bispecific	NA	Phase II/III (NCT04082364)	HER2+ GC, HER2+ GJC	38
Verzistobart	TIM-3	NA	Phase II (NCT06056895)	MCC	25
Cobolimab	TIM-3	NA	Phase II (NCT03680508)	HCC	25
Ociperlimab	TIGIT	NA	Phase II (NCT04952597)	SCLC	25
SX-682	CXCR1, CXCR2	NA	Phase I (NCT03161431) Phase Ib/II (NCT04599140)	mMEL RAS-mutated MSS with or without mCRC	39
AZD5069	CXCR2	NA	Phase I/II (NCT03177187)	mCRPC	40
Emactuzumab	CSFR1	NA	Phase III (NCT05417789)	TGCT	41
Pexidartinib	CSF1R, KIT, PDGFR	Turalio	Approved in 2019	TGCT	42,43
Eganelisib	PI3Kγ	NA	Phase II (NCT03961698)	TNBC, TCC, HNSCC, others	44-48
Ruxolitinib	JAK1/2	Jakafi	Approved in 2011	Myelofibrosis	24
Itacitinib	JAK1	NA	Phase II (NCT03425006) Phase I/Ib (NCT04358185)	mNSCLC, HCC	23
Cabozantinib	MERTK/AXL	Cabometyx	Approved in 2016	RCC, HCC, DTC	49-51
PY314	TREM2	NA	Phase Ia/Ib (NCT04691375)	Advanced solid tumors	52

NOTE. A summary of select immune-oncology therapeutics that have been FDA-approved and/or evaluated in clinical trials for the treatment of cancer. Details include assigned drug name, molecular target, commercial name, clinical trial or approval status, medical indication, and select literature references.

Abbreviations: BCC, basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; CTLA-4, cytotoxic T lymphocyte associated protein 4; DTC, differentiated thyroid cancer; EC, endometrial cancer; FDA, US Food and Drug Administration; GC, gastric cancer; GJC, gastroesophageal junction cancer; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HNSCC, head and neck squamous cell carcinoma; MCC, Merkel cell carcinoma; mCRC, metastatic colorectal cancer; mCRPC, metastatic castration-resistant prostate cancer; MEL, melanoma; mMEL, metastatic melanoma; mNSCLC, metastatic non-small cell lung cancer; MSS, microsatellite-stable; NA, not applicable; nivo, nivolumab; NSCLC, non-small cell lung cancer; PI3Kγ, phosphoinositide 3-kinase gamma isoform; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TCC, urothelial carcinoma; TGCT, tenosynovial giant cell tumor; TNBC, triple-negative breast cancer.

signaling that inhibits T-cell migration, proliferation, and survival.⁵⁵ Tumor microenvironments have been classified into three broad categories based on the presence and localization of T cells: T-cell–inflamed, in which abundant CD8⁺ T cells are closely associated with tumor cells; T-cell–excluded, in which T cells are present in larger numbers but are unable to approach tumor cells; and T-cell deserts, in which no T cells are present.⁵⁶ Of these subsets, T-cell–inflamed tumors are the most responsive to ICB therapy.⁵⁶ Consequently, there is a need to understand key signals and cellular features that maintain suppressive TMEs to develop innovative strategies to enhance patient response and survival (Table 2).

MYELOID CELL–MEDIATED RESISTANCE TO THERAPY

Immunosuppressive myeloid cells, which can include macrophages, dendritic cells, and immune-suppressive monocytes and granulocytes (sometimes called myeloid-derived suppressor cells [MDSCs]), play significant roles in promoting resistance to immune therapy within the TME.⁵⁷ Tumors are often characterized by large increases in immune-suppressive CD206⁺ macrophages or granulocytes when compared with normal tissues.⁵⁴ Immunosuppressive myeloid cells can enhance the stemness, survival, and proliferation of cancer cells through the secretion of cytokines such as insulin-like growth factor, transforming

TABLE 2. Advantages and Disadvantages of Immune Therapy Approaches

Target	Therapies	Clinical Status	Advantages	Disadvantages
CTLA-4	Ipilimumab	Approved	Increased T-cell activity, durable clinical responses	Grade 3-5 irAEs more frequent than with other ICBs; variable responses; lack of biomarkers for predicting response
PD-1	Nivolumab Pembrolizumab and others	Approved	Increases T-cell activity; enhances patient survival	Resistance can develop; grade 3-4 irAEs are frequent; grade 5 irAE is possible
PD-L1	Atezolizumab Durvalumab and others	Approved	Increased T-cell activity, durable clinical responses	Resistance can develop; irAEs are possible
LAG-3	Relatlimab	Approved	Synergy with anti-PD-1, increased T-cell activity when combined with anti-PD-1	Grade 3-4 irAEs. No definitive biomarkers associated with response to anti-LAG-3
TIM-3	Verzistobart Cobolimab	Phase II	Synergy with anti-PD-1, increased T-cell proliferation and immune function	Limited clinical activity as monotherapy
TIGIT	Ociperlimab	Phase III	Synergy with PD-1, increases T-cell and NK functions and memory T cells	Variable response rates; lack of biomarkers for predicting immunotherapy response
CAR-T	Tisagenlecleucel, brexucabtagene autoleucel, axicabtagene ciloleucel, lisocabtagene maraleucel, ciltacabtagene autoleucel	Approved for hematologic tumors	Efficient in hematologic cancer	Not yet effective in solid tumors Secondary hematologic malignancies after CAR-T therapy Grade 3-4 irAEs
CAR-M	CT-0525 CT-0508	Phase I	Synergy with ICB Reduced ctDNA levels, remodeled TME, T-cell activation	Lack of durable responses (first generation)
CSF1R	Pexidartinib	Approved	In combination with paclitaxel, potential for mitigating macrophage tumor infiltration	Reversible aminotransferase elevation. Severe or permanent adverse events (cholestatic hepatotoxicity) possible
JAK1/2	Ruxolitinib	Approved	Prevents T-cell exhaustion, breaks resistance to ICB, reduces suppressive myeloid cell content	Resistance induced by mutations Infectious adverse events
PI3K γ	Eganelisib	Phase II	Myeloid cell–mediated T-cell activation; synergy with chemotherapy, ICB	Elevation of ALT and AST; limited clinical activity as monotherapy
TREM2	PY314	Phase I/II	Modulates the immunosuppressive TME, synergy with ICB	Variable impact in tumor growth, may lead to resistance, can impede maturation and function of NK cells

NOTE. This table presents a summary of the advantages and disadvantages of select immune-oncology therapeutics that have been FDA-approved and/or evaluated in clinical trials for the treatment of cancer. Details include assigned drug name, molecular target, commercial name, clinical status, benefits of the named therapeutic, and disadvantages of the therapeutic.

Abbreviations: CAR-M, chimeric antigen receptor macrophage; CAR-T, chimeric antigen receptor T; ctDNA, circulating tumor DNA; CTLA-4, cytotoxic T lymphocyte associated protein 4; FDA, US Food and Drug Administration; ICBs, immune checkpoint blockades; irAEs, immune-related adverse events; NK, natural killer; PI3K γ , phosphoinositide 3-kinase gamma isoform; TME, tumor microenvironment.

growth factor β , and interleukin 6 family member; facilitate angiogenesis through the production of vascular endothelial growth factors (VEGFs), platelet derived growth factors, and other factors; stimulate fibrotic responses through direct and indirect regulation of extracellular matrix protein secretion; and suppress innate and adaptive immune responses.⁵⁴ Tumor-associated macrophages promote resistance to immune checkpoint inhibitors as they express checkpoint ligands, such as PD-L1, PD-L2, CD80, CD86, and CD155, a TIGIT ligand.⁵⁸ However, macrophages are versatile, exhibit tissue-specific differences, and can

adopt proinflammatory phenotypes, whereupon they can stimulate adaptive immune responses and eliminate tumor cells.⁵⁹ Attempts to modulate the trafficking and gene expression of these populations to enhance immunotherapy are currently underway.⁵⁴ Strategies to target myeloid cell–mediated immune suppression clinically have included inhibitors of the macrophage growth factor receptor CSF1R,⁴² myeloid cell trafficking receptors such as CCR2⁶⁰ and³⁹ CXCR2,³⁹ macrophage signaling receptors MERTK/AXL,⁴⁹ regulators of lipid processing, such as TREM2,⁵² and myeloid cell–specific kinases such as phosphoinositide 3-kinase

gamma isoform (PI3K γ).⁶¹ While none of these approaches have yet been approved for widespread use in cancer, their examination in combination therapies with ICB and targeted therapies is actively under investigation, and current studies suggest that these novel therapeutic approaches will provide clinical benefit to a wide range of patients with cancer.

PI3K γ INHIBITORS IN CANCER IMMUNE THERAPY

One therapeutic approach that has shown promise in animal models of cancer and in early clinical trials is the use of selective inhibitors of PI3K γ . The PI3K family of lipid kinases phosphorylates phosphatidylinositol in response to growth factor or G protein–coupled receptor (GPCR) signaling, thereby playing crucial roles in regulating receptor signaling leading to cell proliferation, migration, vascular permeability, and metabolic changes and immune responses.⁶² The class 1A PI3K isoform alpha (PIK3CA) has been identified as a frequently mutated driver of cancer progression that also regulates glucose metabolism.⁶² For this reason, inhibitors of this PI3K isoform have proven to be too toxic for broad use in cancer therapy.⁶² However, among the four class I PI3Ks, the class 1B PI3K γ isoform emerged from studies at the University of California, San Diego, as a promising target for myeloid cell–based cancer immunotherapy, with evaluations in several clinical trials demonstrating safety and survival benefits in phase II clinical trials of this therapeutic approach.^{44–48,63–66} PI3K γ is predominantly expressed in myeloid cells and endothelial cells, where it facilitates the trafficking and infiltration of monocytes and granulocytes into tissues and promotes vascular leak.^{48,65} PI3K γ is activated by cytokines in the TME that are ligands for myeloid cell surface receptors, such as CSF1R, VEGFR, IL6 receptor family members, toll-like receptors, and GPCRs.⁴⁸ By controlling a cascade of signal transduction events that include rapid activation of BTK, PLC γ , Rap1a, RIAM, talin, paxillin, and myosin light chain kinase, PI3K γ orchestrates changes in the ordered structure of integrin cytoplasmic tails to promote integrin unfolding and activation, leading to myeloid cell adhesion to endothelium and extravasation of myeloid cells, including MDSCs, into tumors.^{48,66} Inhibition of PI3K γ and other components of this signaling cascade blocks immune-suppressive myeloid cell trafficking to tumors and thereby reduces tumor growth.^{48,66} Thus, PI3K γ plays an essential role in tumor immune suppression by promoting myeloid cell trafficking to tumor tissues.

Tumor-associated macrophages are characterized by fatty acid oxidation, which, in turn, elevates PI3K γ expression, thereby fostering an immune-suppressive macrophage phenotype that promotes weight gain, insulin resistance, and immune suppression.⁶⁷ PI3K γ controls immune-suppressive myeloid cell polarization by inhibiting NF κ B activation and promoting mammalian target of rapamycin/S6 kinase activation, leading to C/CAAT enC/CAAT enhancer binding protein beta-dependent transcription and inhibition of NF κ B-dependent transcription, thereby regulating expression of immune-suppressive factors, such as arginase,⁶³

and preventing expression of IL12, tumor necrosis factor alpha (TNF α), and other proinflammatory factors.⁶³ However, PI3K γ inhibition reprograms myeloid cells to a proinflammatory phenotype that recruits and activates CD8⁺ T cells and NK cells and promotes tumor regression mediated by cytotoxic T cells in mouse models of cancer.⁶³ Inhibition of this kinase reduces myeloid cell trafficking to tumors and changes the microenvironments of some tumors from cold to hot.

PI3K γ inhibition promoted tumor regression and long-term survival and suppressed resistance to ICB in mouse models of head and neck cancer, pancreatic cancer, and melanoma.^{44,63,64} PI3K γ inhibitors were most effective when administered concurrently with checkpoint inhibitors in mouse models. The clinical PI3K γ inhibitor, eganelisib, enhanced responses to nivo in patients with nivo-resistant melanoma and head and neck carcinoma in the phase I trial MARIO1 and enhanced survival when combined with nivo in patients with platinum-refractory urothelial cancer in the phase II trial MARIO275.^{45–47} When combined with atezolizumab and nab-paclitaxel in patients with triple-negative breast cancer in the phase II trial MARIO-3, eganelisib decreased circulating monocytic MDSCs and increased circulating Ki67⁺ memory T cells. Treatment with eganelisib, atezolizumab, and nab-paclitaxel increased human leukocyte antigen-DR⁺ macrophages and granzyme⁺ CD8⁺ T cells in tumors. This therapy also altered the TME by decreasing expression of epithelial mesenchymal transformation genes, such as SPP1, PDGFs, integrins, and matrix metalloproteins while increasing expression of MHC class I and MHC class II antigen-presentation genes, IFN γ signaling genes, and biomarkers of T-cell activation.^{45–47} Thus, PI3K γ inhibitors show promise as effective immune-oncology agents that overcome resistance to ICB in cancer therapy.

Spatial transcriptomics and immune profiling of squamous cell carcinomas revealed that tumors are characterized by the gradual development of an extensive tumor cell–cancer associated fibroblast (CAF) barrier characterized by SPP1⁺ macrophage-CAF interactions, the presence of a dense fibrillar collagen network, and isolation of T cells distant from tumor cells (T-cell exclusion).⁶⁸ The presence of this dense collagen network is associated with a poor prognosis. Macrophages participate in the formation of this dense matrix by expressing proteins that crosslink collagens, fibronectin, and other extracellular matrix components into dense fibrils that appear to entrap T cells. Interestingly, PI3K γ inhibition strongly suppressed tumor desmoplasia/fibrosis and prevented T-cell exclusion in mouse models of cancer.⁶³ Notably, PI3K γ inhibition reduced expression of the gene for osteopontin, *SPP1* (secreted phosphoprotein 1), and upregulated expression of the chemokines *CXCL9* and *CXCL10* in triple-negative breast cancer tumors during recent clinical trials. A low SPP1/*CXCL9* ratio has been shown to be prognostic of good outcomes from ICB therapy.⁶⁹

FUTURE DIRECTIONS FOR MYELOID CELL-TARGETED THERAPY

Some novel cell therapeutic approaches take advantage of unique properties of myeloid cells: chimeric antigen receptor macrophages (CAR-Ms), which are presently undergoing clinical evaluation, are genetically engineered autologous monocyte/macrophage constructs that express CAR with phagocytic and proinflammatory signaling capabilities.⁷⁰ First-generation CAR-Ms were derived from monocytes or macrophages and expressed chimeric antigen constructs targeting tumor cell antigens. These constructs consisted of a single-chain variable region fragment derived from an antibody targeting a tumor cell antigen (eg, EGFR), a hinge domain, a transmembrane domain, and a cytosolic signaling domain such as CD3 ζ or Fc gamma receptor.⁷⁰ These CAR-Ms were capable of promoting tumor cell phagocytosis but were susceptible to reprogramming by the tumor microenvironment and did not have durable impacts on tumor growth.⁷⁰ Second-generation CAR-Ms derived from inducible pluripotent stem cells and transduced to express CAR constructs containing a toll/like interleukin receptor signaling domain of toll-like receptor could sustainably activate NF κ B and proinflammatory transcription and immune stimulation.⁷¹ Sustained inhibition of nuclear factor-erythroid factor 2-related factor 2 also maintained CAR-M activity.⁷² These approaches have shown success in animal studies and have proven to be safe in early-phase clinical trials. CAR-M therapy has also demonstrated synergy with anti-PD-1 and anti-CD47 therapy.⁷⁰ It is interesting to speculate that CAR-Ms and CAR-T cells might 1 day be used together, or their functionalities merged for improved

cellular therapeutic approaches. Combinatorial therapies targeting myeloid cells and T cells offer the potential to enhance and synergize with current therapies (Fig 1).

T-CELL CHECKPOINTS AND RESISTANCE TO THERAPY

Exhausted T cells in the TME chronically express multiple inhibitory receptors (IRs) on their surface, including PD-1, LAG-3, TIM3, CTLA-4, and TIGIT.⁷³ Combinatorial strategies to reinvigorate T cells via blockade of multiple IRs have shown increased benefits in the clinic, with the most common being the combination of nivo (anti-PD-1) and ipilimumab (anti-CTLA4).²⁹ While this regimen leads to enhanced OS in metastatic melanoma, this combination also leads to a higher incidence of severe immune-related adverse events (irAEs). Therefore, investigators are actively searching for IR combinations to enhance antitumor immunity without causing intolerable side effects (Fig 2).

LAG-3 DISCOVERY AND FUNCTION

LAG-3 was originally characterized in the 1990s by Frederic Triebel as a marker of T- and NK cell activation closely related in structure to CD4.⁷⁴ Interest in LAG-3 rose when tumor-infiltrating CD4⁺ and CD8⁺ T cells were noted to coexpress both PD-1 and LAG-3 across multiple tumor models. When these IRs were targeted together, they elicited greater tumor clearance in a preclinical model than either IR alone,⁷⁵ creating the rationale to evaluate anti-LAG-3 in the clinic both alone and in combination with other therapies. There are currently 22 monospecific and bispecific LAG-3-targeted antibody drug candidates in clinical trials (Fig 3).³¹

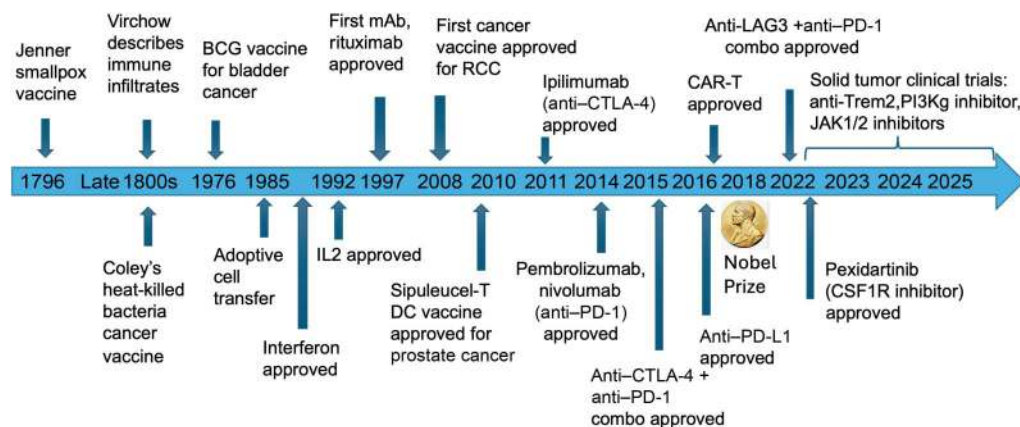


FIG 1. Timeline of cancer immune therapy developments. Key developments in the discovery and clinical use or approval of immune therapy approaches to cancer treatment are depicted in a timeline extending from the late 1700s to the present day. Beginning with Edward Jenner's development of the first formal vaccine against smallpox in 1796 and William Coley's use of heat-killed bacteria to treat patients with sarcoma, the field of cancer immune therapy has enjoyed a long history. The development and approval of precise and targeted immune therapy approaches are accelerating; in the past 15 years, numerous T-cell checkpoints have been described, their checkpoint inhibitors have been developed, and their clinical use has been refined. CAR-T cells have been clinically approved and are being refined. The first myeloid targeted therapy has been approved, and numerous others are in clinical or preclinical development. BCG, Bacillus Calmette-Guerin; CAR-T, chimeric antigen receptor T; CTLA-4, cytotoxic T lymphocyte associated protein 4; DC, dendritic cell; IL2, interleukin-2; mAb, monoclonal antibodies; RCC, renal cell carcinoma.

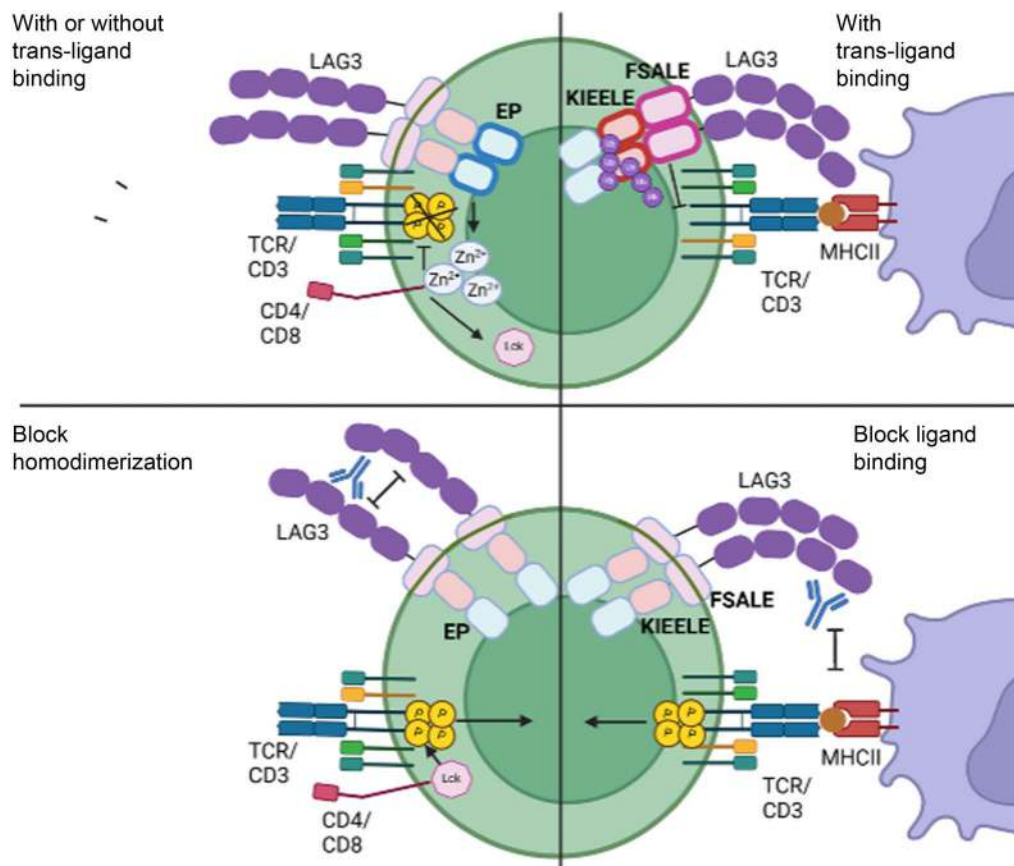


FIG 2. Function and blockade of LAG-3. LAG-3 inhibits TCR signaling both through the function of the glutamic acid–/proline-rich EP motif, which occurs in both the absence and the presence of trans-ligand binding (top left), and through the function of the KIEELE and FSALE motifs in the presence of trans-ligand binding (top right). With LAG-3 bound to the TCR/CD3 complex (in cis), the EP motif alters local pH by sequestering zinc ions, leading to Lck dissociation from CD4/CD8 and blockade of TCR phosphorylation. The KIEELE domain is non-K48-polyubiquitinated in the presence of ligand binding, which frees the FSALE domain from the cell membrane (where it is otherwise buried) to inhibit TCR signaling. These mechanisms can be inhibited by blocking the homodimerization of LAG-3 (bottom left), which excludes it from the TCR/CD3 synapse and allows Lck function, or by blocking the binding of LAG-3 to MHCII (bottom right), which prevents KIEELE ubiquitination, leaving FSALE in the membrane and unable to inhibit TCR signaling. EP, glutamic acid/proline rich motif; MHCII, major histocompatibility complex II; TCR, T cell receptor.

LAG-3 is a type I cell surface molecule induced on TCR stimulation. When LAG-3 binds its ligands, it inhibits proximal TCR signaling, leading to reduced expansion and effector function of the expressing T cells. The intracellular EP motif of LAG-3 is known to lower the pH near CD4/CD8, sequestering Zn^{2+} and leading to Lck dissociation,⁷⁶ which can occur even in the absence of ligand binding, termed tonic LAG-3 signaling. Recently, the intracellular KIEELE and FSALE motifs were implicated in increasing LAG-3 inhibitory function in the setting of ligand binding.⁷⁷ LAG-3 undergoes rapid ubiquitination after ligand binding at the KIEELE motif, releasing the FSALE motif from the cell membrane and enabling its inhibitory function. The roles of other intracellular domains are an ongoing focus of current research.³²

Two different strategies to target LAG-3 function have been identified although only one has made its way to the

clinic. The first is to block the LAG-3 ligand-binding domain to prevent interaction between LAG-3 and its most well-studied ligand, major histocompatibility complex II (MHCII).⁷⁸ LAG-3 binds to MHCII at the same sites as CD4 but with approximately 1,000-fold greater affinity, suggesting that part of LAG-3 function may be competitive MHCII binding with CD4.⁷⁹ Disrupting this interaction improves tumor clearance in murine models and humans.^{33,80} There are other LAG-3 ligands although no antibodies to block these interactions are in the clinic. These include fibrinogen-like protein 1 (FLG1), which is expressed by certain cancers including hepatocellular carcinoma (HCC) and NSCLC.^{81–83} Blocking the FLG1-LAG-3 interaction promoted antitumor immunity in a murine colorectal cancer model.⁸¹ There are other proposed though less well-characterized ligands for LAG-3, including the TCR-CD3 complex, LSECtin, and galectin-3.⁷⁶

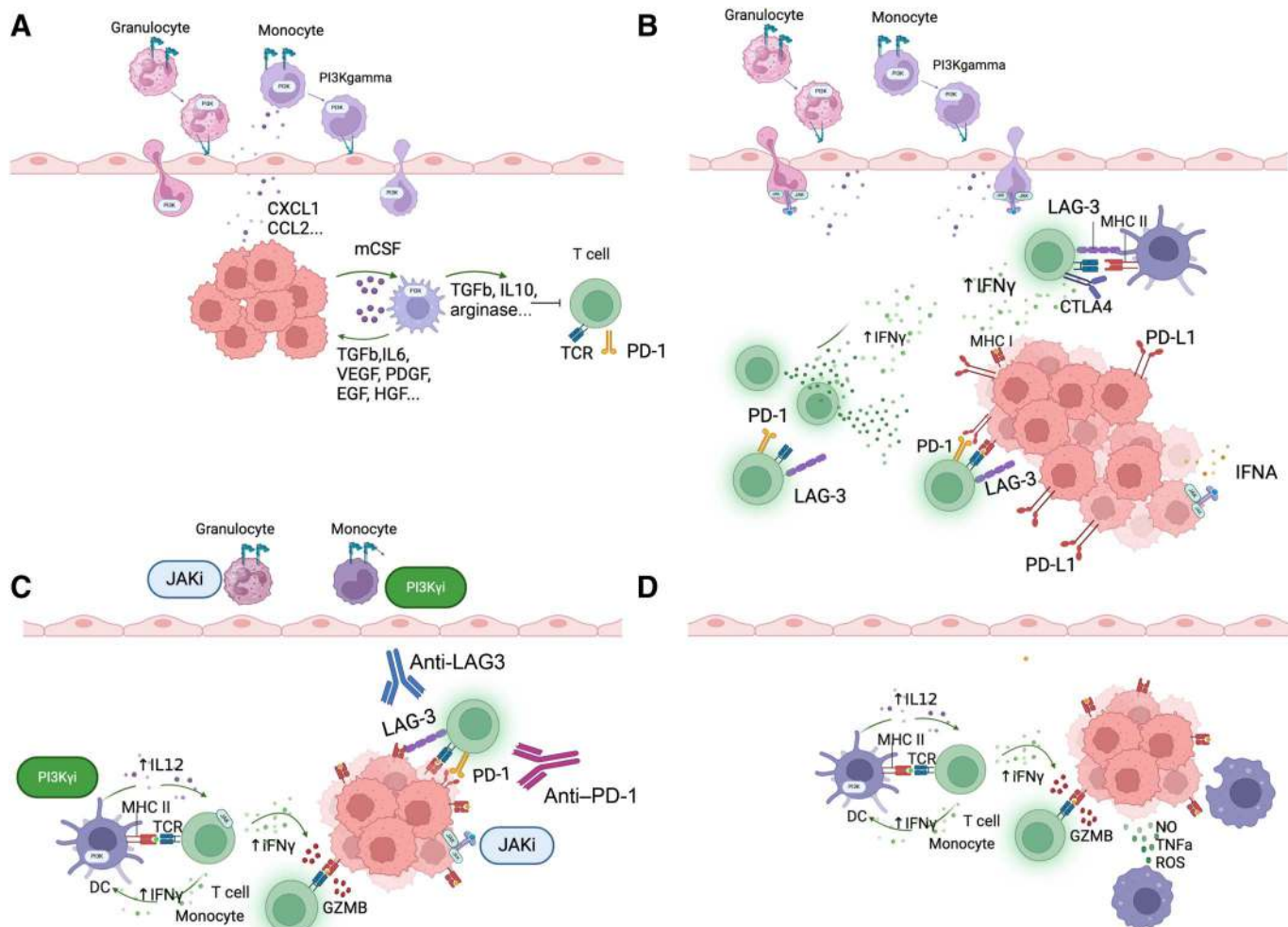


FIG 3. Therapeutic approaches to prevent resistance to immune therapy. (A) The TME is characterized by immune-suppressive monocytes and granulocytes (sometimes called myeloid derived suppressor cells), which are recruited from circulation by chemokines and cytokines released from tumor cells, myeloid cells, fibroblasts, or T cells. These stimuli activate PI3K γ , which promotes integrin activation and trafficking of myeloid cells into tumors. Tumor-associated monocytes and macrophages secrete cytokines and enzymes in a PI3K γ -dependent manner that suppresses T-cell activation and promotes tumor cell proliferation. (B) Chronic T-cell activation in the TME can lead to persistent IFN γ expression that promotes expression of immune checkpoints, including PD-1, LAG-3, and PD-L1, and that can induce IFN α expression and JAK1 activation in tumor cells. (C) Three therapeutic approaches, PI3K γ inhibitors, LAG-3 antibody inhibitors, and JAK1 inhibitors, have been tested to prevent or combat resistance to anti-PD-1 and other immune therapies. (D) PI3K γ and JAK1 inhibitors dampen recruitment of immune-suppressive myeloid cells into tumors. PI3K γ inhibitors also block expression of immune-suppressive cytokines and promote T-cell activation by IL12 secretion. JAK inhibitors block IFN α -mediated signaling in tumor cells and enhance T-cell activation. LAG-3 antibodies prevent the immune-suppressive effect of LAG-3 expression. These three approaches similarly boost responses and prevent resistance to immune therapy. CTLA-4, cytotoxic T lymphocyte associated protein 4; DC, dendritic cell; EGF, epidermal growth factor; HGF, hepatocyte growth factor; IFN α , interferon alpha; IFN γ , interferon gamma; IL6, interleukin 6; IL10, interleukin 10; IL12, interleukin 12; MHC, major histocompatibility complex; mCSF, macrophage colony stimulating factor; NO, nitric oxide; PDGF, platelet derived growth factor; PI3K γ , phosphoinositide 3-kinase gamma isoform; ROS, reactive oxygen species; TCR, T cell receptor; TGF β , transforming growth factor beta; TME, tumor microenvironment; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

The second strategy to block LAG-3 function, which has not yet been tested in the clinic, targets the need for LAG-3 to homodimerize to bind its ligands and signal downstream.⁸⁴ Mutations in the LAG-3 domain required for homodimerization prevented tracking to the TCR/CD3 complex within the immune synapse in murine CD8⁺ T cells, blocking LAG-3 signaling and improving antitumor function in a murine melanoma model.⁸⁵ While these are promising preclinical

data, as noted above, the efficacy of mAbs directed at blocking LAG-3 homodimerization has not yet been assessed in clinical trials.

SYNERGY BETWEEN ANTI-LAG-3 AND ANTI-PD-1

Early studies in multiple murine tumor models demonstrated synergy between anti-PD-1 and anti-LAG-3.⁷⁸

Importantly, recent work in mice has shown that CD8⁺ T cells lacking both PD-1 and LAG-3 demonstrated significantly improved antitumor activity compared with either IR deleted alone.⁸⁶ These double deficient cells were found to be transcriptionally distinct from the cells with single deletions, again highlighting synergistic effects of dual blockade.⁷⁸ PD-1 deletion alone increased proliferation but led to more exhausted T cells within the TME, whereas LAG-3 deletion alone led to reduced expression of TOX, a transcription factor that is critical for the development of T-cell exhaustion. The knockout (KO) of both ligands together in tumor antigen-specific T cells increased the proportion of self-renewing stem-like CD8⁺ T cells and created more polyfunctional effectors. Dual KO CD8⁺ T cells were able to secrete more IFN γ and TNF α than either single KO or wild-type CD8⁺ T cells. Importantly, while IFN γ can have significant antitumor activity on its own, the increased IFN γ produced by the dual KO T cells was critical for boosting the antitumor T-cell response cell intrinsically. Deleting the IFN γ receptor from the tumor or the host did not limit the efficacy of dual KO CD8⁺ T cells, but loss of the IFN γ receptor on the CD8⁺ T cells abrogated the improved antitumor efficacy of the dual-KO cells. Therefore, the combination of PD-1 and LAG-3 engagement on antitumor T cells hinders autocrine IFN γ -dependent antitumor activity of CD8⁺ T cells in mice, shedding light on the increased benefit of dual blockade. Indeed, these data are in line with observations from human studies demonstrating increased IFN γ signature in T-cell clones expanded after combination therapy.⁸⁷

PD-1/LAG-3 synergy has been additionally studied in chronic viral infection models, in which persistent viral antigen mimics the T-cell exhaustion seen within the TME.^{85,88} In this setting, PD-1 was again found to be primarily responsible for limiting proliferative capacity, whereas LAG-3 was more involved with hampering cytotoxic function. LAG-3 was similarly found to sustain the expression of TOX in chronically stimulated cells, while also repressing expression of NKG2C, an activating receptor on CD8⁺ T cells. While PD-1 KO alone led to higher expression of additional IRs, the addition of LAG-3 KO reduced overall IR expression, again suggesting a functional benefit to the dual blockade. Furthermore, higher expression of activating NK receptors improved functionality of dual-blockade cells. Importantly, the alteration in activating/inhibitory NK receptors seen in the murine model was consistent with studies performed on the peripheral blood of patients with melanoma after dual anti-PD-1/anti-LAG-3 therapy.

To assess the role of PD-1/LAG-3 synergy in humans, a randomized phase II trial was designed in which patients with advanced melanoma received nivo (anti-PD-1) alone, relatlimab (rela; anti-LAG-3) alone, or both rela and nivo therapy for a 4-week lead-in phase, followed by combination therapy with rela and nivo for all patients (ClinicalTrials.gov identifier: [NCT03743766](#)).⁸⁷ Single-cell transcriptomic analysis of CD8⁺ T cells from patients initially treated with rela/nivo demonstrated increased T cell

receptor signaling, cytotoxic and effector gene modules, and, surprisingly, retention of exhaustion gene modules, in contrast to the transcriptional signature of blockade of either IR alone. Collectively, these observations highlight parallels between the mechanisms that lead to increased CD8⁺ T-cell activation after dual PD-1/LAG-3 deletion in murine models compared with dual blockade in humans.^{86,89}

LAG-3 IN THE CLINIC—ANTI-LAG-3 mAbs

There are currently over 40 clinical trials evaluating 22 anti-LAG-3 therapeutics. Relatlimab from Bristol Myers Squibb (BMS) was the first anti-LAG-3 therapeutic to be approved by the FDA following the benefits observed in the RELATIVITY-047 trial.³³ In this study, patients received the fixed-dose combination opduvalag (480 mg of nivo and 160 mg of rela) once every 4 weeks. The median progression-free survival in patients with previously untreated metastatic or unresectable melanoma was 10.1 months (95% CI, 6.4 to 15.7), which was more than double that seen with nivo alone at 4.6 months (95% CI, 3.4 to 5.6; hazard ratio, 0.75 [95% CI, 0.62 to 0.92]; $P = .0055$).³³ Impressively, this improvement in PFS was not associated with a worsening safety profile, as was seen with the ipilimumab/nivo combination. This highlighted that combinatorial strategies could be synergistic without amplifying off-target effects and has led to additional trials testing this combination in other tumor types, including Hodgkin and non-Hodgkin lymphoma (ClinicalTrials.gov identifier: [NCT05255601](#)), HCC (ClinicalTrials.gov identifier: [NCT04658147](#)), and glioblastoma (ClinicalTrials.gov identifier: [NCT06325683](#)).

Another phase I trial by Regeneron Pharmaceuticals and Sanofi (ClinicalTrials.gov identifier: [NCT03005782](#)) is testing their anti-LAG-3 mAb fianlimab in combination with the anti-PD-1 mAB cemiplimab. Importantly, this trial significantly increased the dose of the fianlimab (1600 mg once every 3 weeks [20 mg/kg per 80 kg person]) over the dose of rela used in the RELATIVITY-047 trial (160 mg once every 4 weeks).^{33,36} This difference in formulation reflects the ongoing debate on the optimal dosing of LAG-3 therapeutics. There is concern that the interaction of LAG-3 antibodies with soluble LAG-3 (sLAG-3) can limit their efficacy by acting as sink that limits on-target blockade. LAG-3 is generated when LAG-3 is cleaved from the surface of immune cells, including T cells and dendritic cells, by a disintegrin and metalloproteinase domain-containing (ADAM) proteins, ADAM10 and ADAM17.⁹⁰ There is currently no known function of sLAG-3—it is believed, rather, that cleavage of LAG-3 from the surface of T cells is a rapid mechanism to limit LAG-3 signaling. In line with this, a high LAG-3/ADAM10 ratio on conventional CD4⁺ T cells from melanoma and head and neck squamous cell carcinoma (HNSCC) correlated with poor prognosis.⁹¹ Regardless of its function, there remains concern that sLAG-3 interferes with anti-LAG-3 therapeutics, prompting the tenfold increase in dose seen in this clinical trial. In combination with cemiplimab (350 mg) administered once every 3 weeks over

12 months, therapy elicited an overall response rate (ORR) of 61.2%, with 12 complete responses (CRs) and 48 partial responses (PRs) of a total of 98 patients.³⁶ The Kaplan-Meier estimation of median progression free survival was 15.3 (95% CI, 9.4 to not estimated) months.³⁶ While the safety profile of combination therapy was similar to that of cemiplimab alone, they did note higher incidences of adrenal insufficiency (12% of patients), which were grade ≥ 2 in 64% of cases. There were additionally adverse events reported in 94% of patients, with 44% being grade ≥ 3 . This combination is currently in phase III clinical trial (ClinicalTrials.gov identifier: [NCT05352672](#)), wherein two doses of fianlimab (1,600 mg v 400 mg once every 3 weeks) are being tested. Furthermore, another clinical trial (ClinicalTrials.gov identifier: [NCT06246916](#)) will test opdualag against the fixed-dose combination of fianlimab and cemiplimab head-to-head.

In addition to combination with PD-1, anti-LAG-3 is also being tested in combination with other IR blockade, including CTLA-4, TIM3, and TIGIT, and in combination with anti-VEGF and anti-ICOS monoclonal antibodies. While successes have been observed in melanoma, BMS recently terminated its phase III RELATIVITY-123 trial of opdualag in patients with previously treated, microsatellite-stable metastatic colorectal cancer because of low likelihood of meeting the primary OS end point. This result further highlights the importance of understanding how anti-PD-1/anti-LAG-3 combination therapy works to better identify those cancers that would benefit.

LAG-3 IN THE CLINIC—BsAbs

Bispecific antibody therapy, wherein antibodies are generated to recognize more than one IR, is also gaining popularity to more specifically target exhausted T cells by recognizing IRs together on the same cell or between T cells and target cells. There has also been suggestion that BsAbs can sterically exclude IRs from the immune synapse or accelerate their shedding, thereby blocking their inhibitory function.³¹ This mechanism has been proposed for the first BsAb to enter the clinic, FS118. FS118 is a first-in-class tetravalent BsAb against LAG-3 and PD-L1. To create this BsAb, a LAG-3 binding site was introduced into the antibody constant region of a full-length anti-PD-L1 human mAb, with two additional mutations to abrogate Fc receptor binding.³⁷ The phase I trial observed no dose-limiting toxicities and demonstrated a disease control rate of 54.8% in patients with advanced cancer and PD-L1 resistance. Phase II/III trials are currently ongoing. There is also a trispecific antibody GB266T targeting PD-L1, TIGIT, and LAG-3 alongside a competent Fc domain. The goal of this combination is to increase interactions between tumor cells, T cells, and APCs. Preclinical testing in humanized non-obese diabetic scid gamma mice implanted with an RKO OKT3 human colon cancer cell line demonstrated significant tumor growth suppression with GB266T treatment,⁹² suggesting the utility of this strategy.

There are now a total of five BsAbs currently under evaluation. One of these, tebotelimab (MGD013), is a tetravalent anti-LAG-3/PD-1 BsAb developed by MacroGenics. As monotherapy against solid tumors in a phase I trial (ClinicalTrials.gov identifier: [NCT03219268](#)), irAEs occurred in 68.4% of patients (184 of 269), with 22.3% (60 of 269) being $\geq$ grade 3. However, when tested in combination with an Fc-optimized anti-HER2 antibody, margetuximab, in patients with HER2+ tumors, only 16.7% of patients (14 of 84) developed irAEs of grade ≥ 3 , with an ORR of 19.4% and a median duration of response of 16.7 months (95% CI, 11.04 to NE), suggesting that combination with tumor-directed therapy could reduce off-target effects of IR blockade. In addition, they observed one CR (1.4%), 13 PRs (18.1%), 25 stable diseases (34.7%), and 33 (45.8%) progressive diseases.³⁸ With these promising results, the phase II/III Mahogany trial (ClinicalTrials.gov identifier: [NCT04082364](#)) is now ongoing.

FUTURE DIRECTIONS FOR LAG-3 BLOCKADE

Many questions remain to be answered about LAG-3 targeting, including optimal dosing, optimal combination strategies, and, perhaps most importantly, how to determine which patients/cancers will be most responsive to LAG-3 blockade. There are currently no definitive biomarkers associated with response to LAG-3 treatment, limiting our ability to choose those patients/cancers who would benefit most from targeting this IR. Indeed, the RELATIVITY-047 trial saw no correlation between either LAG-3 expression or PD-L1 expression and response to therapy.³³ There has been some research looking at levels of sLAG-3 in the setting of checkpoint blockade, finding a negative correlation between sLAG-3 serum levels and therapy response, but this analysis did not include patients who had received anti-LAG-3 antibodies.⁹³ Interestingly, a negative correlation between ICB response and the ratio of LAG-3 to ADAM10 on the surface of CD4⁺ T cells has been observed, but again, this was in the setting of anti-PD-1 alone.⁸⁶ Finding correlates with response to anti-LAG-3 blockade is an important area of active research. There were data presented at ASCO 2024 from ClinicalTrials.gov (identifier: [NCT02519322](#)), a phase II trial testing checkpoint blockade in the neoadjuvant setting before surgery in patients with stage III, surgically resectable melanoma, evaluating 30 longitudinal patient samples before and after treatment with rela and nivo using RNAseq. Higher gene expression signatures (GES) for B cells, CD45, CD-8+ T cells, TIGIT, indoleamine 2,3-dioxygenase 1, and IFN γ were found in baseline samples from patients with major pathologic response (MPR), whereas there was higher GES for the immune checkpoint B7-H3 in non-MPR.³⁴ In addition, an on-therapy rela + nivo gene signature that persisted in CD8⁺ T cells 1 month after therapy and correlated with improved responses was identified in ClinicalTrials.gov (identifier: [NCT03743766](#)).⁸⁷ This signature also correlated with an increased percentage of CD38+Tim3+ CD8⁺ T cells in peripheral blood, suggesting that coexpression of these markers could be used as an on-therapy biomarker of

combination therapy. Recently, data were published from ClinicalTrials.gov (identifier: [NCT04080804](#)), a phase II neoadjuvant trial comparing nivo alone, nivo + ipilimumab, and nivo + rela in patients with HNSCC.⁹⁴ This analysis demonstrated that patients with combined LAG-3 and PD-L1 positivity (>1%) from baseline tissue were more likely to have a MPR to the combination of nivo + rela, with no correlation found in either of the other arms. This is in contrast to data from patients with melanoma, where there was no association between LAG-3 and response to combination therapy.³³ Furthermore, in HNSCC, the expression of LAG3 mRNA in baseline CD8⁺ TIL positively correlated with pathologic response. These seemingly conflicting results may reflect differences in the TME found in different cancer types. Analyses from the abovementioned trials and currently enrolling trials are ongoing, with further validation of these findings required.

It is also still not fully understood how LAG-3 synergizes with PD-1 and if LAG-3 could similarly synergize with other IRs. Indeed, analysis of additional data from ClinicalTrials.gov (identifier: [NCT04080804](#)) revealed distinct transcriptional states associated with response to the nivo + ipilimumab and the nivo + rela arms, wherein the former expanded effector CD8⁺ T cells, whereas the latter preferentially unleashed exhausted CD8⁺ T cells.⁹⁴ The fact that these combinations seemingly target different CD8⁺ T-cell populations suggests that further combining these three treatments into triple therapy may lead to even greater responses across a wider variety of patients although toxicity profiles would need to be closely monitored in this setting. Either way, understanding more about the mechanism underlying combination therapy synergy and the changes that occur within the TME in patients who either respond or are resistant to anti-LAG-3 will help to elucidate drivers of ICB escape. With multiple mechanisms driving immunosuppression and reducing T-cell infiltration and function in the TME, it is likely that in cases where ICB fails, other immunosuppressive mechanisms have overwhelmed the ICB-mediated release of antitumor T cells. Identifying these inhibitory adaptations will permit the design of rational combination therapies to simultaneously target multiple immune-limiting mechanisms at once, creating treatment protocols that will make ICB more broadly effective for a higher number of patients. Ongoing research is seeking to answer these important questions, the results of which could help to expand the utility of anti-LAG-3 blockade in the clinic.

CHRONIC INFLAMMATION MEDIATES IMMUNE SUPPRESSION

Several suppressive cellular features (eg, immunosuppressive myeloid cells, exhausted CD8 T cells), signaling pathways (eg, interferon, granulocyte colony-stimulating factor [G-CSF]), and immune checkpoint pathways (eg, PD-1/PDL1 and LAG-3) observed in tumors poorly responsive to immunotherapy likely evolved as a consequence of persistent,

yet ineffective, antitumor immune responses. In normal tissues, persistent activation of the immune response can activate immune-suppressive pathways to avoid immune-mediated pathology.^{95,96} For example, in mice with chronic virus infection, deletion of PD-1 unleashes an aggressive immune response that results in tissue damage, immunopathology, and early mortality.^{97,98} Acting as wounds that never heal, tumors exploit these normal immunoregulatory mechanisms to similarly antagonize immune activation and interfere with immunotherapy efficacy.⁹⁹ Moreover, key cytokine signaling pathways that help to initiate or maintain these immunomodulatory effects of chronic inflammation seen in normal tissue and cancers can play very different roles during the early stages of an immune response, making context-dependent effects important to understand.¹⁰⁰ One such context-dependent cytokine pathway is interferon.¹⁰¹ Although type I interferon (IFN-I) and type II interferon (IFNG) are critical for immune activation, both interferons have important functions in maintaining immune suppression to protect tissues from chronic inflammation. However, because of the opposing roles of interferons in immune activation versus immune suppression, the extent to which interferon is responsible for cancer immunotherapy resistance and the feasibility of targeting it has been unclear.

PERSISTENT INTERFERON SIGNALING PROMOTES IMMUNOTHERAPY RESISTANCE

Predictive GEs that contain ISGs are robustly associated with a higher likelihood of response to anti-PD-1 across many human cancer types.¹⁰² Tumors lacking high expression of these ISG-containing gene signatures likely have inadequate infiltration of T cells, an important producer of interferon gamma, explaining why the absence of the signature predicts a poor response. A closer examination of cell types in tumors that express IFNG-related gene signatures confirmed that T cells and myeloid cells are enriched for interferon response gene expression.¹⁰³ However, high expression of IFNG-related signatures does not ensure immunotherapy response as many patients with signature-positive tumors fail to benefit from anti-PD-1.¹⁰² When gene signatures related to IFN-I signaling are considered, these signatures (called the interferon-I response gene signature, for ISG resistance signature) are found to be enriched in cancer cells compared with T cells and are associated with a lower likelihood of response to ICB.^{103,104} A similar pattern has been reported in patients with lymphoma treated with CAR-T cells, where IFNG-related signatures predict durable response, whereas the ISG.RS predicts the nondurable response.¹⁰⁵ Thus, IFNG-related genes enriched in immune cells are associated with T-cell infiltration and favorable response, whereas IFN-I-related genes, such as the ISG.RS, can be enriched in cancer cells, thereby antagonizing immunotherapy response.

Clinical and preclinical evidence suggests that IFN-I-related gene signatures (ISG.RS) in cancer cells are initiated by exposure to chronic IFNG and maintained by persistent IFN-

I, thereby leading to immunotherapy resistance. In a variety of mouse cancer cell lines, chronic IFNG stimulation is sufficient to confer immunotherapy resistance.¹⁰⁶ Chronic IFNG stimulation and acquired resistance result in epigenetic changes and higher levels of autocrine and paracrine IFN- γ production by cancer cells.^{103,104} This increased IFN- γ signaling by cancer cells contributes to high ISG expression, which promotes exhaustion and reduces IFNG production by intratumoral CD8 T cells. Accordingly, tumors from patients with NSCLC who relapsed after anti-PD-1 treatment exhibited a pattern of high resistance-associated ISGs and features of CD8 T-cell exhaustion in half of the relapsed patients.²² Moreover, in patients with NSCLC who were treated with nivo and ipilimumab in the CHECKMATE-012 trial, pathogenic somatic mutations in IFN pathway genes were associated with better progression-free survival.¹⁰³ Similar findings have been observed in other cancers as well.¹⁰⁷ Together, these observations in mice and humans point toward the therapeutic potential of targeting persistent IFN signaling to improve response to checkpoint blockade.

JAK1/2 INHIBITION TARGETS ACQUIRED IMMUNOTHERAPY RESISTANCE

Because interferons are essential for initial immune activation but chronic signaling can lead to immune suppression, these opposing context-dependent functions make targeting interferon and other similar pathways a challenge. In mouse tumor models, JAK inhibitors and IFN- γ receptor (IFNAR1)-blocking antibodies can be properly dosed and sequenced to prevent persistent interferon and/or JAK-dependent cytokine signaling yet preserve interferon signaling critical for immune activation.¹⁰⁶ Consequently, combining a JAK inhibitor or anti-IFNAR1-blocking antibody with ICB can improve response or resensitize immunotherapy-resistant tumors across multiple mouse tumor models.^{23,24} This improved tumor response can be accompanied by improvements in CD8 T-cell differentiation, resulting in less T-cell exhaustion, and favorable changes to myeloid populations, including upregulation of antigen-presentation molecules.

Building on preclinical studies aimed at blocking the immune-suppressive effects of persistent interferon and cytokine signaling, two recent early phase clinical trials have examined the combination of anti-PD-1 with a JAK1 inhibitor (itacitinib) or a JAK1/2 inhibitor (ruxolitinib).^{23,24} In a phase two study for patients with first-line metastatic NSCLC with PDL1 $\geq 50\%$, itacitinib was administered for 6 weeks after two cycles of pembrolizumab, a sequential dosing strategy that starts JAK inhibition after ICB similar to an approach used in mice. The best overall response rate was 67%, which was higher than the expected response rate for this NSCLC patient population treated with pembrolizumab alone. Among the responders were many patients who initially failed to respond to the first two cycles of pembrolizumab but responded after receiving itacitinib. Longitudinal immune profiling studies revealed that

itacitinib altered CD8 T-cell differentiation, pivoting early progenitor or precursor populations away from exhaustion and toward nonexhausted CD8 T-cell subsets. By contrast, nonresponders appeared refractory to JAK inhibition, characterized by persistently elevated levels of serum inflammatory proteins and cytokine signaling along with continuous development of CD8 T-cell exhaustion.²³ In a separate phase one clinical trial, patients with Hodgkin lymphoma previously refractory to anti-PD-1 (nivo) were treated with ruxolitinib in combination with nivo. The best overall response rate was 53%, with 6 of 19 patients achieving a complete metabolic response. A reduction in neutrophil-to-lymphocyte ratios along with a decrease in myeloid cells with suppressive features was among the favorable immune changes that correlated with response. Consistent with improvements in myeloid cells, transcriptomic signatures for G-CSF signaling, a JAK-dependent cytokine, were significantly downregulated by ruxolitinib.²⁴

In total, these early-phase clinical trials using JAK inhibitors corroborate numerous immune-related changes expected from mouse models examining the impact of blocking chronic interferon and cytokine signaling on immune function. Moreover, the studies also highlight the therapeutic potential of targeting chronic inflammation and cytokine signaling to mitigate acquired immunotherapy resistance across different cancer types.

irAEs

Immune checkpoint blockade relies on interfering with the function of naturally expressed inhibitory ligands on the surface of antitumor T cells. While this strategy effectively releases exhausted T cells in the tumors of treated patients, it also has the unintended side effect of causing autoinflammation within healthy organ systems. The natural purpose of inhibitory ligands is to preserve tolerance to self-antigens, limiting the activity of autoreactive cells while similarly downregulating the immune response to avoid bystander tissue damage.¹⁰⁸ By interrupting this complex system of checks and balances, autoinflammatory responses can be triggered, which have been given the name irAEs. In any given patient, irAEs can present as single-organ inflammation or demonstrate multisystem involvement, and while most present within the first few months of treatment, inflammation can occur throughout the ICB course.¹⁰⁹ Low-grade irAEs (grade 1-2) occur in nearly 90% of treated patients, whereas higher-grade irAEs (grades 3-5) can range from 20% to 60%.¹¹⁰ The sites most often affected include barrier tissues like the skin, GI tract/liver, and respiratory epithelium, particularly when PD-1 is used in combination with CTLA-4.¹¹¹ Endocrine tissues can also be affected,¹¹² which can lead to the need for lifelong endocrine supplementation. Similarly, joint toxicities can also be long-lasting, with ongoing pain and mobility issues long after treatment cessation.¹¹³ While cardiac and neurologic toxicities are more rare, they develop rapidly and are more often fatal.¹¹⁴ Currently, the mainstay of treatment of high-grade

irAEs is high-dose steroid therapy with discontinuation of the ICBs although newer therapies are actively being developed.¹¹⁵ The mechanisms driving irAEs are still an area of active study. There is likely a combination of inappropriate activation of tissue-resident memory cells, particularly at epithelial barriers,¹¹⁶ alongside the concept of epitope spreading, whereby inflammation leads to shedding of otherwise self-antigens, which, when coupled with the inflammatory microenvironment and blockade of normal checkpoints, leads to activation of autoreactive T cells.¹⁰⁸ Outside of conventional T cells, checkpoints are also expressed by Tregs (particularly CTLA-4), B cells, and myeloid cells, which could also contribute to irAE-mediated pathology.¹⁰⁸ Because of these varied and often significant side effects, it is the goal of newer combination therapies to avoid further worsening ICB toxicity. Indeed, data reviewing trials completed thus far demonstrate that grade 3/4 irAE rates are considerably lower with relat-nivo (19%) compared with ipilimumab-nivo (59%), likely because of the exclusion of CTLA-4.¹¹⁷ A better understanding of how irAEs are triggered will be required to effectively design better tolerated therapeutic options.

CONCLUSIONS AND FUTURE DIRECTIONS

A key goal of cancer immunotherapy is to eradicate tumor cells without harming normal cells. In general, immune therapy relies on recruitment and activation of CD8⁺ T cells, which can eliminate tumor cells. However, a number of intrinsic resistance mechanisms can develop to prevent checkpoint inhibitors, CAR-T cells, or other therapeutic approaches from achieving tumor control. Here, we have identified several key means by which tumors develop resistance to therapy: a TME that is rich in immune-suppressive macrophages and granulocytes; a stromal cell-/collagen-rich microenvironment that precludes the

close contact between T cells and tumor cells; mutations in antigen-presentation machinery that reduces T-cell recognition of target cells; persistent expression of type II interferon (IFN γ) and type I interferons (IFN α , IFN β), which can upregulate expression of interferon response genes (ISGs); and expression of additional immune checkpoints, including LAG-3, TIM-3, and TIGIT. New therapies designed to circumvent these resistance mechanisms offer promise to improve cancer outcomes. We have described here the foundational studies that led to development of novel approaches to prevent resistance to checkpoint inhibitors. These studies of the myeloid cell protein PI3K γ , the T-cell checkpoint LAG-3, and the signaling protein JAK1 have led to development of novel therapeutic approaches that have shown benefit in preventing resistance to therapy in cancer clinical trials and have led to FDA approval of the LAG-3 antibody relat-n in conjunction with nivo for cancer therapy. PI3K γ and LAG-3 inhibitors to date have been found to be effective if administered concurrent with checkpoint blockade, whereas JAK1 inhibitors were found to be most effective if administered after two cycles of immune checkpoint blockers. Future clinical trials should determine optimal strategies and biomarkers of response and patient selection criteria for these immune therapies. The field of cancer immunotherapy has advanced new strategies aimed at overcoming tumor resistance. In addition to the development of new agents such as those described here, the future of cancer immune therapy will rely on personalized approaches to treatment, where identification of biomarkers such as specific mutations, presence and patterns of T cells, macrophages, granulocytes, and stroma will guide the selection of specific treatments for each patient. Continuous research and refinement of therapeutic approach efforts such as those presented here will bring the promise of immune therapy closer to fruition.

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REFERENCES

- Leach DR, Rummel MF, Allison JP: Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 271:1734-1736, 1996
- Nishimura H, Nose M, Hiai H, et al: Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 11:141-151, 1999
- Hirano F, Kaneko K, Tamura H, et al: Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res* 65:1089-1096, 2005
- Wolchok JD, Hodi FS, Weber JS, et al: Development of ipilimumab: A novel immunotherapeutic approach for the treatment of advanced melanoma. *Ann N Y Acad Sci* 1291:1-13, 2013
- Hodi FS, O'Day SJ, McDermott DF, et al: Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 363:711-723, 2010
- Topalian SL, Hodi FS, Brahmer JR, et al: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 366:2443-2454, 2012
- Wolchok JD, Chiarion-Sileni V, Rutkowski P, et al: Final, 10-year outcomes with nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 392:11-22, 2025
- Wykes M, Lewin S: Immune checkpoint blockade in infectious diseases. *Nat Rev Immunol* 18:91-104, 2018
- Zhou S, Yang H: Immunotherapy resistance in non-small-cell lung cancer: From mechanism to clinical strategies. *Front Immunol* 14:1129465, 2023
- Mariniello A, Borgeaud M, Weiner M, et al: Primary and acquired resistance to immunotherapy with checkpoint inhibitors in NSCLC: From bedside to bench and back. *BioDrugs* 39:215-235, 2025
- Lim SY, Shklovskaya E, Lee JH, et al: The molecular and functional landscape of resistance to immune checkpoint blockade in melanoma. *Nat Commun* 14:1516, 2023
- Postow MA, Sidlow R, Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 378:158-168, 2018
- Srouf SA, Akin S: Chimeric antigen receptor T-cell therapy for solid tumors: The past and the future. *J Immunother Precip Oncol* 6:19-30, 2023
- Maalej KM, Merhi M, Inchakalody VP, et al: CAR-cell therapy in the era of solid tumor treatment: Current challenges and emerging therapeutic advances. *Mol Cancer* 22:20, 2023
- Young RM, Engel NW, Uslu U, et al: Next-generation CAR T-cell therapies. *Cancer Discov* 12:1625-1633, 2022
- Yang X-M, Lin X-D, Shi W, et al: Nanobody-based bispecific T-cell engager (Nb-BiTE): A new platform for enhanced T-cell immunotherapy. *Sig Transduct Target Ther* 8:328, 2023
- Sha D, Jin Z, Budczies J, et al: Tumor mutational burden as a predictive biomarker in solid tumors. *Cancer Discov* 10:1808-1825, 2020
- Chowell D, Morris LGT, Grigg CM, et al: Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy. *Science* 359:582-587, 2018
- Kawazu M, Ueno T, Saeki K, et al: HLA class I analysis provides insight into the genetic and epigenetic background of immune evasion in colorectal cancer with high microsatellite instability. *Gastroenterology* 162:799-812, 2022
- Zaretsky JM, Garcia-Diaz A, Shin DS, et al: Mutations associated with acquired resistance to PD-1 blockade in melanoma. *N Engl J Med* 375:819-829, 2016
- Matsushita H, Vesely MD, Koboldt DC, et al: Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. *Nature* 482:400-404, 2012
- Memon D, Schoenfeld AJ, Ye D, et al: Clinical and molecular features of acquired resistance to immunotherapy in non-small cell lung cancer. *Cancer Cell* 42:209-224.e9, 2024
- Mathew D, Marmarelis ME, Foley C, et al: Combined JAK inhibition and PD-1 immunotherapy for non-small cell lung cancer patients. *Science* 384:eadf1329, 2024
- Zak J, Pratumchai I, Marro BS, et al: JAK inhibition enhances checkpoint blockade immunotherapy in patients with Hodgkin lymphoma. *Science* 384:eade8520, 2024
- Lu C, Tan Y: Promising immunotherapy targets: TIM3, LAG3, and TIGIT joined the party. *Mol Ther Oncol* 32:200773, 2024
- Philip M, Schietinger A: CD8⁺ T cell differentiation and dysfunction in cancer. *Nat Rev Immunol* 22:209-223, 2022
- Shiravand Y, Khodadadi F, Kashani SMA, et al: Immune checkpoint inhibitors in cancer therapy. *Curr Oncol* 29:3044-3060, 2022
- Yost KE, Satpathy AT, Wells DK, et al: Clonal replacement of tumor-specific T cells following PD-1 blockade. *Nat Med* 25:1251-1259, 2019
- Postow MA, Chesney J, Pavlick AC, et al: Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med* 372:2006-2017, 2015
- Twomey JD, Zhang B: Cancer immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics. *AAPS J* 23:39, 2021
- Adam K, Butler SC, Workman CJ, et al: Advances in LAG3 cancer immunotherapeutics. *Trends Cancer* 11:37-48, 2025
- Maruhashi T, Sugiyura D, Okazaki I-M, et al: LAG-3: From molecular functions to clinical applications. *J Immunother Cancer* 8:e001014, 2020
- Tawbi HA, Schadendorf D, Lipson EJ, et al: Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med* 386:24-34, 2022
- Burton EM, Wani KM, Milton DR, et al: Biomarker analysis and updated clinical outcomes: Neoadjuvant systemic treatment (NST) with nivolumab (nivo) and relatlimab (rela) in surgically resectable melanoma. *J Clin Oncol* 42, 2024 (suppl 16; abstr 9587)
- Chocarro L, Bocanegra A, Blanco E, et al: Cutting-edge: Preclinical and clinical development of the first approved lag-3 inhibitor. *Cells* 11:2351, 2022
- Hamid O, Lewis KD, Weise A, et al: Phase I study of flanimab, a human lymphocyte activation gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma. *J Clin Oncol* 42:2928-2938, 2024
- Yap TA, LoRusso PM, Wong DJ, et al: A phase 1 first-in-human study of FS118, a tetravalent bispecific antibody targeting LAG-3 and PD-L1 in patients with advanced cancer and PD-L1 resistance. *Clin Cancer Res* 29:888-898, 2023
- Luke JJ, Patel MR, Blumenschein GR, et al: The PD-1- and LAG-3-targeting bispecific molecule tebotelimumab in solid tumors and hematologic cancers: A phase 1 trial. *Nat Med* 29:2814-2824, 2023
- Patel SP, Dimou A, Victor AI, et al: Safety and efficacy of first-in-class CXCR1/2 inhibitor SX-682 in combination with pembrolizumab (pem) in patients (pts) with metastatic melanoma (mMEL) with disease progression on anti-PD-1 therapy. *J Clin Oncol* 42, 2024 (suppl 16; abstr 9508)
- Guo C, Sharp A, Gurel B, et al: Targeting myeloid chemotaxis to reverse prostate cancer therapy resistance. *Nature* 623:1053-1061, 2023
- Gomez-Roca CA, Italiano A, Le Tourneau C, et al: Phase I study of emactuzumab single agent or in combination with paclitaxel in patients with advanced/metastatic solid tumors reveals depletion of immunosuppressive M2-like macrophages. *Ann Oncol* 30:1381-1392, 2019
- Wesolowski R, Sharma N, Reebel L, et al: Phase Ib study of the combination of pexidartinib (PLX3397), a CSF-1R inhibitor, and paclitaxel in patients with advanced solid tumors. *Ther Adv Med Oncol* 11:1758835919854238, 2019
- Monestime S, Lazaridis D: Pexidartinib (TURALIO™): The first FDA-indicated systemic treatment for tenosynovial giant cell tumor. *Drugs* 80:189-195, 2020
- Kaneda MM, Cappello P, Nguyen AV, et al: Macrophage PI3Kγ drives pancreatic ductal adenocarcinoma progression. *Cancer Discov* 6:870-885, 2016
- Hong DS, Postow M, Chmielowski B, et al: Eganalisib, a first-in-class PI3Kγ inhibitor, in patients with advanced solid tumors: Results of the phase 1/1b MARIO-1 trial. *Clin Cancer Res* 29:2210-2219, 2023
- Tomczak P, Popovic L, Barthelemy P, et al: Preliminary analysis of a phase II, multicenter, randomized, active-control study to evaluate the efficacy and safety of eganalisib (IPI 549) in combination with nivolumab compared to nivolumab monotherapy in patients with advanced urothelial carcinoma. *J Clin Oncol* 39, 2021 (suppl 6; abstr 436)
- O'Connell BC, Hubbard C, Zizlsperger N, et al: Eganalisib combined with immune checkpoint inhibitor therapy and chemotherapy in frontline metastatic triple-negative breast cancer triggers macrophage reprogramming, immune activation and extracellular matrix reorganization in the tumor microenvironment. *J Immunother Cancer* 12:e009160, 2024

48. Schmid MC, Avraamides CJ, Dippold HC, et al: Receptor tyrosine kinases and TLR/IL1Rs unexpectedly activate myeloid cell PI3K γ , a single convergent point promoting tumor inflammation and progression. *Cancer Cell* 19:715-727, 2011
49. Lopiz D, Silva L, Ruiz M, et al: MERTK inhibition improves therapeutic efficacy of immune checkpoint inhibitors in hepatocellular carcinoma. *Oncoimmunology* 14:2473165, 2025
50. Chen YW, Panian J, Rose B, et al: Recent developments in the management of renal cell cancer. *JCO Oncol Pract* 10.1200/OP-24-00875 [epub ahead of print on March 6, 2025]
51. Duke ES, Barone AK, Chatterjee S, et al: FDA approval summary: Cabozantinib for differentiated thyroid cancer. *Clin Cancer Res* 28:4173-4177, 2022
52. Molgora M, Esaulova E, Vermi W, et al: TREM2 modulation remodels the tumor myeloid landscape enhancing anti-PD-1 immunotherapy. *Cell* 182:886-900.e17, 2020
53. Jeong H, Koh J, Kim S, et al: Cell-intrinsic PD-L1 signaling drives immunosuppression by myeloid-derived suppressor cells through IL-6/Jak/Stat3 in PD-L1-high lung cancer. *J Immunother Cancer* 13:e010612, 2025
54. Pathria P, Louis TL, Varner JA: Targeting tumor-associated macrophages in cancer. *Trends Immunol* 40:310-327, 2019
55. Okuyama K, Tsuchiya M, Debnath KC, et al: Desmoplastic reaction in the microenvironment of head and neck and other solid tumors: The therapeutic barrier. *Ther Adv Med Oncol* 17:17588359251317144, 2025
56. Hegde PS, Karanikas V, Evers S: The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition. *Clin Cancer Res* 22:1865-1874, 2016
57. Lyu A, Fan Z, Clark M, et al: Evolution of myeloid-mediated immunotherapy resistance in prostate cancer. *Nature* 637:1207-1217, 2025
58. Brom VC, Burger C, Wirtz DC, et al: The role of immune checkpoint molecules on macrophages in cancer, infection, and autoimmune pathologies. *Front Immunol* 13:837645, 2022
59. Mantovani A, Marchesi A, Marchesi F, Di Mitri D, et al: Macrophage diversity in cancer dissemination and metastasis. *Cell Mol Immunol* 21:1201-1214, 2024
60. Zhai T, Mitamura T, Wang L, et al: Combination therapy with bevacizumab and a CCR2 inhibitor for human ovarian cancer: An in vivo validation study. *Cancer Med* 12:9697-9708, 2023
61. Mognol GP, Ghebremedhin A, Varner JA: Targeting PI3K γ in cancer. *Trends Cancer*, 2025
62. Vasan N, Cantley LC: At a crossroads: How to translate the roles of PI3K in oncogenic and metabolic signalling into improvements in cancer therapy. *Nat Rev Clin Oncol* 19:471-485, 2022
63. Kaneda MM, Messer KS, Ralainirina N, et al: PI3K γ is a molecular switch that controls immune suppression. *Nature* 539:437-442, 2016
64. De Henau Q, Rausch M, Winkler D, et al: Overcoming resistance to checkpoint blockade therapy by targeting PI3K γ in myeloid cells. *Nature* 539:443-447, 2016
65. Shepard RM, Ghebremedhin A, Pratumchai I, et al: PI3K γ inhibition circumvents inflammation and vascular leak in SARS-CoV-2 and other infections. *Sci Transl Med* 16:eadi6887, 2024
66. Schmid MC, Kang SW, Chen H, et al: PI3K γ stimulates a high molecular weight form of myosin light chain kinase to promote myeloid cell adhesion and tumor inflammation. *Nat Commun* 13:1768, 2022
67. Kobayashi N, Ueki K, Okazaki Y, et al: Blockade of class IB phosphoinositide-3 kinase ameliorates obesity-induced inflammation and insulin resistance. *Proc Natl Acad Sci U S A* 108:5753-5758, 2011
68. Chang J, Lu J, Liu Q, et al: Single-cell multi-stage spatial evolutionary map of esophageal carcinogenesis. *Cancer Cell* 43:380-397.e7, 2025
69. Bill R, Wirapati P, Messemaker M, et al: CXCL9:SPPI macrophage polarity identifies a network of cellular programs that control human cancers. *Science* 381:515-524, 2023
70. Pierini S, Gabbasov R, Oliveira-Nunes MC, et al: Chimeric antigen receptor macrophages (CAR-M) sensitize HER2+ solid tumors to PD1 blockade in pre-clinical models. *Nat Commun* 16:706, 2025
71. Lei A, Yu H, Lu S, et al: A second-generation M1-polarized CAR macrophage with antitumor efficacy. *Nat Immunol* 25:102-116, 2024
72. Wang X, Su S, Zhu Y, et al: Metabolic reprogramming via ACOD1 depletion enhances function of human induced pluripotent stem cell-derived CAR-macrophages in solid tumors. *Nat Commun* 14:5778, 2023
73. Wherry EJ: T cell exhaustion. *Nat Immunol* 12:492-499, 2011
74. Triebel F, Jitsukawa S, Baixeras E, et al: LAG-3, a novel lymphocyte activation gene closely related to CD4. *J Exp Med* 171:1393-1405, 1990
75. Woo SR, Turnis ME, Goldberg MV, et al: Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res* 72:917-927, 2012
76. Guy C, Mitrea DM, Chou P-C, et al: LAG3 associates with TCR-CD3 complexes and suppresses signaling by driving co-receptor-Lck dissociation. *Nat Immunol* 23:757-767, 2022
77. Jiang Y, Dai A, Huang Y, et al: Ligand-induced ubiquitination unleashes LAG3 immune checkpoint function by hindering membrane sequestration of signaling motifs. *Cell* 10.1016/j.cell.2025.02.014 [epub ahead of print on March 6, 2025]
78. Huard B, Gaulard P, Faure F, et al: Cellular expression and tissue distribution of the human LAG-3-encoded protein, an MHC class II ligand. *Immunogenetics* 39:213-217, 1994
79. Ming Q, Antfolk D, Price DA, et al: Structural basis for mouse LAG3 interactions with the MHC class II molecule I-Ab. *Nat Commun* 15:7513, 2024
80. Maruhashi T, Sugiura D, Okazaki I-M, et al: Binding of LAG-3 to stable peptide-MHC class II limits T cell function and suppresses autoimmunity and anti-cancer immunity. *Immunity* 55:912-924.e8, 2022
81. Wang J, Sanmamed MF, Datar I, et al: Fibrinogen-like protein 1 is a major immune inhibitory ligand of LAG-3. *Cell* 176:334-347.e12, 2019
82. Yang C, Qian Q, Zhao Y, et al: Fibrinogen-like protein 1 promotes liver-resident memory T-cell exhaustion in hepatocellular carcinoma. *Front Immunol* 14:1112672, 2023
83. Lehtio J, Arslan T, Siavelis I, et al: Proteogenomics of non-small cell lung cancer reveals molecular subtypes associated with specific therapeutic targets and immune evasion mechanisms. *Nat Cancer* 2:1224-1242, 2021
84. Silberstein JL, Du J, Chan K-W, et al: Structural insights reveal interplay between LAG-3 homodimerization, ligand binding, and function. *Proc Natl Acad Sci U S A* 121:e2310866121, 2024
85. Adam K, Lipatova Z, Abdull Ghafoor Raja M, et al: Cutting edge: LAG3 dimerization is required for TCR/CD3 interaction and inhibition of antitumor immunity. *J Immunol* 213:7-13, 2024
86. Andrews LP, Butler SC, Cui J, et al: LAG-3 and PD-1 synergize on CD8+ T cells to drive T cell exhaustion and hinder autocrine IFN- γ -dependent anti-tumor immunity. *Cell* 187:4355-4372.e22, 2024
87. Cillo AR, Cardello C, Shan F, et al: Blockade of LAG-3 and PD-1 leads to co-expression of cytotoxic and exhaustion gene modules in CD8+ T cells to promote antitumor immunity. *Cell* 187:4373-4388.e15, 2024
88. Blackburn SD, Shin H, Haining WN, et al: Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. *Nat Immunol* 10:29-37, 2009
89. Ngilow SF, Manne S, Huang YJ, et al: LAG-3 sustains TOX expression and regulates the CD94/NKG2-Qa-1b axis to govern exhausted CD8 T cell NK receptor expression and cytotoxicity. *Cell* 187:4336-4354.e19, 2024
90. Li N, Wang Y, Forbes K, et al: Metalloproteases regulate T-cell proliferation and effector function via LAG-3. *EMBO J* 26:494-504, 2007
91. Andrews LP, Somasundaram A, Moskovitz JM, et al: Resistance to PD1 blockade in the absence of metalloprotease-mediated LAG3 shedding. *Sci Immunol* 5:eabc2728, 2020
92. Yang R, Huang S, Huang C, et al: Fc-competent multispecific PDL-1/TIGIT/LAG-3 antibodies potentiate superior anti-tumor T cell response. *Sci Rep* 13:9865, 2023
93. Gorgulho J, Roderburg C, Beier F, et al: Soluble lymphocyte activation gene-3 (sLAG3) and CD4/CD8 ratio dynamics as predictive biomarkers in patients undergoing immune checkpoint blockade for solid malignancies. *Br J Cancer* 130:1013-1022, 2024
94. Li H, Zandberg DP, Kulkarni A, et al: Distinct CD8+ T cell dynamics associate with response to neoadjuvant cancer immunotherapies. *Cancer Cell* 10.1016/j.ccell.2025.02.026 [epub ahead of print on March 12, 2025]
95. McInnes IB, Gravelle EM: Immune-mediated inflammatory disease therapeutics: Past, present and future. *Nat Rev Immunol* 21:680-686, 2021
96. Sharpe AH, Wherry EJ, Ahmed R, et al: The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nat Immunol* 8:239-245, 2007
97. Frebel H, Nindl V, Schuepbach RA, et al: Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. *J Exp Med* 209:2485-2499, 2012
98. Jubel JM, Barbati ZR, Burger C, et al: The role of PD-1 in acute and chronic infection. *Front Immunol* 11:487, 2020
99. Hua Y, Bergers G: Tumors vs. chronic wounds: An immune cell's perspective. *Front Immunol* 10:2178, 2019
100. Mangalmurti N, Hunter CA: Cytokine storms: Understanding COVID-19. *Immunity* 53:19-25, 2020
101. Snell LM, McGaha TL, Brooks DG: Type I interferon in chronic virus infection and cancer. *Trends Immunol* 38:542-557, 2017
102. Cristescu R, Mogg R, Ayers M, et al: Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. *Science* 362:eaar3593, 2018
103. Benci JL, Johnson LR, Chao R, et al: Opposing functions of interferon coordinate adaptive and innate immune responses to cancer immune checkpoint blockade. *Cell* 178:933-948.e14, 2019
104. Qiu J, Xu B, Ye D, et al: Cancer cells resistant to immune checkpoint blockade acquire interferon-associated epigenetic memory to sustain T cell dysfunction. *Nat Cancer* 4:43-61, 2023
105. Jain MD, Zhao H, Wang X, et al: Tumor interferon signaling and suppressive myeloid cells are associated with CAR T-cell failure in large B-cell lymphoma. *Blood* 137:2621-2633, 2021
106. Benci JL, Xu B, Qiu Y, et al: Tumor interferon signaling regulates a multigenic resistance program to immune checkpoint blockade. *Cell* 167:1540-1554.e12, 2016
107. Song E, Chow RD: Mutations in IFN- γ signaling genes sensitize tumors to immune checkpoint blockade. *Cancer Cell* 41:651-652, 2023
108. Morad G, Helmink BA, Sharma P, et al: Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. *Cell* 184:5309-5337, 2021
109. Martins F, Sofiya L, Sykietis GP, et al: Adverse effects of immune-checkpoint inhibitors: Epidemiology, management and surveillance. *Nat Rev Clin Oncol* 16:563-580, 2019
110. Pauken KE, Dougan M, Rose NR, et al: Adverse events following cancer immunotherapy: Obstacles and opportunities. *Trends Immunol* 40:511-523, 2019
111. Dougan M, Luoma AM, Dougan SK, et al: Understanding and treating the inflammatory adverse events of cancer immunotherapy. *Cell* 184:1575-1588, 2021
112. de Filette J, Andreescu CE, Cools F, et al: A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. *Horm Metab Res* 51:145-156, 2019
113. Cappelli LC, Gutierrez AK, Bingham CO, et al: Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: A systematic review of the literature. *Arthritis Care Res (Hoboken)* 69:1751-1763, 2017

114. Wang DY, Salem JE, Cohen JV, et al: Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. *JAMA Oncol* 4:1721-1728, 2018
 115. Esfahani K, Elkrief A, Calabrese C, et al: Moving towards personalized treatments of immune-related adverse events. *Nat Rev Clin Oncol* 17:504-515, 2020
 116. Luoma AM, Suo S, Williams HL, et al: Molecular pathways of colon inflammation induced by cancer immunotherapy. *Cell* 182:655-671.e22, 2020
 117. Au L, Larkin J, Turajlic S: Relatlimab and nivolumab in the treatment of melanoma. *Cell* 185:4866-4869, 2022
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Gut Microbiota in Immuno-Oncology: A Practical Guide for Medical Oncologists With a Focus on Antibiotics Stewardship

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OVERVIEW

The gut microbiota has emerged as a critical determinant of immune checkpoint inhibitor (ICI) efficacy, resistance, and toxicity. Retrospective and prospective studies profiling the taxonomic composition of intestinal microbes of patients treated with ICI have revealed specific gut microbial signatures associated with response. By contrast, dysbiosis, which can be caused by chronic inflammatory processes (such as cancer) or comedications, is a risk factor of resistance to ICI. Recent large-scale meta-analyses have confirmed that antibiotic (ATB) use before or during ICI therapy alters the microbiota repertoire and significantly shortens overall survival, even after adjusting for prognostic factors. These results underscore the importance of implementing ATB stewardship recommendations in routine oncology practice. Microbiota-centered interventions are now being explored to treat gut dysbiosis and optimize ICI responses. Early-phase clinical trials evaluating fecal microbiota transplantation (FMT) from ICI responders or healthy donors have shown that this approach is safe and provided preliminary data on potential efficacy to overcome both primary and secondary resistance to ICI in melanoma, non-small cell lung cancer, and renal cell carcinoma. More targeted interventions including live bacterial products including *Clostridium butyricum* and *Akkermansia massiliensis* represent novel microbiome-based adjunct therapies. Likewise, dietary interventions, such as high-fiber diets, have shown promise in enhancing ICI activity. In this ASCO Educational Book, we summarize the current state-of-the-evidence of the clinical relevance of the intestinal microbiota in cancer immunotherapy and provide a practical guide for ATB stewardship.

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INTRODUCTION

Immune checkpoint inhibitors (ICI) have transformed the therapeutic landscape in oncology, improving survival in the metastatic setting in non-small cell lung cancer (NSCLC),^{1,2} melanoma,^{3,4} and renal cell carcinoma (RCC),^{5,6} among other cancers. More recently, the field has evolved toward incorporating ICI in the adjuvant^{7,8} and neoadjuvant settings,^{9–12} leading to improved event-free survival. Despite these groundbreaking advances, most patients will experience disease progression because of primary or acquired resistance to ICI.¹³ In addition, the onset of off-target immune-related adverse events (irAEs) occurring in up to 60% of patients⁴ treated with combination ICI remains a significant challenge for both clinicians and patients.

In 2018, three back-to-back publications unraveled the role of the gut microbiota—a rich organ within the gastrointestinal tract primarily composed of 10¹³ commensal bacteria—in modulating ICI activity.^{14–16} These studies focused on melanoma, and genitourinary malignancies, melanoma, and profiled baseline fecal samples of patients treated with ICI, discerning distinct signatures of bacteria enriched in

responders compared with nonresponder patients.^{14–16} Specifically, high gut bacterial richness (or diversity) and the relative overrepresentation of health-related species were associated with an immunostimulatory tumor microenvironment (TME) dominated by an interferon- γ -related signature and clinical benefit to ICI. By contrast, gut dysbiosis, defined by the relative dominance of immunosuppressive pathobionts and disruption of the gut vascular and epithelial barrier integrities, was associated with resistance to ICI. Gut dysbiosis can be caused by chronic inflammation (such as cancer), dietary factors, and/or concomitant medications (particularly antibiotics [ATB] and proton pump inhibitors). Causal links between gut dysbiosis and resistance to ICI were demonstrated in germ-free or ATB-treated tumor bearing mice, colonized by complex or restricted (isolated or a compendium of live commensal strains) ecosystems. The efficacy of immunotherapy was restored upon oral supplementation with specific species and strains (such as *Akkermansia muciniphila*,¹⁴ *Bifidobacterium longum*,¹⁷ *Faecalibacterium prausnitzii*,¹⁶ and *Coprobacillus cateniformis*¹⁸) or through fecal microbiota transplantation (FMT) derived from responder patients.^{14,15,19} These studies contributed to establishing the polymorphic microbiome as

PRACTICAL APPLICATIONS

- The baseline composition of the gut microbiota represents a promising biomarker for predicting outcomes to immune checkpoint inhibitors (ICI) in patients with solid tumors.
- Antibiotics (ATB) lead to the relative overrepresentation of immunosuppressive gut bacteria and depletion of commensal bacteria culminating in resistance to ICI.
- Several retrospective and prospective studies showed that ATB, particularly broad-spectrum ATB exposure before and during ICI therapy are associated with significantly decreased overall survival.
- Judicious ATB prescription in the peri-ICI period is recommended to mitigate ATB-related dysbiosis.
- Several strategies (fecal microbiota transplantation, diet, live biotherapeutics, and prebiotics) are currently being explored to correct and improve microbiota composition in clinical trials.

one of the hallmarks of cancer²⁰ owing to the deleterious role of distinct bacteria in cancer initiation,²¹ progression,²² and therapeutic response.²³ The role of the microbiome in cancer initiation and progression is beyond the scope of this review, and they have been reviewed in detail elsewhere.²⁴

On the basis of these experimental findings, concerns emerged regarding the use of ATB before ICI initiation²⁵ because of their potential impact on the healthy commensalism. Subsequently, several studies showed that in patients amenable to ICI, ATB reduced microbiota diversity at the relative expense of favorable gut microbiota family members (such as *Ruminococcus* species), promoting the relative dominance of immunosuppressive or proinflammatory *Enterocloster* spp, and *Hungatella*.^{26,27} These harmful bacteria can impair ICI efficacy by downregulating the mRNA and protein expression of the mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1)²⁷ in the ileum, Peyer patches, and mesenteric lymph nodes, which leads to the influx of enterotropic T regulatory cells into tumor deposits. Soon thereafter, the negative role of ATB on ICI overall survival (OS) was demonstrated across multiple retrospective and prospective cohorts, as shown in a seminal meta-analysis.²⁸ This finding was further corroborated by a large updated meta-analysis, which included over 100 published studies and data from 46,000 patients.²⁹ These results underscored the need for the judicious use of ATB³⁰ in patients treated with ICI and catalyzed the development of microbiome-centered intervention (MCI) clinical trials to

beneficially shift the gut microbiota in patients undergoing ICI therapy. Several of these trials, particularly those involving FMT,^{31–33} have demonstrated both safety and encouraging preliminary activity.

In this comprehensive ASCO Educational Book dedicated to the gut microbiota, we will summarize the current state-of-the-evidence linking the gut microbiota to the clinical benefit of ICI. Additionally, we will provide guidance for oncologists on the negative role of ATB (and other comedications), and discuss emerging diagnosis tools to define gut dysbiosis, which may pave the way for designing MCI.

MAIN

Cancer-Associated Dysbiosis

The role of gut dysbiosis in human health is well established, yet it is still a matter of debate whether dysbiosis is an independent pathologic entity or a symptom secondary to chronic disease. Chronic conditions, including cancer distal from the gut,³⁴ cardiovascular disease,³⁵ GI and neurologic disorders, and unhealthy aging^{36,37}—compounded by iatrogenic insults³⁸—exhibit similar perturbations in the microbiota compared with healthy individuals, suggesting shared microbial imbalances may contribute to their pathogenesis. In preclinical models of cancer, tumorigenesis induced ileal mucosa atrophy, with villous microvascular constriction, disrupting epithelial barrier integrity.³⁴ This increased epithelial permeability, even if transient, resulted in marked and sustained gut microbiota dysbiosis dominated by the prototype unhealthy gut microbiota characterized by gram-positive *Clostridium* (including *Enterocloster*) species. In addition, individual studies³⁹ and meta-analyses⁴⁰ have profiled the gut microbiota composition of patients with cancer compared with controls and revealed distinct changes in cancer not present in the healthy population.³⁹ In cancers developing in the colon, specific bacteria including *Streptococcus bovis*⁴¹ and *Fusobacterium nucleatum*²¹ in consortia or biofilms may play etiologic roles in carcinogenesis, and specific gut microbiota signatures can distinguish benign adenomas from malignant lesions, which may have future developmental applications as screening method for colorectal cancer (Piccinno, *Nat Med* In Press). Altogether, the concept of the cancer-associated microbiota or tumor-resident microbiota²³ provides rationale for investigating its role in cancer initiation, progression, and response to therapy.

Signatures of Response and Resistance to ICI in NSCLC, Melanoma, and Other Tumor Types

NSCLC

In addition to distinguishing healthy people from cancer entities, the specific Gut OncoMicrobiome Signatures (GOMS)⁴⁰ can influence patient outcome to ICI (Fig 1). Early studies, including one with 100 patients with NSCLC and RCC

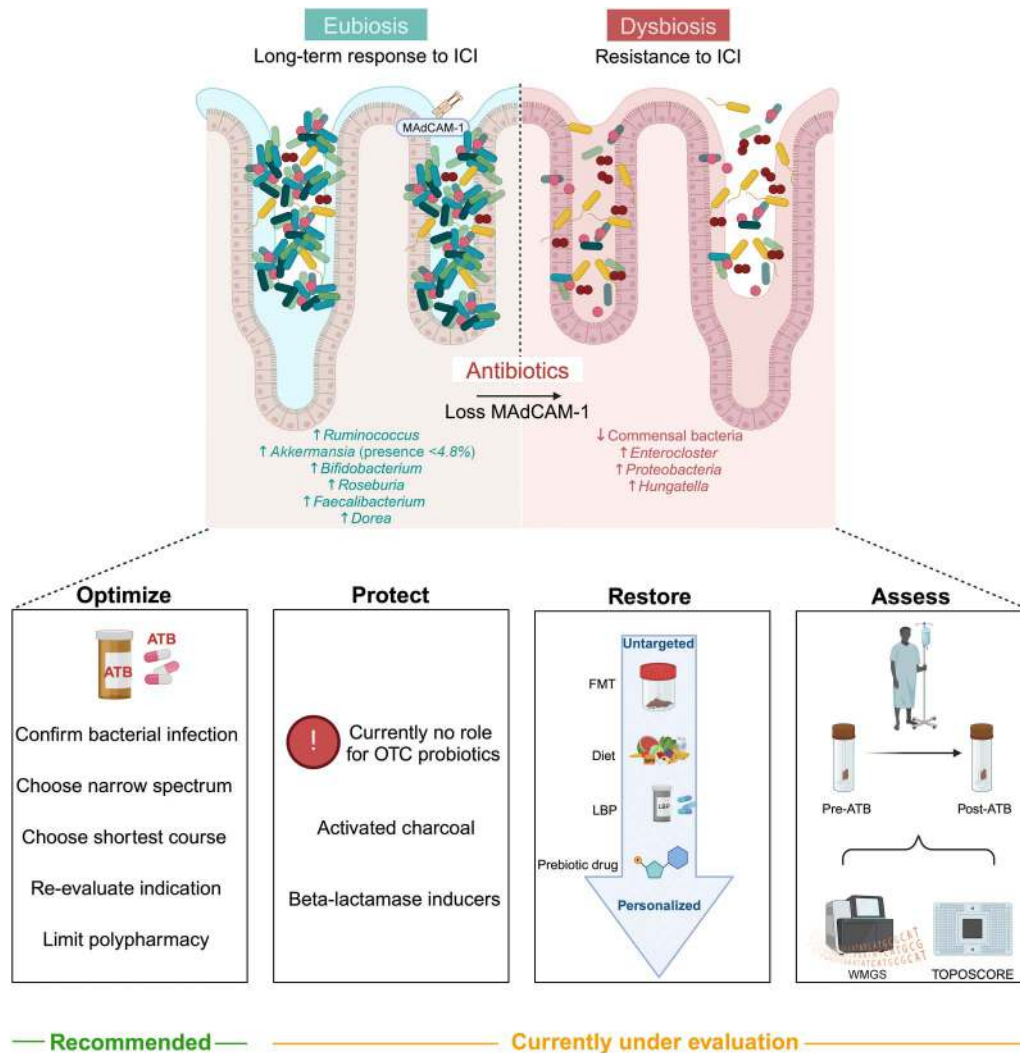


FIG 1. GOMS and emerging strategies to mitigate ATB-related dysbiosis. ATB, particularly broad-spectrum ATB, induce dysbiosis characterized by the proliferation of anaerobic bacteria called *Enterocloster* spp. This disrupts the expression of MAdCAM-1, the ligand for integrin $\alpha 4\beta 7$, which helps to retain Tr17 immunosuppressive T cells within the gut. As a result, these cells rapidly migrate to the tumor and tumor-draining lymph nodes, impairing ICI effectiveness and contributing to decreased OS. Current strategies to mitigate ATB-related dysbiosis focus on optimizing ATB use through stewardship and limiting polypharmacy. Strategies under investigation include protecting the gut microbiota, restoring its balance, as well as developing diagnostic methods to assess its recovery after ATB use. ATB, antibiotics; FMT, fecal microbiota transplantation; GOMS, Gut OncoMicrobiome Signatures; ICI, immune checkpoint inhibitors; LBP, live bacterial product; MAdCAM-1, mucosal addressin cell adhesion molecule-1; OS, overall survival; OTC, over the counter; WMGS, shotgun metagenomics sequencing.

receiving second-line anti-PD-1 therapy, identified *Akkermansia muciniphila*, *Eubacterium* spp, *Lachnospiraceae* spp, *Firmicutes* spp, and *Alistipes indistinctus* as enriched in patients achieving partial response or prolonged stable disease, in contrast to enrichment of *Parabacteroides distasonis*, *Bacteroides clarus*, *B. nordii*, and *Proteobacteria* in those with progressive disease.¹⁴ A large prospective study in a cohort of 338 patients with NSCLC with a prespecified objective response rate (ORR) primary end point confirmed that *A. muciniphila* was associated with 10% increase in ORR, demonstrating its independent impact on outcomes,

irrespective of age, sex, or PD-L1 expression.⁴² This study unraveled the importance of the relative abundance of *A. muciniphila*—pointing to the nonlinear dose effect of distinct bacteria required for optimal ICI response. Specifically, the benefit attributed to *A. muciniphila* was most pronounced when its relative abundance was detected below 4.8%—where it was also associated with other beneficial bacteria such as *Lachnospiraceae* and *Oscillospiraceae* family members. By contrast, resistance to ICI was observed when *Akkermansia* spp was not detectable or when its relative abundance exceeded the 4.8% threshold (observed in 12% of patients).

This scenario corresponded to a relative overrepresentation of pathobionts (*Enterocloster* species, *Hungatella hathewayi*, *Clostridium scindens*, *C. innocuum*) in the stool, often associated with ATB exposure. In addition to *A. muciniphila*, other key bacterial taxa have been identified as beneficial in patients with NSCLC treated with ICI, such as a relative enrichment in *Ruminococcus*²⁶ and *Faecalibacterium prausnitzii* in responders⁴³ contrasting with oral taxa (*Streptococcaceae*, *Veillonellaceae*, and *Eggerthellaceae* family members) in nonresponders.⁴⁴

Importantly, the prognostic relevance of GOMS was recently extended to the neoadjuvant setting in NSCLC as well, with enrichment of *A. muciniphila* and *Ruminococcus* spp in patients experiencing a major pathologic response to neoadjuvant nivolumab + ipilimumab ± chemotherapy.^{45,46} In the advanced-stage setting using chemoimmunotherapy combinations, a post hoc analysis of stool from patients enrolled in the phase III NIPPON trial—primarily designed to evaluate the efficacy and safety of nivolumab, ipilimumab, and platinum chemotherapy versus pembrolizumab plus platinum chemotherapy in treatment-naïve NSCLC—revealed an enrichment of butyrate-producing bacteria such as *Butyricoccus* spp and *Fusicatenibacter* spp, in patients with prolonged OS. By contrast, the presence of *Oscillibacter* spp was associated with decreased OS.⁴⁷ Notably, the impact of microbiota composition varied depending on the ICI regimen (pembrolizumab + platinum chemotherapy v nivolumab + ipilimumab + platinum chemotherapy), highlighting the potential for regimen-specific microbiota biomarkers.

Melanoma

In melanoma, early single-cohort analyses identified relative enrichment of beneficial species such as *F. prausnitzii*, *Bifidobacterium longum*, and *Bacteroides caccae* in responders to ICI.¹⁶ A more recent meta-analysis identified specific bacterial genera confirming the importance of *Bifidobacterium* spp, *F. prausnitzii* specifically, and *Ruminococcus* spp.⁴⁸ By contrast, nonresponders demonstrated a relative dominance of *Streptococcaceae* family members linked to inflammatory gene signatures and poor clinical outcomes.⁴⁸ Another multicentric cohort study of patients with melanoma revealed *Bacteroides stercoris* associated with response to ICI.⁴⁹ A recent multicenter study confirmed the importance of *Bifidobacterium pseudocatenulatum* and *A. muciniphila*.⁵⁰ In the neoadjuvant setting in 103 patients, prospective gut microbiome profiling confirmed the importance of *Ruminococcus* spp.⁵¹

Genitourinary Malignancies

For genitourinary malignancies, gut microbiota signatures were extensively reviewed as part of the ASCO GU Educational Book.⁵² Briefly, the gut microbiota has shown to have a prognostic role in RCC,⁵³ urothelial carcinoma,¹⁴ bladder cancers,⁵⁴ and prostate cancers.⁵⁵

Cross-Cancer Analyses With a Focus on Rare Cancers

Thomas et al⁴⁰ performed a recent meta-analysis across 12 cohorts from eight published studies in NSCLC and melanoma, with 248 responders and 513 nonresponders to ICI.⁴⁹ A challenge in predicting treatment benefit lies in the genetic diversity and functional differences at the subspecies and strain level. Thomas et al⁴⁰ reanalyzed previously published data sets using species-level genome bins (SGBs). This meta-analysis revealed that despite the different cancer histologies, common bacteria were relatively enriched in nonresponders including bacteria associated with immunosuppressive (*Hungatella hathewayi* and *Clostridium symbiosum*, and the genus *Enterocloster*), or proinflammatory properties, including members of the *Veillonellaceae*, *Eggerthellaceae*, *Enterobacteriaceae*, and *Erysipelotrichaceae* families, along with oral genera such as *Streptococcus* and *Actinomyces*. Similarly, when pooling the responders' microbiota from the different studies, the gut microbiota of responders included genera commonly found in healthy individuals and known for producing short-chain fatty acids (SCFAs). These included members of the *Lachnospiraceae* family, such as *Roseburia*, *Coprococcus*, *Blautia*, *Eubacterium*, and *Dorea*, as well as members of the *Ruminococcaceae* family and *A. muciniphila*. Additionally, organisms involved in dietary fiber fermentation and butyrate production, such as *F. prausnitzii*, *Eubacterium rectale*, *Roseburia*, *Fusicatenibacter saccharivorans*, and *Anaerobutyricum hallii*, were relatively prominent in responders. These results indicate that specific groups of bacteria are consistently linked to outcomes across malignancies.

Conversely, a recent investigation studied the microbiota at a deeper taxonomy level using strain (one bacterial species can have several strains) analysis on a diverse cohort of 106 patients with rare cancers, including upper GI, neuroendocrine, and gynecologic cancers, treated with combination nivolumab and ipilimumab ICI.⁵⁶ By focusing on strain-level variation and not at the species level as done in previous studies, these results highlighted the importance of intra-species diversity, revealing a new layer of complexity in establishing the microbiota as a biomarker of response to ICI. Notably, *Faecalibacterium* strains emerged as robust positive predictors. The study demonstrated the cross-cancer applicability of these microbial signatures across various cancer types, contingent on consistent ICI regimens. Importantly, microbial strain markers trained on combination ICI cohorts did not generalize to ICI monotherapy cohorts, underscoring the potential regimen-dependent nature of microbiota-host interactions seen in previous studies. This finding suggests the potential necessity of regimen-specific microbiota diagnostics and interventions in future studies.

Gut Microbiota Signatures of Immune-Related Adverse Events

Given the multiple interactions between the gut microbiota and the systemic immune tone, it is not surprising that the gut microbiota has also been linked to the development

and severity of irAE. In two independent cohorts of patients with melanoma treated with ICI using shotgun metagenomic analysis of the fecal microbiome, taxa from the Bacteroidales order (*Bacteroides intestinalis* and *Copro bacter* spp) and supraglottic bacteria belonging to the Peptostreptococcaceae family (*Intestinibacter bartlettii*) were increased in patients who developed irAE.⁴⁹ In 94 patients with melanoma treated with ICI, supraglottic bacteria (*Streptococcus oralis*) was associated with immune-related colitis,⁵ with *Streptococcus* also relatively enriched in irAE in a separate cohort of 165 patients with melanoma.¹⁹ More recently, a cohort study of 18 patients with immune-related colitis demonstrated enrichment of Proteobacteria such as *Escherichia coli* or *Klebsiella pneumoniae*, as well as *Streptococcus* spp in patients at the time of colitis.⁵⁷ In sum, taxa associated with resistance to therapy are also frequently found associated with irAE. These results have led to the development of strategies to manipulate the microbiota to palliate irAE, including FMT,^{58,59} discussed in detail below.

Point-of-Care Tools for Implementation of Gut Microbiome Profiling Into Clinical Practice

Despite the above studies and robust meta-analyses demonstrating the importance of the gut microbiome in ICI outcome, a consistent signature of dysbiosis associated with ICI resistance distinct from that of response remains to be precisely defined and prospectively validated. This is in part due to the current limitations in analyzing metagenomics data, which do not account for bacterial interactions, networks, and functions. Additionally, the methodology faces challenges related to abundance thresholds and the frequent updates of database, which can lead to changes in species names, thereby introducing variability in microbial signatures. This variability may contribute to the inconsistencies observed across studies, complicating efforts to identify robust and reproducible dysbiosis patterns associated with clinical outcomes. In addition to these challenges, complexity also exists in computing ratios between beneficial and deleterious bacteria. Recently, Derosa et al, represented the microbiome network composition of 249 patients with NSCLC in two species interacting groups (SIG) and revealed that SIG1 was composed of 37 bacteria (including the *Enterocloster* genus, *Streptococcaceae*, *Veillonellaceae*, and *Lactobacillaceae* families) preferentially increased in patients with OS inferior to one year compared with the 45 bacteria from SIG2 (including *Faecalibacterium prausnitzii*, *Ruminococcus bicirculans*, and *Blautia* spp)⁶⁰ associated with long-term survival. The seesaw balance between these two interactive groups was quantified using a SIG1/SIG2 ratio, termed S-score for each sample from each patient. For patients not belonging to either SIG1 or SIG2—thereby existing in an intermediate gray zone—a classification on the basis of the trichotomic distribution of *A. muciniphila* relative abundance could be used to create a custom topological scoring system, or TOPOSCORE, to predict the response to ICI on the basis of baseline gut microbiota composition.⁴² The TOPOSCORE was validated in

independent cohorts, including 254 additional patients with NSCLC and 216 patients with GU cancer. It demonstrated consistent performance in stratifying patients into risk categories on the basis of their microbiota composition. Patients classified as SIG2+ (favorable TOPOSCORE) had significantly prolonged survival compared with those classified as SIG1+. Recognizing the need for clinical feasibility, the TOPOSCORE was focused into a simplified 21-bacteria qPCR-based assay, prospectively validated in NSCLC. Importantly, the 21-bacteria qPCR-based TOPOSCORE's applicability was also extended to patients with melanoma and colorectal cancer, demonstrating its cross-cancer utility. This streamlined diagnostic tool provided results within 48 hours, making it accessible for routine clinical use.

ATB Negatively Affect the Gut Microbiota and Immuno-therapy Activity

Although ATB stand as one of the most profound revolutions in medicine, their overuse and misuse have had significant implications in global health. Indeed, ATB can result in quantitative, qualitative, and cumulative disruptions in the gut microbiota composition, a term collectively known as dysbiosis characterized by low bacterial biomass, low alpha diversity, and shifts in composition with enrichment of pathobiont organisms (such as the *Enterocloster* genus) and relative depletion of healthy organisms.

Murine models consistently described that broad-spectrum ATB abrogates anti-PD-1 and anti-cytotoxic T-cell lymphocyte-4 activity in murine models.^{14-17,19} Given these results, the next logical question was to examine the role of ATB-related dysbiosis in patients. In the first study to do so, Routy et al¹⁴ examined the impact of ATB exposure two months before and up to one month after initiation of ICI in 249 patients with advanced NSCLC (n = 140), RCC (n = 67), and urothelial carcinoma (UC, n = 42). ATB were associated with primary progressive disease, worse progression-free survival (PFS), and OS. This observation was then further extended in a study of 239 patients with NSCLC treated with ICI at Memorial Sloan Kettering Cancer Center and 121 patients with RCC treated with ICI at Institut Gustave Roussy.²⁵ The negative association of ATB on OS in NSCLC and in PFS in RCC was consistent despite adjusting for standard prognostic factors including age, sex, PD-L1 tumor proportion score, hospitalization, and route of ATB (oral v intravenous).

Since then, more than 100 separate studies have confirmed these findings in multiple retrospective and prospective observational cohorts of solid tumors, culminating in several, large meta-analyses. The largest meta-analysis thus far conducted in 46,232 patients (n = 12,646, 27% on ATB) examined data from 105 retrospective and prospective studies, including data obtained from randomized phase III clinical trials. This meta-analysis confirmed a deleterious association between ATB exposure and OS (pooled hazard ratio [HR] for OS, 1.71 [95% CI, 1.59 to 1.83]), consistent across tumor types (NSCLC, melanoma, GI, genitourinary,

and head and neck cancer) and geographic location (Europe, United States, Canada, and Asia). Importantly, this meta-analysis found a negative association irrespective of the time window of ATB exposure—ATB exposure before or after ICI administration was associated with worse outcomes, even up to 90 days after ICI initiation. A slightly older meta-analysis demonstrated a similar negative HR for survival irrespective of window of ATB exposure in 41,663 patients ($n = 11,785$, 28% on ATB).⁶¹

In addition to retrospective cohort studies, post hoc analyses of pooled data from phase III randomized controlled trials have been analyzed to assess the impact of comedications on ICI outcome. In analyses from the POPLAR (ClinicalTrials.gov identifier: [NCT01903993](#)) and OAK (ClinicalTrials.gov identifier: [NCT02008227](#)) trials, which included a total of 1,512 patients with previously treated NSCLC, patients were randomly assigned to receive either atezolizumab ($n = 757$) or docetaxel ($n = 755$). Multivariable analysis demonstrated that ATB were associated with reduced OS in the atezolizumab arms, whereas no significant association was found in the docetaxel-treated arms.⁶² A later study performed a post hoc analysis of the IMpower130 (ClinicalTrials.gov identifier: [NCT02367781](#)), IMpower131 (ClinicalTrials.gov identifier: [NCT02367794](#)), IMpower150 (ClinicalTrials.gov identifier: [NCT02366143](#)), OAK, and POPLAR studies combined.⁶³ This study did not find differences between the ATB-exposed and unexposed groups, but only considered ATB exposure 30 days before initiation of ICI, and pooled efficacy estimates from different backbones including ICI monotherapy, chemoimmunotherapy, and VEGF-inhibition, potentially explaining the lack of difference observed.⁶⁴ In later individual studies and

meta-analyses, ATB in the context of chemoimmunotherapy regimens was consistently associated with inferior ORR, PFS, and OS in patients with NSCLC.²⁹

ATB Class and Route

Several of these studies examined the differential impact of ATB class, duration, dose, and route (Table 1). Broad-spectrum ATB including piperacillin-tazobactam, meropenem, and fluoroquinolones have been associated with comparatively worse outcomes.⁶⁶ In addition, combinations of different classes of ATB are associated with worse outcome.²⁹ Specific ATB classes, including metronidazole, are currently being studied for potential beneficial impact.⁶⁷ However, until prospective and mechanistic data are available, all ATB drug classes should continue to be used judiciously in patients with cancer before or during ICI treatment. Sequential multiple courses, or courses over a period of 10 days or longer have been associated with worse outcomes compared with shorter courses.^{30,66,68,69} Although some studies have found that intravenous exposure was worse than oral exposure, a more recent and larger study revealed similar deleterious outcomes between the intravenous and oral routes compared with the control groups.²⁹

Addressing the Criticisms and Understanding the Mechanism of ATB-Related Dysbiosis

Despite the abundance of data pointing to the negative role of ATB on ICI outcome, critics have cited inability to disentangle whether this was a true biological signal or merely confounding by indication/severity bias, as patients who are

TABLE 1. ATB Drug Classes and Differential Impact on the Gut Microbiome

Antibiotic Drug Class	Examples	Alterations in Gut Microbiome	Findings on ICI Response
Cephalosporins	Ceftriaxone, cefuroxime	Broad spectrum activity especially for third (eg, ceftazidime) and fourth (eg, cefepime) generations Narrow spectrum activity for first generation, eg, cephalixin, cefazolin	Negative association with OS and PFS in patients receiving chemoimmunotherapy for advanced NSCLC in Canada. The shortest PFS and OS were observed when combined with other ATB, particularly sulphonamides. In ICI monotherapy, cephalosporin use showed OS and PFS outcomes comparable with those not exposed to ATB ²⁹ Negative association of ceftazidime and cefepime (and to a lesser extent ceftriaxone and cefuroxime) with CAR T-cell therapy outcomes in patients with solid and hematologic malignancies ⁶⁵
Sulphonamides	Sulfamethoxazole, trimethoprim-sulfamethoxazole	Broad spectrum activity	Negative association with OS and PFS in patients treated with chemoimmunotherapy or ICI monotherapy for advanced NSCLC. The shortest PFS and OS were observed when combined with cephalosporins ²⁹
Quinolones	Ciprofloxacin, levofloxacin	Broad spectrum activity	Negative association of fluoroquinolones (within up to one year before treatment) with OS in elderly patients undergoing ICI for various cancer types ⁶⁶
Carbapenem	Meropenem, imipenem, ertapenem	Broad spectrum activity	Negative association of meropenem with CAR T-cell therapy outcomes ⁶⁵
B-lactam/B-lactamase inhibitors	Penicillins, including amoxicillin and ampicillin	Narrow spectrum activity, eg, penicillin G Broad spectrum activity, eg, amoxicillin-clavulanate	Negative association of piperacillin-tazobactam with CAR-T cell therapy outcomes ⁶⁵

Abbreviations: ATB, antibiotics; CAR T, chimeric antigen receptor T-cell therapy; ICI, immune checkpoint inhibitor; OS, overall survival; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

on ATB are often those with inherently poorer prognosis. In addition to the multivariable analyses performed in many of these studies adjusting for overall sickness, several elements point to the causal link between ATB-related dysbiosis on impaired antitumor immunity including (1) control cohorts examining the impact of ATB exposure on chemotherapy⁶² or mTOR inhibitors⁷⁰ alone without ICI showing no impact of ATB on outcome, (2) murine proof-of-concept that ATB-treated mice exhibited blunted antitumor immune responses,¹⁴⁻¹⁶ (3) ATB affect the systemic immune tone, increasing circulating exhausted CD8⁺ T cells in patients with gastric cancer treated with anti-PD-1 therapy,⁷¹ and promoting the PD-L2 binding to its receptor repulsive guidance molecule b in the TME¹⁸; and (4) mechanistic insight in mice and humans that ATB induce a bloom of a specific gram-positive, anaerobic bacteria called *Enterocloster*—which downregulated the expression of MAdCAM-1 (Fig 1), the ligand for integrin $\alpha 4\beta 7$ that helps to retain Tr17 immunosuppressive T cells within the gut, leading to efflux of these immunosuppressive cells to the tumor and tumor-draining lymph nodes, where they abrogate ICI effectiveness.²⁷ Indeed, in patients with NSCLC treated with ICI, soluble MAdCAM-1 levels were lower in those who received ATB, which was associated with treatment resistance. In addition to identifying the mechanism, soluble MAdCAM-1 levels may serve as a novel and rapidly available biomarker for resistance to ICI.

Not only do ATB affect the efficacy of ICI, but recent studies have also suggested that ATB may also be associated with increased incidence and severity of irAE. One notable example was a retrospective analysis of 767 patients with solid tumors, in addition to aggregate data from the adverse event database of the US Food and Drug Administration (FDA; n = 38,705 reports) and WHO (n = 25,122 reports), demonstrating increased risk of irAE in ATB-exposed patients.⁷² In addition, a recent interventional study demonstrated recurrence of immune-related colitis after exposure to ATB, which was successfully treated with salvage FMT.⁵⁷

Finally, the deleterious consequences of ATB on the anti-cancer immune response are not limited to ICI treatment. Building on decades-long work showing the critical role of the gut microbiota diversity and composition in allogeneic bone marrow transplantation recipient mortality,⁷³ recent studies demonstrated that ATB were associated with inferior outcomes to CAR-T-based therapy,^{65,74} casting an even wider net into the importance of the gut microbiota in the immune response against cancer and importance for ATB stewardship.

Recommendations to Counter ATB-Related Dysbiosis

Altogether, a growing body of evidence, spanning mechanistic studies to large meta-analyses, provide robust evidence on the deleterious impact of ATB. Limitations include that, to our knowledge, to date, no strong data suggest that certain class of ATB are significantly less deleterious than

BOX 1. Recommendations for Judicious Use of ATB in Patients Treated With Immune Checkpoint Inhibitors

Oncologists should follow the joint IDSA/ASCO guidelines, which recommend antibiotic (ATB) stewardship in patients with cancer, particularly for those treated with ICI, given the known negative impact of ATB on ICI efficacy. Specifically, ATB should be used judiciously by:

1. Confirming and documenting the presence of a bacterial infection using a culture, when possible
2. Following local ATB stewardship guidelines
3. Opting for the narrowest-spectrum ATB for the shortest effective duration when ATB are necessary
4. Continuously reassessing the need for ATB
5. Establishing multidisciplinary care with infectious disease experts

others. Moreover, from a clinical trial design perspective, testing the hypothesis of ATB-related dysbiosis as part of a randomized trial would be ethically challenging. Therefore, on the basis of the current literature, we proposed guidance summarized in Box 1 with a focus on ATB stewardship³⁰ (Fig 1, optimize panel) as the primary line of defense against ATB-related dysbiosis until prospective data become available:

1. Confirming and documenting the presence of a bacterial infection using a culture, when possible
2. Following local ATB stewardship guidelines
3. When ATB are required, choosing the narrowest spectrum for the shortest course possible
4. Continuously reassessing the need for ATB
5. Establishing multidisciplinary care with infectious disease experts

In addition to ATB stewardship, several other strategies to restore disrupted microbiota after ATB are currently being evaluated (Fig 1, protect panel). A commonly suggested approach in community pharmacies or practices is to prescribe probiotics,⁷⁵ despite the lack of supporting evidence for their effectiveness.⁷⁶ In addition to the well-documented lack of regulation surrounding probiotics, two significant lines of evidence suggest that this approach may, in fact, be harmful. First, a retrospective analysis in 158 patients with melanoma revealed that patients consuming probiotics had worse outcomes to ICI.⁷⁷ Second, a study in healthy volunteers demonstrated that probiotics after ATB exposure paradoxically prolonged gut microbiota recovery time.⁷⁸

An alternative option is to eliminate ATB from the colon to protect the gut microbiota when ATB are truly indicated (Fig 1, protect panel). In a randomized phase I study in healthy volunteers, DAV132, a colon-targeted activated charcoal adsorbent, was able to adsorb broad-spectrum ATB

including piperacillin-tazobactam, ceftriaxone, or ceftazidime, allowing for systemic absorption without detection of ATB in the stool, which ultimately preserved participants' microbiota diversity, accelerated the recovery of their gut microbiome, and protected key beneficial bacteria.⁷⁹ DAV132 also preserved the activity of ICI in preclinical murine cancer models. In a similar vein, several strategies are currently under evaluation in the context of decreasing the incidence of *Clostridium difficile* infection after ATB such as supplementation of beta-lactamase enzymes to hydrolyze the beta-lactam ring (Fig 1, protect panel), thereby decreasing negative impact of ATB on the gut microbiota.⁸⁰ Whether these strategies have implications in the ICI landscape requires further evaluation. Taken together, although ATB stewardship is the mainstay strategy, there are multimodal

ways that the gut microbiota can be protected after ATB exposure. Other interventions to restore or enhance the microbiota are actively being studied and discussed in the Clinical Trials section below (Fig 1; restore panel).

Finally, although ATB are certainly the most well-studied comedications affecting ICI activity, increasing polypharmacy⁸¹ has revealed that other medications can also disrupt the gut microbiota (Table 2). Notably, proton pump inhibitors cause oralization of the gut microbiota, allowing migration of deleterious oral bacteria such as *Streptococcus* spp within the gut epithelium, also leading to compromised ICI activity.⁶³ Other less well-studied comedications with possible negative impact on the gut microbiota and ICI activity include corticosteroids,⁹⁷ laxatives,⁸⁸ opioids,⁹⁵ benzodiazepines,⁹²

TABLE 2. List of Comedications With Demonstrated Negative Impact on ICI Activity

Drug Class	Proposed Mechanism of Microbiome Modification and/or Antitumor Immune Response	Alterations in Gut Microbiome	Findings on ICI Response
Antibiotics	Dysbiosis characterized by low bacterial biomass, low alpha diversity, enrichment of pathobiont organisms and relative depletion of commensal organisms ²⁹ Migration of Tr17 cells from the gut to the tumor site after ATB-induced downregulation of MAdCAM-1 ²⁷	Generalized and ATB-specific perturbation In ICI-treated patients ↑ <i>Enterobacter</i> , <i>Hungatella</i> spp, ²⁹ <i>Clostridium</i> bolteae, <i>Bilophila wadsworthia</i> , <i>Akkermansia</i> overabundance ⁴² ↓ <i>Ruminococcus</i> , ²⁹ <i>C. aerofaciens</i> , <i>Dorea longicatena</i> , <i>Dorea formicigenerans</i> , <i>Eubacterium</i> sp. CAG38 ^{26,42,53,71}	Negative association with OS and PFS in NSCLC, RCC, and urothelial carcinoma ¹⁴ Negative association with OS in NSCLC, melanoma, GI, genitourinary, and head and neck cancer across Europe, United States, Canada, and Asia ²⁹ Increased risk of irAEs ⁷²
Proton pump inhibitors	Increase of gastric pH facilitating translocation of bacteria across barrier into intestine ⁸² as well as direct inhibition of bacterial growth ⁸³	↑ Oral bacteria and pathobionts, eg, Gammaproteobacteria, Enterobacteriaceae, Streptococcaeae, Staphylococcaeae, Veillonellaceae, and Clostridiaceae ⁸⁴ ↓ Bifidobacteriaceae, ^{82,84} Ruminococcaceae	Negative association with OS and PFS in NSCLC, urothelial cancer, anti-PD-L1 administered in second line or further, in European and Asian patients ^{53,62,85}
Laxatives	Alteration of mucus barrier during osmotic perturbation permitting bacteria colonization	↑ <i>Alistipes</i> and <i>Bacteroides</i> spp. ⁸⁶ ↓ Muribaculaceae, Bacteroidaceae <i>Akkermansia</i> ⁸⁷ starch degradation pathways ⁸⁶	Time to treatment failure with ICI shorter in patients with NSCLC with laxatives ⁸⁸
Antipsychotics	Further investigation required ⁸⁹	↑ Firmicutes with use of risperidone ⁸⁹	Penfluridol shown to cause glycosylation of PD-L1, disrupting interactions between PD-1 and PD-L1, and resulting in activation of T-cell tumor immunity ⁹⁰
Benzodiazepines	Further investigation required ⁸⁶	↓ Alpha diversity; Benzodiazepine derivatives showed broad and long-lasting impact on the gut microbiome, similar to ATB (Aas-mets et al ¹²⁷) ↑ <i>Haemophilus parainfluenzae</i> , ⁸⁶ <i>Eisenbergiella tayi</i> , several <i>Clostridiales</i> spp. <i>Streptococcus parasanguinis</i> , <i>Streptococcus mutans</i> ⁹¹	Negative association with OS and PFS in patients with NSCLC undergoing chemioimmunotherapy ⁹²
Opioids	Modulation of gut barrier function ⁹³	↑ Streptococcaeae ⁹⁴ ↓ <i>Bacteroides</i> , <i>Roseburia</i> , <i>Bilophila</i> ⁹³	Suppression of antitumor immunity via T cell-mediated mu opioid receptor 1 (OPRM1) signaling ⁹⁵
Corticosteroids	Direct immune modulation (immunosuppression) Modulation of gut barrier function ⁹⁶	↑ Firmicutes, Actinobacteria ↓ Bacteroidetes ⁹⁶	Negative association with ORR, PFS, and OS in patients with NSCLC with baseline corticosteroid use of ≥10 mg ⁹⁷

Abbreviations: ATB, antibiotic; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MAdCAM-1, mucosal addressin cell adhesion molecule-1; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

and antipsychotics.⁹⁰ A comprehensive prospective study of the impact of comedications on the gut microbiota composition in immuno-oncology is lacking. In the absence of prospective data, exercising best practices to avoid polypharmacy and reduce unnecessary medications may be of benefit to patients treated with ICI.

Clinical Trials to Beneficially Shift the Gut Microbiota in Patients Treated With Cancer Immunotherapy

Building on the above evidence linking GOMS to ICI outcome and toxicity coupled to the deleterious effect of ATB, MCIs are emerging to correct dysbiosis and enhance ICI outcomes. These approaches span a spectrum (Fig 1, restore panel), from complex and untargeted techniques such as FMT seeking to reset the entirety of the host microbiota or to dietary interventions, to more precise methods involving individual metabolites or formulations of selected bacterial strains. Active and planned clinical trials using MCI are described in Table 3.

FMT

FMT is the administration of a solution of fecal matter from a donor into a recipient's GI tract (upper or lower) to modify or replace the recipient's gut microbial composition. FMT is an approved treatment for prevention of recurrent *C. difficile* infection.¹⁰⁷ In melanoma, three phase I studies have demonstrated the role of FMT in reinstating sensitivity to ICI in the resistant setting or preventing the development of primary resistance to ICI.^{31,32} The first two studies carried out in the ICI-refractory setting demonstrated that adding FMT using stool from patients with melanoma who were responders to ICI restored ICI activity in 20%–30% of the patients.^{31,32} FMT can be carried out using multiple modalities—through direct delivery in the colon through colonoscopy,¹⁰⁸ nasogastric tube, or more recently, through oral capsules.¹⁰⁹ The latter strategy has opened new opportunities for more harmonized clinical studies using the same donor stool material for different participating sites. The most recent published study³³ evaluated FMT capsules from healthy donor volunteers to first-line nivolumab or pembrolizumab and confirmed that the addition of FMT to ICI monotherapy was safe and showed the promising potential of FMT to decrease primary resistance to ICI with an ORR of 65%. Similar to the earlier studies, clinical response correlated with the relative elimination of deleterious bacteria and augmentation of beneficial *Ruminococcus* spp.

In addition to melanoma, FMT is evaluated in clinical trials in other malignancies. The final clinical results of the TACITO trial in 50 patients with advanced RCC undergoing pembrolizumab plus axitinib treatment who were randomly assigned to FMT or placebo (ClinicalTrials.gov identifier: [NCT04758507](#)) were presented at ESMO Barcelona 2024.¹¹⁰ Donor specimens were sourced from a single patient having achieved complete response to ICI combination without targeted therapy. FMT was then administered by

colonoscopy within eight weeks of treatment initiation and subsequently repeated at 12 and 24 weeks by frozen oral capsules. It is important to note that both cohorts received bowel preparation with laxative therapy before intervention. Preliminary results have demonstrated a positive effect of FMT on one-year PFS rate (66.7% in FMT arm v 35% in placebo, $P = .036$). Another single-arm phase IIa trial is currently being led by Ullern et al,¹²⁸ studying several metastatic malignancies including metastatic RCC to determine the safety of FMT in combination with ICI and effect on ORR (ClinicalTrials.gov identifier: [NCT05286294](#)). Initial results reveal only grade 1 FMT-related adverse events in three of nine patients and no objective response. Furthermore, a phase I trial is being conducted by Fernandes et al¹²⁹ on patients with metastatic RCC undergoing FMT with nivolumab plus ipilimumab, with the primary end point of occurrence of immune-related colitis (ClinicalTrials.gov identifier: [NCT04163289](#)). Initial results reveal grade 3 events in four of 10 patients. Another ongoing phase I trial led by Graff et al¹³⁰ on patients with metastatic castration-resistant prostate cancer is looking at FMT in combination with enzalutamide with pembrolizumab (ClinicalTrials.gov identifier: [NCT04116775](#)), for which results are eagerly awaited.

Although FMT brings forward an important proof-of-concept, there are inherent limitations to this technique. Unless the capsules are lyophilized, FMT capsules are kept at -80°C to maintain the viability of microbial populations, which requires cold-chain transportation, limiting the wide adoption of this technique to peripheral centers. In addition, the optimal source of FMT remains to be defined, as FMT for oncology programs can be obtained from patients whose tumors had responded favorably to ICI or from healthy volunteer donors. To our knowledge, no studies have directly compared these two strategies. The specific advantages for using healthy donor stool include lack of regulatory limitations of using responder stool in some countries, the theoretical advantage to using healthy donor stool to avoid the potential for a cancer-related dysbiosis phenotype, and the practical aspect of scalability.

Regardless of the donor source, any FMT program requires an extensive donor screening protocol including history, physical examination, and extensive testing of the stool for all known pathogens and, more recently, viruses, including SARS-CoV-2 or monkeypox virus, to prevent infectious transmission from the donor to the host.^{111–113} In addition, donors must follow strict lifestyle habits including safe sexual practices, no smoking, limited alcohol use, and limited travel. Therefore, donor attrition is a major limitation to implementing FMT into clinical practice.

Finally, although Health Canada does not allow for mixing donor stool, the European Medicines Agency and more recently the FDA do, also termed modified FMT, allowing for superior scale-up of FMT products. However, it remains to be seen whether mixing feces from multiple donors would

TABLE 3. Gut Microbiome–Centered Interventions and Clinical Trials

Drug or Study Name, Sponsor	Type	Description	Stage (when available), Status
FMT-LUMINATE, Centre hospitalier de l'Université de Montréal (CHUM)	FMT	FMT (capsules) from healthy volunteers in patients with advanced NSCLC, melanoma, and uveal melanoma	Phase II, NCT04951583 ³³
LND101, Canadian Cancer Trials Group	FMT	FMT (capsules) from healthy donors in patients with previously untreated advanced melanoma	Phase II, NCT06623461
University of Pittsburgh	FMT	FMT (colonoscopy) from responding patients in patients with PD-1–refractory melanoma	Phase II, NCT03341143 ³¹
Portland VA Medical Center	FMT	FMT (endoscopy) from responding patients in patients with immunotherapy-refractory metastatic castration-resistant prostate cancer	Phase II, NCT04116775
TACITO, Fondazione Policlinico Universitario Agostino Gemelli IRCCS	FMT	FMT (colonoscopy and capsules) from responding patients in patients with advanced RCC	Phase II, NCT04758507
PERFORM, Lawson Health Research Institute	FMT	FMT (capsules) from healthy volunteers in patients with RCC	Phase I, NCT04163289 ⁹⁸
MIMic, Lawson Health Research Institute	FMT	FMT (capsules) from healthy volunteers in patients with melanoma	Phase I, NCT03772899
Sheba Medical Center	FMT	FMT (capsules and colonoscopy) from responding patients in patients with immunotherapy-refractory melanoma	Phase I, NCT03353402 ³²
MaaT013, MaaT Pharma, Assistance Publique–Hôpitaux de Paris	FMT	Fecal transplant (pooled from 3 to 8 healthy donors) in melanoma in combination with ipilimumab and nivolumab	Phase I, NCT04988841
MaaT033, MaaT Pharma, Gustave Roussy, Regeneron	FMT	Fecal transplant (pooled from 3 to 8 healthy donors) in NSCLC in combination with cemiplimab	Randomized Phase II, European Union Clinical Trial number, EUCT No: 2024-517018-14-00
SER401, Seres	FMT	Firmicutes-enriched spore formulation purified from fecal sample in patients with metastatic melanoma	Phase I, discontinued, NCT03817125 ⁹⁹
M.D. Anderson Cancer Center	FMT	FMT (colonoscopy) in patients with genitourinary cancer to treat ICI-induced diarrhea or colitis	Phase I, NCT04038619
M.D. Anderson Cancer Center	FMT	FMT in patients with melanoma or genitourinary cancer to prevent adverse events	Phase II, NCT03819296 ⁵⁸
M.D. Anderson Cancer Center	FMT	FMT (colonoscopy and capsules) in patients with immunotherapy-refractory metastatic colorectal cancer	Phase II, NCT04729322
University of Arhus	FMT	FMT (capsules) in patients with genitourinary cancer or melanoma to treat ICI-induced diarrhea or colitis	Phase II, NCT06206707
Memorial Sloan Kettering Cancer Center	FMT	FMT in patients with any malignancy to prevent ICI-related diarrhea	Phase I, NCT04883762 ⁵⁷
MITRIC, Oslo University Hospital	FMT	FMT from responder patients in immunotherapy-refractory patients of all solid malignancies	Phase IIa, NCT05286294
University of Zurich	FMT	FMT (colonoscopy) in patients with any refractory stage IV malignancy	Phase I, NCT05273255
Soroka University Medical Center	FMT	FMT (capsules) from responder patients in patients with stage IV lung cancer	Phase II, NCT05502913
The Netherlands Cancer Institute	FMT	FMT (gastroduodenoscopy) from responder v non-responder patients in patients with refractory metastatic melanoma	Phase Ia/Ib, NCT05251389
University of Pittsburgh	FMT	FMT (colonoscopy) from responders in patients with refractory stage IV NSCLC	Phase II, NCT05669846
University of Pittsburgh	FMT	FMT (colonoscopy and sigmoidoscopy) from responders in patients with advanced melanoma treated with pembrolizumab and lenvatinib	Phase II, NCT06030037
FMT-ELIMINATE, University of Pittsburgh	FMT	FMT (capsules) in patients with refractory immune-related cutaneous and colitis events	Phase II, NCT06499896
Shanghai Zhongshan Hospital	FMT	FMT (capsules) in patients with stage III/IV NSCLC	Phase I, NCT05008861

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TABLE 3. Gut Microbiome–Centered Interventions and Clinical Trials (continued)

Drug or Study Name, Sponsor	Type	Description	Stage (when available), Status
Medical University of Graz	FMT	Allogenic FMT from responder patients v autologous FMT in patients with refractory advanced melanoma	Terminated, NCT04577729
FLORA, University Hospital Heidelberg	FMT	FMT (capsules) in conjunction with vancomycin in patients with advanced hepatocellular carcinoma	Phase II, NCT05690048
Peking University	FMT	FMT (capsules) in patients with advanced GI solid tumors	Phase I, NCT04130763
Chinese Academy of Medical Sciences	FMT	FMT (capsules) in patients with advanced colorectal cancer in combination with ICI plus sintilimab and fruquintinib	Phase II, NCT05279677
Changhai Hospital	FMT	FMT (capsules) in patients with advanced gastric cancer undergoing chemoimmunotherapy	NCT06346093
Changzhou No.2 People's Hospital	FMT	FMT in patients with advanced gastric cancer undergoing SOX and sintilimab	Phase II, NCT06405113
Changzhou No.2 People's Hospital	FMT	FMT in patients with advanced NSCLC undergoing chemoimmunotherapy	Phase II, NCT06403111
China-Japan Friendship Hospital	FMT	FMT in patients with resectable NSLC undergoing neoadjuvant chemoimmunotherapy	NCT06613308
Asan Medical Center	FMT	FMT in patients with refractory advanced solid tumors in conjunction with nivolumab	Phase II, NCT05533983
Fundacion para la Investigacion Biomedica del Hospital Universitario Ramon y Cajal	FMT	FMT (capsules) from donor with high abundance of select bacteria in patients with advanced NSCLC	NCT04924374
TALENP004, Fujian Provincial Hospital	FMT	FMT (capsules) from healthy donors in refractory unresectable HCC	NCT06643533
Sun Yet-Sen University Cancer Center	FMT	FMT (capsules) in patients with oligometastatic nasopharyngeal carcinoma undergoing chemoimmunotherapy	Phase III, NCT06486220
FAB-HCC, Medical University of Vienna	FMT	FMT in patients with refractory advanced HCC	Phase II, NCT05750030
ProgenaBiome	FMT	FMT (colonoscopy) from healthy donor in patients with metastatic melanoma	Phase I, NCT04056026
Masonic Cancer Center, University of Minnesota	FMT	FMT (capsules) in patients with unresectable NSCLC	Phase II, NCT04105270
Ella Therapeutics Ltd	FMT	FMT (capsules) from responder patients in patients with advanced melanoma, NSCLC, or dMMR GI cancers	Phase Ib, NCT04521075
MET-4, NuBiyota, University Health Network, Toronto	LBP	Microbial Ecosystem Therapeutics (MET-4) consortia of 30 bacterial strains (PO, daily) in patients with advanced solid tumors	Phase II/III, NCT03686202 ¹⁰⁰
VE800, Vedanta Biosciences	LBP	Consortia of 11 bacterial strains	Phase I, discontinued, NCT04208958
BMC128, Biomica	LBP	Consortia of 4 bacterial strains in patients with NSCLC, melanoma, or RCC	Phase I, NCT05354102
Oncobax-AK, EverImmune	LBP	Akkermansia massiliensis p2261 strain (1 capsule daily) in patients with NSCLC or RCC	Phase II, NCT05865730 ¹⁴
CBM588, City of Hope Medical Center	LBP	Clostridium butyricum CBM 588 probiotic strain (PO, BID) in patients with metastatic RCC (in combination with nivolumab and ipilimumab)	Phase I, NCT03829111 ¹⁰¹
CBM588, City of Hope Medical Center	LBP	Clostridium butyricum CBM 588 probiotic strain (PO, twice a day) in patients with metastatic RCC (in combination with nivolumab and cabozantinib)	Phase I, NCT05122546 ¹²⁶
CBM588, Osel	LBP	Clostridium butyricum CBM 588 probiotic strain (PO, twice a day) in patients with advanced-stage RCC	Phase I, NCT06399419
EDP1503, University of Chicago	LBP	Bifidobacterium animalis subsp. lactis strain EDP1503 (capsules, twice a day) in patients with advanced melanoma	Phase II, suspended, NCT03595683 ¹⁷
GEN-001, Genome & Company	LBP	Lactococcus lactis GEN-001(PO, daily) in patients with immunotherapy-refractory metastatic solid tumors	Phase I, completed, NCT04601402

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TABLE 3. Gut Microbiome–Centered Interventions and Clinical Trials (continued)

Drug or Study Name, Sponsor	Type	Description	Stage (when available), Status
GEN-001, Genome & Company	LBP	Lactococcus lactis GEN-001 (PO, daily) in patients with advanced gastric cancer	Phase II, NCT05419362
MRx0518, 4D pharma plc	LBP	Enterococcus gallinarum (PO, twice a day) in patients with solid tumors refractory to immunotherapy in combination with pembrolizumab	Phase I/II, terminated, NCT03637803 ^{103,104}
VSL#3 450B, Mayo Clinic	LBP	Live freeze-dried lactic acid bacteria probiotic (PO, daily) in patients to prevent ICI-induced colitis	NCT06508034
Tianjin Medical University Second Hospital	LBP	Bifidobacterium spp, Lactobacillus spp, and Enterococcus spp (PO, twice a day) in patients with urothelial carcinoma	Phase IV, NCT05220124
CJRB-101, CJ Bioscience, Inc	LBP	CJRB-101 (PO, daily or twice a day) in patients with advanced melanoma, NSCLC, and head and neck squamous cell carcinoma	Phase I and II, NCT05877430
EXL01, GERCOR–Multidisciplinary Oncology Cooperative Group	LBP	Single strain of Faecalibacterium prausnitzii (PO, daily) for patients with PD-L1–positive metastatic gastric cancer	Phase II, NCT06253611
EXL01, Center Eugene Marquis	LBP	Single strain of Faecalibacterium prausnitzii (PO, daily) for patients with advanced HCC	Phase II, NCT06551272
EXL01, University Hospital, Lille	LBP	Single strain of Faecalibacterium prausnitzii (PO, daily) for patients with refractory advanced NSCLC	Phase I and II, NCT06448572
BiFico, Xiangya Hospital of Central South University	LBP	Bifidobacterium trifidum live powder (PO, twice a day) in patients undergoing neoadjuvant chemioimmunotherapy for resectable NSCLC	Phase II, NCT04699721
Shenzhen Third People's Hospital	LBP	Enterobacter spp (PO, six/day) for patients with unresectable HCC	Phase II, NCT06563947
Symbioflor, AC Camargo Cancer Center	LBP	Suspension containing Escherichia coli (PO, daily) in combination with probiotic-rich diet in patients with localized anal canal squamous cell carcinoma	Phase II, NCT03870607
Kex02, Jiangxi Provincial Cancer Hospital	LBP	Lactobacillus spp and Bifidobacterium spp (PO, daily) in patients with NSCLC undergoing platinum-based chemotherapy with cariluzumab	NCT05094167
BL-04, Necmettin Erbakan University	LBP	Bifidobacterium animalis subsp. lactis BL-04 strain (PO, QID) in patients with advanced NSCLC	NCT06428422
R-5780, Rise Therapeutics LLC	LBP	R-5780 in patients with solid tumors including advanced melanoma, basal cell carcinoma, and squamous cell carcinoma	Phase I, NCT06398418
Probio-M9, Jiangxi Provincial Cancer Hospital	LBP	Lactobacillus rhamnosus Probio-M9 (PO, daily) in patients with advanced HCC	NCT05032014
Lactobacillus johnsonii, Second Affiliated Hospital, School of Medicine, Zhejiang University	LBP	Lactobacillus johnsonii supplement in patients with pMMR metastatic colorectal cancer	NCT06823323
Camu camu, Centre hospitalier de l'Université de Montréal (CHUM)	Prebiotic	Camu camu berry lyophilized extract (capsules) in patients with NSCLC or melanoma	Phase I, NCT05303493 ¹⁰⁵
Camu camu, City of Hope Medical Center	Prebiotic	Camu camu berry lyophilized extract (capsules) in patients with metastatic RCC	Phase I, NCT06049576
Inulin, Fondazione del Piemonte per l'Oncologia	Prebiotic	Inulin supplement in patients with relapsed metastatic head and neck squamous cell carcinoma	NCT05821751
Resistant starch, University of Michigan Rogel Cancer Center	Prebiotic	Resistant starch in patients with solid cancer undergoing treatment with ICI	Phase I, NCT04552418
MS-20, Microbio Co Ltd	Prebiotic	Fermented soybean solution in patients with NSCLC	Phase II, NCT04909034 ¹⁰⁶
N-3 PUFA, Universidade Federal do Rio de Janeiro	Prebiotic	Fish oil tablet supplementation for four months in patients with NSCLC	NCT04965129
Eicosapentaenoic acid, University of Leeds	Prebiotic	Icosapent ethyl oral capsules for patients with liver metastases from colorectal cancer	NCT04682665
Eicosapentaenoic acid, Massachusetts General Hospital	Prebiotic	Icosapent ethyl oral capsules for patients with resectable colorectal cancer	Terminated, NCT03661047
Biolosion, Sun Yat-sen University	Prebiotic	Biolosion capsules in triple-negative breast cancer undergoing neoadjuvant chemioimmunotherapy	Phase II, NCT06768931

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TABLE 3. Gut Microbiome–Centered Interventions and Clinical Trials (continued)

Drug or Study Name, Sponsor	Type	Description	Stage (when available), Status
DIET-LUNG, Centre hospitalier de l'Université de Montréal (CHUM)	Diet	Increased fiber intake in patients with NSCLC undergoing immunotherapy	NCT05805319
DIET, M.D. Anderson Cancer Center	Diet	Whole-food, fiber-rich diet in patients with melanoma	Phase II, NCT04645680
PreFED, M.D. Anderson Cancer Center	Diet	PreFED in patients with ICI-refractory melanoma	Phase II, NCT06250335
MINI-MD, University Hospital Rijeka	Diet	Mediterranean diet in patients with metastatic melanoma	NCT06236360
Intermittent fasting, H. Lee Moffitt Cancer Center and Research Institute	Diet	14 hours of PNF in patients with advanced head and neck cancer	NCT05083416
Time-restricted eating, Duke University	Diet	14 hours of nightly fasting period in patients with advanced head and neck squamous cell cancer	NCT06603155
Fasting-mimicking diet, VA Office of Research and Development	Diet	Fasting-mimicking diet with plant-based diet program in patients with metastatic NSCLC undergoing pembrolizumab	NCT06671613
Fasting-mimicking diet, Mayo Clinic	Diet	Calorie-restrictive, low-protein, high-complex-carbohydrate, high-fat diet in advanced stage solid tumors	NCT06438588
Ketogenic diet, Gustave Roussy Cancer Campus	Diet	Ketogenic diet in patients with metastatic RCC	Terminated, NCT05119010
Ketogenic diet, Ohio State University Comprehensive Cancer Center	Diet	Ketogenic diet in patients with metastatic melanoma and renal cancer	Phase I, NCT06391099
Mediterranean diet, University Hospital Rijeka	Diet	Personalized nutrition plan on the basis of Mediterranean diet in patients with metastatic melanoma	NCT06236360
Fermented foods and fiber, University of Pittsburgh	Diet	Fermented foods and fiber supplementation in patients with melanoma and NSCLC	NCT06475807
Fermented foods, H. Lee Moffitt Cancer Center and Research Institute	Diet	3-6 servings of fermented foods per day in patients with stage II-IV NSCLC and locally advanced rectal cancer	NCT06337552
Fiber, Universitair Ziekenhuis Brussel	Diet	High-fiber supplementation in patients with solid tumors treated with ICI	NCT05832606
Fiber, Scripps Health	Diet	High-fiber dietary counseling in patients with triple-negative breast cancer undergoing neoadjuvant chemioimmunotherapy	NCT06610097
Paricalcitol, Translational Genomics Research Institute	Supplements	Paricalcitol supplementation in patients with metastatic pancreatic treated with pembrolizumab	Phase II, NCT03331562
Calcium pantothenate, University Health Network, Toronto	Supplements	Calcium pantothenate supplementation in patients with advanced melanoma undergoing dual ICI	Phase I, NCT06377111
Acarbose, University of Alabama at Birmingham	Pharmacologic drugs	Acarbose in patients with metastatic RCC	Phase II, NCT05487859
Antibiotics, Icahn School of Medicine at Mount Sinai	Pharmacologic drugs	Ciprofloxacin (PO, twice a day) and metronidazole (PO, three times a day) for 21 days in patients with resectable pancreatic cancer treated with pembrolizumab	Phase II, NCT05462496
Antibiotics, NYU Langone Health	Pharmacologic drugs	Ciprofloxacin (PO, twice a day) and metronidazole (PO, three times a day) for 29 days in patients with resectable pancreatic cancer treated with pembrolizumab	Phase IV, suspended, NCT03891979
DUO Trial, Dana-Farber Cancer Institute	Lifestyle	High-fiber diet in combination with high-intensity exercise in advanced melanoma	NCT06298734
EDEN, National Cancer Institute	Lifestyle	Plant-based, high-fiber diet in combination with exercise in patients with melanoma	NCT04866810

Abbreviations: dMMR, deficient DNA mismatch repair; FMT, fecal microbiota transplantation; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; LBP, live bacterial product; NSCLC, non–small cell lung cancer; pMMR, proficient mismatch repair; PNF, prolonged nightly fasting; PO, orally; PreFED, prebiotic food-enriched diet; RCC, renal cell carcinoma.

negatively affect microbial communities owing to incompatible cohabitation among organisms. The MaaT Pharma product, which combines a stool mixture obtained from 3 to 8 healthy volunteer donors (MaaT013), finished enrollment in a 1:1 randomized phase IIa trial of 70 patients with advanced-stage melanoma treated with dual ICI (ClinicalTrials.gov identifier: [NCT04988841](#)). Results are eagerly awaited. In addition, a larger study in 128 patients with advanced-stage melanoma will be randomized 1:1 between physician's choice ICI, including nivolumab and relatlimab combination in the Canadian Canbiome2 trial (ClinicalTrials.gov identifier: [NCT06623461](#)).

Dietary and Lifestyle Interventions

Among the external factors influencing a person's gut microbiota structure and function, diet is one of the most important.^{114,115} Diet has been linked to the pathophysiology of several inflammatory and cardiovascular diseases. Habitual diet varies according to geographical locations among other factors; therefore, different dietary patterns may contribute to the regional variations observed in gut microbiota signatures and some of the inconsistencies in identifying taxa linked to favorable ICI responses across different parts of the world. Despite the important role that diet plays on cancer development and likely also on cancer treatment response, there is insufficient evidence to recommend a specific diet type, as described in the most recent ASCO Guidelines.¹¹⁶

In preclinical studies, specific diets such as ketogenic diet have been linked to enhanced ICI responses and proinflammatory TME characterized by enhanced cytotoxic CD8⁺ T cells in the tumor in a microbiome-mediated fashion,¹¹⁷ and supplementation of fiber has been linked to improved ICI response through binding carcinogenic bile acids.⁷⁷

Fiber

Dietary fiber is defined as nondigestible carbohydrates and lignin that are intrinsic and intact in plants. Therefore, high dietary fiber is a hallmark of plant-based diets. SCFAs (butyrate, acetate, and propionate) are the products of dietary fiber fermentation by gut bacteria. In patients with melanoma, Spencer et al⁷⁷ described that increased dietary fiber consumption was associated with improved PFS in a US cohort of patients with melanoma treated with ICI. Interestingly, although the increase in Ruminococcaceae family and Faecalibacterium genus in responder patients observed in a previous cohort¹⁶ was corroborated in this study, the increase was not statistically significant in patients with a sufficient versus insufficient fiber diet. This underscores the challenge of attributing the beneficial effect of fibers on specific bacterial taxa. Importantly, the increased response to ICI with fiber was reproduced in a conventional mouse melanoma model fed a fiber-rich versus fiber-poor diet, with an associated increase in Ruminococcaceae. The impact of increased dietary fiber was not as clear in patients with NSCLC in a

separate study, likely owing to the lower fiber intake in NSCLC compared with patients with melanoma. As a result, several prospective trials are ongoing to increase the dietary fiber intake in patients with cancer (ClinicalTrials.gov identifiers: [NCT03950635](#), [NCT04645680](#), [NCT05805319](#)).

Prebiotics

Complex Prebiotics

Complex glycans such as fructo-oligosaccharides, inulin, and galacto-oligosaccharides reach the colon intact, where they are broken down by the gut microbiota.^{118,119} In return, the metabolic products of this fermentation, such as SCFAs, can be used by colonocytes or absorbed systemically.

The fructan inulin has been shown to induce favorable changes in the gut microbiota in humans¹²⁰ and potentiated the effect of ICI in different models. Inulin was associated with an increase in *A. muciniphila*, *Lactobacillus* spp, and *Roseburia* spp¹²¹ as well as systemic memory T-cell responses. Inulin is currently being evaluated in a clinical trial in patients with metastatic head and neck squamous cell carcinoma ([Table 2](#)).

Polyphenol-Based Prebiotics

Polyphenols are secondary metabolites found in fruits, vegetables, nuts, and tree heartwood.¹²² Polyphenols are often large, hydrophilic molecules that have poor bioavailability and reach the large intestine intact, where they can interact with the gut microbiota.¹²³ In the context of cancer immunotherapy, polyphenols such as castalagin found in the camu camu berry have been shown to circumvent resistance to anti-PD-1 immunotherapy by modulating the composition and function of the microbiota^{105,124} in murine models. Although the mechanisms of action remain unclear, polyphenols are known to have pleiotropic activities that affect bacteria directly, as well as community structure and activity indirectly. For instance, castalagin supplementation in a murine cancer model leads to an increase in Ruminococcaceae and *A. muciniphila* and the recruitment of CD8⁺, PD-L1⁺CD8⁺, and CD8⁺/FOXP3⁺CD4⁺ T cells within the TME.¹⁰⁵ Camu camu is currently being evaluated in clinical trials in combination with ICI in melanoma, NSCLC, and RCC ([Table 2](#)).¹²⁵

Probiotics and Live Biotherapeutic Products

Probiotics are live microorganisms that, when administered in adequate amounts (between 10⁸ and 10⁹ CFU/serving or per day), confer a health benefit on the host,¹¹⁶ and can be marketed as either a food supplement or drug depending on intent/claim (to improve health v prevent/treat disease, respectively). The FDA has defined a new live biotherapeutic products (LBP) category to meet the increasing need for regulatory oversight of probiotics. Probiotics can be regulated differently depending on their intended use (dietary

supplement or drug). Although dietary supplements do not require the approval of the FDA and many other regulatory bodies, probiotics intended for human diseases must submit to the same regulatory procedures as any other investigational new drug.

More recent understanding of the role of specific gut bacterial strains in local immunomodulation, colonization resistance, or other benefits attributed to the microbiota has spurred a wave of next-generation probiotics on the basis of individual strains or well-defined consortia and their potential systemic bioactivity. In the context of ICI, the next-generation probiotics are classified within LBP, including a wide range of strains such as *A. muciniphila*¹⁴ (reclassified in the updated taxonomy as *A. massiliensis*) or rationally selected consortia of up to 30 species such as in the Microbial Ecosystem Therapeutic 4 (MET4 product)¹⁰⁰ (Table 2). Several clinical trials testing LBP are currently underway (Table 2). In one of these phase I studies, CBM588, a bifidogenic probiotic strain, did not affect the overall abundance of *Bifidobacterium* spp. However, an increase in *Bifidobacterium longum* was observed in responders to ICI, and patients receiving the probiotic in combination with ipilimumab and nivolumab had significantly improved PFS compared with those receiving ipilimumab plus nivolumab alone.¹⁰¹ The same group recently published similar results combining CBM588 with nivolumab and cabozantinib.¹²⁶ Another phase I study evaluated a 30-species microbial consortium MET4 designed for coadministration with ICI. A total of 40 patients with solid malignancies were enrolled. There were no statistically significant differences in the primary ecologic outcomes, and no clear differences have emerged regarding clinical benefit so far.¹⁰⁰

CONCLUSIONS AND FUTURE DIRECTIONS

As demonstrated by the preclinical studies, cohort studies, and clinical trials discussed in this Educational Book, there exists an intricate interplay between the gut microbiota and

ICI efficacy, which has reached clinical implications. The growing body of evidence underscores the necessity of preserving microbiota integrity before and during ICI, particularly in the context of ATB use, which has been repeatedly linked to adverse oncologic outcomes in all immunotherapy-based regimens. These findings cast a wide net over the broader implications of microbiome modulation, extending beyond ICI to other immunotherapeutic modalities such as HSCT and CAR-T therapy. The most important recommendation to date is that of ATB stewardship. This involves confirming the presence of a bacterial infection before starting ATB, selecting the narrowest-spectrum ATB when necessary, prescribing it for the shortest effective duration, and following ATB stewardship guidelines.

Emerging strategies, ranging from complex strategies such as FMT or diet, to more personalized interventions such as LBPs, in addition to techniques to restore the microbiota after ATB, hold promise for optimizing the gut microbiota to improve patient responses to ICI. However, significant challenges remain in refining these approaches, including the need for patient selection and stratification, identification of optimal bacterial consortia, and consideration of regimen-specific microbiome diagnostics.

Looking ahead, a precision-medicine approach leveraging point-of-care gut microbiota profiling may enable patient stratification for personalized MCI, including after ATB. Large-scale clinical trials are needed to validate these therapeutic interventions, ensuring their safety, efficacy, and long-term feasibility. Harnessing the gut microbiota as a therapeutic target in cancer immunotherapy is a groundbreaking yet still nascent frontier—one that holds the potential to revolutionize treatment paradigms. As research accelerates, MCIs have the potential to transform ICI from a one-size-fits-all approach into a precision-guided therapy. This breakthrough approach could unlock new possibilities to enhance treatment response, overcoming resistance, and mitigating toxicity.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Reck M, Rodríguez-Abreu D, Robinson AG, et al: Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 375:1823-1833, 2016
- Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 378:2078-2092, 2018
- Tawbi HA, Schadendorf D, Lipson EJ, et al: Relatlimab and nivolumab versus nivolumab in Untreated advanced melanoma. *N Engl J Med* 386:24-34, 2022
- Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al: Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 377:1345-1356, 2017
- Motzer RJ, Tannir NM, McDermott DF, et al: Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 378:1277-1290, 2018
- Rini BI, Plimack ER, Stus V, et al: Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 380:1116-1127, 2019
- Eggermont AMM, Blank CU, Mandala M, et al: Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med* 378:1789-1801, 2018
- Weber J, Mandala M, Vecchio MD, et al: Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med* 377:1824-1835, 2017
- Forde PM, Spicer J, Lu S, et al: Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* 386:1973-1985, 2022
- Wakelee H, Liberman M, Kato T, et al: Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med* 389:491-503, 2023
- Blank CU, Lucas MW, Scolyer RA, et al: Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. *N Engl J Med* 391:1696-1708, 2024
- Patel SP, Othus M, Chen Y, et al: Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma. *N Engl J Med* 388:813-823, 2023
- Piper M, Kluger H, Ruppert E, et al: Immune resistance mechanisms and the road to personalized immunotherapy. *Am Soc Clin Oncol Educ Book* 43:e390290, 2023
- Routy B, Le Chatelier E, Derosa L, et al: Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 359:91-97, 2018
- Matson V, Fessler J, Bao R, et al: The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 359:104-108, 2018
- Gopalakrishnan V, Spencer CN, Nezi L, et al: Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 359:97-103, 2018
- Sivan A, Corrales L, Hubert N, et al: Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 350:1084-1089, 2015
- Park JS, Gazzaniga FS, Wu M, et al: Targeting PD-L2-RGMb overcomes microbiome-related immunotherapy resistance. *Nature* 617:377-385, 2023
- Vétizou M, Pitt JM, Daillière R, et al: Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 350:1079-1084, 2015
- Hanahan D: Hallmarks of cancer: New dimensions. *Cancer Discov* 12:31-46, 2022
- Zepeda-Rivera M, Minot SS, Bouzek H, et al: A distinct *Fusobacterium nucleatum* clade dominates the colorectal cancer niche. *Nature* 628:424-432, 2024
- Bullman S, Pedamallu CS, Sicinska E, et al: Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. *Science* 358:1443-1448, 2017
- Elkrief A, Montesion M, Sivakumar S, et al: Intratumoral escherichia is associated with improved survival to single-agent immune checkpoint inhibition in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 42:3339-3349, 2024
- LaCourse KD, Johnston CD, Bullman S: The relationship between gastrointestinal cancers and the microbiota. *Lancet Gastroenterol Hepatol* 6:498-509, 2021
- Derosa L, Hellmann MD, Spaziano M, et al: Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. *Ann Oncol* 29:1437-1444, 2018
- Hakozaki T, Richard C, Elkrief A, et al: The gut microbiome associates with immune checkpoint inhibition outcomes in patients with advanced non-small cell lung cancer. *Cancer Immunol Res* 8:1243-1250, 2020
- Fidelle M, Rauber C, Alves CSC, et al: A microbiota-modulated checkpoint directs immunosuppressive intestinal T cells into cancers. *Science* 380:eabo2296, 2023
- Derosa L, Routy B, Desilets A, et al: Microbiota-centered interventions: The next breakthrough in immuno-oncology? *Cancer Discov* 11:2396-2412, 2021
- Elkrief A, Méndez-Salazar EO, Maillou J, et al: Antibiotics are associated with worse outcomes in lung cancer patients treated with chemotherapy and immunotherapy. *NPJ Precis Oncol* 8:143, 2024
- Elkrief A, Derosa L, Kroemer G, et al: The negative impact of antibiotics on outcomes in cancer patients treated with immunotherapy: A new independent prognostic factor? *Ann Oncol* 30:1572-1579, 2019
- Davar D, Dzutssev AK, McCulloch JA, et al: Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. *Science* 371:595-602, 2021
- Baruch EN, Youngster I, Ben-Betzalel G, et al: Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 371:602-609, 2021
- Routy B, Lenehan JG, Miller WH, et al: Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial. *Nat Med* 29:2121-2132, 2023

34. Yonekura S, Terrisse S, Alves CSC, et al: Cancer induces a stress ileopathy depending on β -adrenergic receptors and promoting dysbiosis that contributes to carcinogenesis. *Cancer Discov* 12: 1128-1151, 2022
35. Festi D, Schiumerini R, Eusebi LH, et al: Gut microbiota and metabolic syndrome. *World J Gastroenterol* 20:16079-16094, 2014
36. Ghosh TS, Shanahan F, O'Toole PW: The gut microbiome as a modulator of healthy ageing. *Nat Rev Gastroenterol Hepatol* 19:565-584, 2022
37. López-Otín C, Blasco MA, Partridge L, et al: The hallmarks of aging. *Cell* 153:1194-1217, 2013
38. Gemikonakli G, Mach J, Zhang F, et al: Polypharmacy with high drug burden index (DBI) alters the gut microbiome overriding aging effects and is reversible with deprescribing. *J Gerontol A Biol Sci Med Sci* 78:213-222, 2023
39. Xavier JB, Young VB, Skufca J, et al: The cancer microbiome: Distinguishing direct and indirect effects requires a systemic view. *Trends Cancer* 6:192-204, 2020
40. Thomas AM, Fidelle M, Routy B, et al: Gut OncoMicrobiome Signatures (GOMS) as next-generation biomarkers for cancer immunotherapy. *Nat Rev Clin Oncol* 20:583-603, 2023
41. Abdulamir AS, Hafidh RR, Abu Bakar F: The association of *Streptococcus bovis/gallolyticus* with colorectal tumors: The nature and the underlying mechanisms of its etiological role. *J Exp Clin Cancer Res* 30:11, 2011
42. Derosa L, Routy B, Thomas AM, et al: Intestinal Akkermansia muciniphila predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer. *Nat Med* 28:315-324, 2022
43. Bredon M, Danne C, Pham HP, et al: Faecalibacterium prausnitzii strain EXL01 boosts efficacy of immune checkpoint inhibitors. *Oncoimmunology* 13:2374954, 2024
44. Dora D, Ligeti B, Kovacs T, et al: Non-small cell lung cancer patients treated with Anti-PD1 immunotherapy show distinct microbial signatures and metabolic pathways according to progression-free survival and PD-L1 status. *Oncoimmunology* 12:2204746, 2023
45. Yi Y, Shen L, Shi W, et al: Gut microbiome components predict response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer: A prospective, longitudinal study. *Clin Cancer Res* 27:1329-1340, 2021
46. Cascone T, Leung CH, Weissferdt A, et al: Neoadjuvant chemotherapy plus nivolumab with or without ipilimumab in operable non-small cell lung cancer: The phase 2 platform NEOSTAR trial. *Nat Med* 29:593-604, 2023
47. Hakoziaki T: Exploration of gut microbiota biomarkers in treatment-naïve advanced NSCLC patients undergoing chemo-immunotherapy: Insights from the phase III trial, JCOG2007 (NIPPON). *Ann Oncol* 24:1-16, 2024 (suppl 1)
48. McCulloch JA, Davar D, Rodrigues RR, et al: Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1. *Nat Med* 28: 545-556, 2022
49. Andrews MC, Duong CPM, Gopalakrishnan V, et al: Gut microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade. *Nat Med* 27:1432-1441, 2021
50. Lee KA, Thomas AM, Bolte LA, et al: Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in advanced melanoma. *Nat Med* 28:535-544, 2022
51. Simpson RC, Shanahan ER, Batten M, et al: Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome. *Nat Med* 28:2344-2352, 2022
52. Nguyen CB, Vaishampayan UN: Clinical Applications of the Gut Microbiome in Genitourinary Cancers. *Am Soc Clin Oncol Educ Book* 44:e100041, 2024
53. Derosa L, Routy B, Fidelle M, et al: Gut bacteria composition drives primary resistance to cancer immunotherapy in renal cell carcinoma patients. *Eur Urol* 78:195-206, 2020
54. Mani S: Gut microbiome and bladder cancer: A new link through nitrosamine metabolism. *Cell Host Microbe* 32:1637-1639, 2024
55. Lachance G, Robitaille K, Laaraj J, et al: The gut microbiome-prostate cancer crosstalk is modulated by dietary polyunsaturated long-chain fatty acids. *Nat Commun* 15:3431, 2024
56. Gunjur A, Shao Y, Rozday T, et al: A gut microbial signature for combination immune checkpoint blockade across cancer types. *Nat Med* 30:797-809, 2024
57. Elkrief A, Waters NR, Smith N, et al: Immune-related colitis is associated with fecal microbial dysbiosis and can be mitigated by fecal microbiota transplantation. *Cancer Immunol Res* 12:308-321, 2024
58. Halsey TM, Thomas AS, Hayase T, et al: Microbiome alteration via fecal microbiota transplantation is effective for refractory immune checkpoint inhibitor-induced colitis. *Sci Transl Med* 15: eabq4006, 2023
59. Wang Y, Wiesnoski DH, Helmink BA, et al: Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. *Nat Med* 24:1804-1808, 2018
60. Derosa L, Iebba V, Silva CAC, et al: Custom scoring based on ecological topology of gut microbiota associated with cancer immunotherapy outcome. *Cell* 187:3373-3389.e16, 2024
61. Crespin A, Le Bescop C, de Gunzburg J, et al: A systematic review and meta-analysis evaluating the impact of antibiotic use on the clinical outcomes of cancer patients treated with immune checkpoint inhibitors. *Front Oncol* 13:1075593, 2023
62. Chalabi M, Cardona A, Nagarkar DR, et al: Efficacy of chemotherapy and atezolizumab in patients with non-small-cell lung cancer receiving antibiotics and proton pump inhibitors: Pooled post hoc analyses of the OAK and POPLAR trials. *Ann Oncol* 31:525-531, 2020
63. Hopkins AM, Badaoui S, Kichenadasse G, et al: Efficacy of atezolizumab in patients with advanced NSCLC receiving concomitant antibiotic or proton pump inhibitor treatment: Pooled analysis of five randomized control trials. *J Thorac Oncol* 17:758-767, 2022
64. Cortellini A, Facchinetti F, Derosa L, et al: Antibiotic exposure and immune checkpoint inhibitors in patients with NSCLC: The backbone matters. *J Thorac Oncol* 17:739-741, 2022
65. Stein-Thoeringer CK, Saini NY, Zamir E, et al: A non-antibiotic-disrupted gut microbiome is associated with clinical responses to CD19-CAR-T cell cancer immunotherapy. *Nat Med* 29:906-916, 2023
66. Eng L, Sutradhar R, Niu Y, et al: Impact of antibiotic exposure before immune checkpoint inhibitor treatment on overall survival in older adults with cancer: A population-based study. *J Clin Oncol* 41:3122-3134, 2023
67. Medik YB, Zhou Y, Kahn LM, et al: Outcome of concurrent treatment with a-CTLA4 and metronidazole in murine model of colon adenocarcinoma. *J Clin Oncol* 39, 2021 (suppl 15; abstr e14566)
68. Rounis K, Makrakis D, Papadakis C, et al: Prediction of outcome in patients with non-small cell lung cancer treated with second line PD-1/PDL-1 inhibitors based on clinical parameters: Results from a prospective, single institution study. *PLoS One* 16:e0252537, 2021
69. Kapoor A, Noronha V, Patil VM, et al: Concomitant use of antibiotics and immune checkpoint inhibitors in patients with solid neoplasms: Retrospective data from real-world settings. *Ecancermediscience* 14:1038, 2020
70. Lalani AA, Xie W, Braun DA, et al: Effect of antibiotic use on outcomes with systemic therapies in metastatic renal cell carcinoma. *Eur Urol Oncol* 3:372-381, 2020
71. Kim CG, Koh JY, Shin SJ, et al: Prior antibiotic administration disrupts anti-PD-1 responses in advanced gastric cancer by altering the gut microbiome and systemic immune response. *Cell Rep Med* 4:101251, 2023
72. Jing Y, Chen X, Li K, et al: Association of antibiotic treatment with immune-related adverse events in patients with cancer receiving immunotherapy. *J Immunother Cancer* 10:e003779, 2022
73. Peled JU, Gomes ALC, Devlin SM, et al: Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N Engl J Med* 382:822-834, 2020
74. Smith M, Dai A, Ghilardi G, et al: Gut microbiome correlates of response and toxicity following anti-CD19 CAR T cell therapy. *Nat Med* 28:713-723, 2022
75. Draper K, Ley C, Parsonnet J: Probiotic guidelines and physician practice: A cross-sectional survey and overview of the literature. *Benef Microbes* 8:507-519, 2017
76. Suez J, Zmora N, Segal E, et al: The pros, cons, and many unknowns of probiotics. *Nat Med* 25:716-729, 2019
77. Spencer CN, McQuade JL, Gopalakrishnan V, et al: Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. *Science* 374:1632-1640, 2021
78. Suez J, Zmora N, Zilberman-Schapira G, et al: Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. *Cell* 174:1406-1423.e16, 2018
79. Messaoudene M, Ferreira S, Saint-Lu N, et al: The DAV132 colon-targeted adsorbent does not interfere with plasma concentrations of antibiotics but prevents antibiotic-related dysbiosis: A randomized phase I trial in healthy volunteers. *Nat Commun* 15:8083, 2024
80. Kokai-Kun JF, Roberts T, Coughlin O, et al: Use of ribaxamase (SYN-004), a β -lactamase, to prevent *Clostridium difficile* infection in β -lactam-treated patients: A double-blind, phase 2b, randomised placebo-controlled trial. *Lancet Infect Dis* 19:487-496, 2019
81. Weersma RK, Zernakova A, Fu J: Interaction between drugs and the gut microbiome. *Gut* 69:1510-1519, 2020
82. Kiecka A, Szczepanik M: Proton pump inhibitor-induced gut dysbiosis and immunomodulation: Current knowledge and potential restoration by probiotics. *Pharmacol Rep* 75:791-804, 2023
83. Maier L, Pruteanu M, Kuhn M, et al: Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* 555:623-628, 2018
84. Imhann F, Bonder MJ, Vich Vila A, et al: Proton pump inhibitors affect the gut microbiome. *Gut* 65:740-748, 2016
85. Lopes S, Pabst L, Dory A, et al: Do proton pump inhibitors alter the response to immune checkpoint inhibitors in cancer patients? A meta-analysis. *Front Immunol* 14:1070076, 2023
86. Vich Vila A, Collij V, Sanna S, et al: Impact of commonly used drugs on the composition and metabolic function of the gut microbiota. *Nat Commun* 11:362, 2020
87. Tropini C, Moss EL, Merrill BD, et al: Transient osmotic perturbation causes long-term alteration to the gut microbiota. *Cell* 173:1742-1754.e17, 2018
88. Katayama Y, Yamada T, Tanimura K, et al: Impact of bowel movement condition on immune checkpoint inhibitor efficacy in patients with advanced non-small cell lung cancer. *Thorac Cancer* 10: 526-532, 2019
89. Dias MF, Nogueira YJA, Romano-Silva MA, et al: Effects of antipsychotics on the gastrointestinal microbiota: A systematic review. *Psychiatry Res* 336:115914, 2024
90. Xu W, Wang Y, Zhang N, et al: The antipsychotic drug penfluridol inhibits N-linked glycoprotein processing and enhances T-cell-mediated tumor immunity. *Mol Cancer Ther* 23:648-661, 2024
91. Zernakova A, Kurilshikov A, Bonder MJ, et al: Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science* 352:565-569, 2016

92. Montégut L, Derosa L, Messaoudene M, et al: Benzodiazepines compromise the outcome of cancer immunotherapy. *Oncoimmunology* 13:2413719, 2024
93. Gicquelais RE, Bohnert ASB, Thomas L, et al: Opioid agonist and antagonist use and the gut microbiota: Associations among people in addiction treatment. *Sci Rep* 10:19471, 2020
94. Jackson MA, Verdi S, Maxan M-E, et al: Gut microbiota associations with common diseases and prescription medications in a population-based cohort. *Nat Commun* 9:2655, 2018
95. McIlvried LA, Martel Matos AA, Yuan MM, et al: Morphine treatment restricts response to immunotherapy in oral squamous cell carcinoma. *J Immunother Cancer* 12:e009962, 2024
96. Tena-Garitaonandia M, Arredondo-Amador M, Mascaraque C, et al: Modulation of intestinal barrier function by glucocorticoids: Lessons from preclinical models. *Pharmacol Res* 177:106056, 2022
97. Arbour KC, Mezquita L, Long N, et al: Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol* 36:2872-2878, 2018
98. Ninkov M, Schmerk CL, Moradizadeh M, et al: Improved MAIT cell functions following fecal microbiota transplantation for metastatic renal cell carcinoma. *Cancer Immunol Immunother* 72:1247-1260, 2023
99. Glitza IC, Seo YD, Spencer CN, et al: Randomized placebo-controlled, biomarker-stratified phase Ib microbiome modulation in melanoma: Impact of antibiotic preconditioning on microbiome and immunity. *Cancer Discov* 14:1161-1175, 2024
100. Spreafico A, Heirali AA, Araujo DV, et al: First-in-class Microbial Ecosystem Therapeutic 4 (MET4) in combination with immune checkpoint inhibitors in patients with advanced solid tumors (MET4-IO trial). *Ann Oncol* 34:520-530, 2023
101. Dizman N, Meza L, Bergerot P, et al: Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: A randomized phase 1 trial. *Nat Med* 28:704-712, 2022
102. Reference deleted
103. Laute-Caly DL, Raftis EJ, Cowie P, et al: The flagellin of candidate live biotherapeutic *Enterococcus gallinarum* MRx0518 is a potent immunostimulant. *Sci Rep* 9:801, 2019
104. Parra ER, Adriani M, Lima CFP, et al: Baseline biomarkers associated with clinical benefit in patients with solid tumors refractory to immune checkpoint inhibitors (ICIs) treated with live biotherapeutic MRx0518 in combination with pembrolizumab. *Ann Oncol* 32:S858-S859, 2021
105. Messaoudene M, Pidgeon R, Richard C, et al: A natural polyphenol exerts antitumor activity and circumvents anti-PD-1 resistance through effects on the gut microbiota. *Cancer Discov* 12:1070-1087, 2022
106. Hung CM, Chu WC, Huang WY, et al: Safety assessment of a proprietary fermented soybean solution, Symbiota®, as an ingredient for use in foods and dietary supplements: Non-clinical studies and a randomized trial. *Food Sci Nutr* 12:2346-2363, 2024
107. Raffie E, Zugman M, Pal SK, et al: What is the role of fecal microbiota transplantation in immunotherapy trials? Current perspectives and future directions. *Eur Urol Focus* 10:882-885, 2024
108. Skjveling LK, Hanssen HM, Valle PC, et al: Colonic distribution of FMT by different enema procedures compared to colonoscopy—proof of concept study using contrast fluid. *BMC Gastroenterol* 23:363, 2023
109. Kao D, Roach B, Silva M, et al: Effect of oral capsule- vs colonoscopy-delivered fecal microbiota transplantation on recurrent *Clostridium difficile* infection: A randomized clinical trial. *JAMA* 318:1985-1993, 2017
110. Ciccarese C, Porcari S, Buti S, et al: LBA77 Fecal microbiota transplantation (FMT) versus placebo in patients receiving pembrolizumab plus axitinib for metastatic renal cell carcinoma: Preliminary results of the randomized phase II TACITO trial. *Ann Oncol* 35:S1264, 2024
111. Craven LJ, Nair Parvathy S, Tat-Ko J, et al: Extended screening costs associated with selecting donors for fecal microbiota transplantation for treatment of metabolic syndrome-associated diseases. *Open Forum Infect Dis* 4:ofx243, 2017
112. Kassam Z, Dubois N, Ramakrishna B, et al: Donor screening for fecal microbiota transplantation. *N Engl J Med* 381:2070-2072, 2019
113. Rondinella D, Quaranta G, Rozera T, et al: Donor screening for fecal microbiota transplantation with a direct stool testing-based strategy: A prospective cohort study. *Microbes Infect*:105341, 2024
114. Asnicar F, Berry SE, Valdes AM, et al: Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat Med* 27:321-332, 2021
115. Nguyen NA, Jiang Y, McQuade JL: Eating away cancer: The potential of diet and the microbiome for shaping immunotherapy outcome. *Front Immunol* 15:1409414, 2024
116. Ligibel JA, Bohlke K, May AM, et al: Exercise, diet, and weight management during cancer treatment: ASCO guideline. *J Clin Oncol* 40:2491-2507, 2022
117. Ferrere G, Tidjani Alou M, Liu P, et al: Ketogenic diet and ketone bodies enhance the anticancer effects of PD-1 blockade. *JCI Insight* 6:e145207, 2021
118. El Kaoutari A, Armougom F, Gordon JL, et al: The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nat Rev Microbiol* 11:497-504, 2013
119. Koropatkin NM, Cameron EA, Martens EC: How glycan metabolism shapes the human gut microbiota. *Nat Rev Microbiol* 10:323-335, 2012
120. Vandeputte D, Falony G, Vieira-Silva S, et al: Prebiotic inulin-type fructans induce specific changes in the human gut microbiota. *Gut* 66:1968-1974, 2017
121. Han K, Nam J, Xu J, et al: Generation of systemic antitumor immunity via the in situ modulation of the gut microbiome by an orally administered inulin gel. *Nat Biomed Eng* 5:1377-1388, 2021
122. Quideau S, Deffieux D, Douat-Casassus C, et al: Plant polyphenols: Chemical properties, biological activities, and synthesis. *Angew Chem Int Ed Engl* 50:586-621, 2011
123. van Duynhoven J, Vaughan EE, Jacobs DM, et al: Metabolic fate of polyphenols in the human superorganism. *Proc Natl Acad Sci USA* 108:4531-4538, 2011 (suppl 1)
124. Lv J, Jia Y, Li J, et al: Gegen Qinlian decoction enhances the effect of PD-1 blockade in colorectal cancer with microsatellite stability by remodelling the gut microbiota and the tumour microenvironment. *Cell Death Dis* 10:415, 2019
125. Pang SA, Elkrief A, Capella MP, et al: Two cases of durable and deep responses to immune checkpoint inhibition-refractory metastatic melanoma after addition of camu camu prebiotic. *Curr Oncol* 30:7852-7859, 2023
126. Ebrahimi H, Dizman N, Meza L, et al: Cabozantinib and nivolumab with or without live bacterial supplementation in metastatic renal cell carcinoma: A randomized phase 1 trial. *Nat Med* 30:2576-2585, 2024
127. Aasmets O, Krigul KL, Lüll K, et al: Gut metagenome associations with extensive digital health data in a volunteer-based Estonian microbiome cohort. *Nat Commun* 13:869, 2022
128. Ullern A, Garborg KK, Holm K, et al: 669 MITRIC: Microbiota transplant to cancer patients progressing on immunotherapy using feces from clinical responders. *J Immunother Cancer* 12:A1-A1683, 2024 (suppl 2; abstr 669)
129. Fernandes R: Preventing toxicity in renal cancer patients treated with immunotherapy using fecal microbiota transplantation (PERFORM). 2023. <https://clinicaltrials.gov/study/NCT04163289>
130. Graff J: Fecal microbiota transplant and pembrolizumab for men with metastatic castration resistant prostate cancer. 2022. <https://clinicaltrials.gov/study/NCT04116775>

Autologous T-Cell Therapies in Solid Tumor Malignancies: Current Landscape and Future Opportunities

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OVERVIEW

Modified, autologous T-cell immunotherapies have been transformative in the treatment of hematologic malignancies with several approvals of chimeric antigen receptor T-cell therapies to treat lymphoma, leukemia, and multiple myeloma. Treatment in these settings has resulted in durable response rates as high as 80%–90%. These findings have not been replicated in clinical trials of solid tumor malignancies because of the complex tumor microenvironment, antigen heterogeneity, and immunosuppressive mechanisms that hinder antitumor T-cell responses in solid tumors. Several strategies are being investigated and have proven successful in overcoming these hurdles. This paper provides an overview of the current landscape of autologous T-cell therapies, with a particular focus on their use as treatments for refractory solid tumor malignancies, highlighting promising targets being investigated in ongoing clinical trials and toxicities associated with these therapeutic approaches.

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INTRODUCTION

The use of modified T-cell therapies as an immunotherapeutic approach has been transformative in the treatment of cancer. Clinical trials of chimeric antigen receptor T (CAR T) cell, T-cell receptor (TCR) T-cell, and tumor-derived autologous T-cell therapies have yielded both promising results warranting further clinical investigation and unprecedented outcomes leading to US Food and Drug Administration (FDA) approvals. CAR T-cell therapies consist of a patient's own T cells, engineered ex vivo to express receptors directed at target tumor antigens to induce potent antitumor responses. These products have proven successful in treating hematologic malignancies primarily using cells directed at CD19 and B-cell maturation antigen (BCMA).^{1,2} Starting in 2017, the FDA has approved seven CAR T-cell therapies in total to treat several subtypes of leukemia and lymphoma and multiple myeloma in adults and children (Fig 1). Despite these advancements, the effects observed in hematological cancers have largely not been replicated in solid tumor malignancies.

The less robust antitumor effects of CAR T-cell therapies when evaluated in patients with solid tumor malignancies have been attributed to the complex tumor microenvironment, antigen heterogeneity, and immunosuppressive mechanisms that hinder antitumor T-cell responses often found in solid tumors.³ Alternative strategies to CAR T-cell therapies have been used to address the challenges of implementing this therapeutic approach in solid tumor malignancies. These include the use of TCR T-cell therapy, which harnesses the natural ability of T cells to recognize

tumor antigens presented by human leukocyte antigen (HLA) molecules on the tumor cell surface.^{4,5} With this approach, T cells are engineered to express a tumor antigen reactive TCR, enabling the recognition of intracellular tumor antigens in addition to surface proteins, thereby broadening the spectrum of targetable antigens.⁶ Another strategy involves the transfer of autologous tumor-derived T cells, expanded ex vivo using interleukin (IL)-2, as an infusion to treat solid tumors. This approach was first evaluated in patients with metastatic melanoma⁷ and subsequent studies have confirmed its effectiveness.

This chapter provides an overview of the current landscape of cell therapies with a particular focus on their use as treatments for refractory solid tumor malignancies, highlighting promising targets being investigated in ongoing clinical trials and toxicities associated with these therapeutic approaches.

CAR T-CELL THERAPY

In 2017, tisagenlecleucel, a CD19-directed, genetically modified, autologous T-cell immunotherapy, received approval as the first gene-modified cell therapy approved in the United States.⁸ The approval was for the treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse. Tisagenlecleucel consists of autologous T cells, collected through leukapheresis, that are genetically modified using a lentiviral vector containing an anti-CD19 CAR transgene. This allows the genetically modified T cells to identify and eliminate CD19-expressing normal and malignant cells in patients treated

PRACTICAL APPLICATIONS

- Chimeric antigen receptor T (CAR T) cell therapies have revolutionized treatment of hematologic malignancies, with seven US Food and Drug Administration (FDA)–approved products demonstrating unprecedented efficacy. However, translating this success to solid tumors presents unique challenges because of the complex tumor microenvironment, antigen heterogeneity, and immunosuppressive mechanisms.
- Novel CAR T-cell targets showing promising results in solid tumors include GD2 for diffuse midline gliomas and neuroblastoma, Claudin18.2 for gastric cancers, Claudin6 for various solid tumors, and other innovative targets. Several strategies to enhance efficacy are being developed, which include dual-targeting CAR T cells, T-cell receptor (TCR) fusion constructs, and combinational therapies with immune checkpoint inhibitors.
- TCR T-cell therapies represent a breakthrough in solid tumor treatment by targeting intracellular antigens presented by human leukocyte antigen molecules, expanding potential treatment applications across various solid tumors. This approach achieved validation with the FDA approval of afamitresgene autoleucel for melanoma-associated antigen A4–positive synovial sarcoma. Novel investigational TCR therapies targeting cancer-testis antigens such as preferentially expressed antigen in melanoma and New York esophageal squamous cell carcinoma oncoprotein 1 have demonstrated efficacy across diverse malignancies.
- Autologous tumor-derived T-cell immunotherapy has shown efficacy in metastatic melanoma leading to the FDA approval of lifileucel for pretreated melanoma. This treatment strategy has also demonstrated efficacy in other tumor types such as human papillomavirus–associated cancers and non–small cell lung cancer.
- The use of modified autologous T-cell therapies is associated with specific, sometimes life-threatening, toxicities. These include cytokine release syndrome, immune effector cell–associated neurotoxicity syndrome, and on-target off-tumor toxicity. Rapid identification and treatment of these potential toxicities is necessary to avoid life-threatening or even fatal complications.

with this product. Using CAR T cells directed at CD19, it was shown that complete remission rates of 80%–90% could be achieved for this indication.⁷ Since this landmark approval,

six more CAR T-cell therapies have received FDA approval (axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, idecabtagene vicleucel, ciltacabtagene autoleucel, and obecabtagene autoleucel) for the treatment of hematologic malignancies, targeting CD19 or BCMA (Fig 1).^{6,8–13}

The use of CAR T-cell therapies for the treatment of solid tumors has proven to be less effective when compared with outcomes observed in hematologic malignancies, although successful production of CAR T-cell products for various solid tumor indications has been possible.¹⁴ Several hypotheses have been generated regarding the reasons underlying the lack of success. These include the lack of available target antigens, off-target effects because of target antigen expression on nonmalignant tissues, CAR T-cell extravasation from the bloodstream and their infiltration into solid tumors, and the immunosuppressive tumor microenvironments.^{2,15–17} Notwithstanding these hurdles, clinical trials investigating the applicability of CAR T-cell therapy to solid tumors have shown considerable potential. Below, we highlight some CAR T-cell targets that are under investigation, some of which have yielded encouraging preliminary responses.

CAR T-CELL THERAPY FOR THE TREATMENT OF BRAIN TUMORS AND NEUROBLASTOMA

Recently published results from a phase I clinical trial (ClinicalTrials.gov identifier: [NCT04196413](https://clinicaltrials.gov/ct2/show/study/NCT04196413)) showed encouraging data for patients with H3K27M-mutant diffuse midline gliomas (DMGs), known for their rapid progression and poor prognosis.¹⁸ The trial evaluated an autologous CAR T-cell product targeting disialoganglioside GD2, which was found to be highly and uniformly expressed by H3K27M-mutant DMGs. Patients with H3K27M-mutant DMGs, including diffuse intrinsic pontine glioma and spinal DMG, received sequential intravenous (IV) and intracerebroventricular (ICV) administration of the product. Thirteen patients were enrolled, of whom 11 received one IV dose of autologous GD2–CAR T cells at two dose levels (DL1, $1 \times 10^6 \text{ kg}^{-1}$, DL2, $3 \times 10^6 \text{ kg}^{-1}$) following a regimen of lymphodepleting chemotherapy with cyclophosphamide and fludarabine.^{18,19} Patients who exhibited clinical or radiologic benefit were eligible for subsequent ICV infusions, receiving $10\text{--}30 \times 10^6$ GD2–CAR T cells. Results showed that the manufacturing process for GD2 CAR T cells was successful for all patients and no dose-limiting toxicities were observed in patients treated at DL1, while three patients at DL2 experienced high-grade cytokine release syndrome (CRS). These results established DL1 as the maximally tolerated IV dose. Nine patients underwent ICV infusions without any dose-limiting toxicities. Remarkably, the sequential IV–ICV approach yielded significant clinical benefits in these difficult-to-treat malignancies, with four of 13 patients achieving major tumor reductions (52%–100%), including one complete response. In the most recently published update, this complete response was ongoing more than

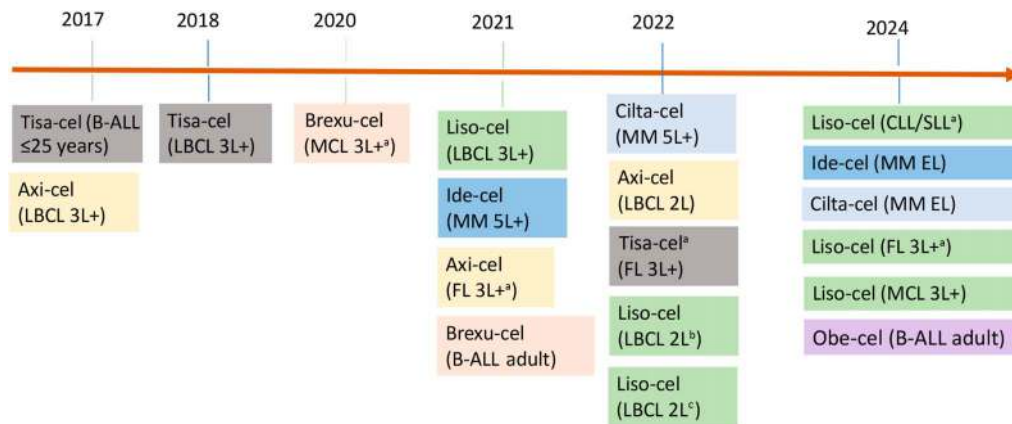


FIG 1. FDA CAR T-cell therapy approvals: 2017-2024. ^aAccelerated approval. ^bRefractory to 1L CIT or relapsed (≤12 months). ^cRefractory to 1L CIT or relapsed (HSCT ineligible). 1L, first-line; 2L, second-line; 3L, third-line; 5L, fifth-line; Axi-cel, axicabtagene ciloleucel; B-ALL, precursor B cell ALL; Brexu-cel, brexucabtagene autoleucel; CAR T, chimeric antigen receptor T; Cilta-cel, ciltacabtagene autoleucel; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; EL, early line; FDA, US Food and Drug Administration; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplantation; Ide-cel, idecabtagene vicleucel; L, line of therapy; LBCL, large B-cell lymphoma; Liso-cel, lisocabtagene maraleucel; MCL, mantle cell lymphoma; MM, multiple myeloma; Obe-cel, obecabtagene autoleucel; SLL, small lymphocytic lymphoma; Tisa-cel, tisagenlecleucel.

40 months since enrollment.⁸⁸ Moreover, nine patients experienced neurologic benefit, showing improved motor coordination, hearing, and taste sensation.¹⁸ These results provide the first evidence that CAR T-cell therapy can effectively penetrate the blood-brain barrier and induce meaningful responses in these historically treatment-resistant brain tumors, offering hope for patients.¹⁸

Clinical trials investigating CAR T-cell therapy for the treatment of gliomas are currently ongoing, targeting various antigens, including B7-H3, epidermal growth factor receptor (EGFR), CD70, chlorotoxin, human epidermal growth factor receptor 2 (HER2), interleukin-13 receptor alpha 2 (IL-13Rα2), interleukin-7Rα, matrix metalloproteinase 2, and NKG2D.²⁰ These studies have shown varying outcomes, mainly demonstrating safety without dose-limiting toxicity, but often lacking clinical efficacy. To improve outcomes for patients, new strategies are being explored, including dual-targeting CAR T-cell therapies, which have shown intrathecally delivered bivalent CAR T cells targeting EGFR and IL-13Rα2 to result in tumor shrinkage in all six patients with recurrent glioblastoma treated.²¹ In addition to dual-targeting CAR T cells, researchers have developed CAR T cells (CARv3-T-cell-engaging antibody molecule [TEAM]-E) that target EGFR variant III (EGFRvIII) while secreting TEAMs against wild-type EGFR.²² In a first-in-human phase I clinical trial (ClinicalTrials.gov identifier: [NCT05660369](https://clinicaltrials.gov/ct2/show/study?term=NCT05660369)), three patients treated with a single, intraventricular infusion of CARv3-TEAM-E T cells showed tumor regression within days, although response was temporary in two patients.²² This study also highlights the potential utility of locoregional administration of CAR T-cell therapy. The efficacy of this approach contrasts with a previous study of a peripherally infused

EGFRvIII-directed CAR T-cell therapy, which did not lead to radiologic responses in any of the 10 patients treated on study.²³ Although these studies show that achievement of antitumor responses is feasible using CAR T-cell therapies in the treatment of malignant gliomas, accomplishing durable responses remains a challenge. Optimizing the number of infused cells, administering repeated cell infusions, incorporating a lymphodepleting chemotherapy regimen before infusion, and targeting multiple antigens may all contribute to overcoming this challenge to increase responses and persistence.²

Investigations of CAR T cells for the treatment of extracranial solid tumors have also shown promising results. GD2 targeting CAR T-cell therapy has been investigated for the treatment of relapsed or refractory (r/r) high-risk neuroblastoma.²⁴ In a phase I-II trial (ClinicalTrials.gov identifier: [NCT03373097](https://clinicaltrials.gov/ct2/show/study?term=NCT03373097)), 27 heavily pretreated children showed no dose-limiting toxicities, with mild CRS occurring in 74% of patients. Treatment at the recommended phase II dose of 10×10^6 CAR-positive T cells kg^{-1} yielded an objective response rate (ORR) of 63%, including eight patients who had partial responses and nine who had complete responses.²⁴ This investigational CAR T-cell therapy incorporated an inducible caspase 9 safety switch designed to rapidly eliminate CAR T cells in case of severe toxicity. This safety switch functions by dimerizing inactive caspase 9 monomers upon administration of the small molecule rimiducid, thereby triggering apoptosis of CAR T cells and providing a critical additional layer of control to enhance the therapy's safety profile.²⁴ Activation of the suicide gene safety system proved effective in the single case where it was required, highlighting its potential to improve the therapeutic index of CAR T-cell therapy in solid tumors.²⁴

CAR T-CELL THERAPY IN OTHER SOLID TUMOR MALIGNANCIES

The claudin gene family encodes a group of tight junction proteins essential for maintaining epithelial and endothelial barrier function. More than 20 claudin isoforms have been identified, each with distinct tissue distribution patterns and biological roles.²⁵ Aberrant expression of certain claudins is associated with tumorigenesis, making them attractive targets for cancer therapies.^{26,27} Claudin18.2 (CLDN18.2) is overexpressed in gastric/gastroesophageal junction (GEJ) cancers and has been identified as an actionable target in patients with gastric cancer.²⁸ In October 2024, FDA approved zolbetuximab-clzb, a Claudin18.2 (CLDN18.2)-directed cytolytic antibody, with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors are CLDN18.2-positive.²⁹

CLDN18.2-targeted CAR T therapy has shown promising results in patients with advanced gastric/GEJ cancer.¹⁴ In a phase I clinical trial (ClinicalTrials.gov identifier: [NCT03874897](#)) of satricabtagene autoleucel ([satri-cel]/CT041) after pretreatment with lymphodepleting chemotherapy, the overall response rate and disease control rate (DCR) in 47 efficacy-evaluable patients with gastric cancer who received monotherapy were 57.4% and 83.0%, respectively.³⁰ No dose-limiting toxicities, treatment-related deaths, and neurotoxicity syndrome were observed. Grade 1–2 CRS occurred in 96.6% of patients. A pooled analysis of two 1/1b trials evaluated satri-cel in 24 heavily pretreated patients with refractory metastatic pancreatic cancer and demonstrated an ORR of 16.7% and a DCR of 70.8%.³¹

Claudin 6 (CLDN6) has also been identified as a potential target for the treatment of various solid tumors. This oncofetal antigen is widely expressed in a range of solid tumors, whereas expression on healthy tissues is very rare.³² Tumor types with highest expression of CLDN6 include germ cell tumors (GCTs), gastric cancer, ovarian cancer and endometrial carcinoma.³³ A phase I-II clinical trial (ClinicalTrials.gov identifier: [NCT04503278](#)) investigating a CLDN6 targeting CAR T-cell product in combination with an RNA vaccine containing messenger RNA encoding the target antigen to stimulate expansion of CAR T cells is currently ongoing.³⁴ The trial enrolled patients with a variety of r/r CLDN6-positive solid tumors, including GCT, ovarian carcinoma, sarcoma, breast tumors, and gastric adenocarcinoma. Interim results from this trial on 21 heavily pretreated patients showed an ORR of 33% and a DCR of 67%. Interestingly, in patients with testicular GCTs exhibiting strong CLDN6 expression (>80% tumor cells with intermediate/strong staining), treatment yielded an ORR of 57% at the higher dose studied, highlighting a potential benefit for this subgroup of patients. Furthermore, a manageable adverse event profile was reported, with 46% of patients

experiencing CRS (including one grade 3 event) and one with grade 1 neurotoxicity.³⁴ Together, these studies show encouraging results regarding manufacturing feasibility as well as promising safety and efficacy profiles for various CAR T-cell therapies in solid tumors.

Other targets for CAR T-cell therapy in solid tumors are under investigation and preliminary results highlight their potential as treatments for solid tumor malignancies. These include prostate-specific membrane antigen (ClinicalTrials.gov identifier: [NCT03873805](#)) and six-transmembrane epithelial antigen of prostate-2 (ClinicalTrials.gov identifier: [NCT06267729](#)) directed CAR T-cell products for the treatment of metastatic castration-resistant prostate cancer,³⁵ glypican-3 CAR T-cell therapy for several solid tumors, including hepatocellular carcinoma (ClinicalTrials.gov identifier: [NCT02395250](#)), mesothelin targeting CAR T cells for refractory, mesothelin-expressing cancers including malignant pleural or peritoneal mesothelioma, non-small cell lung cancer (NSCLC), ovarian cancer, and cholangiocarcinoma (ClinicalTrials.gov identifier: [NCT3907852](#)),³⁶ and HER2-specific CAR T cells for the treatment of advanced sarcomas (ClinicalTrials.gov identifier: [NCT00902044](#)).³⁷

Ongoing clinical investigations are also evaluating the potential for innovative constructs to improve the efficacy of CAR T-cell therapies in solid tumors. For example, gavo-cabtagene autoleucel is a CAR T-cell product that uses the novel T-cell receptor fusion construct (TRuC) technology.³⁶ Unlike CAR T-cell products that only contain the CD3 ζ subunit, TRuC technology integrates directly into the native TCR complex by fusing a mesothelin-targeting llama-derived antibody to CD3 ϵ , enabling engineered T cells to harness all six TCR subunits for more physiological activation. This unique design has demonstrated improved T-cell trafficking and enhanced persistence in preclinical studies. In clinical studies of this product, treatment had shown promising activity in 30 patients with mesothelin-expressing solid tumors (predominantly mesothelioma) with a 20% overall response rate (13% confirmed) and a high DCR of 77%, with 70% of patients alive at 6 months. These findings suggest that TRuC's more complete engagement of T-cell signaling machinery may help overcome traditional solid tumor resistance to cell therapy. Combinatorial approaches are also under investigation to evaluate the potential to drive efficacy, such as the innovative combination of intrapleural mesothelin-targeted CAR T-cell therapy with pembrolizumab in malignant pleural mesothelioma.³⁸

TCR T-CELL THERAPY

Another therapeutic strategy under investigation as a treatment for solid tumor malignancies is the use of autologous T cells that are engineered to express an affinity-enhanced TCR that recognize a naturally processed peptide. The success of this approach is reflected in the historic FDA

TABLE 1. Food and Drug Administration Approved T-Cell Therapies for Solid Tumors

Therapy/Approval Year	Product Type	Trial Design/Primary End Point	Indication/Approved Dosage
Lifileucel/2024	Tumor-derived autologous T-cell immunotherapy	Single-arm, multicenter, multicohort study ORR: 31.5% (95% CI, 21.1 to 43.4) DoR ≥6 months: 56.5% DoR ≥12 months: 43.5%	Treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if <i>BRAF</i> V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor ^a A single dose containing 7.5×10^9 to 72×10^9 viable tumor-derived T cells administered intravenously
Afamitresgene autoleucel/2024	MAGE-A4-directed genetically modified autologous T-cell immunotherapy	Single-arm, multicenter, multicohort study ORR: 43.2% (95% CI, 28.4 to 59.0) DoR ≥6 months: 45.6% DoR ≥12 months: 39.0%	Treatment of adults with unresectable or metastatic synovial sarcoma who have received previous chemotherapy, are HLA-A*02:01P-, HLA-A*02:02P-, HLA-A*02:03P-, or HLA-A*02:06P-positive, and whose tumor expresses the MAGE-A4 antigen as determined by FDA approved or cleared companion diagnostic devices ^a Recommended dose between 2.68×10^9 to 10×10^9 MAGE-A4 TCR-positive T cells administered as a single intravenous infusion

NOTE. Information derived from approved US Prescribing Information.

Abbreviations: DoR, duration of response; FDA, US Food and Drug Administration; HLA, human leukocyte antigen; MAGE-A4, melanoma-associated antigen A4; ORR, objective response rate; TCR, T-cell receptor.

^aIndication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

approval of afamitresgene autoleucel (afami-cel) for the treatment of synovial sarcoma in 2024 (Table 1).³⁹ Afami-cel consists of autologous CD4⁺ and CD8⁺ T cells engineered via a self-inactivating lentiviral vector to express an affinity-enhanced TCR targeting melanoma-associated antigen A4 (MAGE-A4).⁴⁰

Initial clinical investigation of a TCR-transduced T-cell product in patients with cancer were conducted in patients with advanced melanoma. In a published report, tumor responses were observed in two of 13 patients receiving autologous T cells with MART-1-reactive TCR T-cell therapy.⁴¹ In subsequent trials featuring high-avidity TCRs, objective clinical responses were seen in six of 20 patients (30%) treated with autologous T cells transduced with a MART-1-reactive TCR, and in three of 16 patients (19%) treated with a gp100-reactive TCR. These early trials established proof of concept for the further development of TCR T-cell therapy.^{41,42} The FDA approval of afami-cel was based on the results of a multicenter, single-arm, multicohort clinical trial, SPEARHEAD-1 (cohort 1).⁴³ The study enrolled HLA-A*02:01P-, HLA-A*02:02P-, HLA-A*02:03P-, and 383 HLA-A*02:06P allele-positive patients with inoperable or metastatic synovial sarcoma who had received previous systemic therapy with either doxorubicin and/or ifosfamide and whose tumor expressed the MAGE-A4 tumor antigen. Before receiving afami-cel as a single infusion,

patients received lymphodepleting chemotherapy with fludarabine 30 mg/m²/d for 4 days (day -7 to day -4) and cyclophosphamide 600 mg/m²/d for 3 days (day -7 to day -5). The overall response rate was 43.2% with two of 19 responding patients achieving complete responses. The median duration of response was 6 months, and 45.6% of responders maintained their responses for 6 or more months.

Ongoing trials are investigating TCR T-cell products in solid tumors expressing other targets, including preferentially expressed antigen in melanoma (PRAME) and New York esophageal squamous cell carcinoma oncoprotein 1 (NY-ESO-1). PRAME is a cancer testis antigen widely expressed in various solid cancers, including ovarian cancer, triple-negative breast cancer, and melanoma, but minimally present on healthy tissues. PRAME targeting TCR T-cell therapy is currently being investigated and preclinical studies have shown potent cytotoxicity. Multiple clinical trials examining the maximum tolerated dose, safety, tolerability, and antitumor activity of TCR T-cell therapies with high affinity against HLA-A*02:01-presented peptide derived from PRAME in r/r solid tumors have been initiated (ClinicalTrials.gov identifiers: [NCT05958121](#), [NCT03686124](#)). Results from phase Ia dose escalation and phase Ib dose expansion cohorts showed manageable toxicities and an initial objective response in 57% of patients

and confirmed in 51% of patients. Reduction in tumor volume was described in 89% of patients across multiple tumor types, including cutaneous melanoma, mucosal and uveal melanoma, ovarian cancer, synovial sarcoma, breast angiosarcoma, breast cancer, and small cell lung cancer.⁴⁴ Based on these findings, a randomized-controlled phase III trial (ClinicalTrials.gov identifier: [NCT06743126](https://clinicaltrials.gov/ct2/show/study/NCT06743126)) investigating PRAME-directed TCR T cells in patients with previously treated, unresectable or metastatic cutaneous melanoma has been initiated.

NY-ESO-1 is a member of the MAGE-4 cancer testis antigen family and a promising target that is highly expressed in melanoma, multiple myeloma, and esophageal squamous cell carcinoma. Letetresgene autoleucel (lete-cel) is an autologous T-cell receptor therapy targeting NY-ESO-1 that is under investigation for the treatment of patients with advanced HLA-A*02-positive synovial sarcoma and myxoid round cell liposarcoma (MRCLS).⁴⁵⁻⁴⁸ Observed responses in early trials led to the further evaluation of lete-cel in the phase II IGNYTE-ESO trial for patients with synovial sarcoma and MRCLS. The study enrolled HLA-A*02-positive patients with NY-ESO-1-expressing ($\geq 30\%$ staining at 2+/3+ per immunohistochemistry) advanced disease. All patients were previously treated with an anthracycline-based chemotherapy and showed disease progression on their last treatment line. In the first planned interim analysis of 45 evaluable patients with at least 6 months of follow-up, lete-cel displayed a 40% overall response rate. Response rates were similar for both tumor types: 39% in synovial sarcoma and 41% in MRCLS, with two complete and 16 partial responses. The median response duration was 10.6 months. The study met its primary end point by achieving 14 responders among the first 45 patients, indicating that lete-cel may be a promising treatment for advanced or metastatic synovial sarcoma and MRCLS expressing NY-ESO-1.⁴⁹

Other TCR therapies in development include TCRs targeting E7 for patients with metastatic human papillomavirus (HPV)-associated epithelial cancers,⁵⁰ KRAS G12V,⁵¹ KRAS G12D,⁵² and others. The next generation of SPEAR T-cell therapies is also in development. One such agent is ADP-A2M4CD8, a TCR T-cell therapy that targets MAGE-A4 and is modified with a CD8 α coreceptor. In the SURPASS phase I trial, 51 patients with advanced MAGE-A4-positive solid tumors were treated with ADP-A2M4CD8 T cells, resulting in an ORR of 35.6%.⁵³ Expanded cohorts of ADP-A2M4CD8, either alone or combined with anti-PD-1, are underway in head and neck, gastroesophageal, bladder, and platinum-resistant ovarian cancers.⁵⁴⁻⁵⁷

AUTOLOGOUS TUMOR-DERIVED T-CELL IMMUNOTHERAPY

The first reports describing the use of autologous CD4⁺ and CD8⁺ T cells that had been isolated from tumor masses, expanded ex vivo using IL-2,⁷ and administered to patients with metastatic melanoma as IV infusions originated at the National Cancer Institute. Subsequent trials in patients with

melanoma demonstrated that this therapeutic approach could produce robust and lasting clinical responses.⁵⁸⁻⁶¹ More recently, progression-free survival was shown to be significantly improved for patients with unresectable stage IIIC or IV melanoma refractory to anti-PD-1 therapy, receiving this therapeutic modality compared with the anti-cytotoxic T-lymphocyte antigen 4 therapy, ipilimumab (7.2 v 3.1 months; HR, 0.50).⁶²

These advances culminated in the approval of the first such therapy in 2024, based on the results of a multicenter, multicohort, single-arm trial that enrolled patients with unresectable or metastatic melanoma who had previously been treated with at least one systemic therapy, including a PD-1-blocking antibody, and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor with MEK inhibitor. Patients received lifileucel after lymphodepletion with cyclophosphamide 60 mg kg⁻¹ once daily with mesna for 2 days followed by fludarabine 25 mg/m² of body surface area once daily for 5 days. In the trial, patients received IL-2 (aldesleukin) at 600,000 International Unit kg⁻¹ every 8-12 hours for up to six doses 3-24 hours after infusion to support cell expansion in vivo. FDA granted approval based on an ORR of 31.5%, consisting of 20 partial responses and three complete responses. Among responders, 56.5% maintained their response for 6 or more months, and 43.5% maintained their response for 12 months or more.

This treatment strategy has also demonstrated efficacy in different tumor types. Tumor responses were reported in HPV-associated cancers, with responses in 5 of 18 patients (28%) with cervical cancer and two of 11 patients (18%) with other HPV-associated cancers, including oropharyngeal cancer.⁶³ Preliminary efficacy data from a phase II clinical study in patients with recurrent, metastatic, or persistent cervical cancer, demonstrated an ORR of 44%, which included one complete response, nine partial responses, and two unconfirmed partial responses.⁶⁴ Early data from a study of LN-145 showed promising activity in patients with advanced NSCLC who had previously received immune checkpoint inhibitors.⁶⁵ Among the 28 treated patients, the ORR was 21.4%, with 83% of responses ongoing at a median follow-up of 8.2 months, including one complete metabolic response lasting beyond 20 months. Notably, responses were observed regardless of PD-L1 status, suggesting potential utility across different patient subgroups. In a different trial, autologous tumor-derived T-cell therapy followed by maintenance with nivolumab demonstrated promising clinical activity in patients with metastatic NSCLC.⁶⁶ Among 13 evaluable patients, three achieved confirmed responses including two durable (>1.5 years) complete responses. Exploratory analyses revealed the presence and persistence of neoantigen-reactive T-cell clonotypes in responding patients.

In another report, a patient with metastatic, castrate-resistant prostate cancer treated with autologous tumor-infiltrating lymphocytes, combined with immune checkpoint blockade, achieved a complete and durable response lasting over 3.5

years.⁶⁷ These examples collectively highlight the potential promise of this approach in a wide range of tumor types.

The potential for improved outcomes with combinatorial approaches consisting of autologous tumor-derived T cells plus immune checkpoint inhibitors is under investigation in clinical trials (eg, ClinicalTrials.gov identifier: [NCT05727904](#)). Other approaches to improve outcomes include the use of tumor-derived T cells that are screened and selected for neoantigen recognition. The potential of this strategy was demonstrated in a recent phase II study of gastrointestinal cancers (ClinicalTrials.gov identifier: [NCT01174121](#)). In this study, patients treated with unselected tumor-derived lymphocytes achieved no clinical responses (zero of 18). By contrast, among patients treated with neoantigen-specific tumor-derived lymphocytes, three responses were observed out of 39 patients. Furthermore, in the cohort treated with neoantigen-specific tumor-infiltrating lymphocytes combined with pembrolizumab, eight responses were observed among 34 patients.⁶⁸

TOXICITIES

Although modified autologous T-cell therapies have revolutionized the field of cancer immunotherapy, their use is hampered by the association with specific, sometimes life-threatening, toxicities. The most prevalent toxicity seen in patients who receive CAR T-cell therapy is CRS, which is a systemic inflammatory response that results from a potent production of inflammatory cytokines and chemokines from activated CAR T cells and tumor-resident myeloid cells.^{69,70} After recognition of the target antigen, CAR T cells become activated and start proliferating, leading to the production of a wide range of proinflammatory cytokines, including interferon- γ , tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor.⁶⁹ Subsequently, myeloid cells produce IL-6, IL-1 α , IL-1 β , IL-1 receptor antagonist, and IL-8 to reinforce CAR T-cell activation.⁵⁹ This leads to the recruitment of monocytes, which further amplifies the positive feedback loop, resulting in a systemic cytokine storm.⁶⁹

Clinically, symptoms of fevers, myalgias, anorexia, and fatigue develop, which commence during the first few days after infusion.^{71,72} If progressive, CRS can lead to life-threatening symptoms, including capillary leak syndrome, leading to vasodilatory shock and organ hypoperfusion and dysfunction.^{71,72} In addition, the cytokine release leads to loosening of the blood-brain barrier, allowing immune cells and cytokines into the cerebrospinal fluid and brain.⁶⁹ This in turn may result in immune effector cell-associated neurotoxicity syndrome (ICANS) associated with neurologic symptoms such as confusion, dysphasia, aphasia, somnolence, and in more severe cases, seizures, motor weakness, and cerebral edema.⁷³ Although the mechanisms underlying ICANS are not fully understood, patients who develop ICANS often show concomitant or previous CRS, suggesting a relationship between these adverse reactions. However, ICANS can also develop without preceding or concomitant CRS.^{69,73}

In some cases, CRS and ICANS can be self-limited, requiring only supportive care, however, the absence of clear understanding of factors predicting the severity of these events and their potential to be life-threatening or fatal necessitates prompt intervention with directed therapies including blocking the IL-6 receptor (IL-6R) with tocilizumab, a monoclonal antibody directed at IL-6R, or corticosteroids in more severe cases.^{71,72,74}

As a result of the lymphodepleting chemotherapy regimen often given in the context of CAR T-cell therapy and CRS, late immune effector cell-associated hematotoxicity (ICAH) is seen in 30%-40% of patients.⁶⁹ Although ICAH often occurs shortly after the lymphodepleting chemotherapy, cytopenias can be long-lasting and may persist for months after CAR T-cell infusion as a result of bone marrow aplasia.⁷⁵ As a result, patients may need repeated blood transfusions and can become extremely susceptible to severe infections, which may require additional treatments or hospital admissions. In addition to ICAH, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) may also occur, although this is described less often.⁶⁹ IEC-HS is treated with high-dose corticosteroids, sometimes in combination with targeted therapies such as anakinra, ruxolitinib, and emapalumab.^{76,77} These risks led to FDA approval of CAR T-cell therapies for hematologic malignancies with black box warnings for CRS, neurologic toxicities, and a requirement for a risk evaluation and mitigation strategy. Additionally, because CAR T-cell therapies are produced using viral vectors transduced with the transgene of interest, treatment with approved CAR T-cell therapies carries a risk of for insertional oncogenesis. US Prescribing Information of approved products provide up-to-date description of these risks.

In addition to the aforementioned toxicities, a major challenge in the development of CAR T-cell therapies for the treatment of solid tumors is on-target off-tumor toxicity (OTOT), which is the result of target antigens being coexpressed on healthy tissues.⁷⁸ OTOT of varying severity have been observed in many clinical trials investigating CAR T-cell therapy in solid tumors.⁷⁹⁻⁸¹ Thoughtful target antigen selection is critical to ensuring the safety and efficacy of CAR T-cell therapies. In addition, novel strategies are being explored to improve CAR T-cell specificity and reduce OTOT in patients with solid tumor malignancies. These approaches mainly focus on regulating CAR T activity and include fine-tuning of CAR domains, logic-gating CAR T cells using Boolean logic-gating approaches, and controlling CAR T cell therapy products after infusion with approved drugs or suicide switches.^{69,78}

Similar to toxicities seen with CAR T-cell therapy, patients treated with TCR T-cell therapy may also develop CRS and ICANS, although it has been reported to occur less frequently.^{82,83} As for CAR T-cell therapy, TCR T-cell therapy is also associated with OTOT, which has led to severe adverse events and even fatalities in clinical trials.⁸⁴ For instance, treatment of patients with metastatic melanoma with TCR

T cells targeting MAGE-A3 has previously caused fatal cardiotoxicity in patients.^{83,85} Additionally, autoimmune reactions may occur after TCR T-cell infusion, because of cross-reactions between endogenous and exogenous TCR heterodimers, causing potentially new autoimmune specificity, thereby leading to graft-versus-host-like disease.^{82,86} TCR T-cell-related toxicities are managed similarly to CAR T-cell-related toxicities and are treated mainly with tocilizumab and corticosteroids. Current investigations to reduce TCR T-cell-related toxicities are ongoing, for example, by adding disulfide bonds to stabilize engineered TCRs, silencing endogenous TCRs to prevent mispairing between exogenous and endogenous TCRs, and enhancing TCR T-cell specificity and affinity to prevent OTOT.⁸²

The safety profile of autologous tumor-derived T-cell therapy observed in clinical trials has generally been characterized by transient hematologic toxicities attributed to preparative lymphodepleting chemotherapy, together with decreases in immune cells, leading to an increased incidence of infections, including severe infections. Autoimmune manifestations have also been observed. For example, in patients with advanced melanoma,^{62,86} autoimmune melanocyte destruction with ensuing vitiligo has been reported; uveitis and hearing impairment have also been described. Capillary leak syndrome, likely related to IL-2, has also been reported in clinical trials. Treatment-related deaths have also been described in clinical trials.⁵⁸ FDA product labeling for lifileucel includes a black box warning for treatment-related mortality, prolonged severe cytopenia, severe infection, and cardiopulmonary and renal impairment.⁸⁷

CONCLUSION

CAR T, TCR T, and tumor-derived T-cell immunotherapies, which leverage the immune system to selectively target

tumors with remarkable precision, represent a paradigm shift in the treatment of cancer, including solid tumor malignancies. CAR T-cell therapy has shown unprecedented efficacy in hematologic malignancies and its application is currently being translated into solid tumors, with numerous promising targets exhibiting potent efficacy and manageable toxicity profiles. Likewise, TCR T-cell therapy offers a unique advantage by targeting intracellular antigens presented by HLA molecules, thereby expanding its applicability to a broader range of solid tumors. However, CAR T-cell and TCR T-cell therapies are associated with significant challenges due to toxicities such as CRS, ICANS and OTOT, which can result in life-threatening or even fatal complications. For FDA-approved products, prescriber labeling describes toxicities and risk mitigation measures to ensure their safe and effective use. Ongoing clinical investigations aim to mitigate these risks by refining target antigen selection, enhancing T-cell engineering, optimizing lymphodepleting chemotherapy regimens, and developing innovative toxicity management strategies. In parallel, understanding mechanisms of therapeutic resistance, including tumor antigen escape and the development of immunosuppressive microenvironments, is critical to improving long-term efficacy. Similarly, the identification of biomarkers of T-cell exhaustion may enable earlier intervention and the development of strategies to sustain T-cell functionality over time. Furthermore, the advancement of safer, better-tolerated cell therapies raises the potential for outpatient administration, which could significantly expand patient access and reduce health care burdens. The integration of advanced preclinical models that more accurately predict human toxicities, alongside the design of safer and more controllable constructs, will be essential for the continued evolution of these therapies. With ongoing research and optimization, these therapies hold immense potential to improve outcomes in patients with otherwise refractory malignancies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Sterner RC, Sterner RM: CAR-T cell therapy: Current limitations and potential strategies. *Blood Cancer J* 11:69, 2021
2. Uslu U, June CH: Beyond the blood: Expanding CAR T cell therapy to solid tumors. *Nat Biotechnol* 43:506-515, 2025
3. Guzman G, Reed MR, Bielamowicz K, et al: CAR-T therapies in solid tumors: Opportunities and challenges. *Curr Oncol Rep* 25:479-489, 2023
4. Tsimberidou A-M, Van Morris K, Vo HH, et al: T-cell receptor-based therapy: An innovative therapeutic approach for solid tumors. *J Hematol Oncol* 14:102, 2021
5. Baulu E, Gardet C, Chuvin N, et al: TCR-engineered T cell therapy in solid tumors: State of the art and perspectives. *Sci Adv* 9:eadf3700, 2023
6. Albarrán V, San Román M, Pozas J, et al: Adoptive T cell therapy for solid tumors: Current landscape and future challenges. *Front Immunol* 15:1352805, 2024
7. Rosenberg SA, Packard BS, Aebersold PM, et al: Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. *N Engl J Med* 319:1676-1680, 1988
8. O'Leary MC, Lu X, Huang Y, et al: FDA approval summary: Tisagenlecleucel for treatment of patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. *Clin Cancer Res* 25:1142-1146, 2019
9. Braendstrup P, Levine BL, Ruella M: The long road to the first FDA-approved gene therapy: Chimeric antigen receptor T cells targeting CD19. *Cytotherapy* 22:57-69, 2020
10. Sharma P, Kasamon YL, Lin X, et al: FDA approval summary: Axicabtagene ciloleucel for second-line treatment of large B-cell lymphoma. *Clin Cancer Res* 29:4331-4337, 2023
11. Sharma P, Kanapuru B, George B, et al: FDA approval summary: Idecabtagene vicleucel for relapsed or refractory multiple myeloma. *Clin Cancer Res* 28:1759-1764, 2022
12. Natrajan K, Kaushal M, George B, et al: FDA approval summary: Ciltacabtagene autoleucel for relapsed or refractory multiple myeloma. *Clin Cancer Res* 30:2865-2871, 2024
13. Bouchkouj N, Przepiorka D, Fashoyin-Aje LA: Obecabtagene autoleucel for B-cell acute lymphoblastic leukemia. *JAMA* 333:1354-1355, 2025
14. Albelda SM: CAR T cell therapy for patients with solid tumours: Key lessons to learn and unlearn. *Nat Rev Clin Oncol* 21:47-66, 2024
15. Ai K, Liu B, Chen X, et al: Optimizing CAR-T cell therapy for solid tumors: Current challenges and potential strategies. *J Hematol Oncol* 17:105, 2024
16. Zhang K, Chen H, Li F, et al: Bright future or blind alley? CAR-T cell therapy for solid tumors. *Front Immunol* 14:1045024, 2023
17. Akbari P, Katsarou A, Daghighian R, et al: Directing CAR T cells towards the tumor vasculature for the treatment of solid tumors. *Biochim Biophys Acta Rev Cancer* 1877:188701, 2022
18. Monje M, Mahdi J, Majzner R, et al: Intravenous and intracranial GD2-CAR T cells for H3K27M+ diffuse midline gliomas. *Nature* 637:708-715, 2025
19. Majzner RG, Ramakrishna S, Yeom KW, et al: GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas. *Nature* 603:934-941, 2022
20. Park S, Maus MV, Choi BD: CAR-T cell therapy for the treatment of adult high-grade gliomas. *npj Precis Oncol* 8:279, 2024
21. Bagley SJ, Logun M, Fraietta JA, et al: Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: Phase 1 trial interim results. *Nat Med* 30:1320-1329, 2024
22. Choi BD, Gerstner ER, Frigault MJ, et al: Intraventricular CARv3-TEAM-E T cells in recurrent glioblastoma. *N Engl J Med* 390:1290-1298, 2024
23. O'Rourke DM, Nasrallah MP, Desai A, et al: A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. *Sci Transl Med* 9:eaad0984, 2017
24. Del Bufalo F, De Angelis B, Caruana I, et al: GD2-CART01 for relapsed or refractory high-risk neuroblastoma. *N Engl J Med* 388:1284-1295, 2023
25. Krause G, Winkler L, Mueller SL, et al: Structure and function of claudins. *Biochim Biophys Acta* 1778:631-645, 2008
26. Morin PJ: Claudin proteins in human cancer: Promising new targets for diagnosis and therapy. *Cancer Res* 65:9603-9606, 2005
27. Swisshelm K, Macek R, Kubbies M: Role of claudins in tumorigenesis. *Adv Drug Deliv Rev* 57:919-928, 2005
28. Nakayama I, Qi C, Chen Y, et al: Claudin 18.2 as a novel therapeutic target. *Nat Rev Clin Oncol* 21:354-369, 2024
29. US Food and Drug Administration package insert—VYLOY. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761365s000lbl.pdf
30. Qi C, Liu C, Gong J, et al: Claudin18.2-specific CAR T cells in gastrointestinal cancers: Phase 1 trial final results. *Nat Med* 30:2224-2234, 2024
31. Qi C, Zhang P, Liu C, et al: Safety and efficacy of CT041 in patients with refractory metastatic pancreatic cancer: A pooled analysis of two early-phase trials. *J Clin Oncol* 42:2565-2577, 2024
32. Du H, Yang X, Fan J, et al: Claudin 6: Therapeutic prospects for tumors, and mechanisms of expression and regulation (review). *Mol Med Rep* 24:677, 2021
33. Simon AG, Lyu SI, Laible M, et al: The tight junction protein claudin 6 is a potential target for patient-individualized treatment in esophageal and gastric adenocarcinoma and is associated with poor prognosis. *J Transl Med* 21:552, 2023
34. Mackensen A, Haanen JBAG, Koenecke C, et al: CLDN6-specific CAR-T cells plus amplifying RNA vaccine in relapsed or refractory solid tumors: The phase 1 BNT211-01 trial. *Nat Med* 29:2844-2853, 2023
35. Dorff TB, Blanchard MS, Adkins LN, et al: PSCA-CAR T cell therapy in metastatic castration-resistant prostate cancer: A phase 1 trial. *Nat Med* 30:1636-1644, 2024
36. Hassan R, Butler M, O'Cearbhaill RE, et al: Mesothelin-targeting T cell receptor fusion construct cell therapy in refractory solid tumors: Phase 1/2 trial interim results. *Nat Med* 29:2099-2109, 2023
37. Hegde M, Navai S, DeRenzo C, et al: Autologous HER2-specific CAR T cells after lymphodepletion for advanced sarcoma: A phase 1 trial. *Nat Cancer* 5:880-894, 2024
38. Adusumilli PS, Zauderer MG, Riviere I, et al: A phase I trial of regional mesothelin-targeted CAR T-cell therapy in patients with malignant pleural disease, in combination with the anti-PD-1 agent pembrolizumab. *Cancer Discov* 11:2748-2763, 2021
39. US Food and Drug Administration—TECELRA approval letter. <https://www.fda.gov/media/180568/download?attachment>
40. US Food and Drug Administration package insert—TECELRA. <https://www.fda.gov/media/180565/download?attachment>
41. Morgan RA, Dudley ME, Wunderlich JR, et al: Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science* 314:126-129, 2006
42. Johnson LA, Morgan RA, Dudley ME, et al: Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. *Blood* 114:535-546, 2009
43. D'Angelo SP, Araujo DM, Abdul Razak AR, et al: Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): An international, open-label, phase 2 trial. *Lancet* 403:1460-1471, 2024
44. Wermke M, Alsdorf W, Araujo DM, et al: 687 ACTengine IMA203 TCR-T targeting PRAME shows deep and durable anti-tumor activity in heavily pretreated solid cancer patients. *J Immunother Cancer* 12:A788, 2024 (suppl 2)
45. Robbins PF, Kassim SH, Tran TLN, et al: A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: Long-term follow-up and correlates with response. *Clin Cancer Res* 21:1019-1027, 2015
46. Ramachandran I, Lowther DE, Dryer-Minnerly R, et al: Systemic and local immunity following adoptive transfer of NY-ESO-1 SPEAR T cells in synovial sarcoma. *J Immunother Cancer* 7:276, 2019
47. Gyurdieva A, Zajic S, Chang YF, et al: Biomarker correlates with response to NY-ESO-1 TCR T cells in patients with synovial sarcoma. *Nat Commun* 13:5296, 2022
48. D'Angelo SP, Druta M, Van Tine BA, et al: Letetresgene autoleucel in advanced/metastatic myxoid/round cell liposarcoma. *J Clin Oncol* 10.1200/JCO-24-01466 [epub ahead of print on January 21, 2025]
49. D'Angelo SP, Furness AJS, Thistlethwaite F, et al: Lete-cel in patients with synovial sarcoma or myxoid/round cell liposarcoma: Planned interim analysis of the pivotal IGNYTE-ESO trial. *J Clin Oncol* 42, 2024 (suppl 16; abstr 2500)
50. Nagarsheth NB, Norberg SM, Sinkov AL, et al: TCR-engineered T cells targeting E7 for patients with metastatic HPV-associated epithelial cancers. *Nat Med* 27:419-425, 2021
51. Mitchell S, Khan B, Payumo F, et al: AFNT-211: A phase 1 study of autologous CD4+ and CD8+ T cells engineered to express a high avidity HLA-A*11:01-restricted, KRAS G12V-specific, transgenic TCR, a CD8α/β coreceptor, and a FAS41BB switch receptor in patients with advanced/metastatic solid tumors. *J Clin Oncol* 42, 2024 (suppl 16; abstr TPS8650)
52. Punekar SR, Pelster M, Becerra CR, et al: An open-label, phase 1, multicenter study to evaluate the safety and preliminary anti-tumor activity of NT-112 in human leukocyte antigen-C*08:02-positive adult patients with unresectable, advanced, and/or metastatic solid tumors that are positive for the KRAS G12D mutation. *J Clin Oncol* 42, 2024 (suppl 16; abstr TPS2677)
53. Moreno Garcia V, Calvo E, Asch A, et al: 10190 Clinical and translational data from the phase I SURPASS trial of ADP-A2M4CD8 T cell receptor (TCR) T cell therapy alone or combined with nivolumab in solid tumors. *Ann Oncol* 34:S620-S621, 2023
54. Murphy MAB, Ajani JA, Van Tine BA, et al: Safety and efficacy from the phase 1 SURPASS trial of ADP-A2M4CD8, a next-generation T-cell receptor T-cell therapy, in patients with advanced esophageal, esophagogastric junction, or gastric cancer. *J Clin Oncol* 41, 2023 (suppl 4; abstr 349)
55. Ho A, Garcia-Consuegra A, Saro J, et al: First-line ADP-A2M4CD8 T-cell receptor T-cell therapy plus pembrolizumab in head and neck cancers: An additional cohort of the phase 1 SURPASS trial. *Int J Radiat Oncol Biol Phys* 118:e84-e85, 2024
56. Aggen DH, Garcia A, Saro Suarez JM, et al: New phase 1 SURPASS trial cohort: Early-line ADP-A2M4CD8 T-cell receptor T-cell therapy plus pembrolizumab in urothelial carcinoma. *J Clin Oncol* 42, 2024 (suppl 4; abstr TPS708)
57. Moore K, Oaknin A, Ray-Coquard I, et al: GOG-3084: A phase II trial of ADP-A2M4CD8 TCR-T cell therapy, alone or in combination with nivolumab, among patients with recurrent ovarian cancers. *Gynecol Oncol* 190:S281-S282, 2024 (suppl 1)
58. Sarnaik AA, Hamid O, Khushalani NI, et al: Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. *J Clin Oncol* 39:2656-2666, 2021
59. Besser MJ, Shapira-Frommer R, Treves AJ, et al: Clinical responses in a phase II study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients. *Clin Cancer Res* 16:2646-2655, 2010

60. Goff SL, Dudley ME, Citrin DE, et al: Randomized, prospective evaluation comparing intensity of lymphodepletion before adoptive transfer of tumor-infiltrating lymphocytes for patients with metastatic melanoma. *J Clin Oncol* 34:2389-2397, 2016
61. Rosenberg SA, Yang JC, Sherry RM, et al: Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clin Cancer Res* 17:4550-4557, 2011
62. Rohaan MW, Borch TH, van den Berg JH, et al: Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. *N Engl J Med* 387:2113-2125, 2022
63. Stevanović S, Helman SR, Wunderlich JR, et al: A phase II study of tumor-infiltrating lymphocyte therapy for human papillomavirus-associated epithelial cancers. *Clin Cancer Res* 25:1486-1493, 2019
64. Jazaeri AA, Zsiros E, Amaria RN, et al: Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma. *J Clin Oncol* 37, 2019 (suppl 15; abstr 2538)
65. Schoenfeld A, Lee S, Paz-Ares L, et al: First phase 2 results of autologous tumor-infiltrating lymphocyte (TIL; LN-145) monotherapy in patients with advanced, immune checkpoint inhibitor-treated, non-small cell lung cancer (NSCLC). *J Immunother Cancer* 9:A486-A487, 2021 (suppl 2)
66. Creelan BC, Wang C, Teer JK, et al: Tumor-infiltrating lymphocyte treatment for anti-PD-1-resistant metastatic lung cancer: A phase 1 trial. *Nat Med* 27:1410-1418, 2021
67. Karbach J, Kiselicki D, Brand K, et al: Tumor-infiltrating lymphocytes mediate complete and durable remission in a patient with NY-ESO-1-expressing prostate cancer. *J Immunother Cancer* 11:e005847, 2023
68. Lowery FJ, Goff SL, Gasmi B, et al: Neoantigen-specific tumor-infiltrating lymphocytes in gastrointestinal cancers: A phase 2 trial. *Nat Med* 10.1038/s41591-025-03627-5 [epub ahead of print on April 1, 2025]
69. Mulvey A, Trueb L, Coukos G, et al: Novel strategies to manage CAR-T cell toxicity. *Nat Rev Drug Discov* 10.1038/s41573-024-01100-5 [epub ahead of print on February 3, 2025]
70. Brudno JN, Kochenderfer JN: Toxicities of chimeric antigen receptor T cells: Recognition and management. *Blood* 127:3321-3330, 2016
71. Frey N, Porter D: Cytokine release syndrome with chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant* 25:e123-e127, 2019
72. Morris EC, Neelapu SS, Giavridis T, et al: Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol* 22:85-96, 2022
73. Gu T, Hu K, Si X, et al: Mechanisms of immune effector cell-associated neurotoxicity syndrome after CAR-T treatment. *WIREs Mech Dis* 14:e1576, 2022
74. Rejeski K, Jain MD, Shah NN, et al: Immune effector cell-associated haematotoxicity after CAR T-cell therapy: From mechanism to management. *Lancet Haematol* 11:e459-e470, 2024
75. Rejeski K, Subklewe M, Aljurf M, et al: Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. *Blood* 142:865-877, 2023
76. Hines MR, Knight TE, McNeerney KO, et al: Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome. *Transplant Cell Ther* 29:438.e1-438.e16, 2023
77. Flugel CL, Majzner RG, Krenciute G, et al: Overcoming on-target, off-tumour toxicity of CAR T cell therapy for solid tumours. *Nat Rev Clin Oncol* 20:49-62, 2023
78. Feng K, Liu Y, Guo Y, et al: Phase I study of chimeric antigen receptor modified T cells in treating HER2-positive advanced biliary tract cancers and pancreatic cancers. *Protein Cell* 9:838-847, 2018
79. Thistlethwaite FC, Gilham DE, Guest RD, et al: The clinical efficacy of first-generation carcinoembryonic antigen (CEACAM5)-specific CAR T cells is limited by poor persistence and transient pre-conditioning-dependent respiratory toxicity. *Cancer Immunol Immunother* 66:1425-1436, 2017
80. Morgan RA, Yang JC, Kitano M, et al: Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. *Mol Ther* 18:843-851, 2010
81. Liu Y, Yan X, Zhang F, et al: TCR-T immunotherapy: The challenges and solutions. *Front Oncol* 11:794183, 2021
82. Golikova EA, Alshevskaya AA, Alrhoun S, et al: TCR-T cell therapy: Current development approaches, preclinical evaluation, and perspectives on regulatory challenges. *J Transl Med* 22:897, 2024
83. van den Berg JH, Gomez-Eerland R, van de Wiel B, et al: Case report of a fatal serious adverse event upon administration of T cells transduced with a MART-1-specific T-cell receptor. *Mol Ther* 23:1541-1550, 2015
84. Bouchkouj N, Lin X, Wang X, et al: FDA approval summary: Brexucabtagene autoleucel for treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. *Oncologist* 27:892-899, 2022
85. Bendle GM, Linnemann C, Hooijkaas AI, et al: Lethal graft-versus-host disease in mouse models of T cell receptor gene therapy. *Nat Med* 16:565-570, 2010
86. Dudley ME, Wunderlich JR, Yang JC, et al: Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol* 23:2346-2357, 2005
87. US Food and Drug Administration package insert—AMTAGVI. <https://www.fda.gov/media/176417/download?attachment>
88. The road to CAR-T-cell therapy for lethal childhood brain tumours. *Nature* 10.1038/d41586-024-04156-w [epub ahead of print on January 15, 2025]

Capturing Unicorns: Targeting Cancers With *TP53* Mutations, *RAS* Alterations Beyond G12C, and *MTAP* Loss—No Target Is Out of the Realm of Possibility

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OVERVIEW

In cancer genomics, there is the realization that some very frequently mutated genes like *TP53* or *KRAS* are extremely hard to approach from a therapeutic perspective. In the realm of cancer treatment, the development of agents capable of transforming these alterations into actionable targets would be like capturing unicorns. These unicorns of oncology—drugs targeting undruggable targets that span various cancer types—offer an exciting opportunity for the development of histology-agnostic therapies. Among these, recent developments in targeting *TP53* mutations, *KRAS* alterations, and *MTAP* loss mark pivotal advancements for innovative treatment strategies. *TP53* mutations, which occur in nearly every cancer type, are central to tumorigenesis and contribute to resistance against conventional therapies. *KRAS* mutations, especially in cancers like pancreatic and lung cancers, are notoriously difficult to target but are now yielding promising therapeutic avenues. Similarly, *MTAP* is frequently deleted in cancers such as lung, pancreatic, and mesothelioma and plays a critical role in cellular metabolism and epigenetics, making its loss a significant vulnerability in tumor cells. Recent developments in drug discovery provide a broad foundation for the clinical testing of drugs that target common mechanisms across diverse tumor types, offering hope for a more universal approach to cancer treatment.

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INTRODUCTION

This study delves into the latest research on targeting cancers driven by *TP53* mutations, *KRAS* alterations, and *MTAP* loss. These genetic alterations are frequently observed across a broad spectrum of cancers, contributing significantly to tumorigenesis, metastasis, and resistance to conventional therapies. Mutations in the tumor suppressor gene *TP53* and the *KRAS* oncogene pose substantial challenges to current treatment paradigms because of their complex roles in cellular signaling, DNA repair, and apoptosis. Similarly, *MTAP* loss disrupts key metabolic pathways and has been linked to poor prognosis in several cancers. Recent research has shifted toward developing novel therapeutic strategies that specifically target some of these variants, offering new avenues for more personalized and effective cancer treatments. By examining the molecular mechanisms underlying these genetic events and the latest breakthroughs in therapeutic interventions, this study aims to provide a comprehensive overview of how these targeted approaches could revolutionize the treatment landscape for cancers with these challenging genetic features.

TUMOR SUPPRESSOR p53 AND TARGETED CANCER THERAPY

p53 was discovered in 1979 as a cellular protein that forms a complex with the SV40 virus large T antigen.¹⁻⁴ The normal

function of p53 remained obscure until transfection experiments showed that wild-type (WT) but not mutant p53 cDNA could inhibit cell growth in vitro.^{5,6} Moreover, DNA sequencing revealed frequent mutations in the p53 gene (*TP53*) in common human tumors,^{7,8} and mice that completely lacked p53 developed spontaneous tumors at a high rate.⁹ Thus, *TP53* emerged as an important tumor suppressor gene. The finding that p53 could trigger cell death by apoptosis provided a mechanism by which p53 can suppress tumor growth.¹⁰ p53 had also been shown to accumulate in cells on DNA damage¹¹ and was dubbed the Guardian of the Genome.¹²

Subsequent studies showed that the p53 protein is a DNA-binding transcription factor that regulates a wide range of cellular processes, most notably cell cycle progression and cell death in response to cellular stress.^{13,14} p53 executes these responses through its capacity to bind specific DNA binding motifs and activate transcription of more than 100 target genes, including *CDKN1A* (p21), *PUMA*, *FAS*, and *ZMAT3*.^{15,16} The ability of p53 to respond to oncogenic stress serves to eliminate incipient tumors cells. Thus, p53 forms a crucial barrier against tumor development.¹⁷

The key role of p53 as a tumor suppressor gene is highlighted by the frequent *TP53* mutations in cancer. Whole-genome sequencing and mutation analysis of 3,281 tumors from The Cancer Genome Atlas (TCGA), representing 12 common

PRACTICAL APPLICATIONS

- Targeting undruggable mutations: the growing potential of targeting previously considered undruggable genetic alterations, such as *TP53*, *KRAS*, and *MTAP*, offers hope for the development of therapies that could treat multiple cancer types more effectively.
- Histology-agnostic therapies: by focusing on common mutations across various cancers, this approach could lead to the development of histology-agnostic therapies, which could simplify treatment strategies and improve outcomes for patients with diverse cancer types.
- Broad clinical testing for universal treatments: the emerging therapies targeting shared mechanisms in different tumors provide a robust platform for clinical trials, potentially leading to more universally applicable cancer treatments and better clinical outcomes across cancer types.

tumor types, revealed *TP53* mutations in 42% of cases, the highest among all genes. *PIK3CA* followed with a 17.8% mutation rate, and *PTEN* at 9.7%. *KRAS*- and *NRAS*-activating mutations were found in 6.7% and 1.5%, with the highest frequencies in colorectal cancer (CRC; 45% and 8.8%, respectively).¹⁸ The rate of *TP53* mutation ranged from 94.6% in ovarian serous carcinoma to 2.2% in kidney renal clear cell carcinoma.¹⁸ These results indicate a strong selection pressure for *TP53* inactivation during tumor development although the *TP53* mutation rate varies considerably between different tumor types. Inherited *TP53* mutations cause the cancer-prone Li-Fraumeni syndrome (LFS) with a high lifetime risk of various types of cancers.^{19–21} Overall, the *TP53* mutational spectrum in LFS is similar that of tumors with somatic *TP53* mutations (The *TP53* Database²² [2025]).²³

Most tumor suppressor genes are inactivated by deletions or truncating mutations that are usually distributed over a large part of the coding sequence. By contrast, a majority of *TP53* mutations (>70%) are missense mutations that lead to amino acid substitutions in the DNA-binding core domain (DBD), approximately residues 100–300.^{23,24} Many missense *TP53* mutations result in lower thermostability of the DNA-binding domain and failure to bind specifically to DNA and transactivate transcription of *p53* target genes. The most common so-called hot spot *TP53* mutations include R175H, R248Q, R273H, and R282H. Missense *p53* mutants can be broadly subdivided into two main categories: (1) mutants with substitutions of residues that make direct contact with DNA, for example, R248Q (DNA contact mutants), and (2) mutants with substitution of residues which are critical for the structural integrity of the DBD, for example, R175H

(structural mutants).²⁵ Structural mutants show variable degrees of misfolding of the DBD. Missense mutant *p53* can exert a dominant negative effect by forming mixed tetramers with WT *p53*, preventing the tetramer from binding to DNA and activating its target genes.²⁶ In some contexts, missense mutant *p53* can also acquire gain-of-function (GOF) oncogenic properties, as demonstrated in *Trp53* missense mutant knock-in mouse models.^{27,28} However, other studies using cell culture, organoid, and mouse models have failed to detect evidence for *p53* GOF.^{26,29}

The selection of *TP53* mutations in tumors is driven by multiple factors. Loss of *p53* function leads to dysregulated cell proliferation, evasion of apoptosis, genomic instability, and accelerated tumor progression (Fig 1). One important feature of *p53* is the fragility of its DBD, which makes *p53* vulnerable to inactivation by missense mutations.³⁰ Moreover, the selection for *p53* inactivation probably involves a trade-off between oncogenic fitness and immunogenicity.³¹

TP53 nonsense mutations are less common than missense mutations but nevertheless represent around 10% of all *TP53* mutations in cancer. These mutations give rise to a premature termination codon in *TP53* and expression of truncated and inactive *p53* protein. The most common *TP53* nonsense mutation is R213X, followed by R196X and R306X.^{24,32}

Studies on the *TP53* mutational landscape using cDNA-based transfection assays^{33–35} and recently CRISPR-Cas9-based saturation genome editing³⁶ have confirmed complete loss of function for common hot spot mutants and variable loss of function for many less frequent missense mutants. The CRISPR-Cas9 approach identified additional subtle loss-of-function variants, including splicing alterations and temperature-sensitive mutants that could be reactivated pharmacologically. These results should facilitate the interpretation of *TP53* mutation data in the clinic and ultimately enable better management and treatment for patients with cancer with somatic or inherited *TP53* mutations.

Therapeutic Targeting of *TP53* Missense Mutant Tumors

Restoration of normal *p53* function in tumor cells by various means was shown to elicit cell death and elimination of tumors in vivo in mice (Fig 1).^{37–39} This suggests that functional *p53* can induce tumor cell death even in the presence of multiple other genetic alterations. A number of strategies for mutant *p53* reactivation in cancer have been explored over the past two decades. This research area has been covered in several recent comprehensive reviews.^{40–42} Here, we shall highlight a few examples, including molecules that have been or are being tested in the clinic.

Compound PRIMA-1 was identified in a chemical library screen for compounds with a preferential effect on tumor

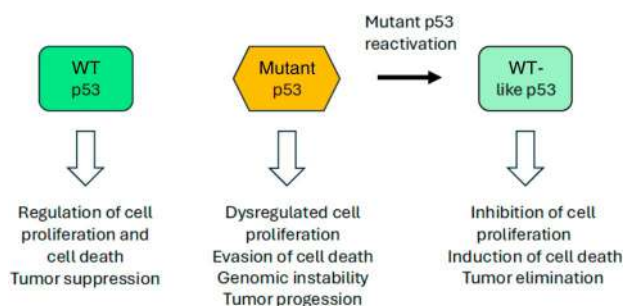


FIG 1. Schematic representation of p53-mediated regulation of cell proliferation and cell death in normal cells (left); the consequences of TP53 loss of function by mutation in incipient tumor cells, leading to genomic instability and tumor progression (middle); and the impact of mutant p53 reactivation in tumor cells, driving tumor cell death and tumor elimination (right). The aim of therapeutic reactivation of p53 is either refolding of missense mutant p53 protein or induction of translational readthrough across a premature termination codon in nonsense mutant TP53. WT, wild-type.

cells that carry missense mutant *TP53*.⁴³ PRIMA-1 and its analog APR-246 are converted to methylene quinuclidinone (MQ), a compound that reacts covalently with cysteine residues in p53's core domain.⁴⁴ Similarly, a series of 2-sulfonylpyrimidines including compound PK11007 were shown to target p53 cysteines and trigger both p53-dependent and p53-independent effects in tumor cells.⁴⁵ X-ray crystallography demonstrated MQ binding to C124, C229, and C277 and indicated two mechanisms for stabilization of complexes between p53 tetramers and DNA: (1) MQ binding to C277 stabilizes the protein-DNA interface and (2) MQ binding to C124 and C229 supports the interface between p53 dimers.⁴⁶ APR-246, via MQ, also perturbs cellular redox homeostasis in a number of ways.^{47–52} The depletion of glutathione by APR-246/MQ can trigger cell death by ferroptosis.⁵² These redox effects most likely contribute to the anticancer activity and observed clinical effects of APR-246. This is also supported by studies that failed to detect a p53-dependent effect of APR-246 in cancer cells.^{53,54} Phase II clinical studies with APR-246 (eprenetapopt) in combination with azacitidine (AZA) in *TP53*-mutant AML and myelodysplastic syndrome (MDS) showed promising anti-tumor efficacy and relatively mild side effects.^{55,56} However, a phase III trial in *TP53*-mutant MDS did not show a statistically significant effect as compared with AZA alone. Eprenetapopt has also been tested in other clinical trials, including one study in solid tumors in combination with pembrolizumab.⁴¹

Another cysteine-based approach relies on repurposing of the drug arsenic trioxide (ATO) that is commonly used for treatment of acute promyelocytic leukemias where it induces differentiation of the leukemic cells by promoting degradation of the PML-RAR α fusion protein. ATO was shown to refold mutant p53 by binding three cysteine residues (C124, C135, and C141) and restore proper folding and transcriptional activity of a subset of mutant p53 proteins,

mainly structural mutants.^{54,57} A screen of 800 p53 missense mutants demonstrated rescue by ATO at variable efficiency for 390 mutants, suggesting a potentially broad clinical utility.⁵⁸ A clinical phase I trial with ATO in combination with decitabine has been initiated in patients with AML or MDS (ClinicalTrials.gov identifier: [NCT03855371](#)), and a phase II trial with ATO as monotherapy has been initiated in patients with *TP53*-mutant solid tumors (ClinicalTrials.gov identifier: [NCT04869475](#)).

The structural heterogeneity of p53 missense mutants is a major challenge for the development of anticancer drugs that target a wide range of *TP53*-mutant tumors. An alternative approach is to focus on a specific and more easily druggable mutant with well-defined structural features. The p53-mutant Y220C that occurs in around 1% of all solid tumors has a unique solvent-accessible crevice at the periphery of the beta-sandwich, which makes it particularly attractive as a drug target.²⁵ The rationally designed carbazole derivative PhiCan083 was shown by X-ray crystallography to bind specifically to the unique solvent-accessible crevice in the Y220C mutant, stabilizing the mutant protein and increasing its melting temperature, which indicates enhanced thermal stability and potential restoration of partial p53 function.⁵⁹ Liu et al⁶⁰ subsequently identified the molecule PK7088 that binds the same crevice and stabilizes the Y220C mutant. PK7088 also induced p53 target genes *CDKN1A* and *NOXA* and p53-Y220C-dependent cell cycle arrest and apoptosis. The company PMV Pharma has developed the molecule PC14586⁶¹ that targets and stabilizes the Y220C mutant in a similar manner and restores its DNA-binding and transcriptional transactivation function, as demonstrated by upregulation of p53 target genes in vitro and in vivo.⁶² Furthermore, clinical responses (reduction of tumor lesions, decrease in *TP53* Y220C ctDNA) have been observed in an ongoing phase I/II clinical trial with PC14586 (rezatapopt) in patients with solid tumors carrying Y220C-mutant *TP53* (PYNNAACLE; ClinicalTrials.gov identifier: [NCT04585750](#)).⁶³ An objective response rate (ORR) at 2,000 mg once daily of 46.2% was observed in patients with *TP53* Y220C and *KRAS* WT tumors (n = 13).⁶⁴

A different way of targeting the p53 Y220C mutant is illustrated by the compound KG13 that binds covalently to the Y220C-mutant cysteine and enhances p53 stability, and promotes WT conformation, DNA-binding, and transactivation of p53 target genes.⁶⁵

Therapeutic Targeting of *TP53* Nonsense Mutant Tumors

TP53 nonsense mutations lead to a premature termination codon in the coding sequence and, as a consequence, expression of a truncated inactive p53 protein. In tumors with such *TP53* mutations, expression of full-length p53 can be restored by induction of translational readthrough across the premature termination codon.⁶⁶ Natural termination codons are much less sensitive to induction of readthrough as a

result of the proximity to the poly(A)-binding protein, which enhances termination of translation. Known inducers of translational readthrough include aminoglycoside antibiotics.⁶⁷ Aminoglycosides G418 and gentamicin have been shown to induce translational readthrough of several common *TP53* nonsense mutations, including R213X.⁶⁸ Unfortunately, side effects of these aminoglycosides (nephrotoxicity, ototoxicity) make them unsuitable for clinical use. Therefore, efforts have been directed at the identification and characterization of other readthrough inducers with lower toxicity.

Examples of readthrough inducers of nonsense mutant *TP53* include the synthetic glycoside ELX-02 (NB124),⁶⁹ the nucleoside analog clitocine,⁷⁰ and the fluorouracil metabolite 5-fluorouridine.⁷¹ Readthrough induction by clitocine or 5-fluorouridine has been shown to occur through their incorporation into mRNA. Full-length p53 protein expressed on induction of readthrough by these agents is capable of transactivating p53 target genes such as *CDKN1A* and *PUMA* and inducing cell death by apoptosis. Thus, translational readthrough is potentially a promising strategy for targeting tumors with *TP53* nonsense mutations. However, no readthrough inducer of nonsense mutant *TP53* has so far been approved for clinical use.⁶⁶

THE EXCITEMENT AND CHALLENGES OF TARGETING RAS BEYOND KRAS^{G12C}

The RAS pathway is one of the most commonly deregulated pathways in human cancer.⁷² Mutations occur in genes that function upstream or downstream of RAS; however, nearly one fifth of all cancers harbor a direct mutation in *K-*, *H-*, or *NRAS*.⁷³ *KRAS* mutations are most prevalent and represent 80% of RAS mutations overall. In addition, they drive three of the most common deadly malignancies: pancreatic ductal adenocarcinoma (PDAC; 86%), CRC (41%), and non-small cell lung cancer (NSCLC; 32%).⁷⁴ These observations have fueled a 40-year quest for clinical *KRAS* inhibitors, which has now been actualized. Moreover, the initial breakthrough of developing *KRAS*^{G12C} inhibitors has stimulated broader efforts to target other oncogenic RAS alleles and WT RAS proteins and to design more effective combinatorial therapeutic strategies. The recent pace of progress in this area has been astounding and should progressively reshape the standard of care for these and other RAS-driven malignancies for years to come.

Approved *KRAS*^{G12C} Inhibitors

RAS proteins were thought to be undruggable until 2013, when Ostrem et al⁷⁵ discovered small molecules that covalently bound the altered cysteine residue in *KRAS*^{G12C}. This finding paved the way for the development and accelerated US Food and Drug Administration (FDA) approval of the first two clinical *KRAS*^{G12C} inhibitors, sotorasib (2021) and adagrasib (2022) for the treatment of advanced NSCLC.^{76,77} Nevertheless, limitations of these agents continue to motivate the development of more effective treatments. First, while *KRAS*^{G12C} inhibitors have changed the standard of care for NSCLC,

response rates are still relatively moderate. For example, for perspective, the ORRs to the EGFR inhibitor osimertinib and the ALK inhibitor alectinib in relevant tumors were 80% and 82.9%, respectively,^{78,79} whereas sotorasib and adagrasib only conferred ORRs of 41.0% and 42.9%.^{77,80} Second, most RAS oncogenes cannot be targeted by *KRAS*^{G12C} inhibitors, including *KRAS*^{G12D} mutations which are prevalent in CRC and PDAC. Finally, responses to these *KRAS*^{G12C} inhibitors are not as durable as anticipated and efficacy varies between tissues, with CRCs being more refractory.^{81,82}

Additional *KRAS*^{G12C} Inhibitors

To improve efficacy, one approach has been to strive to develop more potent *KRAS*^{G12C} inhibitors. To that end, the *KRAS*^{G12C} inhibitor, divarasib, appeared to exhibit better responses in NSCLC and CRC in phase I studies although these agents were not directly compared.⁸³ However, drugs with different mechanisms of action have also been developed. For example, sotorasib, adagrasib, and divarasib all bind to *KRAS*^{G12C} in its inactive, GDP-bound form, thereby preventing RAS reactivation.⁷⁴ By contrast, BBO-8520 is a *KRAS*^{G12C}-selective covalent inhibitor that binds both *KRAS*-GDP and *KRAS*-GTP, and in doing so, it also blocks effector binding, which should suppress some mechanisms of resistance (discussed below).⁸⁴ Phase I studies of BBO-8520 are underway (ClinicalTrials.gov identifier: [NCT06343402](#)). In addition, a newer class of inhibitors known as molecular glues have been developed, which bring together cyclophilin A and *KRAS*^{G12C}, thereby preventing RAS signaling by steric hindrance.⁸⁵ These agents also bind and target RAS in its GTP-bound ON state, which may ultimately be more effective because of the fact that feedback activation of RAS signaling can drive resistance.^{86,87} Indeed, preclinical studies have shown that RAS (ON) inhibitors remain effective in tumors that have become resistant to RAS (OFF) agents.⁸⁸ RMC-6291 and other additional *KRAS*^{G12C} (ON) agents are currently being evaluated in the clinic. Several recent reviews provide comprehensive, albeit ever evolving, lists of trials with these and other classes of RAS inhibitors described below.^{86,89-91}

KRAS^{G12D} Inhibitors

KRAS^{G12D} mutations represent 28% of all *KRAS* mutations, and therefore, developing agents that target this mutant allele has been a priority for the field.⁷³ Similar to *KRAS*^{G12C} inhibitors, a variety of *KRAS*^{G12D} inhibitors have been developed, which can bind to RAS in its GDP-bound form, function as molecular glues, or degrade RAS proteins.^{89,90} At least 15 *KRAS*^{G12D} inhibitors have been generated. The most clinically advanced agent, RMC-9805, *KRAS*^{G12D} (ON), appears to be well tolerated and exhibits promising activity in PDAC (ClinicalTrials.gov identifier: [NCT06040541](#)).

Multi-*KRAS* Inhibitors

In addition to mutation-selective *KRAS* inhibitors, agents that target multiple *KRAS* mutations and the WT *KRAS* allele

have been developed. While these agents do not suppress every *KRAS* mutation, BI-3706674 inhibits the majority of common *KRAS* mutations and should also be effective in tumors with *KRAS* amplifications⁹⁰ (ClinicalTrials.gov identifier: [NCT06056024](#)). QTX3034, which is also being evaluated in phase I studies, inhibits *KRAS*^{G12D} and *KRAS*^{G12V} mutants and WT *KRAS*⁹⁰ (ClinicalTrials.gov identifier: [NCT06227377](#)).

Multi-RAS (ON) Inhibitors

Perhaps the most surprising class of agents target several mutant RAS alleles and WT H-, K-, and NRAS proteins. The tool compound RMC-7977 and the related clinical compound RMC-6236 are most effective against *KRAS*^{G12X} and *NRAS*^{G61X} mutations, but the unexpected finding is that they appear to be tolerated, despite their ability to suppress all three WT RAS proteins.^{92,93} RMC-6236 is currently being evaluated in solid tumors, with preliminary signs of activity in PDAC and NSCLC (ClinicalTrials.gov identifier: [NCT05379985](#)).⁹³ Again, these agents should, in theory, be more effective than mutant-selective inhibitors alone if tolerated as they should also block RAS activation caused by some resistance mechanisms.

Promising Drug Combinations Designed to Combat Resistance

The most effective RAS inhibitor in each setting will ultimately be determined in clinical trials. However, none of these agents will likely be curative. This is because tumors can exhibit intrinsic, acquired, or adaptive resistance, conferred by both genetic and nongenetic mechanisms.^{86,89,90,94}

Nevertheless, investigators have been working on rational combination therapies designed to combat specific resistance mechanisms. Expanding upon a previous review, the most promising drug combinations thus far tend to fall into one of five categories (Fig 2).⁸⁶ Examples of each type of strategy are discussed below although many additional approaches falling into each of these categories have been presented elsewhere.^{86,89-91}

Vertical Inhibition/Deeper Pathway Suppression

Previous studies of BRAF, MEK, EGFR, and ALK inhibitors demonstrate that deeper pathway suppression leads to more potent and durable therapeutic responses. These historical observations have fueled the charge to develop more potent RAS inhibitors. However, two of the primary mechanisms of resistance to current RAS inhibitors are either (1) on-target genetic alterations in RAS pathway components or (2) feedback activation of signals that enhance RAS signaling.^{86,94} Therefore, one promising approach has been to cotarget the driving mutant RAS allele along with a second component in the RAS pathway. An example of this type of approach has been approved for the treatment of CRC. Specifically, *KRAS*^{G12C} inhibitors are not very effective in CRC, in part, because the EGFR pathway is hyperactivated in response RAS pathway inhibitors.⁸⁷ However, these signals can be thwarted by combining *KRAS*^{G12C} inhibitors with EGFR-directed antibodies. Based on promising responses, adagrasib and cetuximab received accelerated FDA approval in 2024 (ClinicalTrials.gov identifier: [NCT03785249](#)) and sotorasib and panitumumab were also recently FDA-approved in chemotherapy-refractory CRC (ClinicalTrials.gov identifier: [NCT05198934](#)).

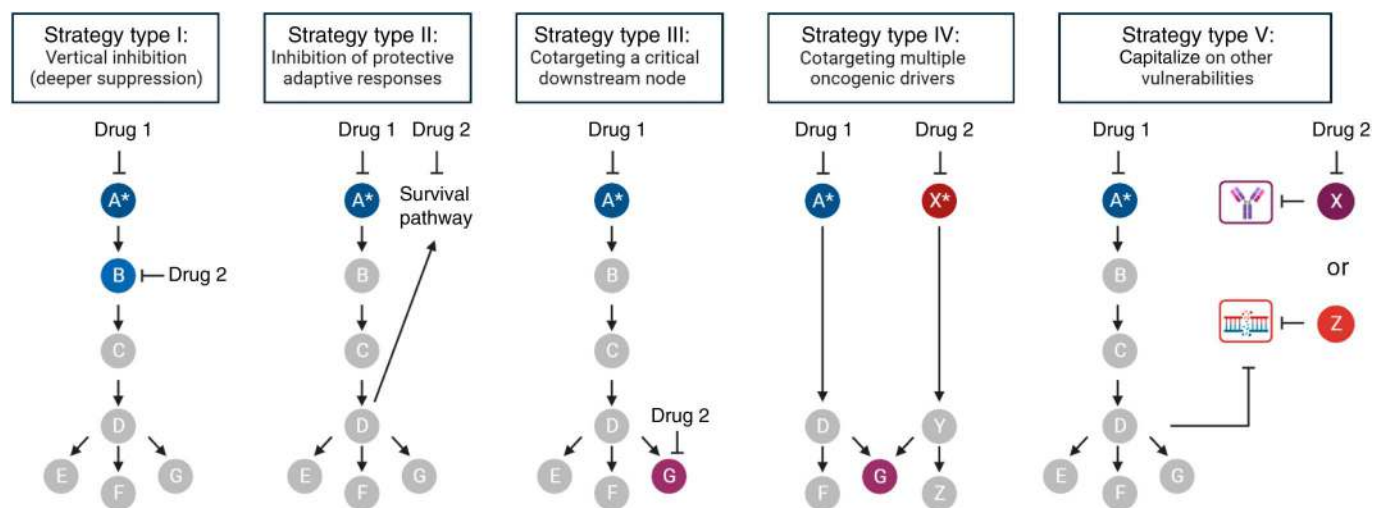


FIG 2. Strategies for developing combination therapies for RAS-driven cancers. Several promising categories of combination therapies have been studied in preclinical models and, in some instances, clinical trials, as discussed in the Vertical Inhibition/Deeper Pathway Suppression, Inhibition of Protective/Adaptive Responses, Cotargeting RAS and a Distal Downstream Effector, Cotargeting Multiple Oncogenic Pathways, and Capitalizing on Other Cancer-Associated Vulnerabilities sections. In each case, drug number one could represent any type of RAS inhibitor. Drug number 2 could represent a different class of RAS inhibitors (in strategy type I only) or target a different protein in strategy types II-V. The antibody and DNA damage cartoons in strategy type V are intended to depict agents that target immune suppressive responses or DNA repair mechanisms, respectively.

A second related approach is to combine two RAS inhibitors with different mechanisms of action. For example, the *KRAS*^{G12C} (OFF) inhibitor, RMC-6291, is currently being evaluated with the multi-RAS(ON) drug RMC-6236 (ClinicalTrials.gov identifier: [NCT06128551](#)). A similar approach could be exploited by combining a *KRAS*^{G12D} inhibitor and multi-RAS agents. These drug combinations could and should exert cooperate effects by targeting both the mutant oncogenic driver and any feedback or mutations that activate WT RAS proteins. Of note, a plethora of drug combinations that combine two RAS pathway inhibitors are currently being evaluated in clinical trials and preclinical studies.^{86,89,90} The ultimate success of any of these combinations will likely be dictated by the tolerability of the specific drugs examined.

Inhibition of Protective/Adaptive Responses

Approximately 45% of *KRAS*^{G12C}-mutant tumors develop mutations in the RAS pathway; however, the remaining 55% of resistance is thought to be regulated by non-mutational mechanisms.⁹⁴ Feedback activation of the RTK/RAS signaling is one example of an adaptive response and certainly contributes to resistance. However, many other adaptive pathways have been shown to promote resistance and offer new therapeutic vulnerabilities. For example, RAS pathway inhibitors have been shown to trigger the induction of autophagy, which serves as a survival signal in PDAC and other tumor types.^{95,96} Accordingly, RAS pathway inhibitors are currently being evaluated in combination with chloroquine⁸⁶ or the ULK inhibitor (ClinicalTrials.gov identifier: [NCT04892017](#)), each of which suppresses aspects of autophagy.

Cotargeting RAS and a Distal Downstream Effector

A third approach is to cotarget RAS along with a critical effector that functions farther downstream in the pathway. In this way, the second agent sensitizes tumor cells to the inhibition of a particularly important downstream component, which could mitigate the need for deep suppression of the entire pathway in all tissues. For example, one of the consequences of aberrant RAS signaling is transcriptional upregulation of cyclin D1, enhanced formation of cyclin D1:CDK4/6 complexes, and subsequent phosphorylation and inactivation of retinoblastoma protein.⁹⁷ Because of the importance of this downstream node, various RAS pathway inhibitors have been shown to synergize with CDK4/6 inhibitors in preclinical models, and as such, multiple clinical trials are underway⁸⁶ and specifically in combination with *KRAS*^{G12C} inhibitors (ClinicalTrials.gov identifiers: [NCT05178888](#), [NCT04185883](#), [NCT04956640](#), [NCT05358249](#)). A second powerful example is the cosuppression of RAS and components of cap-dependent translation. In addition to the RAF-MEK-ERK cascade, RAS also activates the PI3K-AKT-mTORC1-eIF4F pathway. Interestingly, mutant-selective *KRAS* inhibitors have been shown to potentially cooperate with eIF4A inhibitors, the RNA helicase of the eIF4F complex,⁹⁸ or mTORC1 inhibitors⁹⁹ and cause

potent tumor regression in NSCLC models. In both settings, the suppression of RAS and cap-dependent translation were required to inhibit the expression of critical Bcl2-family prosurvival proteins.

Cotargeting Multiple Oncogenic Pathways

The fourth strategy capitalizes on the fact that cancers do not develop from a single oncogenic event. Therefore, one can cotarget the first pathway along with a second oncogenic driver. An example of this type of approach is cotargeting EGFR along with MET, in lung cancers that develop a MET amplification.¹⁰⁰ More recently, RAS pathway inhibitors were shown to potentially synergize with EZH2 inhibitors in CRC.¹⁰¹ EZH2 is an epigenetic enzyme that is frequently overexpressed in CRC. Interestingly, these agents function by cooperatively suppressing WNT signaling, driving differentiation, and subsequently triggering apoptosis in differentiated cells.¹⁰¹ This combination was shown to be effective in multiple patient and mouse-derived models in vivo and may finally provide a means for cosuppressing RAS and WNT in this tissue.¹⁰¹

Capitalizing on Other Cancer-Associated Vulnerabilities

Finally, one can cotarget the driving oncogenic protein and a second cancer-associated vulnerability, such as the need to undergo massive DNA repair or evade the immune system. Again, these strategies appear to be effective because the RAS pathway also converges on DNA repair and immunoregulatory pathways.¹⁰²⁻¹⁰⁶ Promising preclinical studies have led to many combinatorial clinical trials that cotarget the RAS pathway and PD-1 in colon, lung, and pancreatic cancers or the RAS pathway and poly (ADP-ribose) polymerase in endometrial, ovarian, and pancreatic cancers.⁸⁶

Summary

Various classes of RAS inhibitors continue to be developed, with the hope that we will ultimately be able to target every mutant or hyperactivated WT RAS allele in human cancers. Nevertheless, drug combinations will likely be required to achieve durable responses. The approaches listed here are just a few examples of the types of combinations that show promise in preclinical and early clinical studies. However, the clinical success of any drug combination will ultimately depend on tolerability and our ability to prospectively select patients who are likely to respond. Therefore, we must continue these discovery efforts along with a deep dissection of how specific drug combinations function, so that we can identify an optimal treatment for each patient.

TARGETING MTAP LOSS IN HUMAN MALIGNANCIES

Homozygous 9p21 chromosomal deletion is one of the common genomic events in several human malignancies, resulting in the loss of *CDKN2A*, *CDKN2B*, *MTAP*, and the *IFN* cluster located in the vicinity.¹⁰⁷ 5'-methylthioadenosine

phosphorylase (*MTAP*) is deleted in approximately 15% of all human cancers (TCGA), co-occurring in 80%–90% of *CDKN2A*-deleted malignancies, and is associated with poor prognosis as compared with *MTAP*-proficient cancers.^{108,109} Although the majority of *MTAP* loss is attributed to its close proximity to *CDKN2A* on 9p21, increasing evidence supports its independent role as a tumor suppressor gene in breast and T-cell malignancies.^{110,111} Representing one of the largest patient populations in precision oncology, genetic *MTAP* loss is particularly prevalent in rare and aggressive cancers like malignant peripheral nerve sheath tumor (50%–60%), glioblastoma (40%–50%), and mesothelioma (40%) and moderately present in not so rare diseases like pancreatic cancer (25%) and NSCLC (15%–20%). In addition to genomic deletion, recent studies have provided evidence of an epigenetic mechanism for *MTAP* inactivation through promoter hypermethylation, further increasing the overall prevalence of *MTAP* loss in cancer.^{111–113} Therefore, targeting the cellular vulnerability of *MTAP* loss is an attractive strategy for cancer therapy.

Biological Consequences of MTAP Loss

MTAP loss disrupts critical cellular processes, including those involved in metabolism, epigenome regulation, and immune signaling,^{114–117} thus leading to tumorigenesis and immune evasion. *MTAP* WT cells encode *MTAP* enzyme, which is involved in the methionine salvage pathway, catalyzing 5'-methylthioadenosine (MTA) into adenine (building block of DNA and RNA) and methionine.¹¹⁸ Almost all adenine syntheses in the human body are driven by *MTAP*, highlighting its critical role in maintaining essential cellular functions and various metabolic processes. At the same time, methionine adenosyl transferase (*MAT2A*) converts methionine into S-adenosyl methionine (SAM), which

serves as a cofactor for protein arginine methyltransferases (PRMTs).¹¹⁸ PRMT5, a type II PRMT enzyme and a key epigenetic regulator, transfers the methyl group from SAM to substrate proteins, resulting in the formation of symmetric dimethyl arginine (SDMA), a unique post-translational modification.¹¹⁹ These SDMA-tagged proteins, such as histones, are essential for critical cellular functions such as gene expression, splicing, DNA damage response, and cell cycle progression. However, *MTAP*-deficient cells lack the ability to metabolize MTA, leading to its intracellular accumulation. These elevated MTA levels compete with SAM to bind and partially inhibit PRMT5 activity affecting its downstream signaling (Fig 3).^{114,120} Thus, in *MTAP*-WT cells, *MTAP* is key to adjusting the balance between metabolic and epigenetic pathways by increasing adenine availability and lowering MTA levels, thus favoring the formation of the active PRMT5-SAM complex over the inactive PRMT5-MTA complex. Furthermore, accumulation of MTA in the tumor immune microenvironment contributes to an immune suppression, hindering antitumor immune responses by affecting T-cell and natural killer-cell functions.^{117,121,122} Consistent with these findings, recent studies have demonstrated that *MTAP*-deleted tumors exhibit a cold tumor immune microenvironment and resistance to immune checkpoint therapy, driven by the immune-suppressive effects of accumulated MTA.¹²³

Therapeutic Avenues of Targeting MTAP Loss Tumors

The various underlying sensitivities of *MTAP*-deficient cells and the corresponding therapeutic approaches are under active investigation with promising potential for clinical efficacy. Here, we will mainly review the epigenetic and metabolic interventions that have demonstrated improved outcomes in patients with *MTAP* loss.

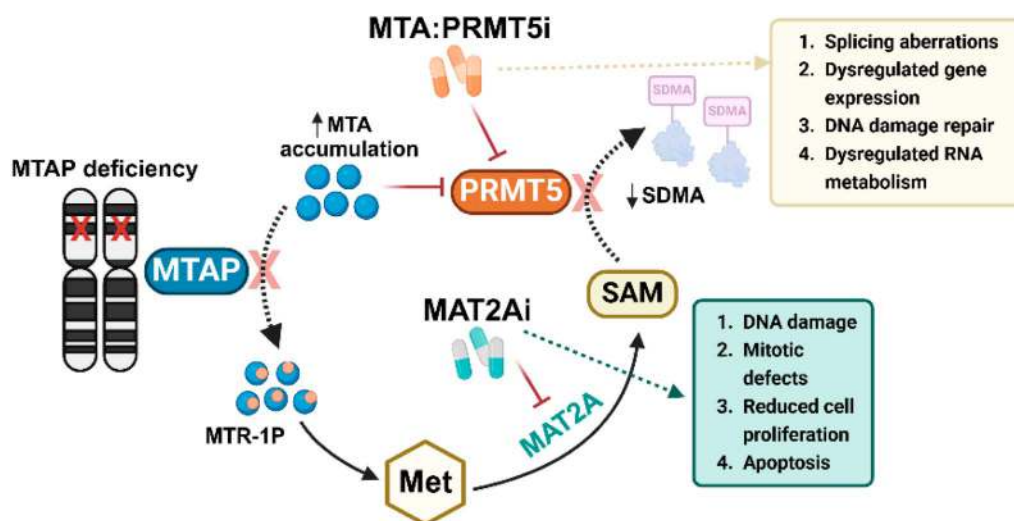


FIG 3. Biological consequence of *MTAP* loss and associated therapeutic vulnerabilities. *MAT2A*, methionine adenosyl transferase; *MAT2Ai*, methionine adenosyl transferase inhibitor; Met, methionine; MTA, methylthioadenosine; MTA:PRMT5i, MTA-cooperative PRMT5 inhibitors; MTR-1P, 5-methylthioribose-1-phosphate; PRMT5, protein arginine methyltransferase 5; SAM, S-adenosyl methionine; SDMA, symmetric dimethyl arginine.

PRMT5 Blockade as a Synthetic Lethal Target in MTAP Loss Tumors—Epigenetic Intervention

In MTAP-deleted cells, the failure of MTA metabolism and subsequent enrichment of MTA-PRMT5 complexes partially inhibit PRMT5 activity, resulting in impaired PRMT5-mediated signaling. This creates a state whereby MTAP loss cancer cells are particularly vulnerable to further inhibition of PRMT5 (Fig 3). The synthetic lethality between MTAP and PRMT5 was first discovered from a series of genetic functional screens in 2016.^{114,115,120} Since then, enormous efforts have been made to develop effective and selective PRMT5 inhibitors (PRMT5i). The first-generation SAM-cooperative or SAM-competitive PRMT5i (JNJ-64619178, GSK3326595, PF-06939999, PRT543, and PRT811) blocked PRMT5 activity efficiently. However, early-phase clinical studies in patients with solid tumors or hematologic malignancies resulted in severe adverse events and heme toxicities.^{124,125} In addition, these agents also demonstrated low ORRs (<10%) to single-agent therapies likely owing to narrow therapeutic index because of mechanism-based toxicities.^{124,125} Since PRMT5 activity is critical for survival of all cells, including immune cells, the clinical development of these non-tumor-selective agents was largely discontinued. To exploit the synthetic lethal relationship of PRMT5 inhibition in MTAP-deficient tumors as an effective therapeutic approach for the clinic, a structure-based drug discovery approach was used to develop second-generation PRMT5i. These agents selectively bind to the PRMT5-MTA complexes, found in high intracellular concentrations in MTAP loss tumor cells. Currently, seven such compounds (AMG193, BMS-986504/MRTX1719, TNG908, TNG462, TNG465, AZD3470, BGB-58067) have entered the early-phase clinical trials for patients with MTAP loss cancers.

In vitro studies on these second-generation MTA-cooperative PRMT5i (MTA:PRMT5i) have shown strong selectivity for MTAP-deleted cells, with dose-dependent tumor growth inhibition in various xenograft models, including lung, colorectal, and other cancer types, without significant toxicity. These inhibitors effectively reduce SDMA levels in MTAP-deleted tumors, with maximal tumor growth inhibition correlating with substantial SDMA reduction, suggesting that nearly complete PRMT5 inhibition is needed for the synthetic lethal effect. The preclinical data indicate that these inhibitors, including BMS-986504/MRTX1719,^{126,127} AMG193,^{128,129} TNG908,¹³⁰ and AZD3470,¹³¹ exhibit strong selectivity for MTAP-deleted tumors, induce changes in RNA splicing and DNA repair pathways, and offer robust antitumor activity without the hematologic toxicities seen with nonselective PRMT5i.

Preliminary clinical data for BMS-986504/MRTX1719 and AMG193 demonstrated promise in treating MTAP-deleted tumors. In a phase I/II trial of BMS-986504, patients with advanced solid tumors showed dose-dependent tumor growth inhibition, with the maximum tolerated dose (MTD) established at 600 mg once daily.^{127,132} AMG193 at the MTD set at 1,200 mg once daily also demonstrated efficacy in a

phase I trial, with an ORR of 12.2% and a disease control rate of 47.3% across several tumor types.¹³³ Both drugs showed tolerability with common treatment-related adverse events (TRAEs) like nausea and fatigue, but without significant hematologic toxicity. AZD3470, TNG908, and TNG462 are in ongoing trials with results expected in 2025. Early clinical data suggest that MTA:PRMT5i have a wider therapeutic window and may require longer follow-up to fully assess their potential clinical benefit.

MAT2Ai and Antifolate Treatment—Metabolic Intervention

MAT2A inhibitors, such as S95033/AG-270 and IDE397, have shown promise in targeting MTAP-deficient tumors. These inhibitors disrupt SAM biosynthesis, inducing synthetic lethality in MTAP-deleted cancers by reducing the natural substrate and thus inhibiting PRMT5 activity, which is already compromised by high MTA levels (Fig 3). Preclinical studies demonstrated that S95033/AG-270 and IDE397 effectively reduced SAM and SDMA levels, exhibiting antitumor activity in MTAP-deficient cell lines and xenograft models.^{134–136} In clinical trials, S95033/AG-270 showed a dose-limiting toxicity at higher doses, with common TRAEs including fatigue and hyperbilirubinemia, but limited objective responses.¹³⁷ IDE397, on the other hand, has shown promising preliminary efficacy, including an ORR of 33% in a phase I trial for advanced solid tumors.¹³⁸

Antifolates, like pemetrexed, have been explored for synthetic lethality in MTAP-deficient tumors by further depleting adenine, a critical component for DNA and RNA syntheses. An early phase II trial with pemetrexed disodium for MTAP-deficient urothelial carcinoma showed a 43% response rate, despite being terminated after only seven patients were enrolled, in favor of another trial that would evaluate pemetrexed-combined ICI for these patients.¹³⁹ Retrospective analyses in metastatic NSCLC also suggested that MTAP deficiency could predict a better response to pemetrexed.¹³⁹ The data align with findings from other studies which indicate that MTAP deficiency is a predictive biomarker for improved pemetrexed response in breast and lung cancers.^{140,141}

Potential Drug Combinations

Research into MTA:PRMT5i, MAT2A inhibitors, and antifolates has highlighted promising drug combinations with synergistic potential for targeting MTAP-deficient cancers. Preclinical studies show that combining MTA:PRMT5i like BMS-986504/MRTX1719, AMG 193, and AZD3470 with MAT2A inhibitors such as S95033/AG-270 or IDE397 may enhance tumor-selective synthetic lethality in MTAP-deficient cancer cells.^{142–144} These combinations leverage the unique vulnerability of MTAP-deleted cells, where PRMT5 inhibition is further augmented by MAT2A inhibition, reducing SAM levels and increasing the efficacy of both drug classes. In addition, early clinical results suggest that combining MTA:PRMT5i with other therapies, including

antifolates like pemetrexed, may lead to better therapeutic outcomes by further depleting adenine availability and exacerbating the already existing purine synthesis perturbations in MTAP-deficient tumors. Although these combinations show potential, careful consideration of safety and toxicity profiles is essential, particularly with respect to hematologic side effects commonly seen with nonselective inhibitors and traditional chemotherapy.

Future Directions

The development of MTA:PRMT5i, MAT2A inhibitors, and antifolates for MTAP-deficient tumors offers promising avenues for future research, including development as single agents in multiple tumor types, synergistic drug combinations, identification of predictive biomarkers, and optimization of patient testing. Clinical trials are also investigating combinations with standard-of-care therapies, like IDE397 with taxanes or AMG193 with KRAS inhibitors, to assess their efficacy in MTAP-deleted cancers. In addition, identifying patient subgroups with specific genetic alterations, such as co-occurring mutations in BRAF, EGFR, and KRAS, will help refine treatment strategies.¹⁴⁵ While MTAP loss in tumors is a key focus, further studies are needed to determine the best testing methods and patient selection criteria for various MTAP alterations, including those beyond homozygous deletions, to optimize therapeutic outcomes across different cancer types.

CONCLUSION

Drug discovery of unicorns, drugs that enable targeting undruggable genetic alterations, such as mutant TP53 and KRAS, and MTAP loss, holds the potential to revisit what is

considered therapeutically actionable. The ability to develop therapies that target these genetic vulnerabilities across various cancer types could lead to more effective and personalized treatments for a wide range of patients. The restoration of TP53 function offers an additional layer of therapeutic opportunity, especially in cancers with high TP53 mutation rates. Recent progress in the Y220C p53 mutant raises hopes for improved treatment of tumors carrying this particular mutant form of TP53. While approaches dedicated to specific p53 mutants will probably have the greatest chances of success, it is also clear that many common p53 mutants will be more challenging as targets than p53 Y220C. Furthermore, targeting KRAS mutations represents one of the most promising yet challenging frontiers in cancer therapy. While the success of KRAS^{G12C} inhibitors has revolutionized treatment paradigms for some cancers, their limitations underscore the need for more comprehensive strategies. Recent advancements in developing multi-KRAS inhibitors and multi-RAS inhibitors, which target mutant and WT RAS proteins, and the discovery of promising drug combinations demonstrate significant progress in overcoming the constraints of mutation-specific therapies. Similarly, drugs like PRMT5i, MAT2A inhibitors, and antifolates have already shown promise in MTAP-deficient cancers, and clinical trials are expanding these possibilities. Collectively, these unicorn drugs are driving the next generation of precision medicine, offering the potential for treatments that transcend traditional histologic boundaries. As research advances, multitargeted strategies that address these key molecular drivers could pave the way for more effective therapies, overcoming resistance mechanisms and improving long-term outcomes for a wide variety of patients with cancer.

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REFERENCES

- Lane DP, Crawford LV: T-antigen is bound to a host protein in SV40-transformed cells. *Nature* 278:261-263, 1979
- Linzer DI, Levine AJ: Characterization of a 54K dalton cellular SV40 tumor antigen present in SV40-transformed cells and uninfected embryonal carcinoma cells. *Cell* 17:43-52, 1979
- Kress M, May E, Cassingena R, et al: Simian virus 40-transformed cells express new species of proteins precipitable by anti-simian virus 40 tumor serum. *J Virol* 31:472-483, 1979
- Chang C, Simmons DT, Martin MA, et al: Identification and partial characterization of new antigens from simian virus 40-transformed mouse cells. *J Virol* 31:463-471, 1979
- Finlay CA, Hinds PW, Levine AJ: The P53 proto-oncogene can act as a suppressor of transformation. *Cell* 57:1083-1093, 1989
- Eliyahu D, Michalovitz D, Eliyahu S, et al: Wild-type P53 can inhibit oncogene-mediated focus formation. *Proc Natl Acad Sci U S A* 86:8763-8767, 1989
- Nigro JM, Baker SJ, Preisinger AC, et al: Mutations in the p53 gene occur in diverse human tumour types. *Nature* 342:705-708, 1989
- Baker SJ, Fearon ER, Nigro JM, et al: Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. *Science* 244:217-221, 1989
- Donehower LA, Harvey M, Slagle BL, et al: Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. *Nature* 356:215-221, 1992
- Yonishrouah E, Resnitzky D, Lotem J, et al: Wild-type p53 induces apoptosis of myeloid leukaemic cells that is inhibited by interleukin-6. *Nature* 352:345-347, 1991
- Maltzman W, Czyzyk L: UV irradiation stimulates levels of P53 cellular tumor-antigen in nontransformed mouse cells. *Mol Cell Biol* 4:1689-1694, 1984
- Lane DP: Cancer. p53, guardian of the genome. *Nature* 358:15-16, 1992
- Kastenhuber ER, Lowe SW: Putting p53 in context. *Cell* 170:1062-1078, 2017
- Boutelle AM, Attardi LD: p53 and tumor suppression: It takes a network. *Trends Cell Biol* 31:298-310, 2021
- Andrysk Z, Galbraith MD, Guarnieri AL, et al: Identification of a core TP53 transcriptional program with highly distributed tumor suppressive activity. *Genome Res* 27:1645-1657, 2017
- Fischer M: Census and evaluation of p53 target genes. *Oncogene* 36:3943-3956, 2017
- Halazonetis TD, Gorgoulis VG, Bartek J: An oncogene-induced DNA damage model for cancer development. *Science* 319:1352-1355, 2008
- Kandoth C, McLellan MD, Vandin F, et al: Mutational landscape and significance across 12 major cancer types. *Nature* 502:333-339, 2013
- Malkin D, Li FP, Strong LC, et al: Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* 250:1233-1238, 1990
- Srivastava S, Zou ZQ, Pirolo K, et al: Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. *Nature* 348:747-749, 1990
- Malkin D: Li-Fraumeni syndrome. *Genes Cancer* 2:475-484, 2011
- Reference deleted
- de Andrade KC, Lee EE, Tookmanian EM, et al: The TP53 Database: Transition from the International Agency for Research on Cancer to the US National Cancer Institute. *Cell Death Differ* 29:1071-1073, 2022
- Soussi T, Wiman KG: TP53: An oncogene in disguise. *Cell Death Differ* 22:1239-1249, 2015
- Joerger AC, Ang HC, Fersht AR: Structural basis for understanding oncogenic p53 mutations and designing rescue drugs. *Proc Natl Acad Sci U S A* 103:15056-15061, 2006
- Boettcher S, Miller PG, Sharma R, et al: A dominant-negative effect drives selection of TP53 missense mutations in myeloid malignancies. *Science* 365:599-604, 2019
- Lang GA, Iwakuma T, Suh YA, et al: Gain of function of a p53 hot spot mutation in a mouse model of Li-Fraumeni syndrome. *Cell* 119:861-872, 2004
- Olive KP, Tuveson DA, Ruhe ZC, et al: Mutant p53 gain of function in two mouse models of Li-Fraumeni syndrome. *Cell* 119:847-860, 2004
- Kato S, Han SY, Liu W, et al: Loss-of-function but not gain-of-function properties of mutant TP53 are critical for the proliferation, survival, and metastasis of a broad range of cancer cells. *Cancer Discov* 14:362-379, 2024
- Joerger AC, Stiewe T, Soussi T: TP53: The unluckiest of genes? *Cell Death Differ* 32:219-224, 2025
- Hoyos D, Zappasodi R, Schulze I, et al: Fundamental immune-oncogenicity trade-offs define driver mutation fitness. *Nature* 606:172-179, 2022
- Tate JG, Bamford S, Jubb HC, et al: COSMIC: The catalogue of somatic mutations in cancer. *Nucleic Acids Res* 47:D941-D947, 2019
- Kato S, Han SY, Liu W, et al: Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. *Proc Natl Acad Sci U S A* 100:8424-8429, 2003
- Kotler E, Shani O, Goldfeld G, et al: A systematic p53 mutation library links differential functional impact to cancer mutation pattern and evolutionary conservation. *Mol Cell* 71:178-190.e8, 2018
- Giacomelli AO, Yang X, Lintner RE, et al: Mutational processes shape the landscape of TP53 mutations in human cancer. *Nat Genet* 50:1381-1387, 2018
- Funk JS, Klimovich M, Drangenstein D, et al: Deep CRISPR mutagenesis characterizes the functional diversity of TP53 mutations. *Nat Genet* 57:140-153, 2025
- Martins CP, Brown-Swigart L, Evan GI: Modeling the therapeutic efficacy of p53 restoration in tumors. *Cell* 127:1323-1334, 2006
- Ventura A, Kirsch DG, McLaughlin ME, et al: Restoration of p53 function leads to tumour regression in vivo. *Nature* 445:661-665, 2007
- Xue W, Zender L, Miething C, et al: Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Nature* 445:656-660, 2007
- Hassin O, Oren M: Drugging p53 in cancer: One protein, many targets. *Nat Rev Drug Discov* 22:127-144, 2023
- Tuval A, Strandgren C, Heldin A, et al: Pharmacological reactivation of p53 in the era of precision anticancer medicine. *Nat Rev Clin Oncol* 21:106-120, 2024
- Peugot S, Zhou XL, Selivanova G: Translating p53-based therapies for cancer into the clinic. *Nat Rev Cancer* 24:192-215, 2024
- Bykov VJ, Issaeva N, Shilov A, et al: Restoration of the tumor suppressor function to mutant p53 by a low-molecular-weight compound. *Nat Med* 8:282-288, 2002
- Lambert JM, Gorzov P, Vepintsev DB, et al: PRIMA-1 reactivates mutant p53 by covalent binding to the core domain. *Cancer Cell* 15:376-388, 2009
- Bauer MR, Joerger AC, Fersht AR: 2-sulfonylpyrimidines: Mild alkylating agents with anticancer activity toward p53-compromised cells. *Proc Natl Acad Sci U S A* 113:E5271-E5280, 2016
- Dejtjarik O, Golovenko D, Diskin-Posner Y, et al: Structural basis of reactivation of oncogenic p53 mutants by a small molecule: Methylene quinuclidinone (MQ). *Nat Commun* 12:7057, 2021
- Peng X, Zhang MQZ, Conserva F, et al: APR-246/PRIMA-1MET inhibits thioredoxin reductase 1 and converts the enzyme to a dedicated NADPH oxidase. *Cell Death Dis* 4:e881, 2013
- Tessoulin B, Descamps G, Moreau P, et al: PRIMA-1Met induces myeloma cell death independent of p53 by impairing the GSH/ROS balance. *Blood* 124:1626-1636, 2014
- Mohell N, Alfredsson J, Fransson Å, et al: APR-246 overcomes resistance to cisplatin and doxorubicin in ovarian cancer cells. *Cell Death Dis* 6:e1794, 2015
- Liu DS, Duong CP, Haupt S, et al: Inhibiting the system x_C^+ /glutathione axis selectively targets cancers with mutant-p53 accumulation. *Nat Commun* 8:14844, 2017
- Ceder S, Eriksson SE, Cheteh EH, et al: A thiol-bound drug reservoir enhances APR-246-induced mutant p53 tumor cell death. *EMBO Mol Med* 13:e10852, 2021
- Fujihara KM, Zhang BZ, Jackson TD, et al: Eprenetapopt triggers ferroptosis, inhibits NFS1 cysteine desulfurase, and synergizes with serine and glycine dietary restriction. *Sci Adv* 8:eabm9427, 2022
- Wang ZL, Hu H, Heitink L, et al: The anti-cancer agent APR-246 can activate several programmed cell death processes to kill malignant cells. *Cell Death Differ* 30:1033-1046, 2023
- Xiao S, Shi F, Song H, et al: Characterization of the generic mutant p53-rescue compounds in a broad range of assays. *Cancer Cell* 42:325-327, 2024
- Cluzeau T, Sebert M, Rahmé R, et al: Eprenetapopt plus azacitidine in TP53-mutated myelodysplastic syndromes and acute myeloid leukemia: A phase II study by the Groupe Francophone des Myélodysplasies (GFM). *J Clin Oncol* 39:1575-1583, 2021
- Sallman DA, DeZern AE, Garcia-Manero G, et al: Eprenetapopt (APR-246) and azacitidine in TP53-mutant myelodysplastic syndromes. *J Clin Oncol* 39:1584-1594, 2021
- Chen S, Wu JL, Liang Y, et al: Arsenic trioxide rescues structural p53 mutations through a cryptic allosteric site. *Cancer Cell* 39:225-239.e8, 2021
- Song H, Wu J, Tang Y, et al: Diverse rescue potencies of p53 mutations to ATO are predetermined by intrinsic mutational properties. *Sci Transl Med* 15:eabn9155, 2023
- Boeckler FM, Joerger AC, Jaggi G, et al: Targeted rescue of a destabilized mutant of p53 by an in silico screened drug. *Proc Natl Acad Sci U S A* 105:10360-10365, 2008
- Liu X, Wilcken R, Joerger AC, et al: Small molecule induced reactivation of mutant p53 in cancer cells. *Nucleic Acids Res* 41:6034-6044, 2013
- Vu BT, Dominique R, Fahr BJ, et al: Discovery of rezatapopt (PC14586), a first-in-class, small-molecule reactivator of p53 Y220C mutant in development. *ACS Med Chem Lett* 16:34-39, 2025
- Puzio-Dunlop AM, Xu L, McBrayer MK, et al: Restoration of the tumor suppressor function of Y220C-mutant p53 by rezatapopt, a small molecule reactivator. *Cancer Discov*:OF1-OF21, 2025
- Dumbrava EE, Johnson ML, Tolcher AW, et al: First-in-human study of PC14586, a small molecule structural corrector of Y220C mutant p53, in patients with advanced solid tumors harboring a TP53 Y220C mutation. *J Clin Oncol* 40, 2022 (suppl 16; abstr 3003)
- Schram AM, Shapiro GI, Johnson ML, et al: Updated phase 1 results from the PYNNALE phase 1/2 study of PC14586, a selective p53 reactivator, in patients with advanced solid tumors harboring a TP53 Y220C mutation. *Mol Cancer Ther* 22:A25, 2023 (suppl 12)
- Guiley KZ, Shokat KM: A small molecule reacts with the p53 somatic mutant Y220C to rescue wild-type thermal stability. *Cancer Discov* 13:56-69, 2023
- Strandgren C, Wiman KG: Therapeutic targeting of TP53 nonsense mutations in cancer. *Upsala J Med Sci* 129:e10719, 2024

67. Keeling KM, Xue X, Gunn G, et al: Therapeutics based on stop codon readthrough. *Annu Rev Genomics Hum Genet* 15:371-394, 2014
68. Floquet C, Deforges J, Rousset JP, et al: Rescue of non-sense mutated p53 tumor suppressor gene by aminoglycosides. *Nucleic Acids Res* 39:3350-3362, 2011
69. Crawford DK, Alroy I, Sharpe N, et al: ELX-02 generates protein via premature stop codon read-through without inducing native stop codon read-through proteins. *J Pharmacol Exp Ther* 374:264-272, 2020
70. Friesen WJ, Trotta CR, Tomizawa Y, et al: The nucleoside analog cliticocine is a potent and efficacious readthrough agent. *Rna* 23:567-577, 2017
71. Palomar-Siles M, Heldin A, Zhang M, et al: Translational readthrough of nonsense mutant TP53 by mRNA incorporation of 5-fluorouridine. *Cell Death Dis* 13:997, 2022
72. Simanshu DK, Nissley DV, McCormick F: RAS proteins and their regulators in human disease. *Cell* 170:17-33, 2017
73. Prior IA, Hood FE, Hartley JL: The frequency of Ras mutations in cancer. *Cancer Res* 80:2969-2974, 2020
74. Moore AR, Rosenberg SC, McCormick F, et al: RAS-targeted therapies: Is the undruggable druggable? *Nat Rev Drug Discov* 19:533-552, 2020
75. Ostrem JM, Peters U, Sos ML, et al: K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature* 503:548-551, 2013
76. Skoulidis F, Li BT, Dy GK, et al: Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med* 384:2371-2381, 2021
77. Jänne PA, Riely GJ, Gadgil SM, et al: Adagrasib in non-small-cell lung cancer harboring a KRAS(G12C) mutation. *N Engl J Med* 387:120-131, 2022
78. Soria JC, Ohe Y, Vansteenkiste J, et al: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 378:113-125, 2018
79. Peters S, Camidge DR, Shaw AT, et al: Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 377:829-838, 2017
80. Dy GK, Govindan R, Velcheti V, et al: Long-term outcomes and molecular correlates of sotorasib efficacy in patients with pretreated KRAS G12C-mutated non-small-cell lung cancer: 2-year analysis of CodeBreak 100. *J Clin Oncol* 41:3311-3317, 2023
81. Hong DS, Fakih MG, Strickler JH, et al: KRAS(G12C) inhibition with sotorasib in advanced solid tumors. *N Engl J Med* 383:1207-1217, 2020
82. Yaeger R, Weiss J, Pelster MS, et al: Adagrasib with or without cetuximab in colorectal cancer with mutated KRAS G12C. *N Engl J Med* 388:44-54, 2023
83. Sacher A, LoRusso P, Patel MR, et al: Single-agent divarasil (GDC-6036) in solid tumors with a KRAS G12C mutation. *N Engl J Med* 389:710-721, 2023
84. Maciag AE, Stice JP, Wang B, et al: Discovery of BBO-8520, a first-in-class direct and covalent dual inhibitor of GTP-bound (ON) and GDP-bound (OFF) KRASG12C. *Cancer Discov* 15:578-594, 2025
85. Perurena N, Cichowski K: Finding the sweet spot: Targeting RAS in tumors while sparing normal tissue. *Cancer Cell* 42:943-945, 2024
86. Perurena N, Situ L, Cichowski K: Combinatorial strategies to target RAS-driven cancers. *Nat Rev Cancer* 24:316-337, 2024
87. Amodio V, Yaeger R, Arcella P, et al: EGFR blockade reverts resistance to KRAS(G12C) inhibition in colorectal cancer. *Cancer Discov* 10:1129-1139, 2020
88. Nokin MJ, Mira A, Patrucco E, et al: RAS-ON inhibition overcomes clinical resistance to KRAS G12C-OFF covalent blockade. *Nat Commun* 15:7554, 2024
89. Isermann T, Sers C, Der CJ, et al: KRAS inhibitors: Resistance drivers and combinatorial strategies. *Trends Cancer* 11:91-116, 2025
90. Cox AD, Der CJ: "Undruggable KRAS": Druggable after all. *Genes Dev* 39:132-162, 2025
91. Miyashita H, Kato S, Hong DS: KRAS G12C inhibitor combination therapies: Current evidence and challenge. *Front Oncol* 14:1380584, 2024
92. Holderfield M, Lee BJ, Jiang J, et al: Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy. *Nature* 629:919-926, 2024
93. Jiang J, Jiang L, Maldonado BJ, et al: Translational and therapeutic evaluation of RAS-GTP inhibition by RMC-6236 in RAS-driven cancers. *Cancer Discov* 14:994-1017, 2024
94. Awad MM, Liu S, Rybkin II, et al: Acquired resistance to KRAS(G12C) inhibition in cancer. *N Engl J Med* 384:2382-2393, 2021
95. Bryant KL, Stalneck CA, Zeitouni D, et al: Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer. *Nat Med* 25:628-640, 2019
96. Kinsey CG, Camolotto SA, Boespflug AM, et al: Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers. *Nat Med* 25:620-627, 2019
97. Aktas H, Cai H, Cooper GM: Ras links growth factor signaling to the cell cycle machinery via regulation of cyclin D1 and the Cdk inhibitor p27KIP1. *Mol Cell Biol* 17:3850-3857, 1997
98. Nardi F, Perurena N, Schade AE, et al: Cotargeting a MYC/ELF4-survival axis improves the efficacy of KRAS inhibitors in lung cancer. *J Clin Invest* 133:e167651, 2023
99. Kitai H, Choi PH, Yang YC, et al: Combined inhibition of KRAS(G12C) and mTORC1 kinase is synergistic in non-small cell lung cancer. *Nat Commun* 15:6076, 2024
100. Feldt SL, Bestvina CM: The role of MET in resistance to EGFR inhibition in NSCLC: A review of mechanisms and treatment implications. *Cancers (Basel)* 15:2998, 2023
101. Loi P, Schade AE, Rodriguez CL, et al: Epigenetic and oncogenic inhibitors cooperatively drive differentiation and kill KRAS-mutant colorectal cancers. *Cancer Discov* 14:2430-2449, 2024
102. Maertens O, Kuzmickas R, Manchester HE, et al: MAPK pathway suppression unmasks latent DNA repair defects and confers a chemical synthetic vulnerability in BRAF-NRAS-and NF1-mutant melanomas. *Cancer Discov* 9:526-545, 2019
103. Sun C, Fang Y, Yin J, et al: Rational combination therapy with PARP and MEK inhibitors capitalizes on therapeutic liabilities in RAS mutant cancers. *Sci Transl Med* 9:eaa15148, 2017
104. Canon J, Rex K, Saiki AY, et al: The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* 575:217-223, 2019
105. Mahadevan KK, McAndrews KM, LeBleu VS, et al: KRAS(G12D) inhibition reprograms the microenvironment of early and advanced pancreatic cancer to promote FAS-mediated killing by CD8(+) T cells. *Cancer Cell* 41:1606-1620 e8, 2023
106. Kemp SB, Cheng N, Markosyan N, et al: Efficacy of a small-molecule inhibitor of KrasG12D in immunocompetent models of pancreatic cancer. *Cancer Discov* 13:298-311, 2023
107. Barriga FM, Tsanov KM, Ho YJ, et al: MACHETE identifies interferon-encompassing chromosome 9p21.3 deletions as mediators of immune evasion and metastasis. *Nat Cancer* 3:1367-1385, 2022
108. Alhalabi O, Zhu Y, Hamza A, et al: Integrative clinical and genomic characterization of MTAP-deficient metastatic urothelial cancer. *Eur Urol Oncol* 6:228-232, 2023
109. Su CY, Chang YC, Chan YC, et al: MTAP is an independent prognosis marker and the concordant loss of MTAP and p16 expression predicts short survival in non-small cell lung cancer patients. *Eur J Surg Oncol* 40:1143-1150, 2014
110. Christopher SA, Diegelman P, Porter CW, et al: Methylthioadenosine phosphorylase, a gene frequently codeleted with p16(cdkN2a/ARF), acts as a tumor suppressor in a breast cancer cell line. *Cancer Res* 62:6639-6644, 2002
111. Woollard WJ, Kalaivani NP, Jones CL, et al: Independent loss of methylthioadenosine phosphorylase (MTAP) in primary cutaneous T-cell lymphoma. *J Invest Dermatol* 136:1238-1246, 2016
112. Ishii M, Nakazawa K, Wada H, et al: Methylthioadenosine phosphorylase gene is silenced by promoter hypermethylation in human lymphoma cell line DHL-9: Another mechanism of enzyme deficiency. *Int J Oncol* 26:985-991, 2005
113. Urošević J, Lynch JT, Meyer S, et al: Epigenetic silencing of MTAP in Hodgkin's lymphoma renders it sensitive to a 2nd generation PRMT5 inhibitor. *Blood* 142:4185, 2023
114. Kryukov GV, Wilson FH, Ruth JR, et al: MTAP deletion confers enhanced dependency on the PRMT5 arginine methyltransferase in cancer cells. *Science* 351:1214-1218, 2016
115. Mavrikis KJ, McDonald ER III, Schlachbach MR, et al: Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5. *Science* 351:1208-1213, 2016
116. Chang WH, Hsu SW, Zhang J, et al: MTAP deficiency contributes to immune landscape remodelling and tumour evasion. *Immunology* 168:331-345, 2023
117. Chen S, Hou J, Jaffery R, et al: MTA-cooperative PRMT5 inhibitors enhance T cell-mediated antitumor activity in MTAP-loss tumors. *J Immunother Cancer* 12:e009600, 2024
118. Fan N, Zhang Y, Zou S: Methylthioadenosine phosphorylase deficiency in tumors: A compelling therapeutic target. *Front Cell Dev Biol* 11:1173356, 2023
119. Branscombe TL, Frankel A, Lee JH, et al: PRMT5 (Janus kinase-binding protein 1) catalyzes the formation of symmetric dimethylarginine residues in proteins. *J Biol Chem* 276:32971-32976, 2001
120. Marjon K, Cameron MJ, Quang P, et al: MTAP deletions in cancer create vulnerability to targeting of the MAT2A/PRMT5/RIOK1 Axis. *Cell Rep* 15:574-587, 2016
121. Gjuka D, Adib E, Garrison K, et al: Enzyme-mediated depletion of methylthioadenosine restores T cell function in MTAP-deficient tumors and reverses immunotherapy resistance. *Cancer Cell* 41:1774-1787 e9, 2023
122. Jacobs B, Schlögl S, Strobl CD, et al: The oncometabolite 5'-deoxy-5'-methylthioadenosine blocks multiple signaling pathways of NK cell activation. *Front Immunol* 11:2128, 2020
123. Han GC, Yang G, Hao D, et al: 9p21 loss confers a cold tumor immune microenvironment and primary resistance to immune checkpoint therapy. *Nat Commun* 12:5606, 2021
124. Vieito M, Moreno V, Spreafico A, et al: Phase 1 study of JNJ-64619178, a protein arginine methyltransferase 5 inhibitor, in advanced solid tumors. *Clin Cancer Res* 29:3592-3602, 2023
125. Rodon J, Rodriguez E, Maitland ML, et al: A phase I study to evaluate the safety, pharmacokinetics, and pharmacodynamics of PF-06939999 (PRMT5 inhibitor) in patients with selected advanced or metastatic tumors with high incidence of splicing factor gene mutations. *ESMO Open* 9:102961, 2024
126. Smith CR, Aranda R, Bobinski TP, et al: Fragment-based discovery of MRTX1719, a synthetic lethal inhibitor of the PRMT5*MTA complex for the treatment of MTAP-deleted cancers. *J Med Chem* 65:1749-1766, 2022
127. Engstrom LD, Aranda R, Waters L, et al: MRTX1719 is an MTA-cooperative PRMT5 inhibitor that exhibits synthetic lethality in preclinical models and patients with MTAP deleted cancer. *Cancer Discov* 13:2412-2431, 2023
128. Rodon J, Yamamoto N, Doi T, et al: Initial results from first-in-human study of AMG 193, an MTA-cooperative PRMT5 inhibitor, in biomarker-selected solid tumors. *Mol Cancer Ther* 22, 2023 (suppl 12; abstr PR006)
129. Belmontes B, Slemmons KK, Su C, et al: AMG 193, a clinical stage MTA-cooperative PRMT5 inhibitor, drives antitumor activity preclinically and in patients with MTAP-deleted cancers. *Cancer Discov* 15:139-161, 2025
130. Briggs KJ, Cottrell KM, Tonini MR, et al: TNG908 is a brain-penetrant, MTA-cooperative PRMT5 inhibitor developed for the treatment of MTAP-deleted cancers. *Transl Oncol* 52:102264, 2025
131. Hong T, Criscione S, Jarnuczak A, et al: Integrative dynamic multiOMICS analysis identifies cell cycle and DNA damage response phenotypes as downstream consequences of using the PRMT5 inhibitor AZD3470. *Cancer Res* 84, 2024 (suppl 7; abstr LB008)

132. Rodon J, Jänne PA, Leventakos K, et al: Results from CA240-0007, a phase 1/2 multiple expansion cohort study of BMS-986504 in patients (pts) with advanced solid tumors with homozygous MTAP deletion (MTAP-del). *Eur J Cancer* 211:S178-S180, 2024
133. Rodon J, Prenen H, Sacher A, et al: First-in-human study of AMG 193, an MTA-cooperative PRMT5 inhibitor, in patients with MTAP-deleted solid tumors: Results from phase I dose exploration. *Ann Oncol* 35:1138-1147, 2024
134. Kalev P, Hyer ML, Gross S, et al: MAT2A inhibition blocks the growth of MTAP-deleted cancer cells by reducing PRMT5-dependent mRNA splicing and inducing DNA damage. *Cancer Cell* 39:209-224.e11, 2021
135. Konteatis Z, Travins J, Gross S, et al: Discovery of AG-270, a first-in-class oral MAT2A inhibitor for the treatment of tumors with homozygous MTAP deletion. *J Med Chem* 64:4430-4449, 2021
136. Fischer MM, Bhola N, Faulhaber J, et al: MAT2A inhibitor, IDE397, displays broad anti-tumor activity across a panel of MTAP-deleted patient-derived xenografts. *Cancer Res* 81:1278, 2021 (suppl 13)
137. Gounder M, Johnson M, Heist RS, et al: MAT2A inhibitor AG-270/S095033 in patients with advanced malignancies: A phase I trial. *Nat Commun* 16:423, 2025
138. Johnson ML, Rodon J, Aljumaily R, et al: A phase I study of synthetic lethal, IDE397 (MAT2A inhibitor) as a monotherapy and in combination with chemotherapy in advanced solid tumors harboring MTAP deletion. *Ann Oncol* 33:S766-S767, 2022
139. Alhalabi O, Chen J, Zhang Y, et al: MTAP deficiency creates an exploitable target for antifolate therapy in 9p21-loss cancers. *Nat Commun* 13:1797, 2022
140. Jing W, Zhu H, Liu W, et al: MTAP-deficiency could predict better treatment response in advanced lung adenocarcinoma patients initially treated with pemetrexed-platinum chemotherapy and bevacizumab. *Sci Rep* 10:843, 2020
141. Bou Zerdan M, Ashok Kumar P, Barrios DM, et al: Metabolic syndrome is independently associated with improved overall survival to first-line therapy with immune checkpoint inhibitors in non-small cell lung cancer. *Front Oncol* 13:1134824, 2023
142. Garbett D, Rao AA, Fischer MM, et al: The mechanistic basis of both deep and durable antitumor activity by combinatorial inhibition of MAT2A and PRMT5 in MTAP-deleted tumors. *Eur J Cancer* 211:S84, 2024
143. Fischer MM, Gerrick K, Belmontes B, et al: Dual inhibition of MAT2A and PRMT5 delivers synergistic anti-tumor responses in preclinical models of MTAP-deleted cancer. *Cancer Res* 83:1644, 2023 (suppl 7)
144. Gerrick KY, Laraio J, Annen K, et al: MAT2A inhibition in MTAP^{-/-} tumors confers mechanistic vulnerabilities to multiple clinically actionable synthetic lethal drug combinations. *Cancer Res* 83:1637, 2023 (suppl 7)
145. Ngoi NYL, Tang TY, Gaspar CF, et al: Methylthioadenosine phosphorylase genomic loss in advanced gastrointestinal cancers. *Oncologist* 29:493-503, 2024

Bispecific Antibodies in Hematologic and Solid Tumors: Current Landscape and Therapeutic Advances

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OVERVIEW

Bispecific antibodies (bsAbs) have emerged as a novel class of therapeutics, offering a dual-targeting strategy to enhance the therapeutic efficacy of monoclonal antibodies, which is often limited by tumor heterogeneity and the occurrence of resistance mechanisms. By simultaneously engaging two distinct antigens or pathways, bsAbs disrupt multiple signaling cascades simultaneously, preventing escape mechanisms and offering a more durable response. Furthermore, they can optimize immune activation, improving immune cell recruitment strategies. In particular, T-cell engager bsAbs facilitate immune cell–mediated tumor destruction by linking T cells to tumor antigens. Instead, dual immune checkpoint inhibitors (CPIs) enhance immune activation by blocking inhibitory signals. Additionally, bsAbs targeting tumor growth factors or receptor tyrosine kinases offer solutions for overcoming drug resistance in solid tumors. Although bsAbs have shown remarkable success in hematologic malignancies, their expansion into solid tumors faces key challenges, including tumor heterogeneity, limited tumor penetration, and the risk of on-target, off-tumor toxicities. Addressing these challenges requires innovative engineering strategies, optimized delivery mechanisms, and careful patient selection to maximize therapeutic benefit while mitigating adverse effects. The efficacy of bsAbs in clinical trials has led to their approval for both hematologic and solid malignancies, with numerous agents in development. Combination strategies with chemotherapy, targeted agents, and immune CPIs could represent a promising strategy to further expand their potential. As research progresses, bsAbs are expected to play a role in reshaping the future of precision oncology, offering more effective and tailored treatment options.

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INTRODUCTION

Over the past two decades, monoclonal antibodies (mAbs) have played a pivotal role in cancer treatment; however, their efficacy as anticancer agents is constrained by tumor heterogeneity and the coexistence of multiple parallel signaling pathways driving resistance.¹ To address these limitations, bispecific antibodies (bsAbs) have been developed and rapidly incorporated in hematologic and solid tumor pharmacopeia.^{2,3} Indeed, bsAbs provide an innovative therapeutic approach simultaneously targeting multiple antigens through diverse mechanisms of action. The dual binding capability of bsAbs allows for synergistic antigen targeting, resulting in more complex mechanisms of action compared with conventional mAbs.⁴

On the basis of their pharmacodynamic profile, bsAbs can be classified into obligate and combinatorial bsAbs. Obligate bsAbs require simultaneous binding to both targets for their therapeutic activity, which depends on the spatially coordinated engagement of two antigens to induce specific downstream signaling. For example, T-cell engagers (TCEs) are bsAbs designed to simultaneously bind CD3 on T cells and

a tumor-associated antigen (TAA) on cancer cells, bringing the T cell and cancer cell into close proximity to promote immune-mediated tumor cell killing.⁵ By contrast, combinatorial bsAbs can interact with each of their targets independently, without the need for concurrent binding. This category includes compounds targeting receptor tyrosine kinases such as amivantamab, which binds to both epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) factor.⁵

Advances in protein engineering technologies have enabled the development of numerous bispecific and multispecific antibody designs, paving the way for a variety of distinct and innovative therapeutic approaches. Indeed, the broad spectrum of mechanisms of action exhibited by bsAbs goes beyond their dichotomous classification. For example, dual immune checkpoint protein (ICP) modulators target ICPs (eg, PD-1, CTLA-4, LAG-3, or TIGIT) on both T cells and tumor cells, enhancing immune system activation and overcoming tumor immune suppression.⁶ Moreover, dual-targeting bsAbs can bind two distinct antigens blocking receptor–ligand interactions, inducing receptor internalization and activating immune effector functions by antibody-dependent cellular

PRACTICAL APPLICATIONS

- Bispecific antibodies (bsAbs) exert their function through diverse strategies including T-cell engagement for immune-mediated tumor cell killing, dual immune checkpoint inhibition to enhance immune activation, and dual receptor targeting to enhance efficacy and prevent drug resistance.
- Tumor heterogeneity, penetration issues, and off-tumor toxicity limit their expansion in the treatment of solid tumors. Innovative designs and delivery strategies are required to overcome these issues.
- Combination strategies have proven to be effective in enhancing bsAbs efficacy.
- Ongoing clinical development and combination approaches are establishing bsAbs as a pivotal component of next-generation cancer therapies, reshaping the future of precision oncology.

phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC).⁶ Dual receptor targeting demonstrated to address tyrosine kinase inhibitor (TKI) resistances caused by compensatory pathway activation. In addition, promising data have been obtained with biparatopic bsAbs, a subtype of bsAbs that target two nonoverlapping epitopes on the same antigen.⁷

Blinatumomab, a TCE targeting CD19 and CD3, was the first bsAb to receive US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval (in 2014 and 2015, respectively) for the treatment of relapsed or refractory B-cell precursor ALL (R/R B-ALL; Fig 1).⁸ Subsequently, other 11 bsAbs have been approved by FDA for hematologic malignancies or solid tumors; the latest was zanidatamab-hrii, a bispecific human epidermal growth factor receptor 2 (HER2)-directed antibody, for previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC).⁹ At present, hundreds of bsAbs are under investigation, many in solid tumors, with a significant proportion of them in later phases.

The aim of our work was to explore current evidence about the clinical use of bsAbs in both hematologic and solid malignancies, providing also a comprehensive overview of current development and future perspectives.

bsAbs FOR DUAL RECEPTOR INHIBITION

mAbs radically changed the treatment landscape of solid and hematologic cancers.¹⁰ However, their design is limited because of a single-target approach that allows compensatory cell pathways to overcome the antineoplastic effects

induced by mAbs. In this regard, bsAbs structure is designed to target two different TAAs simultaneously, potentially limiting resistances to a single-pathway modulation, inherent in the plasticity of cancer cells.^{1,11,12} Moreover, dual receptor inhibition by bsAbs may reduce the incidence of on-target off-tumor toxicities, owing to the need to engage to both receptors to carry out their cytotoxic effect.^{5,6}

Several bsAbs designed for dual receptor inhibition are being evaluated in clinical trials worldwide, both in advanced and early clinical settings, with many others currently in development (Table 1). The first one approved for patients with solid tumors was the anti-EGFRxMET bsAb amivantamab.¹³ In 2021, according to the results of the phase I CHRYSALIS trial, this agent was approved for patients with non-small cell lung cancer (NSCLC) harboring EGFR exon 20 insertion, which represents the third most common EGFR mutation type, resulting in altered TKI binding and intrinsic resistance to EGFR TKIs.¹⁴⁻¹⁶ However, this altered receptor can be targeted by amivantamab, which was demonstrated to promote the blockade of ligand-receptor binding and receptor-antibody complex endocytosis and degradation and induce Fc-dependent trogocytosis by macrophages and antibody-dependent cellular cytotoxicity by natural killer cells (Fig 2).¹⁷⁻¹⁹ Accordingly, the CHRYSALIS trial evaluated amivantamab monotherapy in 81 patients with NSCLC harboring EGFR exon 20 insertion, progressed on or after platinum-based chemotherapy. This study showed an objective response rate (ORR) of 40% (95% CI, 29 to 51), median duration of response (mDOR) of 11.1 months (95% CI, 6.9 to not reached), and median progression-free survival (mPFS) of 8.3 months (95% CI, 6.5 to 10.9).²⁰

Among other TAAs explored for dual signaling inhibitors, one of the major areas of development is represented by the HER2, whose overexpression is a major driver in various solid tumors, such as breast cancer (BC), gastric or gastroesophageal junction cancer (G/GEJC), NSCLC, BTC, endometrial cancer, and colorectal cancer (CRC).^{21,22} In this setting, zanidatamab is anti-HER2 biparatopic bsAb targeting the extracellular domain 4 (ECD4) and extracellular domain 2 (ECD2) of HER2.²³ It has been shown to mediate antitumor activity also through complement-dependent cytotoxicity, a mechanism not observed with trastuzumab and pertuzumab combinations. The phase I ZWI-ZW25-101 basket trial assessed the safety and activity of zanidatamab in HER2-positive advanced tumors, showcasing an acceptable safety profile and an ORR of 37% among all cancer types.²⁴ The phase 2b HERIZON-BTC-01 trial assessed zanidatamab in 87 patients with HER2-amplified advanced BTC progressed on gemcitabine-based therapy and confirmed its activity in this difficult-to-treat setting (in patients with 3+ or 2+ IHC, ORR, 41% [95% CI, 30.4 to 52.8]).^{25,26} Notably, the ORR was especially compelling in patients with 3+ expression with an ORR of 51.6% (95% CI, 38.6% to 64.5%) for IHC 3+ tumors and 5.6% (95% CI, 0.1-27.3) in IHC 2+ tumors. These results led to the FDA approval of zanidatamab in patients with unresectable or metastatic

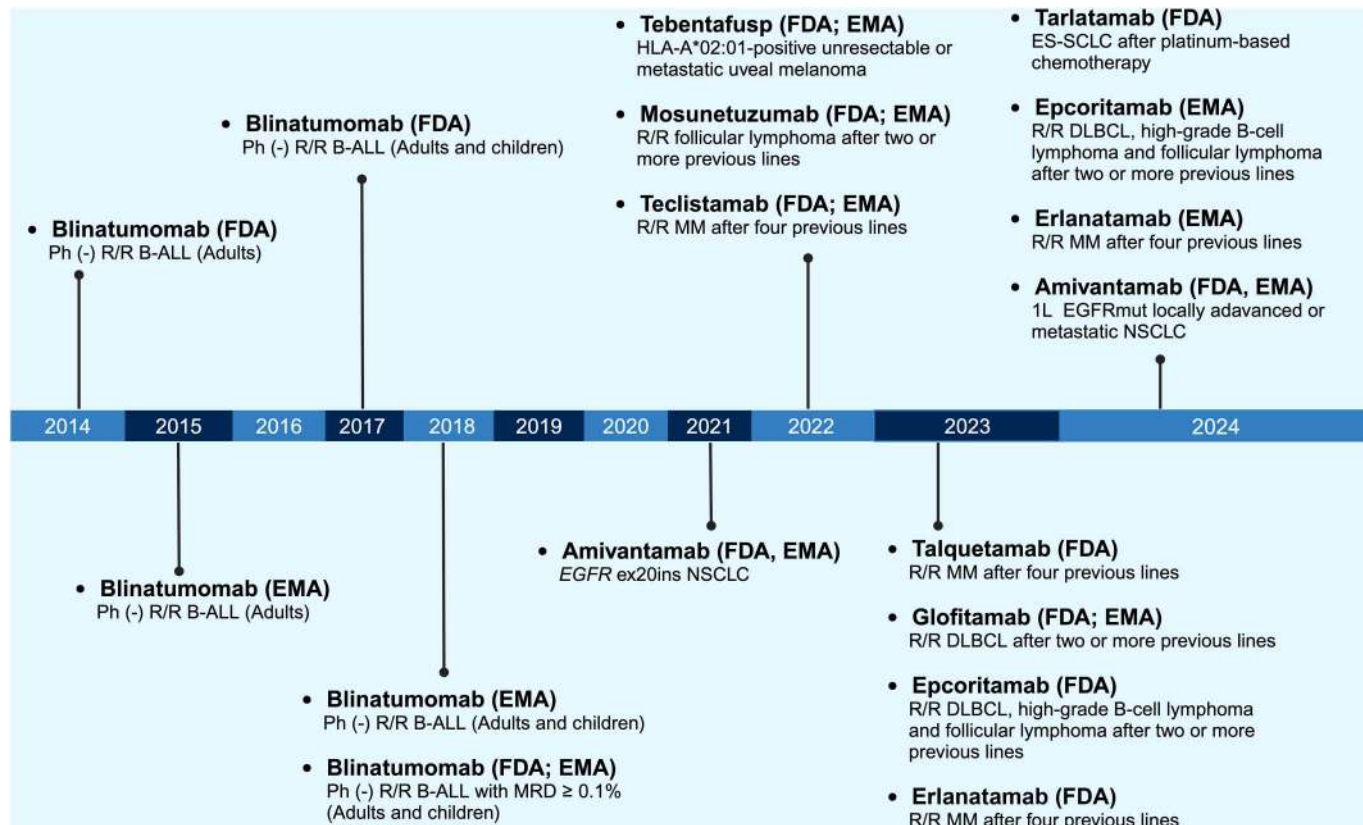


FIG 1. Timeline of FDA and EMA approvals for bispecific antibodies. The image shows key regulatory approvals of bsAbs from 2014 to 2024. 1L, first line treatment; B-ALL, B-cell ALL; DLBCL, diffuse large B-cell lymphoma; bsAbs, bispecific antibodies; EGFR ex20ins, exon 20 insertion; EGFR, epidermal growth factor receptor; EGFRmut, EGFR-mutated; EMA, European Medicines Agency; ES-SCLC, early-stage small cell lung cancer; FDA, US Food and Drug Administration; HLA, human leukocyte antigen; MM, multiple myeloma; MRD, minimal residual disease; NSCLC, non-small cell lung cancer; Ph-, Philadelphia chromosome negative; R/R, refractory or relapsed.

BTC with HER2 3+ IHC in November 2024.²⁷⁻²⁹ Anbenitamab is another biparatropic antibody targeting the ECD2 and ECD4 epitopes of HER2.³⁰ In early phase I-II trials, it demonstrated promising activity and safety in patients with HER2-positive metastatic BC and HER2-positive G/GEJC.³¹⁻³³

Zenocutuzumab, an HER2xHER3 bsAb, is the latest anti-HER2 bsAb to receive an FDA approval in December 2024.³⁴ This agent binds to HER2 and HER3, blocking the interaction of HER3 with neuregulin 1 (NRG1) or NRG1 fusion proteins.³⁵ In the phase I/II eNRGy trial, which included 64 patients with advanced NSCLC and pancreatic adenocarcinoma carrying NRG1 fusions, for NSCLC, zenocutuzumab showed an ORR of 33% (95% CI, 22 to 46) and for pancreatic adenocarcinoma, ORR was 40% (95% CI, 23 to 59).^{31,36-39}

More recently, ivonescimab, a bsAb targeting PD-1 and vascular endothelial growth factor (VEGF), was tested compared with pembrolizumab in the phase III HARMONI-2 trial for patients with advanced PD-L1-positive NSCLC.⁴⁰ On interim analysis, mPFS was significantly longer in those receiving ivonescimab than those receiving pembrolizumab (11.1 months v 5.8 months, hazard ratio [HR], 0.51 [95% CI, 0.38 to 0.69], $P < .0001$); a consistent benefit was observed

across prespecified PD-L1 subgroups, which included patients with PD-L1 tumor proportion score (TPS) 1%-49% (HR, 0.54 [95% CI, 0.37 to 0.78]) and PD-L1 TPS of 50% or higher (HR, 0.48 [95% CI, 0.29 to 0.79]). Ivonescimab had a manageable safety profile, making it a potential first-line treatment option for PD-L1-positive advanced NSCLC. Nonetheless, this trial was limited by the fact that patients with PD-L1 TPS 1%-49% did not receive chemotherapy added to immunotherapy in the control arm, which is a widely used combination in this setting.

Significant attention is also given to bispecific antibody-drug conjugates (ADCs) as a next-generation approach, offering potentially greater efficacy than current ADCs.^{41,42} These include JSKN003, a biparatopic anti-HER2 bsAb linked to a topoisomerase-1 inhibitor (TOP1i), currently being tested in a phase III trial for HER2-low metastatic BC, after having demonstrated substantial activity in patients with platinum-resistant ovarian cancer⁴²⁻⁴⁴; izalontamab brengitecan (an EGFRxHER3 ADC), which showed antitumor activity in HER2-positive solid tumors and in urothelial carcinoma and is being evaluated in a phase III trial for previously treated nasopharyngeal carcinoma^{42,45,46}; zanidatamab zovodotin (HER2xHER2 ADC), which demonstrated

TABLE 1. Results From Trials Assessing Bispecific Antibodies

Trials	Target	Agent	Setting	Phase	Results
Dual receptor inhibition					
CHRYSLIS (NCT02609776)	EGFRxMET	Amivantamab	Previously treated EGFR Exo-n20ins NSCLC	I	ORR, 40%; mPFS, 8.3 months
ZWI-ZW25-101 (NCT02892123)	HER2xHER2	Zanidatamab	HER2+ advanced tumors	I	ORR, 37%
HERIZON-BTC-01 (NCT04466891)	HER2xHER2	Zanidatamab	HER2+ mBTC with disease progression on gemcitabine-based ChT	IIb	ORR, 41.3%
NCT05035836	HER2xHER2	Zanidatamab	Neoadjuvant stage I node-negative HER2+ eBC	II	pCR, 36%
NCT03619681	HER2xHER2	Anbenitamab	Previously treated HER2+ mBC	I	ORR, 32.1%; DCR, 76.8%
NCT03925974	HER2xHER2	Anbenitamab	Previously treated HER2+ (cohort 1) or HER2-low (cohort 2) G/GEJC	II	Cohort 1: ORR, 56%; mDoR, 9.7 months Cohort 2: ORR, 14%; mDoR, 6.2 months
eNRGy (NCT02912949)	HER2xHER3	Zenocutuzumab	Previously treated NRG1+ solid tumors (56% NSCLC, 25% PDAC, 19% others)	II	ORR, 34%; mDoR, 9.1; months
NCT03821233	HER2xHER2	Zanidatamab zovodotin (ZW49; ADC)	Previously treated HER2+ solid tumors (GC 33%, BC 15%)	I	ORR, 31%; DCR, 72%
NCT05194982	EGFRxHER3	Izalontamab brengitecan (BL-B01D1; ADC)	Advanced HER2+ solid tumors (58% NSCLC)	I	ORR, 34%
NCT05785039	EGFRxHER3	Izalontamab brengitecan (BL-B01D1; ADC)	Advanced urothelial cancer	Ib/II	ORR, 43.5% (10/23); DCR, 91.3%
NCT05494918 NCT05744427	HER2xHER2	JSKN003 (ADC)	PROC	I/II	ORR, 59.1% (61.1% in HER2-expression)
Immunotherapy					
TOWER (NCT02013167)	CD3xCD19	Blinatumomab (MT103)	Adults ALL Ph+/-; pediatric ALL Ph+/-	III	mOS, 7.7 v 4.4 months
ALCANTARA (NCT02000427)	CD3xCD19	Blinatumomab (MT103)	R/R B-ALL Ph+	II	mOS, 9.0 months
BLAST (NCT01207388)	CD3xCD19	Blinatumomab (MT103)	MRD positive B-ALL Ph+/-	II	Undetectable MRD, 85% in CR1 and 72% in CR2
NCT02003222	CD3xCD19	Blinatumomab (MT103)	Consolidation of Ph- B-ALL	III	5-year OS rate, 82.4% v 62.5%
G029781 (NCT02500407)	CD3xCD20	Mosunetuzumab	R/R FL after two prior lines of systemic therapy	II	ORR, 80% (CR, 60%)
EPCORE NHL-1 (study GCT3013-01; NCT03625037)	CD3xCD20	Epcoritamab	R/R FL after two or more lines of systemic therapy	II	ORR, 82% (95% CI, 74.1 to 88.2); CR, 60%
NP30179 (NCT03075696)	CD3xCD20	Glofitamab	R/R DLBCL, NOS or LBCL arising from FL, after two or more lines of systemic therapy	I-II	ORR, 56% (CR, 43%)
(continued on following page)					

TABLE 1. Results From Trials Assessing Bispecific Antibodies (continued)

Trials	Target	Agent	Setting	Phase	Results
MajesTEC-1 (NCT03145181 ; NCT04557098)	CD3xBCMA	Teclistamab	R/R MM	I-II	ORR, 63.0%; CR, 39.4%
MagnetisMM-3 (NCT04649359)	CD3xBCMA	Erlanatamab	R/R MM refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one anti-CD38 antibody	II	ORR, 57.7%
MMY1001 (MonumenTAL-1)	CD3xGPRC5D	Talquetamab	R/R MM with previous 4 lines of therapy	II	ORR (0.4 mg/kg once every week), 73%; ORR (receiving 0.8 mg/kg once every 2 weeks), 73.6%
IMCgp100-202 (NCT03070392)	CD3xgp100	Tebentafusp	HLA-A*02:01-positive unresectable or metastatic uveal melanoma	III	mOS, 21.6 months v 16.9 months (mFUP, 36 months)
DeLLphi-301 (NCT05060016)	CD3xDLL3	Tarlatamab	ES-SCLC with disease progression on or after platinum-based chemotherapy	II	ORR, 40% and median DOR, 9.7 months
REDIRECT (NCT04101331)	CD30xCD16A	Acimtamig	(R/R) PTCL	II	ORR, 32.4%; CR, 10.2%
NCT04522323	PD-1xCTLA-4	Volrustomig	Advanced-stage ccRCC	I	ORR, 46.9%; mPFS, 9.9 months (500 mg doses); ORR, 45.5%; mPFS, 11.1 months (750 mg doses)
Combinations					
GIMEMA LAL2116 D-ALBA (NCT02744768)	CD3xCD19	Blinatumomab + dasatinib	1L Ph+ ALL	II	Molecular response 60% after two cycles, 72% after five cycles
NCT03263572	CD3xCD19	Blinatumomab + ponatinib	1L or R/R Ph+ ALL or CML in lymphoid blast phase	II	1L ALL, 87% CMR R/R ALL, 92% ORR CML, 83% ORR
EudraCT 2016-004674-17	CD3xCD19	Blinatumomab + ChT	1L KMT2A-rearranged infant ALL	II	No clinically relevant toxic effects 2-year DFS, 81.6% 2-year OS, 93.3%
NCT03677141	CD3xCD20	Mosunetuzumab + CHOP	1L DLBCL	II	ORR, 95%; CRR, 90%
NCT03671018	CD3xCD20	Mosunetuzumab + polatuzumab vedotin	R/R DLBCL	Ib/II	ORR, 59.2%; CRR, 45.9%
RedirecTT-1 (NCT04586426)	CD3xBCMA CD3xGPRC5D	Teclistamab + talquetamab	R/R MM	Ib/II	ORR, 80%
STARGLO (NCT04408638)	CD3xCD20	Glofitamab + gemcitabine-oxaliplatin	R/R DLBCL	III	mOS, 25.5 v 12.9 months (HR, 0.62)
NCT02665650	CD30xCD16A	Acimtamig + pembrolizumab	R/R HL	Ib	ORR, 83%; CMR, 42%; mDOR, 9.9 months
NCT04074746	CD30xCD16A	Acimtamig + CB-derived NK cells	R/R CD30 ⁺ lymphomas	I-II	ORR, 92.8%; CRR, 66.7%; mEFS, 8 months; mOS, not reached
PAPILLON (NCT04538664)	EGFRxMET	Amivantamab + ChT	1L EGFR Exon20ins NSCLC	III	mPFS, 11.4 v 6.7 months (HR, 0.40)

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TABLE 1. Results From Trials Assessing Bispecific Antibodies (continued)

Trials	Target	Agent	Setting	Phase	Results
MARIPOSA (NCT04487080)	EGFRxMET	Amivantamab + lazertinib	1L EGFR ex19 deletion or L858R NSCLC	III	mPFS, 23.7 v 16.6 months (HR, 0.70)
MARIPOSA-2 (NCT04988295)	EGFRxMET	Amivantamab + lazertinib + ChT	2L EGFR ex19 deletion or L858RC NSCLC after progression on osimertinib	III	mPFS, 8.3 v 6.3 v 4.2 months
NCT04276493	HER2xHER2	Zanidatamab + docetaxel	1L HER2+ mBC	Ib/II	ORR, 86.4%; DCR, 97%; mDOR, not reached
NCT04224272	HER2xHER2	Zanidatamab + fulvestrant-palbociclib	Hormone receptor–positive/HER2+ mBC	II	ORR, 35%; DCR, 93.1%; mPFS, 11.3 months
NCT05427383	HER2xHER2	Anbenitamab + ChT	2L HER2+ G/GEJC	II	ORR, 40%; DCR, 80%
NCT04165993	HER2xHER2	Anbenitamab + docetaxel	1L HER2+ mBC	II	ORR, 76.4%; mDoR, not reached
NCT03321981	HER2xHER3	Zenocutuzumab + trastuzumab + vinorelbine	HER2+ mBC	II	DCR, 77%
NCT05020457	EGFRxHER3	Izalontamab + ChT	2L EGFR/ALKwt NSCLC	II	ORR, 31.3%; DCR, 77.1%
COMPASSION-16 (NCT04982237)	PD-1xCTLA-4	Cadonilimab + ChT ± bevacizumab	1L cervical cancer	III	mPFS, 12.7 v 8.1 months (HR, 0.62) mOS, not reached (27.0 months to not estimable) v 22.8 months (HR, 0.64)
COMPASSION-15 (NCT05008783)	PD-1xCTLA-4	Cadonilimab + ChT	1L HER2- G/GEJC	III	mOS, 14.1 v 11.1 months (HR, 0.66)
NCT04646330	PD-1xCTLA-4	Cadonilimab + anlotinib	1L NSCLC non oncogene-addicted	Ib/II	ORR, 51% (15 mg/kg) and 60% (10 mg/kg)
COMPASSION-08 (NCT04444167)	PD-1xCTLA-4	Cadonilimab + lenvatinib	1L HCC	Ib/II	ORR, 35.5% (cohort A, Q2W) and 35.7% (cohort B, Q3W)
ChiCTR2200066893	PD-1xCTLA-4	Cadonilimab + FLOT	Neoadjuvant G/GEJC	II	pCR, 21.1%
NCT03872791	PD-L1xCTLA-4	Erfonilimab (KN046) + nab-paclitaxel	1L TNBC	II	ORR, 44%; mDoR, not mature mPFS 7.33 months (8.61 months in PD-L1+ v 4.73 months in PD-L1–); mOS, 30.92 months.
NCT04054531	PD-L1xCTLA-4	Erfonilimab (KN046) + ChT	1L NSCLC	II	ORR, 46%; mDoR, 8.1 months
NCT04542837	PD-L1xCTLA-4	Erfonilimab + lenvatinib	1L HCC	II	ORR, 51.9%
NCT04736823	PD-1xVEGF	Ivonescimab + ChT	NSCLC Cohort 1: 1L EGFR/ALKwt Cohort 2: 2L EGFRmut Cohort 3: 2L	II	Cohort 1: ORR, 53.5%; mPFS, not reached (59.1% at 12 months) Cohort 2: ORR, 68.4%; mPFS, 8.5 months Cohort 3: ORR 40%, mPFS 7.5 months
HARMONI-A (NCT05184712)	PD-1xVEGF	Ivonescimab + ChT	EGFRmut NSCLC in PD after EGFR TKI	III	mPFS, 7.1 v 4.8 (HR, 0.46)
	PD-1xVEGF	Ivonescimab + carboplatin-etoposide	1L SCLC	Ib	ORR, 80%; DCR, 91.4%

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TABLE 1. Results From Trials Assessing Bispecific Antibodies (continued)

Trials	Target	Agent	Setting	Phase	Results
NCT05756972	PD-L1xVEGF-A	PM8002/BNT327 + ChT	EGFRmut NSCLC in PD after EGFR TKI	II	ORR, 54.7%; DCR, 95.3%
NCT05918133	PD-L1xVEGF-A	PM8002/BNT327 + ChT	1L TNBC	Ib/II	ORR, 78.6%; DCR, 95.2%
COMPANION-002 (NCT04492033)	DLL4xVEGF	CTX-009 + paclitaxel	2L/3L mBTC	II	ORR, 37.5%

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; ADC, antibody-drug conjugate; ALK, anaplastic lymphoma kinase; B-ALL, B-cell acute lymphoblastic leukemia; BC, breast cancer; BCMA, B-cell maturation antigen; CB, cord blood; ccRCC, clear-cell renal cell carcinoma; CD, cluster of differentiation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ChT, chemotherapy; CML, chronic myeloid leukemia; CMR, complete metabolic response; CR, complete remission; CRR, complete response rate; CTLA-4, cytotoxic T-lymphocyte antigen 4; DCR, disease control rate; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; DLL3, Delta-like ligand 3; DLL4, Delta-like ligand 4; eBC, early breast cancer; EGFR, epidermal growth factor receptor; ES, extensive stage; ES-SCLC, extensive-stage small cell lung cancer; ex, exon; FL, follicular lymphoma; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC, gastric cancer; G/GEJC, gastric or gastroesophageal junction cancer; gp100, glycoprotein 100; GPRC5D, G-protein coupled receptor family C group 5 member D; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HL, Hodgkin lymphoma; HLA, human leukocyte antigen; HR, hazard ratio; ins, insertion; KMT2A, histone-lysine N-methyltransferase 2; LBCL, large B-cell lymphoma; mBC, metastatic breast cancer; mBTC, metastatic biliary tract cancer; mDoR, median duration of response; mEFS, median event-free survival; MET, mesenchymal-epithelial transition factor; mFUP, median follow-up; MM, multiple myeloma; mOS, median overall survival; mPFS, median progression-free survival; MRD, molecular residual disease; NK, natural killer; NOS, not otherwise specified; NRG1, neuregulin 1; NSCLC, non–small-cell lung cancer; ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PD, progression disease; PDAC, pancreatic ductal adenocarcinoma; Ph, Philadelphia; PROC, platinum-resistant ovarian cancer; PTCL, peripheral T-cell lymphoma; Q2W, once every 2 weeks; Q3W, once every 3 weeks; R/R, relapsed and/or refractory; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; VEGF, vascular endothelial growth factor; wt, wild-type.

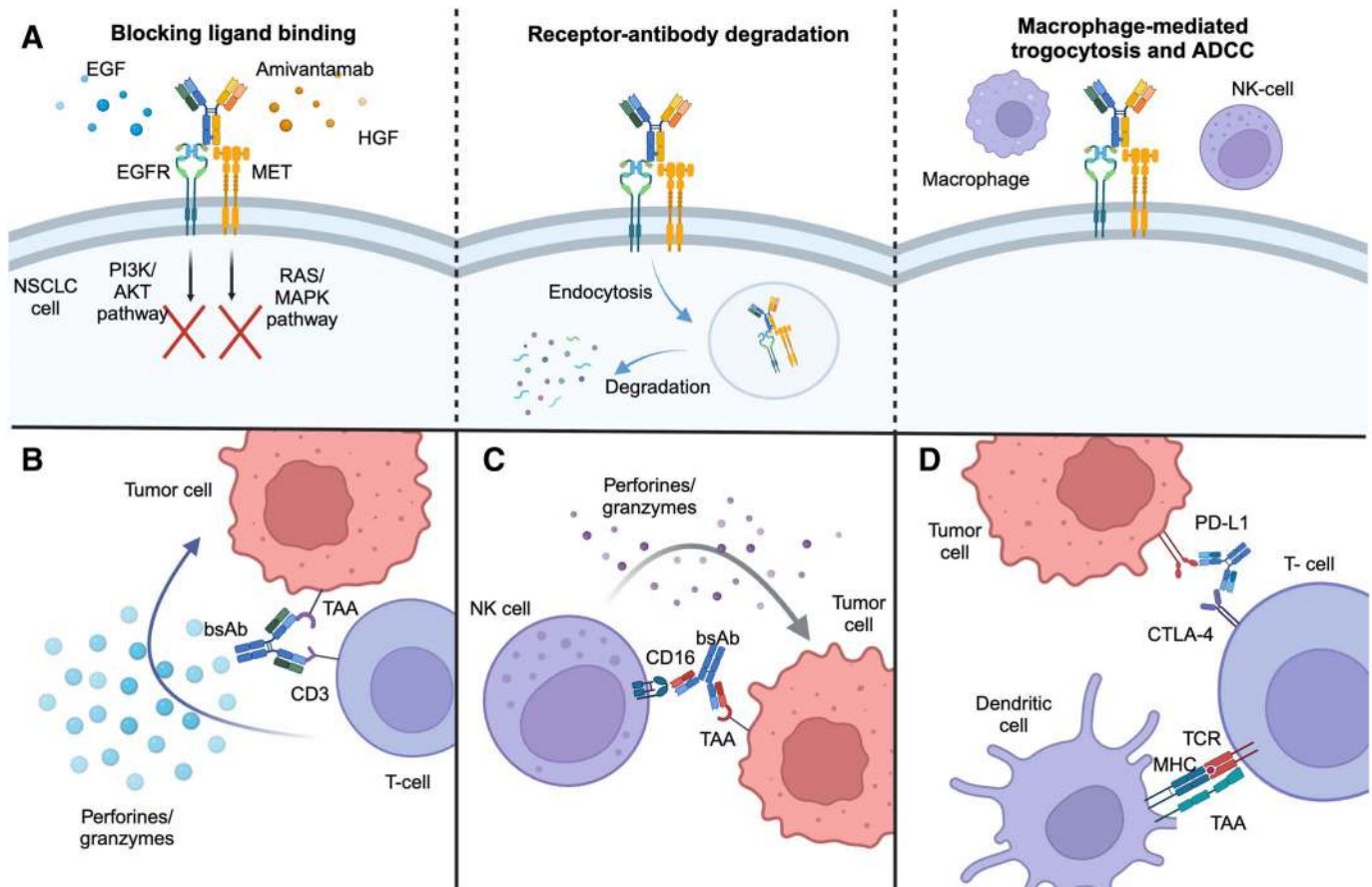


FIG 2. Mechanisms of action of bsAbs. (A) Amivantamab blocks ligand binding to EGFR and MET and promotes receptor-antibody degradation by endocytosis. Also, it induces macrophages-mediated trogocytosis and ADCC by NK cells. (B) TCE bsAbs recruit T cells by CD3 binding to attack tumor cells. (C) NK-cell engagers bsAbs bind CD16 on NK cells, leading to tumor cell killing using perforins and granzymes. (D) Dual checkpoint inhibition: bsAbs targeting PD-L1 and CTLA-4 enhance T-cell activation, while TAA binding promotes dendritic cell-mediated antigen presentation. ADCC, antibody-dependent cellular cytotoxicity; BsAb, bispecific antibody; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; MAPK, mitogen-activated protein kinase; MET, mesenchymal-epithelial transition factor; MHC, major histocompatibility complex; NK, natural killer; NSCLC, non-small cell lung cancer; PI3K, phosphatidylinositol-3 kinase; RAS, rat sarcoma virus; TAA, tumor-associated antigen; TCE, T-cell engager; TCR, T-cell receptor.

encouraging activity in HER2-positive solid tumors.⁴⁷ These and other bispecific ADCs are already broadening the therapeutic potential of bsAbs, especially in patients with solid tumors.⁴²

bsAbs FOR CANCER IMMUNOTHERAPY

Several bsAbs in clinical development are involved in cancer immunotherapy: These agents are classified according to their mechanism of action, namely if they exert their function enhancing natural immunity by a T-cell-driven engagement, recruiting immunity innate cells, or blocking immune checkpoint inhibitors' (CPIs) signals.

T-Cell Engagers

Bispecific TCEs connect native CD4⁺ and CD8⁺ T cells with tumor cells by simultaneous binding to the CD3 ϵ subunit of the T-cell receptor (TCR) complex and a specific TAA. This specific interaction determines T-cell activation, release of

granzymes and perforins, and tumor cell lysis (Fig 2).^{48,49} Currently, TCEs have shown promising results in hematologic malignancies and are under evaluation in clinical trials for solid tumors.

On the basis of the results of the phase III TOWER trial, blinatumomab, a bispecific TCE that simultaneously binds to CD19 on B cells and CD3 on T cells, was the first-in-class bsAb to gain approval by FDA in 2014 for the treatment of adults with Philadelphia chromosome-negative (Ph-) R/R B-ALL.⁵⁰ In the TOWER trial, 405 patients were randomly assigned to receive blinatumomab (271 patients) or chemotherapy (134 patients), and blinatumomab demonstrated a significant advantage in terms of OS compared with standard chemotherapy (median OS, 7.7 months v 4.0; HR, 0.71 [95% CI, 0.55 to 0.93]; $P = .01$). Subsequently, the ALCANTARA and MT103-205 trials evaluated blinatumomab in adult and pediatric patients, respectively, with Philadelphia chromosome-positive (Ph+) B-ALL, showing a complete remission rate (CRR) of 31% in adult patients (95%

CI, 18.2% to 46.6%) and 39% in pediatric patients (95% CI, 27% to 51%).^{51,52} Furthermore, the phase II BLAST trial results led to FDA approval of blinatumomab for patients with minimal residual disease (MRD)-positive B-ALL; of the 86 patients in first and second complete remission with MRD $\geq 0.1\%$, conversion to MRD $< 0.01\%$ was achieved after 1 cycle of blinatumomab by 85.2% (95% CI, 73.8% to 93.0%) and 72.0% (95% CI, 50.6% to 87.9%), respectively; and the estimated median hematologic relapse-free survivals were 35.2 months (95% CI, 0.4 to 53.5) and 12.3 months (95% CI, 0.7 to 42.3), respectively.⁵³ Nevertheless, limitations are present: the need for a continuous administration because of its short half-life, the risk of cytokine release syndrome (CRS) or immune-effector cell-associated neurotoxicity, which require careful handling. Innovative CD3 $\times$ CD19 TCEs are currently under development to overcome these clinical challenges.

Among anti-CD20 TCE bsAbs, mosunetuzumab demonstrated promising results in the phase II GO29781 study, which evaluated its efficacy in patients with relapsed/refractory follicular non-Hodgkin lymphoma (NHL).⁵⁴ The observed CRR of 60% (95% CI, 49.1 to 70.2) led to the FDA-granted accelerated approval for adult patients who received two or more lines of systemic therapy. Moreover, epcoritamab, a similar anti-CD3 $\times$ CD20 bispecific TCE, has also been granted FDA accelerated approval for the same population, on the basis of the results of the EPCORE NHL-1 study, which demonstrated a CRR of 62.5% in the pivotal cohort for patients with relapsed or refractory follicular NHL.^{55,56}

Glofitamab is a heterodimeric 2 + 1 anti-CD3 $\times$ CD20 TCE, whose configuration enables a bivalent binding to CD20 with an enhanced T-cell engagement. In 2023, FDA and EMA granted approval to glofitamab for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), on the basis of the phase I/II NP30179 trial, which evaluated glofitamab in 61 patients with relapsed or refractory DLBCL.^{57,58} In this trial, 39% (95% CI, 32 to 48) of the patients achieved a complete response with a median follow-up of 12.6 months.

In refractory or relapsed multiple myeloma (R/R MM), bsAbs targeting CD3 and plasma cell antigens such as CD38, B-cell maturation antigen (BCMA, which is expressed on myeloma cells), G-protein-coupled receptor class C group 5 member D (GPCR5D), and Fc receptor-homolog 5 (FcRH5) have shown encouraging therapeutic potential. Teclistamab, an anti-CD3 $\times$ BCMA bispecific TCE, was the first bsAb to receive FDA approval for R/R MM in patients after four or more line of therapy,⁵⁹ according to the findings of the phase I/II MajesTEC-1 trial, showing an ORR of 63.0% and a CRR of 39.4%.⁶⁰ However, the study also showed that 72.1% of patients experienced an any-grade CRS, leading to the restriction of this agent under a Risk Evaluation and Mitigation Strategy. Furthermore, erlanatamab, a BCMA-targeted bispecific TCE, has recently gained FDA approval for the treatment of R/R MM after the phase II MagnetisMM trial showed a

benefit in terms of efficacy of erlanatamab with 61.0% (95% CI, 51.8 to 69.6) of patients having a confirmed OR.^{61,62}

Talquetamab is a first-in-class TCE targeting GPRC5D, a cell surface protein that is highly expressed on plasma cells, including malignant B cells in MM. The results of the phase I/II MonumentAL-1 study showed a 70% ORR (95% CI, 51 to 85) in those patients with a once per week dosing schedule and a 64% ORR in those who received a once every 2 weeks schedule.⁶³ According to these results, the FDA approved talquetamab in 2023 for the treatment of R/R MM.⁶⁴

The development of TCEs for solid tumors still faces numerous challenges that are not typically countered in hematologic cancers. In particular, the heterogeneity in antigen expression makes it difficult to identify an appropriate target. Additionally, the expression of shared targets in healthy tissues increases the risk of on-target off-tumor adverse events. To date, only two TCEs have been approved for the treatment of solid tumors.

Tebentafusp is classified as part of immune-mobilizing monoclonal TCRs against cancer (ImmTACs), a subtype of TCEs. It consists of engineered TCRs that specifically recognize a peptide-HLA complex (pHLA) on the surface of cancer cells. These TCRs are typically fused to a single-chain variable fragment (scFv) that targets CD3 on T cells. Tebentafusp gained FDA approval in January 2022 for the treatment of unresectable or metastatic uveal melanoma in patients who are HLA-A*02:01 positive.⁶⁵ This indication was based on the phase III IMCgp100-202 study, which showed an OS benefit in patients who received tebentafusp compared with those who received investigator's choice treatment (pembrolizumab, ipilimumab, or dacarbazine; median OS, 21.6 months v 16.9 months HR, 0.68 [95% CI, 0.54 to 0.87]).⁶⁶

Tarlatamab is an anti-CD3 $\times$ DLL3 bispecific TCE designed to redirect T cells to target DLL3, a protein commonly expressed on small cell lung cancer (SCLC) cells. In May 2024, tarlatamab received FDA accelerated approval for the treatment of R/R extensive-stage SCLC in patients whose disease had progressed after platinum-based chemotherapy.⁶¹ This approval was based on the results of the phase II DeLLphi-301 study, in which tarlatamab demonstrated an ORR of 40% (97.5% CI, 29 to 52) and a mOS of 14.3 months in patients with heavily pretreated SCLC.⁶⁷ The most relevant TRAEs were CRS (51%), mostly grade 1-2 during cycle 1; decreased appetite; and pyrexia. Tarlatamab in SCLC is currently being explored against lurbinectedin or topotecan after failure to platinum-based first-line therapy (ClinicalTrials.gov identifier: [NCT05740566](https://clinicaltrials.gov/ct2/show/study?term=NCT05740566)), after radical chemoradiotherapy in limited-stage disease (ClinicalTrials.gov identifier: [NCT06117774](https://clinicaltrials.gov/ct2/show/study?term=NCT06117774)), as well as in combination with carboplatin, etoposide, and atezolizumab in transformed SCLC after failure to EGFR TKI therapy (ClinicalTrials.gov identifier: [NCT06830694](https://clinicaltrials.gov/ct2/show/study?term=NCT06830694)). Tarlatamab is also being tested in patients with extrapulmonary small cell carcinoma or other

neuroendocrine tumors (TAURUS, [NCT06816394](#)). A subcutaneous formulation of tarlatamab is being developed (ClinicalTrials.gov identifier: [NCT06598306](#)).

The phase I trial (NCT04429087) evaluated BI 764532 (Obixtamig), a bispecific DLL3/CD3 IgG-like TCE in patients with DLL3-positive tumors including SCLC, extrapulmonary neuroendocrine carcinomas and large cell neuroendocrine carcinoma of the lung. Overall, a RR of 23% and median DoR of 8.5 months (6.2–not reached [NR]) were achieved.^{68,69}

Innate-Cell Engagers

Beyond TCEs, significant efforts are underway to develop next-generation innate-cell engagers (ICEs), including NK-cell engagers and bsAbs that recruit myeloid-derived cells—such as neutrophils, macrophages, and monocytes—to promote tumor phagocytosis and enhance antitumor immunity.⁷⁰ Given that tumors often evade T-cell-driven destruction, promoting a downregulation of major histocompatibility complex I expression, innate immune cells represent a promising candidate to overcome this resistance mechanism.

The first molecules developed to activate NK cells against cancer were designed to target CD16A, an activating Fc receptor crucial for NK-cell-mediated ADCC, in combination with a tumor antigen.⁷¹ Currently, several trials are assessing bispecific ICEs that simultaneously target CD16A and various tumor antigens.

Acimtamig (AFM13), an anti-CD30×CD16A bsAb, is the most clinically advanced NK-cell engager. It has been evaluated in patients with R/R Hodgkin lymphoma (HL), CD30-positive T-cell lymphoma, and transformed mycosis fungoides. In a recent phase II trial, AFM13 was promising in a population of 108 patients with R/R peripheral T-cell lymphoma (PTCL), reporting an ORR of 32.4% (95% CI, 23.7 to 42.1) and CR rate of 10.2% (95% CI, 5.2 to 17.5).⁷²

Trispecific NK-cell engagers (TKEs) are a distinct class of antibodies that simultaneously target CD16A, a tumor antigen, and an IL-15 domain. These molecules are designed to enhance NK-cell-mediated tumor killing while also promoting NK-cell expansion through cytokine signaling. Preclinical studies have demonstrated their effectiveness in mouse models of ovarian cancer and AML. To date, the GTB-3550 TKE has demonstrated clinical activity in a phase I/II trial involving patients with high-risk myelodysplastic syndrome (MDS) and R/R AML.⁷³

Other activating receptors, such as NKG2D, Nkp46, and Nkp30, are also being explored as potential targets, beyond CD16A. Notably, the Nkp46-ANKET molecule targeting CD123 (SAR443579) is currently being tested in a phase I/II trial for patients with R/R AML, B-cell ALL, and high-risk MDS. The dose-escalation phase of the study showed no dose-limiting toxicities.⁷⁴ When compared with the CD123×CD3 dual affinity

retargeting (DART) agent in a phase II trial, SAR443579 demonstrated a favorable safety.⁷⁵ The molecule has also received fast-track designation from the FDA.

Furthermore, myeloid cells such as monocytes, macrophages, dendritic cells, and granulocytes are prevalent in the tumor microenvironment (TME) and can either promote or inhibit tumor progression. To leverage their potential for antitumor activity, a new class of molecules has been developed to stimulate myeloid cells by specifically engaging activating Fc receptors, targeting the immunomodulatory protein CD40, or delivering immunostimulatory agents. Although myeloid-cell engagers targeting Fc receptors for IgG(FcγRs) showed promising results in preclinical studies, their development was halted because of a lack of efficacy observed in clinical trials.

Alternatively, activating CD40 signaling has been considered an encouraging approach to overcome TME immunosuppression. In this regard, ABBV-428, a novel tumor-targeting immunomodulator, was designed to bind the mesothelin antigen and activate CD40 within the TME, aiming for localized immune activation without systemic effects. However, minimal activity was observed in a small cohort of patients with advanced mesothelioma or ovarian cancer.⁷⁶

Dual Checkpoint Inhibitors

Dual CPI-blocking bsAbs simultaneously target immune checkpoint receptors by binding 1 receptor (eg, PD-1, CTLA-4, LAG-3, or TIGIT) on the surface of a T cell with one arm, while the other arm engages a second immune checkpoint receptor. This second receptor can be located on the same T cell, tumor cell, or antigen-presenting cell.⁷⁷

Extending the use of bsAbs in the context of CPI agents could offer a promising strategy to enhance both safety and efficacy outcomes. Of note, selective targeting of TAAs and checkpoint proteins could be effective in minimizing auto-immune adverse events. Additionally, the simultaneous binding of two checkpoint proteins has the potential to improve efficacy, boost immune responses, and overcome resistance mechanisms. One of the key advantages of this class of drugs is their selective action on tumor-infiltrating lymphocytes (TILs). In a recent study, various CPIs were found to be highly coexpressed on TILs, including PD-1, CTLA-4, LAG-3, TIM-3, and TIGIT.

The anti-PD-1×CTLA-4 cadonilimab exhibits stronger binding in a context with high PD-1 and CTLA-4 expression, such as the TME, while demonstrating weaker binding in low PD-1 settings, such as normal peripheral tissues.⁷⁸ Cadonilimab has been evaluated in several clinical trials leading to China's National Medical Products Administration (NMPA) approval, in June 2022, for patients with relapsed or metastatic cervical cancer who progressed on or after platinum-based chemotherapy. This achievement was based on the results of a phase

II study that showed an ORR of 33% and a mOS of 17.5 months in this population.⁷⁹ More recently, in the phase III COMPASSION-16 trial, cadonilimab plus platinum-based chemotherapy with or without bevacizumab was tested as first-line treatment of persistent, recurrent or metastatic cervical cancer.⁸⁰ This trial demonstrated a significant improvement in mPFS (12.7 months v 8.1 months, HR, 0.62 [95% CI, 0.49 to 0.80]) and mOS (not reached v 22.8 months HR, 0.64 [95% CI, 0.48 to 0.86]). Moreover, the COMPASSION-03 phase Ib/II trial evaluated cadonilimab in advanced solid tumors, demonstrating activity in the esophageal squamous cell carcinoma cohort (ORR, 18.2% [95% CI, 5.2 to 40.3]) and hepatocellular carcinoma (HCC) cohort (ORR, 16.7% [95% CI, 4.7 to 37.4]).⁸¹ In this study, the most frequent adverse events were hematologic with 28% of grade 3–4 related adverse events and five deaths (one due to myocardial infarction, while the cause remained unknown for the other four). Cadonilimab in combination with anlotinib has been evaluated in patients with advanced, treatment-naïve NSCLC (ClinicalTrials.gov identifier: [NCT0464330](#)). The ORR was 53.6%, while median PFS was 8.8 months (95% CI, 6.9 to NR).⁸² A phase III clinical trial of cadonilimab in combination with chemotherapy has also improved OS in patients with HER2-negative advanced gastric or gastroesophageal junction carcinoma.⁸³

Other anti-PD-1xCTLA-4 bsAbs include erfonrilimab and volrustomig. Erfonrilimab (KNO46) was evaluated in 27 treatment-naïve patients with metastatic triple-negative breast cancer (TNBC) in combination with paclitaxel, achieving an ORR of 44%. Additionally, a phase II trial of erfonrilimab in combination with platinum-based chemotherapy in patients with NSCLC reported an ORR of 46% and a median OS of 26.6 months (95% CI, 16.92 to NR).^{84,85} Volrustomig was analyzed in NSCLC in 105 patients with advanced-stage, nonsquamous histology, EGFR and ALK wild-type, and no prior systemic therapy.⁸⁶ In the single-arm cohort, patients received volrustomig at a dose of 750 mg intravenously once every 3 weeks, while in the randomized cohort, patients received either volrustomig 1500 mg or pembrolizumab 200 mg once every 3 weeks. Both cohorts included carboplatin-pemetrexed backbone for four cycles, followed by pemetrexed maintenance. In the randomized cohort, the median PFS of the volrustomig arm was 15.1 months (5.5-not estimable [NE]), compared with 8.9 months (4.2–15.0) in the pembrolizumab arm. The median OS of the volrustomig arm was NR (16.4–NE) versus 16.5 months in the pembrolizumab arm. Greater rates of grade 3 treatment-related adverse events (70%) led to further exploring the 750-mg dose level. Furthermore, Volrustomig demonstrated activity as first-line therapy in patients with advanced-stage ICP-naïve renal cell carcinoma, with an ORR of 46.9%.⁸⁷

The combination of PD-(L)1 blockade with LAG-3 or TIM-3 inhibition is also being investigated as a strategy for dual inactivation. In this context, the anti-PD-1xLAG-3 tebotelimab demonstrated activity as monotherapy in a phase I

trial including patients with solid tumors or hematologic malignancies.⁸⁸ Of the 172 patients evaluable for response, 59 (34%) obtained a tumor response; however, 68% (184/269) experienced treatment-related adverse events and 22% were grade 3 or more. Noteworthy, a phase I trial confirmed the safety and tolerability of FS118, a bsAb targeting LAG-3 and PD-L1, in patients with advanced cancers resistant to anti-PD-(L)1 therapy.⁸⁹ The trial demonstrated sustained pharmacodynamic activity and reported an overall disease control rate (DCR) of 46.5%, particularly in patients with acquired resistance to anti-PD-(L)1 agents. These findings support further investigation of FS118 in refractory cancers.

A number of compounds targeting TIGIT and PD-(L)1 are under development. Rilvegostomig (AZD2936) is a monovalent bsAb designed to prevent tumor ligands from attaching to TIGIT, revitalizing CD8⁺ cells and activating NK cells more effectively than anti-PD1 or anti-TIGIT separately. Furthermore, the Fc domain is triple mutated, minimizing immune effector function.^{90,91}

The phase I/II ARTEMIDE-01 trial (ClinicalTrials.gov identifier: [NCT04995523](#)) included 83 patients with advanced NSCLC with confirmed progression to ICI and PD-L1 $\geq 1\%$. The RP2D was 750 mg once every 3 weeks. TRAEs occurring in $>5\%$ of patients included fatigue, pruritus, lipase increase, pyrexia, and rash. Concerning efficacy, ORR was 5.6% and median PFS 3.8 months. Rilvegostomig has also shown encouraging activity in ICI-naïve patients, achieving an ORR of 29% and median PFS of 6 months, improving to 61.9% and 10.2 months, respectively, in patients with PD-L1 $\geq 50\%$.^{90,92}

Rilvegostomig is currently being explored in multiple phase III trials as frontline therapy: in advanced squamous NSCLC (ARTEMIDE-Lung02, [NCT06692738](#)), in nonsquamous NSCLC (ARTEMIDE-Lung03, [NCT06627647](#)), or in combination with datopotamab-deruxtecan in nonsquamous NSCLC (TROPION-Lung10, [NCT06357533](#)).

Furthermore, the development of anti-TGF β $\times$ PD-L1 bsAbs introduces an innovative strategy to simultaneously inhibit multiple immunosuppressive pathways in the TME, enhancing the immune system's ability to combat cancer. Numerous compounds are under development into clinical trials, among these bintrafusp alfa (M7824) holds promise in enhancing an effective immune response. In a recent phase II trial, M7824 was tested in patients with recurrent or metastatic cervical cancer after platinum-based treatment failure. Among the 146 patients who received bintrafusp alfa monotherapy, the confirmed ORR was 21.9%. These results support the potential role of anti-TGF β $\times$ PD-L1 bsAbs in recurrent or metastatic cervical cancer.

bsAbs IN COMBINATION STRATEGIES

BsAbs have primarily been developed to overcome drug resistance and improve the efficacy of existing treatments, making their key validation in combination with

chemotherapy and biologic systemic therapies.⁹³ Therefore, the positive results from various trials evaluating the activity and efficacy of bsAbs have prompted further exploration of their effects in combination with other systemic treatments.

BsAbs could potentially overcome resistance mechanisms of current treatments, while combination therapies could produce synergistic effects and enhance their activity, by simultaneously inhibiting key pathways in tumor growth and immune evasion.⁹⁴ For example, given that T-cell energy could reduce the efficacy of TCEs, the combination with ICIs should theoretically improve the antineoplastic activity of TCEs.⁹⁵

TCEs and ICEs

TCEs and ICEs have been tested mainly in oncohematology trials. Glofitamab (anti-CD3×CD20 bsAb) is currently being evaluated in patients with R/R DLBCL in a phase III trial comparing its combination with gemcitabine and oxaliplatin with rituximab plus gemcitabine-oxaliplatin.^{96,97} The mOS was 25.5 versus 12.9 months, in favor of the glofitamab arm.⁹⁸

Blinatumomab is currently being evaluated in combination strategies in various phase II studies, mainly in patients with ALL. The GIMEMA trial evaluated in patients with Ph-positive ALL treated with a consolidation first-line treatment, the combination of blinatumomab and dasatinib (a BCR-ABL TKI), showing a 10-year OS of 94.5% (95% CI, 86 to 97.9).⁹⁹

Another phase II trial evaluated the activity of blinatumomab in association with ponatinib, a multi-TKI, in patients with newly diagnosed or R/R Ph-positive ALL or CML in lymphoid blast phase; among patients with newly diagnosed Ph-positive ALL, 33 of 38 evaluable patients (87%) achieved a complete molecular response. Among those with R/R Ph-positive ALL, 12 of 13 evaluable patients (92%) demonstrated an overall response, with 11 (79%) achieving a complete molecular response. In addition, five of six patients (83%) with CML in the lymphoid blast phase experienced an overall response, while two (33%) achieved a complete molecular response.¹⁰⁰ Blinatumomab has also been associated with chemotherapy in a phase II study including infants with lysine (K)-specific methyltransferase 2A (KMT2A)-rearranged ALL, showcasing a 2-year DFS of 81.6%, in a setting in which with current treatments, the 3-year event-free survival is below 40%.¹⁰¹

The anti-CD20×CD3 mosunetuzumab has been associated with the cyclophosphamide, doxorubicin, vincristine, and prednisone regimen in the first-line treatment of DLBCL, achieving an ORR of 95%.¹⁰² Furthermore, mosunetuzumab has been combined with polatuzumab vedotin, an anti-CD79B ADC, in patients with R/R DLBCL, demonstrating a promising 59.2% ORR.¹⁰³ Furthermore, the CD30×CD16a bispecific ICE AFM13 was tested in combination with pembrolizumab, in a

phase Ib trial; 30 patients with R/R classical HL were enrolled and an ORR of 83% was observed; also, 37% of those patients experienced a complete metabolic response.¹⁰⁴ Moreover, AFM13 demonstrated efficacy in combination with pre-activated and expanded (P + E) cord blood-derived NK cells in a phase I-II trial that included 42 patients with R/R HL; an ORR of 92.8% and CR of 66.7% were observed associated with an OS rate of 76% at a median follow-up (mFUP) of 14 months.¹⁰⁵ Teclistamab (anti-CD3×BCMA bsAb) and talquetamab (anti-CD3×GPRC5D bsAb) have been combined in a phase Ib/II trial for patients with R/R MM, showing that with the recommended phase II regimen, a response occurred in 80% of the patients, and across all dose levels, a response occurred in 78%.¹⁰⁶⁻¹⁰⁸

Dual Signaling Inhibitors

Combination therapies involving dual receptor inhibitors have been tested mainly in the setting of solid tumors. For years, EGFR TKIs have been the backbone of the first-line treatment of patients with NSCLC harboring common *EGFR* mutations (ie, exon 19 deletion or exon 21 L858R mutation) but eventually lead to resistance, driven by many mechanisms including MET pathway activation or secondary mutations in *EGFR*.^{18,109,110} Amivantamab has been designed to overcome these mechanisms of resistance by the concurrent inhibition of both pathways, inducing ADCC, ADCP, and Fc-independent EGFR and MET signal inhibition.¹¹¹ The MARIPOSA clinical trials showed that this agent is effective both in overcoming resistance in patients who progressed on osimertinib and in preventing resistance in untreated patients, leading to its approval in combination with lazertinib (an anti-EGFR TKI of third generation) in the first-line setting or with chemotherapy (with or without lazertinib) in patients who progressed on first-line TKI.¹¹²⁻¹¹⁴ In particular, the MARIPOSA trial patients were randomly assigned into three arms: amivantamab plus lazertinib, osimertinib alone, and lazertinib alone; the results demonstrated that the combination of amivantamab and lazertinib significantly improved PFS compared with osimertinib monotherapy (23.7 v 16.6 months; HR, 0.70 [95% CI, 0.58 to 0.85]). OS analysis is still ongoing; however, current data suggest a positive trend in favor of the combination. The 2-year OS rate was 79% (95% CI, 69 to 78) compared with 69% in the monotherapy arm (95% CI, 64 to 74). Conversely, the MARIPOSA 2 trial evaluated patients with locally advanced or metastatic NSCLC progressed on osimertinib, and a significant improvement in terms of PFS was observed in the amivantamab plus chemotherapy arm compared with the chemotherapy-alone arm (HR, 0.48 [95% CI, 0.36 to 0.64]); similarly, PFS was longer in the amivantamab, lazertinib, and chemotherapy arm compared with the chemotherapy-alone arm (HR, 0.44 [95% CI, 0.35 to 0.56]).^{113,115,116}

The efficacy of amivantamab plus chemotherapy has also been evaluated in patients with NSCLC harboring *EGFR* exon 20 insertion.¹⁴⁻¹⁶ The phase III PAPILLON trial randomized patients with advanced NSCLC with exon 20 *EGFR* insertion

mutation to receive chemotherapy with or without amivantamab as a first-line treatment, resulting in a statistically significant improvement in PFS.¹¹⁷ Even if mature OS data are still awaited, the promising results of the study led to the approval of first-line amivantamab-chemotherapy by the FDA in this setting, and both the National Comprehensive Cancer Network and ASCO guidelines recommend this regimen as a preferred first treatment option for these patients.^{113,118,119}

Various anti-HER2 bsAbs are being explored in combination regimens in phase II trials. Zanidatamab has proven to have a strong antitumor activity in association with chemotherapy in untreated patients with HER2-positive BC showcasing an ORR of 86.4%, DCR of 97%, and mDOR not reached after 7 months of follow-up.¹²⁰ Moreover, fulvestrant and palbociclib were tested in combination in 29 patients with metastatic triple-positive BC; the results showed an ORR was 34.5% (95% CI, 17.9 to 54.3).¹²¹ This biparatopic anti-HER2 bsAb is currently being tested in a phase III trial in patients with untreated, metastatic HER2-positive gastroesophageal adenocarcinoma.¹²² Anbenitamab is under evaluation in registrational studies as second-line treatment of HER2-positive G/GEJC and first-line treatment of HER2-positive mBC.¹²³⁻¹²⁵ These and other anti-HER2 bsAbs, such as zenocutuzumab, are broadening the therapeutic landscape of HER2-positive diseases.¹²⁶⁻¹²⁸

Immunomodulators and VEGF Inhibitors

Among bispecific immunomodulators, cadonilimab (anti-PD-1xCTLA-4 bsAb) is the only approved drug.¹²⁹ The NMPA in China approved cadonilimab in combination with chemotherapy in 2022 as first-line therapy for patients with cervical cancer, on the basis of the results of the phase III COMPASSION-16 trial, and in 2024 as first-line therapy for patients with HER2-negative G/GEJC, on the basis of the results of the phase III COMPASSION-15 trial.^{80,83,130} Both trials demonstrated to provide an approximately 35% relative decrease in the hazard of death regardless of PD-L1 expression.

Two phase II trials showed promising results for cadonilimab in combination with TKIs in previously untreated patients affected by advanced HCC and nononcogene addicted NSCLC, respectively. Of note, 59 patients with advanced HCC were enrolled in a phase Ib/II single-arm trial in which cadonilimab was tested in combination with lenvatinib (cohort A: 6 mg/kg cadonilimab once every 2 weeks plus lenvatinib; cohort B: 15 mg/kg cadonilimab once every 3 weeks plus lenvatinib) at a mFUP of 27.4 months; ORR in cohort A was 35.5% (95% CI, 19.2 to 54.6) and that in cohort B was 35.7% (95% CI, 18.6 to 55.9), and the median DoR was 13.6 months (95% CI, 4.14 to NE) and 13.67 months (95% CI, 3.52 to NE), respectively. The median OS was 27.1 months (95% CI, 15.7 to NE) for cohort A, while it was not reached for cohort B.¹³¹ Concerning advanced NSCLC, a phase Ib/II tested

cadonilimab in combination with anlotinib as first-line treatment in NSCLC without sensitizing mutations, 69 treatment-naïve patients received cadonilimab 15 mg/kg and 10 mg/kg combination and confirmed ORRs of 51% (25/49) and 60% (12/20) were reported.⁸² Provisional results are awaited for cadonilimab in combination therapy in second-line treatment of SCLC, and many other trials exploring cadonilimab applications in combination therapy for advanced cancers are still ongoing (Table 2).¹³²⁻¹³⁴ Considering the early-stage setting, cadonilimab has been tested also in addition to neoadjuvant 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel in patients with locally advanced G/GEJC, showing a pCR rate of 21.1%.¹³⁵

Erfonrilimab (anti-PD-L1xCTLA-4 bsAb) showed impressive results in phase II clinical trials in different settings. Positive results have been observed in addition to first-line chemotherapy in patients with NSCLC (nonsquamous NSCLC, 48 patients, 45.8% [95% CI, 31.4% to 60.8%]; squamous NSCLC, 33 patients, 57.6% [95% CI, 39.2% to 74.5%]), TNBC (25 patients, ORR, 44.0% [95% CI, 24.4% to 65.1%]), and HCC (55 patients, ORR, 45.5% [95% CI, 31.97 to 59.45]).^{31,85,136-138} Moreover, the phase III ENREACH-PDAC-01 trial is evaluating the addition of erfonrilimab to chemotherapy in untreated patients with advanced pancreatic cancer, and another trial is assessing its efficacy in the neoadjuvant treatment of stage IB-IIIB NSCLC in addition to axitinib.^{139,140} Ivonescimab (anti-PD-1xVEGF bsAb) achieved promising results, mainly in patients with advanced lung cancer.¹⁴¹⁻¹⁴³ The phase III HARMONi-2 trial compares ivonescimab with pembrolizumab in patients with treatment-naïve PD-L1+ advanced NSCLC. At data cutoff, the ivonescimab arm has shown superiority in terms of ORR (50% v 38.5%) and median PFS (11.14 v 5.82 months, HR, 0.51) compared with pembrolizumab. A tolerable safety profile was seen in patients with squamous histology.¹⁴⁴ Ivonescimab combined with chemotherapy has also demonstrated improvement in efficacy outcomes in patients with EGFR-mutated NSCLC after failure to third-generation tyrosine kinase inhibitors.¹⁴²

BNT327 (PM002) is a novel BsAb that targets PD-L1 and VEGF-A. In a phase II clinical trial, patients with EGFR-mutated advanced NSCLC and failure to EGFR-targeted therapy received BNT327 at a dose of 30 mg/kg Q3W in combination with platinum-based chemotherapy, followed by maintenance therapy. A total of 64 patients were included. The ORR was 60.9% (95% CI, 47.9 to 72.9) and time to response (TTR) was 2.9 months (95% CI, 1.5 to 4.1). Interestingly, results were enriched in the PD-L1 high population: ORR 92.3% and TTR 1.6 months.¹⁴⁵

A plethora of other bispecific immunomodulators is being tested for several types of advanced and localized cancers.¹⁴⁶⁻¹⁵² Combination strategies are essential to successfully exploit the full potential of bsAb into currently existing cancer treatment algorithms, and further clinical trials are required.

TABLE 2. Ongoing Trials Assessing Bispecific Antibodies

Trials	Target	Agent	Setting	Phase	Current Status
Dual receptor inhibition					
NCT06079983	HER2xHER2	JSKN003 (ADC)	Previously treated HER2-low mBC	III	Not yet recruiting
NCT06561607	HER2xHER2	TQB2102 (ADC)	ChT-naïve HER2-low hormone receptor-positive mBC	III	Not yet recruiting
NCT06118333	EGFRxHER3	Izalontamab brengitecan (BL-B01D1; ADC)	Previously treated nasopharyngeal carcinoma	III	Recruiting
Immunotherapy					
LINKER-MM1 (NCT03761108)	CD3xBCMA	Linvoseltamab (REGN5458)	R/R MM	I/II	Recruiting
MajesTEC-9 (NCT05572515)	CD3xBCMA	Teclistamab	R/R MM	III	Recruiting
DeLLphi-306 (NCT06117774)	CD3xDLL3	Tarlatamab (AMG757)	Limited stage SCLC	III	Recruiting
NCT03888105	CD3xCD20	Odronextamab	Previously treated B-cell NHL	II	Recruiting
GLOBRYTE (NCT06084936)	CD3xCD20	Glofitamab	R/R mantle cell lymphoma	III	Recruiting
TEBE-AM (NCT05549297)	CD3xgp100	Tebentafusp	Previously treated HLA-A*02:01-positive advanced melanoma	III	Recruiting
NCT06337318	CD3xCD20	Mosunetuzumab	Low tumor burden FL	III	Recruiting
NCT05149326	PD-L1xCTLA-4	Erfonrilimab (KN046)	Advanced PDAC	III	Active, not recruiting
NCT04165993	PD-L1xCTLA-4	Erfonrilimab (KN046)	mBC	II	Active, not recruiting
NCT05420220	PD-L1xCTLA-4	Erfonrilimab (KN046)	Advanced NSCLC	II	Recruiting
NCT05086315	CD123xNKp46xCD16	SAR443579	R/R AML, B-ALL, HR-MDS or BPDCN	I/II	Recruiting
NCT04417660	PD-L1xTGFβ	Bintrafusp alfa (M7824)	Thymoma and thymic carcinoma	II	Recruiting
Combinations					
CHRYSLIS-2 (NCT04077463)	EGFRxMET	Amivantamab + lazertinib	ChT-naïve EGFR ex19 deletion or L858RC NSCLC after progression on osimertinib	I	Active, not recruiting
HERIZON-GEA-01 (NCT05152147)	HER2xHER2	Zanidatamab + ChT ± tislelizumab	1L HER2+ GEA	III	Recruiting
JZP598-302 (NCT06282575)	HER2xHER2	Zanidatamab + gemcitabine-cisplatin ± ICI	1L HER2+ BTC	III	Recruiting
NCT05838066	HER2xHER2	Anbenitamab + HB1801	1L HER2+ mBC	III	Not yet recruiting
DESTINY-Gastric03 (NCT04379596)	PD-1xCTLA-4	Volrustomig + T-DXd + fluoropyrimidine	HER2+ and HER2-low G/GEJC	Ib/II	Recruiting
eVOLVE-Lung02 (NCT05984277)	PD-1xCTLA-4	Volrustomig + ChT	1L mNSCLC with PD-L1 TC <50%	III	Recruiting
COMPANION-002 (NCT05506943)	DLL4xVEGF	CTX-009 + paclitaxel	2L mBTC	III	Active, not recruiting
NCT06548412	DLL4xVEGF	CTX-009 + gemcitabine-cisplatin-durvalumab	1L mBTC	I/II	Not yet recruiting
NCT05125016	PSMAxCD3	REGN4336 ± cemiplimab	mCRPC	I/II	Recruiting

(continued on following page)

TABLE 2. Ongoing Trials Assessing Bispecific Antibodies (continued)

Trials	Target	Agent	Setting	Phase	Current Status
NCT05901584	PD-1xCTLA-4	Cadonilimab + ChT	2L SCLC	II	Recruiting
NCT05149326	PD-L1xCTLA-4	Erfonrilmab + gemcitabine-nab-paclitaxel	1L PDAC	III	Active, not recruiting
NCT06767527	PD-1xVEGF	Ivonescimab + nab-paclitaxel	1L TNBC	III	Not yet recruiting
NCT06591520	PD-1xVEGF	Ivonescimab + gemcitabine-cisplatin	1L BTC	III	Not yet recruiting
ARTEMIDE-Biliary01 (NCT06109779)	PD-1xTIGIT	Rilvegostomig + ChT	Adjuvant therapy BTC	III	Recruiting
ARTEMIDE-Lung02 (NCT06692738)	PD-1xTIGIT	Rilvegostomig + ChT	1L sqNSCLC	III	Recruiting
MAHOGANY (NCT04082364)	PD-1xLAG3	Tebotelimab + margetuximab + ChT	1L HER2+ G/GEJC	III	Active, not recruiting
NCT04580498	PD-L1xTGFβ	Retlirafusp alfa + ChT	Neoadjuvant stage III unresectable NSCLC	II	Active, not recruiting
NCT04856787	PD-L1xTGFβ	Retlirafusp alfa + CAPOX-bevacizumab	1L mCRC	II/III	Unknown status

Abbreviations: 1L, first-line; 2L, second-line; ADC, antibody-drug conjugate; B-ALL, B-cell ALL; BCMA, B-cell maturation antigen; BPCDN, blastic plasmacytoid dendritic cell neoplasm; BTC, biliary tract cancer; CAPOX, capecitabine and oxaliplatin; ChT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte antigen 4; DLL3, Delta-like ligand 3; DLL4, Delta-like ligand 4; EGFR, epidermal growth factor receptor; ex, exon; FL, follicular lymphoma; GC, gastric cancer; G/GEJC, gastric or gastroesophageal junction cancer; GEA, Gastroesophageal adenocarcinoma; gp100, glycoprotein 100; HER2, human epidermal growth factor receptor 2; HER2-low, human epidermal growth factor receptor 2 low; HER3, human epidermal growth factor receptor 3; HLA, human leukocyte antigens; HR-MDS, high-risk myelodysplastic syndrome; ICI, immune checkpoint inhibitor; LAG3, lymphocyte activation gene 3; mBC, metastatic breast cancer; mBTC, metastatic biliary tract cancer; mCRC, metastatic colorectal cancer; mCRPC, metastatic castration-resistant prostate cancer; MET, mesenchymal-epithelial transition factor; MM, multiple myeloma; mNSCLC, metastatic non-small cell lung cancer; NK, natural killer; NKp46, natural killer cell protein 6; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; Ph, Philadelphia; PSMA, prostate-specific membrane antigen; R/R MM, refractory or relapsed multiple myeloma; sqNSCLC, squamous non-small cell lung cancer; SCLC, small cell lung cancer; TC, tumor cell score; T-DXd, trastuzumab deruxtecan; TGFβ, transforming growth factor beta; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; VEGF, vascular endothelial growth factor.

CONCLUSIONS

bsAbs are reshaping the pharmacopeia of solid tumors and hematologic malignancies, demonstrating to improve clinical outcomes in clinical trials. However, their application in solid tumors remains challenging: Overcoming this barrier requires innovative approaches to optimize bsAb design, delivery, and patient selection.

Future efforts should focus on identifying tumors that consistently express TAAs to enhance efficacy while minimizing

off-tumor toxicities. Bioinformatic and computational tools may aid in predicting individual HLA-restricted peptide antigens, enabling a more personalized approach to bsAb therapy. Beyond conventional bsAbs, emerging strategies such as bispecific antibody–drug conjugates, multispecific antibodies, and bispecific proteolysis–targeting chimeras may offer new opportunities for targeted cancer treatment. With continued innovation and precision–driven approaches, bsAbs are poised to play a transformative role in the future of oncology, providing more potentially effective and tailored treatment options for patients with hematologic and solid tumors.

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REFERENCES

- Goebeler M-E, Stuhler G, Bargou R: Bispecific and multispecific antibodies in oncology: Opportunities and challenges. *Nat Rev Clin Oncol* 21:539-560, 2024
- Brinkmann U, Kontermann RE: The making of bispecific antibodies. *MAbs* 9:182-212, 2017
- Antonarelli G, Giugliano F, Corti C, et al: Research and clinical landscape of bispecific antibodies for the treatment of solid malignancies. *Pharmaceuticals* 14:884, 2021
- Madsen AV, Pedersen LE, Kristensen P, et al: Design and engineering of bispecific antibodies: Insights and practical considerations. *Front Bioeng Biotechnol* 12:1352014, 2024

5. Klein C, Brinkmann U, Reichert JM, et al: The present and future of bispecific antibodies for cancer therapy. *Nat Rev Drug Discov* 23:301-319, 2024
6. Herrera M, Pretelli G, Desai J, et al: Bispecific antibodies: Advancing precision oncology. *Trends Cancer* 10:893-919, 2024
7. Oganessian V, Peng L, Bee JS, et al: Structural insights into the mechanism of action of a biparatopic anti-HER2 antibody. *J Biol Chem* 293:8439-8448, 2018
8. Bargou R, Leo E, Zugmaier G, et al: Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science* 321:974-977, 2008
9. FDA grants accelerated approval to zanidatamab-hrii for previously treated unresectable or metastatic HER2-positive biliary tract cancer. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zanidatamab-hrii-previously-treated-unresectable-or-metastatic-her2>
10. Köhler G, Milstein C: Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 256:495-497, 1975
11. Brinkmann U, Kontermann RE: Bispecific antibodies. *Science* 372:916-917, 2021
12. Labrijn AF, Janmaat ML, Reichert JM, et al: Bispecific antibodies: A mechanistic review of the pipeline. *Nat Rev Drug Discov* 18:585-608, 2019
13. Chon K, Larkins E, Chatterjee S, et al: FDA approval summary: Amivantamab for the treatment of patients with non-small cell lung cancer with EGFR exon 20 insertion mutations. *Clin Cancer Res* 29:3262-3266, 2023
14. Kumar A, Petri ET, Halmos B, et al: Structure and clinical relevance of the epidermal growth factor receptor in human cancer. *J Clin Oncol* 26:1742-1751, 2008
15. Robichaux JP, Elamin YY, Tan Z, et al: Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. *Nat Med* 24:638-646, 2018
16. Arcila ME, Nafa K, Chaff JE, et al: EGFR exon 20 insertion mutations in lung adenocarcinomas: Prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol Cancer Ther* 12:220-229, 2013
17. Yun J, Lee SH, Kim SY, et al: Antitumor activity of amivantamab (JNJ-61186372), an EGFR–MET bispecific antibody, in diverse models of *EGFR* exon 20 insertion–driven NSCLC. *Cancer Discov* 10:1194-1209, 2020
18. Vijayaraghavan S, Lipfert L, Chevalier K, et al: Amivantamab (JNJ-61186372), an Fc enhanced EGFR/cMet bispecific antibody, induces receptor downmodulation and antitumor activity by monocyte/macrophage trogocytosis. *Mol Cancer Ther* 19:2044-2056, 2020
19. Moores SL, Chiu ML, Bushey BS, et al: A novel bispecific antibody targeting EGFR and cMet is effective against EGFR inhibitor–resistant lung tumors. *Cancer Res* 76:3942-3953, 2016
20. Park K, Haura EB, Leigh NB, et al: Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: Initial results from the CHRYSALIS phase I study. *J Clin Oncol* 39:3391-3402, 2021
21. Zhu K, Yang X, Tai H, et al: HER2-targeted therapies in cancer: A systematic review. *Biomark Res* 12:16, 2024
22. Valenza C, Guidi L, Battaiotto E, et al: Targeting HER2 heterogeneity in breast and gastrointestinal cancers. *Trends Cancer* 10:113-123, 2024
23. Weisser NE, Sanches M, Escobar-Cabrera E, et al: An anti-HER2 biparatopic antibody that induces unique HER2 clustering and complement-dependent cytotoxicity. *Nat Commun* 14:1394, 2023
24. Meric-Bernstam F, Beeram M, Hamilton E, et al: Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: A phase 1, dose-escalation and expansion study. *Lancet Oncol* 23:1558-1570, 2022
25. Harding JJ, Fan J, Oh DY, et al: Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): A multicentre, single-arm, phase 2b study. *Lancet Oncol* 24:772-782, 2023
26. Pant S, Fan J, Oh DY, et al: Zanidatamab in previously-treated HER2-positive (HER2+) biliary tract cancer (BTC): Overall survival (OS) and longer follow-up from the phase 2b HERIZON-BTC-01 study. *J Clin Oncol* 42, 2024 (suppl 16; abstr 4091)
27. Benson AB, D'Angelica MI, Abrams T, et al: NCCN Guidelines® Insights: Biliary tract cancers, version 2.2023. *J Natl Compr Cancer Netw* 21:694-704, 2023
28. Vogel A, Ducreux M; ESMO Guidelines Committee: ESMO clinical practice guideline interim update on the management of biliary tract cancer. *ESMO Open* 10:104003, 2025
29. Mullard A: FDA approves first biparatopic antibody therapy. *Nat Rev Drug Discov* 24:7, 2025
30. Crescioli S, Kaplon H, Wang L, et al: Antibodies to watch in 2025. *MABS* 17:2443538, 2025
31. Xu J, Ying J, Liu R, et al: KN026 (anti-HER2 bispecific antibody) in patients with previously treated, advanced HER2-expressing gastric or gastroesophageal junction cancer. *Eur J Cancer* 178:1-12, 2023
32. Zhang J, Ji D, Cai L, et al: First-in-human HER2-targeted bispecific antibody KN026 for the treatment of patients with HER2-positive metastatic breast cancer: Results from a phase I study. *Clin Cancer Res* 28:618-628, 2022
33. Ji D, Zhang J, Shen W, et al: Preliminary safety, efficacy and pharmacokinetics (PK) results of KN026, a HER2 bispecific antibody in patients (pts) with HER2-positive metastatic breast cancer. *J Clin Oncol* 38, 2020 (suppl 15; abstr 1041)
34. FDA grants accelerated approval to zenocutuzumab-zbco for non-small cell lung cancer and pancreatic adenocarcinoma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zenocutuzumab-zbco-non-small-cell-lung-cancer-and-pancreatic>
35. Schram AM, Odintsov I, Espinosa-Cotton M, et al: Zenocutuzumab, a HER2xHER3 bispecific antibody, is effective therapy for tumors driven by NRG1 gene rearrangements. *Cancer Discov* 12:1233-1247, 2022
36. Schram A, Macarulla T, Cleary J, et al: 1618P Durable efficacy of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced NRG1 fusion positive (NRG1+) pancreatic ductal adenocarcinoma (PDAC). *Ann Oncol* 34:S895-S896, 2023
37. Schram A, Goto K, Kim DW, et al: 1315MO Durable efficacy of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced NRG1 fusion-positive (NRG1+) non-small cell lung cancer (NSCLC). *Ann Oncol* 34:S756-S757, 2023
38. Schram AM, Goto K, Kim DW, et al: Efficacy and safety of zenocutuzumab, a HER2 x HER3 bispecific antibody, across advanced NRG1 fusion (NRG1+) cancers. *J Clin Oncol* 40, 2022 (suppl 16; abstr 105)
39. Schram AM, Drilon A, Mercade TM, et al: A phase II basket study of MCLA-128, a bispecific antibody targeting the HER3 pathway, in NRG1 fusion-positive advanced solid tumours. *Ann Oncol* 30:v317, 2019
40. Xiong A, Wang L, Chen J, et al: Ivonescimab versus pembrolizumab for PD-L1-positive non-small cell lung cancer (HARMONI-2): A randomised, double-blind, phase 3 study in China. *Lancet* 405:839-849, 2025
41. Gu Y, Wang Z, Wang Y: Bispecific antibody drug conjugates: Making 1+1>2. *Acta Pharm Sin B* 14:1965-1986, 2024
42. Zeng H, Ning W, Liu X, et al: Unlocking the potential of bispecific ADCs for targeted cancer therapy. *Front Med* 18:597-621, 2024
43. Rao Q, Chen Y, Gao B, et al: 759P JSKN003, a HER2-targeting antibody-drug conjugate, in patients with platinum-resistant ovarian cancer: A pooled analysis of two studies. *Ann Oncol* 35:S575-S576, 2024
44. Wang P, Guo K, Peng J, et al: JSKN003, A novel biparatopic anti-HER2 antibody-drug conjugate, exhibits potent antitumor efficacy. *Antibody Ther* 6, 2023 (suppl 1)
45. Ye D, Bian X, Yang T, et al: 19590 BL-B01D1, an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic urothelial carcinoma (UC). *Ann Oncol* 35:S1133, 2024
46. Ma Y, Huang Y, Zhao Y, et al: BL-B01D1, a first-in-class EGFR-HER3 bispecific antibody-drug conjugate, in patients with locally advanced or metastatic solid tumours: A first-in-human, open-label, multicentre, phase 1 study. *Lancet Oncol* 25:901-911, 2024
47. Oh D-Y, Bedard PL, Lee KW, et al: Phase 1 study of zanidatamab zovodotin (ZW49): Safety profile and recommended dose (RD) in patients with human epidermal growth factor 2 (HER2)-positive solid cancers. *Mol Cancer Ther* 22, 2023 (suppl 12; abstr B130)
48. Baeuerle PA, Reinhardt C: Bispecific T-cell engaging antibodies for cancer therapy. *Cancer Res* 69:4941-4944, 2009
49. Goebeler M-E, Bargou RC: T cell-engaging therapies—BiTEs and beyond. *Nat Rev Clin Oncol* 17:418-434, 2020
50. Kantarjian H, Stein A, Gökbüget N, et al: Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 376:836-847, 2017
51. Topp MS, Stelljes M, Zugmaier G, et al: Blinatumomab retreatment after relapse in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia. *Leukemia* 32:562-565, 2018
52. Martinelli G, Boissel N, Chevallier P, et al: Long-term follow-up of blinatumomab in patients with relapsed/refractory Philadelphia chromosome–positive B-cell precursor acute lymphoblastic leukaemia: Final analysis of ALCANTARA study. *Eur J Cancer* 146:107-114, 2021
53. Gökbüget N, Dombret H, Bonifacio M, et al: Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood* 131:1522-1531, 2018
54. Budde LE, Sehn LH, Matasar M, et al: Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: A single-arm, multicentre, phase 2 study. *Lancet Oncol* 23:1055-1065, 2022
55. FDA grants accelerated approval to epcoritamab-bysp for relapsed or refractory follicular lymphoma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-epcoritamab-bysp-relapsed-or-refractory-follicular-lymphoma>
56. Linton KM, Vitolo U, Jurczak W, et al: Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): A phase 2 cohort of a single-arm, multicentre study. *Lancet Haematol* 11:e593-e605, 2024
57. FDA grants accelerated approval to glofitamab-gxbm for selected relapsed or refractory large B-cell lymphomas. <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-glofitamab-gxbm-selected-relapsed-or-refractory-large-b-cell>

58. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al: Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med* 387:2220-2231, 2022
59. FDA approves teclistamab-cqyv for relapsed or refractory multiple myeloma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma>
60. Moreau P, Garfall AL, van de Donk NWCJ, et al: Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 387:495-505, 2022
61. FDA grants accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tarlatamab-dlle-extensive-stage-small-cell-lung-cancer>
62. Lesokhin AM, Tomasson MH, Arnulf B, et al: Elranatamab in relapsed or refractory multiple myeloma: Phase 2 MagnetisMM-3 trial results. *Nat Med* 29:2259-2267, 2023
63. Chari A, Minnema MC, Berdeja JG, et al: Talquetamab, a T-cell–redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med* 387:2232-2244, 2022
64. FDA grants accelerated approval to talquetamab-tgvs for relapsed or refractory multiple myeloma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-talquetamab-tgvs-relapsed-or-refractory-multiple-myeloma>
65. FDA approves tebentafusp-tebn for unresectable or metastatic uveal melanoma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tebentafusp-tebn-unresectable-or-metastatic-uveal-melanoma>
66. Hassel JC, Piperno-Neumann S, Rutkowski P, et al: Three-year overall survival with tebentafusp in metastatic uveal melanoma. *N Engl J Med* 389:2256-2266, 2023
67. Ahn M-J, Cho BC, Felip E, et al: Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med* 389:2063-2075, 2023
68. Wermke M, Felip E, Gambardella V, et al: Phase I trial of the DLL3/CD3 bispecific T-cell engager BI 764532 in DLL3-positive small-cell lung cancer and neuroendocrine carcinomas. *Future Oncol* 18:2639-2649, 2022
69. Wermke M, Gambardella V, Kuboki Y, et al: 670P Phase I trial of the delta-like ligand-3 (DLL3)/CD3 IgG-Like T cell engager BI 764532 in patients (pts) with DLL3-positive tumors: Updated data. *Ann Oncol* 35:S525-S526, 2024
70. Fenis A, Demaria O, Gauthier L, et al: New immune cell engagers for cancer immunotherapy. *Nat Rev Immunol* 24:471-486, 2024
71. Wu Z, Cheung NV: T cell engaging bispecific antibody (T-BsAb): From technology to therapeutics. *Pharmacol Ther* 182:161-175, 2018
72. Kim WS, Shortt J, Zinzani PL, et al: A phase II study of acimamig (AFM13) in patients with CD30-positive, relapsed, or refractory peripheral T-cell lymphomas. *Clin Cancer Res* 31:65-73, 2025
73. Warlick ED, Weisdorf DJ, Valleria DA, et al: GTB-3550 TriKE™ for the treatment of high-risk myelodysplastic syndromes (MDS) and refractory/relapsed acute myeloid leukemia (AML) safely drives natural killer (NK) cell proliferation at initial dose cohorts. *Blood* 136:7-8, 2020 (suppl 1)
74. Bajel A, Garcia S, Desai P, et al: First-in-Human study of the CD123 NK cell engager SAR443579 in relapsed or refractory acute myeloid leukemia, B-cell acute lymphoblastic leukemia or high-risk myelodysplasia: Updated safety, efficacy, pharmacokinetics and pharmacodynamics. *Blood* 142:3474, 2023 (suppl 1)
75. Uy GL, Godwin J, Rettig MP, et al: Preliminary results of a phase I study of flotetuzumab, a CD123 x CD3 bispecific Dart® protein, in patients with relapsed/refractory acute myeloid leukemia and myelodysplastic syndrome. *Blood* 130:637, 2017 (suppl 1)
76. Luke JJ, Barlesi F, Chung K, et al: Phase I study of ABBV-428, a mesothelin-CD40 bispecific, in patients with advanced solid tumors. *J Immunother Cancer* 9:e002015, 2021
77. Zhang T, Lin Y, Gao Q: Bispecific antibodies targeting immunomodulatory checkpoints for cancer therapy. *Cancer Biol Med* 20:181-195, 2023
78. Pang X, Huang Z, Zhong T, et al: Cadonilimab, a tetravalent PD-1/CTLA-4 bispecific antibody with trans-binding and enhanced target binding avidity. *Mabs* 15:2180794, 2023
79. Wang J, Lou H, Cai HB, et al: A study of AK104 (an anti-PD1 and anti-CTLA4 bispecific antibody) combined with standard therapy for the first-line treatment of persistent, recurrent, or metastatic cervical cancer (R/M CC). *J Clin Oncol* 40, 2022 (suppl 16; abstr 106)
80. Wu X, Sun Y, Yang H, et al: Cadonilimab plus platinum-based chemotherapy with or without bevacizumab as first-line treatment for persistent, recurrent, or metastatic cervical cancer (COMPASSION-16): A randomised, double-blind, placebo-controlled phase 3 trial in China. *Lancet* 404:1668-1676, 2024
81. Gao X, Xu N, Li Z, et al: Safety and antitumour activity of cadonilimab, an anti-PD-1/CTLA-4 bispecific antibody, for patients with advanced solid tumours (COMPASSION-03): A multicentre, open-label, phase 1b/2 trial. *Lancet Oncol* 24:1134-1146, 2023
82. Chen B, Yao W, Li X, et al: A phase Ib/II study of cadonilimab (PD-1/CTLA-4 bispecific antibody) plus anlotinib as first-line treatment in patients with advanced non-small cell lung cancer. *Br J Cancer* 130:450-456, 2024
83. Shen L, Zhang Y, Li Z, et al: First-line cadonilimab plus chemotherapy in HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma: A randomized, double-blind, phase 3 trial. *Nat Med* 10.1038/s41591-024-03450-4 [epub ahead of print on January 22, 2025]
84. Zhao Y, Chen G, Li X, et al: KN046, a bispecific antibody against PD-L1 and CTLA-4, plus chemotherapy as first-line treatment for metastatic NSCLC: A multicenter phase 2 trial. *Cell Rep Med* 5: 101470, 2024
85. Li Q, Liu J, Zhang Q, et al: The anti-PD-L1/CTLA-4 bispecific antibody KN046 in combination with nab-paclitaxel in first-line treatment of metastatic triple-negative breast cancer: A multicenter phase II trial. *Nat Commun* 15:1015, 2024
86. Ahn M-J, Kim SW, Costa EC, et al: LBA56 MEDI5752 or pembrolizumab (P) plus carboplatin/pemetrexed (CP) in treatment-naïve (1L) non-small cell lung cancer (NSCLC): A phase Ib/II trial. *Ann Oncol* 33:S1423, 2022
87. Voss MH, Garmezby B, Kim S, et al: 1883MO MEDI5752 (volrustomig), a novel PD-1/CTLA-4 bispecific antibody, in the first-line (1L) treatment of 65 patients (pts) with advanced clear cell renal cell carcinoma (aRCC). *Ann Oncol* 34:S1012, 2023
88. Luke JJ, Patel MR, Blumenschein GR, et al: The PD-1- and LAG-3-targeting bispecific molecule tebotelimab in solid tumors and hematologic cancers: A phase 1 trial. *Nat Med* 29:2814-2824, 2023
89. Yap TA, LoRusso PM, Wong DJ, et al: A phase 1 first-in-human study of FS118, a tetravalent bispecific antibody targeting LAG-3 and PD-L1 in patients with advanced cancer and PD-L1 resistance. *Clin Cancer Res* 29:888-898, 2023
90. Chariou P, Rothstein R, Miller C, et al: Dual blockage of PD-1 and TIGIT with rilvegostomig inhibits tumor growth in various in vitro/in vivo/ex vivo tumor models through effector CD8 activation and immune modulation. *J Immunother Cancer* 12:483, 2024
91. Lee K, Malhotra D, Pryts S, et al: Preclinical studies support clinical development of AZD2936, a monovalent bispecific humanized antibody targeting PD-1 and TIGIT. *J Immunother Cancer* 10: A489, 2022
92. Brandao M, Hiltermann J, Wauters E, et al: 1446P Preliminary efficacy and safety of rilvegostomig (AZD2936), a bispecific antibody targeting PD-1 and TIGIT, in checkpoint inhibitor (CPI)-pretreated advanced/metastatic non-smallcell lung cancer (NSCLC): ARTEMIDE-01. *Ann Oncol* 34:S822-S823, 2023
93. Sun Y, Yu X, Wang X, et al: Bispecific antibodies in cancer therapy: Target selection and regulatory requirements. *Acta Pharm Sin B* 13:3583-3597, 2023
94. Gu Y, Zhao Q: Clinical progresses and challenges of bispecific antibodies for the treatment of solid tumors. *Mol Diagn Ther* 28:669-702, 2024
95. Kobold S, Pantelyushin S, Rajat F, et al: Rationale for combining bispecific T cell activating antibodies with checkpoint blockade for cancer therapy. *Front Oncol* 8:285, 2018
96. Hertzberg M, Ku M, Catalani O, et al: A phase III trial evaluating glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). *J Clin Oncol* 39, 2021 (suppl 15; abstr TPS7575)
97. Shirley M: Glofitamab: First approval. *Drugs* 83:935-941, 2023
98. Abramson JS, Ku M, Hertzberg M, et al: Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): A global phase 3, randomised, open-label trial. *Lancet* 404:1940-1954, 2024
99. Foà R, Bassan R, Elia L, et al: Long-Term results of the dasatinib-blinatumomab protocol for adult philadelphia-positive ALL. *J Clin Oncol* 42:881-885, 2024
100. Jabbour E, Short NJ, Jain N, et al: Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: A US, single-centre, single-arm, phase 2 trial. *Lancet Haematol* 10:e24-e34, 2023
101. van der Sluis IM, de Lorenzo P, Kotecha RS, et al: Blinatumomab added to chemotherapy in infant lymphoblastic leukemia. *N Engl J Med* 388:1572-1581, 2023
102. Olszewski AJ, Phillips TJ, Hoffmann MS, et al: Mosunetuzumab in combination with CHOP in previously untreated DLBCL: Safety and efficacy results from a phase 2 study. *Blood Adv* 7: 6055-6065, 2023
103. Budde LE, Olszewski AJ, Assouline S, et al: Mosunetuzumab with polatuzumab vedotin in relapsed or refractory aggressive large B cell lymphoma: A phase 1b/2 trial. *Nat Med* 30:229-239, 2024
104. Bartlett NL, Herrera AF, Domingo-Domenech E, et al: A phase 1b study of AFM13 in combination with pembrolizumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood* 136: 2401-2409, 2020
105. Nieto Y, Banerjee P, Kaur I, et al: Innate cell engager (ICE®) AFM13 combined with preactivated and expanded (P+E) cord blood (CB)-Derived natural killer (NK) cells for patients with refractory CD30-positive lymphomas: Final results. *Blood* 142:774, 2023 (suppl 1)
106. Cohen YC, Magen H, Gatt M, et al: Talquetamab plus teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 392:138-149, 2025
107. Keam SJ: Talquetamab: First approval. *Drugs* 83:1439-1445, 2023
108. Kang C: Teclistamab: First approval. *Drugs* 82:1613-1619, 2022
109. Turke AB, Zejnullahu K, Wu YL, et al: Preexistence and clonal selection of MET amplification in EGFR mutant NSCLC. *Cancer Cell* 17:77-88, 2010
110. Engelman JA, Zejnullahu K, Mitsudomi T, et al: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 316:1039-1043, 2007

111. Cho BC, Simi A, Sabari J, et al: Amivantamab, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) bispecific antibody, designed to enable multiple mechanisms of action and broad clinical applications. *Clin Lung Cancer* 24:89-97, 2023
112. Hendriks LE, Kerr KM, Menis J, et al: Oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol* 34:339-357, 2023
113. Bazhenova L, Ismaila N, Abu Rous F, et al: Therapy for stage IV non-small cell lung cancer with driver alterations: ASCO living guideline, version 2024.2. *J Clin Oncol* 42:e72-e86, 2024
114. Neijssen J, Cardoso RMF, Chevalier KM, et al: Discovery of amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR and MET. *J Biol Chem* 296:100641, 2021
115. Passaro A, Wang J, Wang Y, et al: Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: Primary results from the phase III MARIPOSA-2 study. *Ann Oncol* 35:77-90, 2024
116. Cho BC, Lu S, Felip E, et al: Amivantamab plus lazertinib in previously untreated EGFR-mutated advanced NSCLC. *N Engl J Med* 391:1486-1498, 2024
117. Zhou C, Tang KJ, Cho BC, et al: Amivantamab plus chemotherapy in NSCLC with EGFR exon 20 insertions. *N Engl J Med* 389:2039-2051, 2023
118. Sabari JK, Girard N, Mansfield AS, et al: Plain language summary of PAPILLON: Amivantamab plus chemotherapy in untreated EGFR-mutated non-small-cell lung cancer. *Future Oncol* 20:2409-2421, 2024
119. Killock D: From CHRYSLIS to PAPILLON: The metamorphosis of amivantamab into frontline therapy for NSCLC. *Nat Rev Clin Oncol* 21:5, 2024
120. Lee K-S, Wang X, Im YH, et al: Zanidatamab (zani), a HER2-targeted bispecific antibody, in combination with docetaxel as first-line (1L) therapy for patients (pts) with advanced HER2-positive breast cancer: Preliminary results from a phase 1b/2 study. *J Clin Oncol* 40, 2022 (suppl 16; abstr 1031)
121. Escrivá-de-Romani S, Alba E, Rodríguez-Lescure A, et al: Treatment of HER2-positive (HER2+) hormone-receptor positive (HR+) metastatic breast cancer (mBC) with the novel combination of zanidatamab, palbociclib, and fulvestrant. *Cancer Res* 83:PD18-10, 2023
122. Tabernero J, Shen L, Elimova E, et al: HERIZON-GEA-01: Zanidatamab + chemo ± tislelizumab for 1L treatment of HER2-positive gastroesophageal adenocarcinoma. *Future Oncol* 18:3255-3266, 2022
123. Niquille DL, Fitzgerald KM, Gera N: Biparatopic antibodies: Therapeutic applications and prospects. *MAbs* 16:2310890, 2024
124. Ma J, Wang J, Xu T, et al: Efficacy and safety of KN026 and docetaxel for HER2-positive breast cancer: A phase II clinical trial. *Cancer Commun (Lond)* 10.1002/cac2.12662 [epub ahead of print on January 18, 2025]
125. Xu J, Zhao J, Chen Y, et al: 1425P Efficacy and safety of KN026 in combination with chemotherapy in patients (pts) with unresectable or metastatic HER2 positive gastric or gastroesophageal cancers (GC/GEJC) after first-line treatment with a trastuzumab-containing regimen. *Ann Oncol* 35:S889, 2024
126. Scheck MK, Hoffmeier RD, Lorenzen S: HER2-positive gastric cancer and antibody treatment: State of the art and future developments. *Cancers (Basel)* 16:1336, 2024
127. Fernandes CL, Silva DJ, Mesquita A: Novel HER-2 targeted therapies in breast cancer. *Cancers (Basel)* 16:87, 2023
128. Pistilli B, Wildiers H, Hamilton EP, et al: Clinical activity of MCLA-128 (zenocutuzumab) in combination with endocrine therapy (ET) in ER+/HER2-low, non-amplified metastatic breast cancer (MBC) patients (pts) with ET-resistant disease who had progressed on a CDK4/6 inhibitor (CDK4/6i). *J Clin Oncol* 38, 2020 (suppl 15; abstr 1037)
129. Keam SJ: Cadonilimab: First approval. *Drugs* 82:1333-1339, 2022
130. Romero D: Cadonilimab is effective and safe in recurrent cervical cancer. *Nat Rev Clin Oncol* 22:2, 2025
131. Qiao Q, Han C, Ye S, et al: The efficacy and safety of cadonilimab combined with lenvatinib for first-line treatment of advanced hepatocellular carcinoma (COMPASSION-08): A phase Ib/II single-arm clinical trial. *Front Immunol* 14:1238667, 2023
132. Wahafu W, Wei S, Qiao X, et al: Disitamab vedotin (DV, RC48-ADC) combined with cadonilimab (anti-PD-1/CTLA-4 bispecific antibody) in patients with locally advanced or metastatic urothelial carcinoma (la/mUC): An open-label, single-arm, phase II study. *J Clin Oncol* 42, 2024 (suppl 15; abstr e16572)
133. Chen Q-Y, Guo SS, Luo Y, et al: Efficacy and safety of cadonilimab in previously treated recurrent or metastatic nasopharyngeal carcinoma (COMPASSION-06): A phase II multicenter study. *Oral Oncol* 151:106723, 2024
134. Chen C, Chen M, Bai Y, et al: A single-arm multi-center phase II clinical trial of cadonilimab (anti-PD-1/CTLA-4) in combination with or without conventional second-line treatment for patients with extensive stage small cell lung cancer. *Technol Cancer Res Treat* 23:15330338241249690, 2024
135. Long B, Zhou H, Yu Z, et al: Neoadjuvant cadonilimab plus FLOT chemotherapy in locally advanced gastric/gastroesophageal junction adenocarcinoma: A multicenter, phase 2 study. *Med (N Y)* 6:100531, 2025
136. Xing B, Da X, Zhang Y, et al: A phase II study combining KN046 (an anti-PD-L1/CTLA-4 bispecific antibody) and lenvatinib in the treatment for advanced unresectable or metastatic hepatocellular carcinoma (HCC): Updated efficacy and safety results. *J Clin Oncol* 40, 2022 (suppl 16; abstr 4115)
137. Xing B: 938P KN046 (an anti-PD-L1/CTLA-4 bispecific antibody) in combination with lenvatinib in the treatment for advanced unresectable or metastatic hepatocellular carcinoma (HCC): Preliminary efficacy and safety results of a prospective phase II trial. *Ann Oncol* 32:S822, 2021
138. Yang Y, Fang W, Huang Y, et al: A phase 2, open-label, multicenter study to evaluate the efficacy, safety, and tolerability of KN046 in combination with chemotherapy in subjects with advanced non-small cell lung cancer. *J Clin Oncol* 39, 2021 (suppl 15; abstr 9060)
139. Geng Q, Jiao P: Anti-PD-L1-Based bispecific antibodies targeting Co-inhibitory and Co-stimulatory molecules for cancer immunotherapy. *Molecules* 29:454, 2024
140. Jin G, Guo S, Xu J, et al: A multicenter, randomized, double-blind phase III clinical study to evaluate the efficacy and safety of KN046 combined with nab-paclitaxel and gemcitabine versus placebo combined with nab-paclitaxel and gemcitabine in patients with advanced pancreatic cancer (ENREACH-PDAC-01). *J Clin Oncol* 40, 2022 (suppl 16; abstr TPS4189)
141. Chen Z, Wu L, Wang Q, et al: Brief report: Ivonescimab combined with etoposide plus carboplatin as first-line treatment for extensive-stage SCLC: Results of a phase 1b clinical trial. *J Thorac Oncol* 20:233-239, 2025
142. HARMONI-A Study Investigators, Fang W, Zhao Y, et al: Ivonescimab plus chemotherapy in non-small cell lung cancer with EGFR variant: A randomized clinical trial. *JAMA* 332:561-570, 2024
143. Zhao Y, Chen G, Chen J, et al: AK112, a novel PD-1/VEGF bispecific antibody, in combination with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): An open-label, multicenter, phase II trial. *EclinicalMedicine* 62:102106, 2023
144. Zhou C, Chen J, Wu L, et al: Phase 3 study of ivonescimab (AK112) vs. Pembrolizumab as first-line treatment for PD-L1-positive advanced NSCLC: HARMONI-2. *J Thorac Oncol* 19:S1, 2024
145. Wu Y-L, Wang Z, Cheng Y, et al: 1255MO A phase II safety and efficacy study of PM8002/BNT327 in combination with chemotherapy in patients with EGFR-mutated non-small cell lung cancer (NSCLC). *Ann Oncol* 35:S804, 2024
146. Qiu M-Z, Bai Y, Wang J, et al: Addition of SHR-1701 to first-line capecitabine and oxaliplatin (XELOX) plus bevacizumab for unresectable metastatic colorectal cancer. *Signal Transduct Target Ther* 9:349, 2024
147. Catenacci D, Koshiji Rosales M, Chung H, et al: P-138 Margetuximab combined with anti-PD-1 (retifanlimab) or anti-PD-1/LAG-3 (tebotelimab) +/- chemotherapy in first-line therapy of advanced/metastatic HER2+ gastroesophageal junction or gastric cancer. *Ann Oncol* 32:S146, 2021
148. Catenacci DV, Rosales M, Chung HC, et al: MAHOGANY: Margetuximab combination in HER2+ unresectable/metastatic gastric/gastroesophageal junction adenocarcinoma. *Future Oncol* 17:1155-1164, 2021
149. Wei J, Li W, Zhang P, et al: Current trends in sensitizing immune checkpoint inhibitors for cancer treatment. *Mol Cancer* 23:279, 2024
150. Fan J, Bekaii-Saab TS, Aldighetti LA, et al: A phase 3, randomized study of adjuvant rilvegostomig plus chemotherapy in resected biliary tract cancer: ARTEMIDE-Biliary01. *J Clin Oncol* 42, 2024 (suppl 16; abstr TPS4199)
151. Janjigian YY, Raoofmoghadam S, Sztachelska M, et al: Phase 1b/2, open-label dose-escalation and -expansion study evaluating trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients (pts) with HER2+ and HER2-low gastric cancer (GC): DESTINY-Gastric03 (DG-03). *J Clin Oncol* 42, 2024 (suppl 3; abstr TPS424)
152. Johnson ML, Arriola E, Kato T, et al: eVOLVE-Lung02: A phase 3 study of first-line (1L) volrustomig plus chemotherapy (CT) versus pembrolizumab plus CT in metastatic non-small-cell lung cancer (mNSCLC) with PD-L1 tumor cell (TC) expression <50%. *J Clin Oncol* 42, 2024 (suppl 16; abstr TPS8652)

Liquid Biopsy Approaches for Cancer Characterization, Residual Disease Detection, and Therapy Monitoring

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OVERVIEW

Liquid biopsy encompasses a variety of molecular approaches to detect circulating tumor DNA (ctDNA) and has become a powerful tool in the diagnosis and treatment of solid tumors. Current applications include comprehensive genomic profiling for identifying targetable mutations and therapeutic resistance mechanisms, with emerging applications in minimal residual disease detection and treatment response monitoring. Increasingly, the potential for liquid biopsy in guiding treatment decisions is under active investigation through prospective clinical trials using ctDNA-adaptive interventions in patients with early-stage and metastatic cancers. Limitations arise on the basis of the sensitivity and feasibility of individual liquid biopsy assays; nonetheless, emerging technologies set the stage for improving these shortcomings. As the global oncology community continues to ascertain the clinical value of liquid biopsy across the continuum of patient care, this minimally invasive approach heralds a significant advancement in the promise of precision oncology.

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INTRODUCTION

Liquid biopsies are emerging as a powerful tool in cancer diagnostics with profound implications for patient care. Several analytes fall under the umbrella term of liquid biopsy, including circulating extracellular nucleic acids and cell-free DNA (cfDNA),¹ messenger RNA and microRNA,² circulating tumor cells (CTCs),³ extracellular vesicles,⁴ and tumor-educated platelets.⁵ In the past decade, advances in circulating tumor DNA (ctDNA) analyses are propelling liquid biopsies toward widespread clinical integration. ctDNA detection methods are emerging as a pivotal advancement across the cancer care continuum, enabling comprehensive genomic profiling (CGP) to identify targetable mutations and track tumor evolution, together with minimal residual disease (MRD) detection and therapy response monitoring. Although liquid biopsies are a powerful tool for precision oncology, these approaches are subject to a number of technical and biological limitations. Importantly, not all ctDNA assays are universally applicable across all clinical settings and a careful evaluation is necessary to match the assay's analytical performance and capabilities to its intended use. In this review, we provide an overview of cfDNA biology and liquid biopsy technologies and summarize the established and emerging applications of these approaches, using lung and breast cancers as use cases.

LIQUID BIOPSY TECHNOLOGIES

cfDNA Biology

cfDNA consists of extracellular fragments of DNA that are predominantly released into body fluids such as blood, urine, saliva, and cerebrospinal fluid (CSF) because of cell death through apoptosis and necrosis.^{6–8} In healthy individuals, most cfDNA molecules are derived from leukocytes, and in patients with cancer, a small fraction of cfDNA is tumor-derived, namely ctDNA.^{9,10} ctDNA shedding varies by disease burden, tumor biologic features including tumor proliferation and apoptosis rates, sites of involvement, tumor vascularization, and primary histology.¹¹ ctDNA may therefore have different biologic underpinnings and reflect different processes not only among cancers from diverse primary sites but also across the natural history of the same cancer, influenced by its evolutionary trajectory and the selection pressure of therapy. Importantly, ctDNA lends insights into the genomic footprint of the tumor and several tumor-specific alterations can be detected in the bloodstream, including sequence mutations, translocations, amplifications, deletions, and larger-scale copy-number losses and gains.^{12–15} A deeper understanding of cfDNA biology has revealed that ctDNA molecules also retain the epigenetic features, reflective of chromatin organization and cancer lineage, of the primary tumor, which can be leveraged for minimally invasive cancer detection and have broadened

PRACTICAL APPLICATIONS

- Liquid biopsies are minimally invasive approaches that have been established as means of comprehensive genomic profiling of advanced/metastatic tumors, with emerging clinical applications in minimal residual disease monitoring and therapy response monitoring.
- Selection of the optimal liquid biopsy approach depends on the assay's analytical performance, the diagnostic application, and intended use.
- Limitations of liquid biopsies include analytical performance and variable false-negative rates, biological noise from clonal hematopoiesis mutations, and largely unknown clinical sensitivity in the early-stage setting.
- Emerging technologies leveraging integration of cell-free DNA genomic and epigenetic features may allow for more sensitive detection of circulating tumor DNA (ctDNA) and further inform treatment strategies across the clinical cancer care continuum.
- The clinical value of liquid biopsies is under active investigation in ctDNA-adaptive clinical trials in patients with early-stage and advanced/metastatic cancers.

significantly the diagnostic applications of liquid biopsies.^{16–20} cfDNA fragmentation is a nonrandom process, heavily influenced by nucleosome organization.²¹ Typically, cfDNA is digested into mononucleosomal (approximately 167 bp) or oligonucleosomal fragments, indicative of internucleosomal DNA cleavage by nucleases.⁸ cfDNA fragmentation is related to the nucleosomal positioning, chromatin structure and histone modifications,²² gene expression,^{23–25} and nuclease content of the tissue of origin yielding characteristic signatures in the distribution of fragment size, nucleotide motifs at the fragment ends, single-stranded jagged ends, and the genomic locations of the fragmentation end points.^{16,26–28} Furthermore, actively transcribed promoter regions at transcriptionally active sites display low nucleosomal occupancy and are susceptible to aberrant cleavage by DNaseases. As such, differential ctDNA fragment length, end motifs, and nucleosomal footprinting represent additional alterations that can be detected by liquid biopsy approaches.²¹ In tandem, cancer-specific cfDNA methylation patterns²⁹ have prompted the development of methylation-based cfDNA methods for cancer detection and monitoring.^{30–32} This principle has been predominantly exploited by multicancer early detection tests that target differentially methylated genomic regions for the simultaneous detection of multiple cancers.³³

Tumor-Naïve Mutation-Based Liquid Biopsy Approaches

The advent of mutation-based liquid biopsy approaches began with polymerase chain reaction (PCR) methods that could only identify single or a small number of previously known mutations at specific loci. The sensitivity of traditional PCR techniques was improved by digital PCR-based quantitative methods such as digital droplet PCR (ddPCR) and Beads Emulsions Amplification and Magnetism that enabled a limit of detection (LOD) of 0.1% to 0.01% variant allele frequency (VAF).^{34,35} However, sampling variation and limited multiplexing capacity per reaction prompted the development of next-generation sequencing (NGS) techniques that can interrogate a larger panel of alterations in parallel. Commonly used NGS technologies primarily use two approaches: amplicon-based sequencing where specific primers are designed to hybridize and amplify target sequences, and hybrid capture where biotinylated probes selectively bind to DNA sequences of interest (Fig 1). These approaches can be coupled with *in silico* sequencing error-correction bioinformatic pipelines^{12,36} and methods to filter out variants related to clonal hematopoiesis (CH),^{37,38} and overall have a LOD in the order of 0.01%–0.1%.^{12,13,39,40} Fixed gene panel targeted NGS allows for multimutation detection, is routinely used for ctDNA CGP, and is embedded in consensus guidelines to inform targeted therapy selection across cancer types. Plasma CGP also provides real-time insights into the emergence of therapy resistance mechanisms and systemic tumor burden dynamics by way of longitudinal assessments.⁴¹ The transformative impact of these technologies is reflected in the increasing number of liquid biopsy companion diagnostic assays that are approved by the US Food and Drug Administration (FDA) to inform choice of targeted therapy in select tumor types.⁴⁰ The Cobas EGFR Mutation Test v2 was the first real-time PCR test approved to detect 42 select mutations in exons 18, 19, and 20 of the *EGFR* gene in non-small cell lung cancer (NSCLC). Similarly, the Therascreen *PIK3CA* real-time PCR assay marked the first approved assay used to detect 11 mutations in the *PIK3CA* gene for individuals with breast cancer. Hybrid capture NGS assays have since expanded molecular diagnostics and several assays have been approved as companion diagnostic tests, including the Agilent Resolution ctDx First assay that was FDA-approved for detection of *KRAS* G12C alterations in NSCLC, Guardant360 CDx (74-gene panel) that was FDA-approved for detection of *EGFR*, *ERBB2*, and *KRAS* alterations in NSCLC, as well as *ESR1* mutations in breast cancer, and FoundationOne Liquid CDx (324-gene panel), which is approved for multiple indications, including *NTRK* fusions in solid tumors, *BRCA* alterations in ovarian and prostate cancers, *PIK3CA* mutations in breast cancer, *BRAF* mutations in colorectal cancer, and *EGFR*, *ROS1*, *MET*, *BRAF*, and *ALK* alterations in NSCLC.

Limitations of Plasma Comprehensive Genomic Profiling

Although gene panel NGS is advantageous when tumor specimens are insufficient for molecular testing or when an

additional biopsy is not feasible,⁴² these approaches are subject to technical and biological limitations (Fig 1). A key technical limitation of gene panel targeted NGS approaches lies in their analytical performance especially in the context of small quantities of ctDNA, which can be at or below the LOD of the assay, especially for patients with early-stage disease. An additional technical consideration lies in the differential sensitivity of plasma CGP by type of alteration, especially for fusion detection. In cases where circulating tumor fraction is high (typically >1%), plasma CGP can reliably capture actionable fusions and shows high concordance with tumor tissue NGS.⁴³ Given the differences in assay performance, it is critical to interpret negative liquid biopsy results in the context of the sensitivity and design of the liquid biopsy used. As such, an undetectable ctDNA finding may signify tumor clearance, or presence of ctDNA below the LOD of the assay or presence of genomic alterations that are not captured by the gene panel used. Certain biological factors such as cancer stage,¹¹ histology,⁴⁴ location of the primary tumor,⁴⁵ and distant organ metastasis⁴⁶ have been postulated to effect ctDNA shedding, resulting in false-negative findings. Importantly, tumor-naïve liquid biopsies can be confounded by mutations derived from clonally expanded hematopoietic cells. As discussed above, the majority of cfDNA is released from hematopoietic cells, and therefore, blood-based NGS approaches have the potential to detect CH variants, and these may be misclassified as tumor-specific. Overall, up to 50% of cfDNA mutations may be CH or germline in origin and may occur in genes not canonically associated with CH, which can further confound precision oncology decisions.^{36,47-50}

Ultra-Sensitive Tumor-Informed Liquid Biopsy Approaches for Residual Disease Detection

Previous knowledge of the tumor's mutational profile allows for higher sensitivity of detection compared with tumor-naïve approaches. Such methods, collectively termed tumor-informed liquid biopsies, are currently better suited for the detection of MRD (Fig 1). MRD describes the persistence of a small amount of tumor cells either during or after treatment that is usually not detected by conventional radiologic techniques. Although there are currently no FDA-approved ctDNA assays for MRD detection, certain Clinical Laboratory Improvement Amendments-/College of American Pathologists-certified clinical tests are covered by Medicare for multiple solid tumors including colorectal, breast, and bladder cancers,⁵¹⁻⁵³ while several others are under development. Querying patient-specific alterations in personalized liquid biopsy assays enables ctDNA detection at low concentrations while suppressing biological noise from CH. After molecular profiling of the tumor by whole-exome sequencing, bespoke multiplex PCR-based assays have been developed to track a small number¹⁶⁻⁴⁸ of clonal variants in cfDNA, achieving an LOD from 0.01% to 0.001%.^{51,54,55} The analytical sensitivity of bespoke tumor-informed assays can be

further improved by querying a larger number of tumor-derived variants in cfDNA. To this end, whole-genome sequencing of tumor tissue has been used to identify single-nucleotide variants (SNVs) across the genome, which are in turn used to design custom probe panels per patient. One such assay incorporating approximately 1,800 tumor-specific SNVs reported an LOD of 1.67 parts per million (PPM).⁵⁶ Further improvement of signal-to-noise ratio may be feasible by implementing machine learning methods that use tumor whole-genome sequencing to generate genome-wide mutations profiles instead of relying on the detection of specific ctDNA variants⁵⁷ or focusing on phased variants, which represent two or more mutations occurring on the same DNA strand.⁵⁸ These approaches have allowed the ultra-sensitive detection of ctDNA in patients with early-stage disease with reported LODs in the order of 10 PPM⁵⁷ and approximately 1 PPM, respectively.⁵⁸

Emerging Tumor-Naïve Liquid Biopsy Approaches

Expanding past mutations, consideration of cfDNA epigenetic features including methylation and fragmentation profiles may enhance the sensitivity of tumor-naïve liquid biopsies and potentially alleviate some of the challenges of tumor-informed approaches related to feasibility, complexity, turnaround time, and tissue availability. Cancer-specific large-scale epigenetic alterations can be reliably captured in cfDNA including in patients with early-stage cancers.³⁰ Plasma-only epigenomic MRD assays can capture cancer-specific cfDNA methylation patterns, and one such approach that evaluated >20,000 differentially methylated regions achieved an LOD of 0.01% VAF or 100 PPM.⁵⁹ Although detection of cfDNA methylation has relied on bisulfite conversion, which can be destructive of the input DNA, novel enzymatic conversion methods and direct detection by single-molecule sequencers mitigate input DNA degradation and may result in greater sensitivity and accuracy.¹⁶ As liquid biopsy technologies and analytical frameworks continue to evolve, assays and methods developed for cancer screening and multicancer early detection have the potential to be adapted to the MRD setting. Evaluation of the cfDNA fragmentome coupled with machine learning algorithms has shown promise in cancer early detection and reflects a suite of features (cfDNA fragment lengths, motifs, nucleosomal positioning, repeat elements, and transcription factor binding site occupancy) that can be leveraged in the MRD setting.^{17,18,60,61} cfDNA fragmentation profiles can also be used to infer cfDNA methylation patterns.⁶² Importantly, integration of ctDNA methylation, fragmentation, and mutation profiles holds promise in further improving the detection and interpretation of circulating tumor burden (Fig 1).⁶³

In the following sections, we focus on the clinical implementation of liquid biopsies using NSCLC and breast cancer as use cases and discuss strategies to test the clinical utility of these approaches in clinical trials.

LIQUID BIOPSY IN THE TREATMENT OF PATIENTS WITH NSCLC

Established Role of Plasma-Based CGP in Characterization of Metastatic NSCLC

As discussed above, in 2016, the FDA approved the first liquid biopsy assay, the Cobas EGFR Mutations Test v2, for the detection of activating *EGFR* mutations in patients with metastatic NSCLC unable to undergo tissue biopsy.⁶⁴ Current consensus guidelines recommend ctDNA testing for molecular profiling of patients newly diagnosed with metastatic NSCLC.^{65,66} Testing can be complementary to tissue-based NGS or used as an alternative if tissue analysis is unfeasible. In this setting, liquid biopsy may identify a driver oncogene to target with initial systemic therapy. Liquid biopsy can also be conducted at the time of targeted therapy resistance with the goal of identifying acquired molecular alterations to guide selection of next-line therapy. However, limitations include a reduced sensitivity for detection of oncogene fusions and resistance mechanisms driven by copy-number alterations, as well as reduced assay sensitivity in the setting of CNS-limited disease or low-volume disease limited to the pleural cavity. Furthermore, mutation-based ctDNA approaches do not adequately capture histologic transformation,⁶⁷ thus limiting the value of fixed panel NGS in capturing targeted therapy resistance. If a liquid biopsy returns negative and the suspicion for a primary driver or resistance mechanism remains high, clinicians are encouraged to attempt tissue biopsy for molecular profiling.

In December 2020, the third-generation *EGFR* tyrosine kinase inhibitor (TKI), osimertinib, received the first FDA approval as adjuvant targeted therapy in early-stage *EGFR*-mutated NSCLC.⁶⁸ This approach diverges from the subsequent approvals of adjuvant and perioperative immune checkpoint inhibitors (ICIs) in early-stage NSCLC,⁶⁹⁻⁷¹ providing rationale for biomarker assessment in localized disease.⁷² However, the role of liquid biopsy in this setting is not defined. With its rapid turnaround time, ctDNA CGP may become useful in identifying upfront patients who are less likely to benefit from neoadjuvant ICI on the basis of molecular profiling (eg, *EGFR*, *ALK*, and *ROS1*) and for which alternative neoadjuvant/induction strategies incorporating targeted therapies can be implemented, as in the NeoADAURA (ClinicalTrials.gov identifier: [NCT04351555](#)), NEOLA (ClinicalTrials.gov identifier: [NCT06194448](#)), and NAUTIKA1 (ClinicalTrials.gov identifier: [NCT04302025](#)) clinical trials.

Liquid Biopsies in Early-Stage NSCLC: Refining the Approach to Cure

The literature surrounding liquid biopsy and its evaluation in the definitive treatment of early-stage NSCLC is vast and has been reviewed in depth previously.⁷³ Studies have used both tumor-informed and tumor-naïve approaches implementing various ctDNA assays to risk stratify patients as they progress through each phase of treatment. Findings from selected

studies addressing the role of baseline, postneoadjuvant, and postoperative ctDNA detection in disease prognostication in the neoadjuvant/perioperative setting are summarized in [Table 1](#).

Baseline ctDNA Levels as a Prognostic Marker

Retrospective analyses have revealed the prognostic significance of detectable ctDNA before definitive treatment of early-stage NSCLC, where pretreatment ctDNA has been associated with shorter recurrence-free survival (RFS) and overall survival (OS).⁵⁵ Similarly, when stratified by high versus low pretreatment ctDNA levels as determined by tumor-informed multiplex PCR NGS, high ctDNA levels were associated with a significantly shorter RFS.⁴⁴ In the TRACERx cohort of patients with early-stage NSCLC, a tumor-informed whole-genome sequencing-based assay stratified patients before surgical resection, demonstrating a 5-year OS of 100% in ctDNA-negative patients, 61.4% in ctDNA-low patients, and 48.8% in ctDNA-high patients.⁸⁴ The prognostic value of baseline ctDNA measurements before neoadjuvant therapy is less established. The phase II LCMC3 trial showed that baseline ctDNA negativity neither conferred improved disease-free survival (DFS) nor OS.⁷⁴ By contrast, the phase II NADIM study revealed that low baseline ctDNA mutant allele fraction (<1%) was associated with an improved progression-free survival (PFS) and OS,⁷⁶ which may reflect a higher prognostic relevance in more locally advanced disease.

ctDNA Clearance in Predicting Pathologic Response After Neoadjuvant Therapy

The association between ctDNA clearance after neoadjuvant therapy in predicting pathologic response has been evaluated in several studies, showing variable concordance between ctDNA kinetics and pathologic response ([Table 1](#)). ctDNA clearance was not associated with major pathologic response (MPR) after neoadjuvant atezolizumab,⁷⁵ and in the NADIM study, ctDNA clearance was not associated with pathologic complete response (pCR) after neoadjuvant nivolumab plus chemotherapy,⁷⁶ although both analyses were limited by fairly small sample sizes. By contrast, two randomized phase III trials demonstrated a strong relationship between ctDNA clearance and pathologic response. In CheckMate 816, ctDNA clearance exhibited a dose-response relationship across various thresholds of pathologic response (MPR and pCR) after neoadjuvant therapy.⁷⁷ Similarly, ctDNA clearance was strongly associated with both pCR and MPR in the AEGEAN trial.⁷⁹ These results suggest a potential role for ctDNA clearance in predicting pathologic response with neoadjuvant chemoimmunotherapy, although this requires prospective validation.

ctDNA Clearance as a Predictor of Survival Outcomes

As an independent predictor, ctDNA clearance after neoadjuvant therapy trended toward having an association with DFS and OS in the LCMC3 trial and with PFS in NADIM, while

TABLE 1. ctDNA and MRD Assessment in Selected Neoadjuvant, Perioperative, and Adjuvant Studies in NSCLC

Study Name (phase)	Sample Size ^a ; Stage (%)	Neoadjuvant/Adjuvant Therapy	ctDNA Assay and Description	Baseline ctDNA Detection (%)	Postneoadjuvant ctDNA Clearance (%)	ctDNA MRD Detection (%)	Outcomes by ctDNA Status	References
LCMC3 (phase II single-arm)	137 IB 12% IIA 8% IIB 31% IIIA 39% IIIB 10%	Atezolizumab/ ± atezolizumab + chemotherapy	Avenio Hybrid capture NGS (197-gene panel)	72%	32% of baseline ctDNA+ patients	11.3%	3-year DFS: 85% ctDNA clearance (CL)+ v 63% ctDNA CL- (HR, 0.32 [95% CI, 0.10 to 1.10]; <i>P</i> = NS) 3-year OS: 90% CL+ v 74% CL- (HR, 0.36 [95% CI, 0.08 to 1.61]; <i>P</i> = NS) 3-year DFS: MPR+ CL ± 100% v MPR- CL+ 78% v MPR- CL- 57% (<i>P</i> = NS) 3-year OS: MPR+ CL ± 100% v MPR- CL+ 86% v MPR- CL- 70% (<i>P</i> = NS)^b ctDNA MRD: 3-year DFS: 72% MRD- v 33% MRD- (HR, 0.25 [95% CI, 0.08 to 0.78]; <i>P</i> < .05) 3-year OS: 82% MRD- v 50% MRD+ (HR, 0.26 [95% CI, 0.07 to 0.99]; <i>P</i> < .05) 3-year DFS: MPR+ MRD- 100% v MPR- MRD- 64% v MPR- MRD+ 33% 3-year OS: MPR+ MRD- 100% v MPR- MRD- 77% v MPR- MRD+ 50%	74,75

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TABLE 1. ctDNA and MRD Assessment in Selected Neoadjuvant, Perioperative, and Adjuvant Studies in NSCLC (continued)

Study Name (phase)	Sample Size ^a ; Stage (%)	Neoadjuvant/Adjuvant Therapy	ctDNA Assay and Description	Baseline ctDNA Detection (%)	Postneoadjuvant ctDNA Clearance (%)	ctDNA MRD Detection (%)	Outcomes by ctDNA Status	References
NADIM (phase II single-arm)	43 IIIA 100%	Nivolumab + chemotherapy	Oncomine Pan-Cancer Cell-Free Assay Multiplex PCR NGS (52-gene panel)	70%	68%	NA	<i>5-year PFS:</i> 60.6% CL– v 85.2% CL+ (HR, 3.06 [95% CI, 0.73 to 12.9]; <i>P</i> = .079) <i>5-year OS:</i> 59.2% CL– v 92.3% CL+ (HR, 6.88 [95% CI, 1.29 to 36.8]; <i>P</i> = .007) <i>PFS in CL– v CL+ in nonresected/non-pCR:</i> HR, 3.58, 95% CI, 0.68 to 18.9; <i>P</i> = .073 <i>OS in CL– v CL+ in nonresected/non-pCR:</i> HR, 5.80, 95% CI, 0.93 to 36.3; <i>P</i> = .019 ^c	⁷⁶
CheckMate 816 (phase III randomized)	89 IB to II 44.9% IIIA 55.1%	Nivolumab + chemotherapy v chemotherapy alone	ArcherDX Tumor-informed multiplex PCR NGS (up to 50 tumor variants)	97% (n = 43 in each arm)	56% in nivolumab + chemotherapy v 35% in chemotherapy alone	NA	<i>Median EFS in nivo + chemo:</i> NR in CL+ v 18.9 months in CL– (HR, 0.60 [95% CI, 0.20 to 1.82]) <i>Median EFS in chemo alone:</i> NR in CL+ v 16.9 months in CL– (HR, 0.63 [95% CI, 0.20 to 2.01]) <i>OS in CL+ v CL– in nivo + chemo:</i> HR, 0.31, 95% CI, 0.10 to 0.90 <i>OS in CL+ v CL– in chemo alone:</i> HR, 0.58, 95% CI, 0.20 to 1.64 ^d	^{77,78}

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TABLE 1. ctDNA and MRD Assessment in Selected Neoadjuvant, Perioperative, and Adjuvant Studies in NSCLC (continued)

Study Name (phase)	Sample Size ^a ; Stage (%)	Neoadjuvant/Adjuvant Therapy	ctDNA Assay and Description	Baseline ctDNA Detection (%)	Postneoadjuvant ctDNA Clearance (%)	ctDNA MRD Detection (%)	Outcomes by ctDNA Status	References
AEGEAN (phase III randomized)	175 IIA to IIIB	Durvalumab + chemotherapy v placebo + chemotherapy/ durvalumab v placebo	Invitae personalized cancer monitoring Tumor-informed multiplex PCR NGS (18-50 tumor variants)	90% in durvalumab arm v 94% in placebo arm	66% in durvalumab arm v 41% in placebo arm	11.1% in durvalumab arm v 10.1% in placebo arm	<i>EFS</i> in CL+ v CL- in durva arm: HR, 0.26, 95% CI, 0.13 to 0.54 <i>EFS</i> in CL+ v CL- in placebo arm: HR, 0.47, 95% CI, 0.26 to 0.84 <i>EFS</i> in durva arm with CL+ and pCR+ v CL- and pCR-: HR, 0.14, 95% CI, 0.04 to 0.48 <i>EFS</i> in durva arm with CL+ and pCR- v CL- and pCR-: HR, 0.35, 95% CI, 0.16 to 0.76 <i>EFS</i> in durva arm with CL+ and pCR+ v CL+ and pCR-: HR, 0.39, 95% CI, 0.11 to 1.41^e MRD: <i>DFS</i> in MRD- v MRD+ in durva arm: HR, 0.05, 95% CI, 0.02 to 0.13 <i>DFS</i> in MRD- v MRD+ in placebo arm: HR, 0.07, 95% CI, 0.02 to 0.20 <i>DFS</i> with durva v placebo in MRD- subgroup: HR, 0.56, 95% CI, 0.26 to 1.20 <i>DFS</i> with durva v placebo in MRD+ subgroup: HR, 0.78, 95% CI, 0.26 to 2.36	79,80
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TABLE 1. ctDNA and MRD Assessment in Selected Neoadjuvant, Perioperative, and Adjuvant Studies in NSCLC (continued)

Study Name (phase)	Sample Size ^a ; Stage (%)	Neoadjuvant/Adjuvant Therapy	ctDNA Assay and Description	Baseline ctDNA Detection (%)	Postneoadjuvant ctDNA Clearance (%)	ctDNA MRD Detection (%)	Outcomes by ctDNA Status	References
IMpower010 (phase III randomized)	534 II to IIIA	Adjuvant: Atezolizumab v best supportive care	Signatera Tumor-informed multiplex PCR NGS (16 tumor variants)	NA	NA	19.6% in atezolizumab arm v 22.4% in BSC arm	<i>DFS</i> with atezo v BSC in MRD– subgroup: HR, 0.72, 95% CI, 0.51 to 1.00 <i>DFS</i> with atezo v BSC in MRD+ subgroup: HR, 0.61, 95% CI, 0.39 to 0.94 <i>DFS</i> with atezo v BSC after chemo in MRD– subgroup: HR, 0.7, 95% CI, 0.37 to 1.34 <i>Time to ctDNA+</i> with atezo v BSC after chemo in MRD– subgroup: HR, 0.6, 95% CI, 0.31 to 1.17	^{81,82}
ADAURA (phase III randomized)	220 IB to IIIA	Adjuvant: osimertinib v placebo	RaDaR Tumor-informed multiplex PCR NGS (48 tumor variants)	NA	NA	8.1%	<i>DFS and MRD event-free</i> with osimertinib v placebo: HR, 0.23, 95% CI, 0.15 to 0.36 ^{f,g}	⁸³

Abbreviations: atezo, atezolizumab; BSC, best supportive care; CL, clearance; ctDNA, circulating tumor DNA; DFS, disease-free survival; durva, durvalumab; EFS, event-free survival; HR, hazard ratio; MPR, major pathologic response; MRD, minimal residual disease; NA, not applicable; NGS, next-generation sequencing; NR, not reached; NS, not significant; NSCLC, non–small cell lung cancer; OS, overall survival; pCR, pathologic complete response; PCR, polymerase chain reaction; PFS, progression-free survival.

^aSample size restricted to patients with evaluable ctDNA levels, if available.

^bctDNA CL was not associated with MPR.

^cctDNA CL was not associated with pCR.

^dctDNA CL showed a dose-response inverse relationship with residual viable tumor.

^eAll patients who achieved a pCR and >90% of patients who achieved a MPR had ctDNA clearance presurgery.

^fMRD clearance occurred in 4 of 5 patients receiving osimertinib, and 0 of 13 patients receiving placebo.

^gMRD lead-time to DFS: 4.7 months.

achieving a significant association with OS in the latter.^{74,76} In both the CheckMate 816 and AEGEAN trials, ctDNA clearance after neoadjuvant therapy was associated with improved EFS in each trial arm,^{78,80} and was further associated with improved OS in the chemoimmunotherapy arm of CheckMate 816.⁷⁸ Analyses combining ctDNA clearance with pathologic response demonstrate the potential superior predictive power of integrated pathologic and molecular approaches in this setting. LCMC3 and NADIM are both limited because of small sample sizes, although they provide early proof that ctDNA clearance may point toward improved PFS and OS in the setting of an MPR in the former,⁷⁴ and improved PFS and OS in patients without a pCR in the latter.⁷⁶ AEGEAN most elegantly demonstrated the combined association of ctDNA clearance with pCR in improving EFS over ctDNA clearance without a pCR, and both over the combined absence of ctDNA clearance and pCR.⁸⁰ Furthermore, ctDNA clearance may be informative in dissecting the heterogeneity of the non-pCR, as patients in the non-pCR group who were ctDNA-negative have been shown to attain longer RFS after neoadjuvant immunotherapy.⁸⁵ Altogether, these data suggest that ctDNA clearance combined with pathologic response may be an effective marker in predicting postoperative EFS, although the variable ctDNA assay sensitivity must be taken into consideration.

Predictive Value of ctDNA MRD

ctDNA MRD after definitive therapy has been evaluated as a predictor for survival outcomes in purely adjuvant clinical trials and in perioperative studies (Table 1). In IMpower010, ctDNA MRD was detected using multiplex PCR in approximately 20%–22% of patients, with MRD positivity associated with worse DFS.⁸¹ Adjuvant atezolizumab improved DFS in both ctDNA MRD-positive and MRD-negative subgroups with PD-L1 tumor positivity. After chemotherapy, atezolizumab delayed time to ctDNA positive conversion and this correlated with an improved DFS in the MRD-negative subgroup.⁸² In LCMC3, patients who were ctDNA MRD-negative by hybrid capture NGS had significantly improved DFS and OS.⁷⁴ In AEGEAN, atezolizumab demonstrated DFS benefits in both the MRD-positive and MRD-negative subgroups.⁸⁰ In the phase III ADAURA trial, ctDNA MRD was detected via multiplex PCR NGS in 8.1% of patients with *EGFR*-mutated lung cancers.⁸³ ctDNA MRD clearance occurred at a greater frequency with adjuvant osimertinib versus placebo, and ctDNA MRD detection preceded radiographic recurrence with a median lead-time of 4.7 months. Altogether, these studies support a role for ctDNA MRD in predicting survival outcomes after surgical resection and suggest that MRD detection may be a relevant outcome in itself. Looking ahead, clinical trials involving adaptive designs in which ctDNA MRD guides selection of patients for adjuvant therapy or intensification of therapy are underway.⁸⁶

Liquid Biopsies in Advanced NSCLC: Moving Toward a ctDNA Molecular Response-Adaptive Approach

Multiple studies evaluating metastatic NSCLC have established the prognostic and predictive potential for baseline

ctDNA levels and subsequent clearance (selected studies summarized in Table 2).^{37,41,49,50} These results have heralded interventional studies, which include real-time ctDNA assessments that may guide treatment escalation/de-escalation strategies.

Liquid Biopsy Implementation Into Targeted Therapy Selection for *EGFR*-Mutant NSCLC

In the AURA3 and FLAURA trials of osimertinib for *EGFR*-mutant NSCLC,^{87,89} baseline ctDNA detection correlated with shorter PFS and OS.⁸⁸ Osimertinib improved ctDNA clearance at week 3 compared with chemotherapy and first-generation *EGFR* TKI as well as prolonged PFS particularly in patients who attained ctDNA clearance. Serial ctDNA monitoring demonstrated that ctDNA molecular progression preceded radiographic progression by approximately 3 months, suggesting that ctDNA progression could serve as alternative end point of therapy efficacy.⁸⁸ Previous analyses have revealed that ctDNA molecular response is rapid, often occurring within one treatment cycle of TKI.^{95,96} ctDNA clearance at a prespecified landmark also correlates with radiographic response and survival outcomes with TKIs for other oncogene-driven NSCLCs.^{97–99} In addition to single-agent osimertinib, ctDNA analyses are informative in the context of combination regimens, such as osimertinib plus chemotherapy and amivantamab plus lazertinib.^{100,101} Patients with detectable baseline ctDNA, reflective of a higher burden of disease and a higher-risk patient subgroup,^{54,102} may benefit from the combination regimens.^{90,91} Lack of ctDNA clearance at the prespecified landmark was associated with reduced activity with both combinations—a pattern that was also seen in the PAPILLON trial of amivantamab plus chemotherapy.⁹² These findings underscore the need to improve outcomes in high-risk patients by implementing molecular read-outs of therapy response by liquid biopsies.

ctDNA Molecular Response Predicts Immunotherapy Outcomes

Longitudinal plasma CGP is gaining momentum in ICI response monitoring.^{37,103} Although a higher baseline tumor fraction has been shown to correlate with inferior outcomes, the association between baseline ctDNA and ICI OS, PFS, and response rates is variable across studies.¹⁰⁴ Dynamic ctDNA assessment represents a promising biomarker of ICI response, which has been consistently associated with improved OS, PFS, response rate, and durability of response, despite variability in collection timing across studies.¹⁰⁵ Collectively, these analyses have revealed distinct patterns of ctDNA molecular response that are reflective of patients' clinical outcomes such that patients with ctDNA molecular response have a dramatic reduction in ctDNA to undetectable levels while patients with molecular progression show ctDNA persistence or increase.³⁷ In the first stage of the single-arm BR.36 trial (Table 2), ctDNA molecular response after two cycles of single-agent pembrolizumab showed a sensitivity of 82% and a specificity of 75% for RECIST best

TABLE 2. ctDNA Analyses in Selected Studies of Advanced NSCLC

Study (phase)	Sample Size ^a	Systemic Therapy	ctDNA Assay	Assay Description	ctDNA Assessment	Baseline ctDNA Detection (%)	Outcomes	References
AURA3 (phase III randomized)	291	Osimertinib v chemotherapy	Biodesix ddPCR	ddPCR (select mutations in <i>EGFR</i> , <i>ALK</i> , <i>KRAS</i> , <i>BRAF</i> , <i>ROS1</i> , and <i>RET</i>)	Baseline, Week 3, Week 6	71	<i>Median PFS</i> : 12.4 months in ctDNA– v 6.7 months in ctDNA+ (HR, 0.48 [95% CI, 0.33 to 0.68]) <i>Median PFS in osi</i> : 14.0 months in ctDNA– v 8.3 months in ctDNA+ <i>Median OS</i> : 44.9 months in ctDNA– v 21.6 months in ctDNA+ (HR, 0.40 [95% CI, 0.28 to 0.56]) <i>ctDNA clearance at week 3</i> : 63% in osi v 25% in chemo (OR, 5.0 [95% CI, 2.5 to 10.1]) <i>Median PFS in osi</i> : 10.9 months in week 3 CL+ v 5.7 months in week 3 CL– ^b	^{87,88}
FLAURA (phase III randomized)	499	Osimertinib v first-generation EGFR TKI	Biodesix ddPCR	ddPCR (select mutations in <i>EGFR</i> , <i>ALK</i> , <i>KRAS</i> , <i>BRAF</i> , <i>ROS1</i> , and <i>RET</i>)	Baseline, Week 3, Week 6	71	<i>Median PFS</i> : 19.1 months in ctDNA– v 11.1 months in ctDNA+ (HR, 0.54 [95% CI, 0.41 to 0.70]) <i>Median PFS in osi</i> : 23.5 months in ctDNA– v 15.2 months in ctDNA+ <i>Median OS</i> : NR in ctDNA– v 29.7 months in ctDNA+ (HR, 0.34 [95% CI, 0.25 to 0.45]) <i>ctDNA CL+ at week 3</i> : 65% in osi v 59% in chemo (OR, 1.3 [95% CI, 0.8 to 2.1]) <i>Median PFS in osi</i> : 19.8 months in week 3 CL+ v 11.3 months in week 3 CL– ^c	^{88,89}

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TABLE 2. ctDNA Analyses in Selected Studies of Advanced NSCLC (continued)

Study (phase)	Sample Size ^a	Systemic Therapy	ctDNA Assay	Assay Description	ctDNA Assessment	Baseline ctDNA Detection (%)	Outcomes	References
FLAURA2 (phase III randomized)	421	Osimertinib + chemotherapy v osimertinib alone	Biodesix ddPCR	ddPCR (select mutations in <i>EGFR</i> , <i>ALK</i> , <i>KRAS</i> , <i>BRAF</i> , <i>ROS1</i> , and <i>RET</i>)	Baseline, Week 3, Week 6	73	<i>Median PFS</i>: 30.5 months in ctDNA– v 18.3 months in ctDNA+ (HR, 0.55 [95% CI, 0.42 to 0.73]) <i>Median PFS in osi + chemo</i>: 33.3 months in ctDNA– v 24.8 months in ctDNA+ (HR, 0.64 [95% CI, 0.42 to 0.98]) <i>Median PFS in osi</i>: 30.3 months in ctDNA– v 13.9 months in ctDNA+ (HR, 0.51 [95% CI, 0.35 to 0.76]) <i>Median PFS in baseline ctDNA+</i>: 24.8 months in osi + chemo v 13.9 months in osi (HR, 0.60 [95% CI, 0.45 to 0.80]) <i>Median PFS in baseline ctDNA–</i>: 33.3 months in osi + chemo v 30.3 months in osi (HR, 0.93 [95% CI, 0.51 to 1.72]) <i>ctDNA clearance at week 3</i>: 81% in osi + chemo v 71% in osi <i>Median PFS in CL+ at week 3</i>: 27.6 months in osi + chemo v 15.2 months in osi (HR, 0.51 [95% CI, 0.35 to 0.75]) <i>Median PFS in CL– at week 3</i>: 19.6 months in osi + chemo v 11.1 months in osi (HR, 0.62 [95% CI, 0.33 to 1.14])	90

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TABLE 2. ctDNA Analyses in Selected Studies of Advanced NSCLC (continued)

Study (phase)	Sample Size ^a	Systemic Therapy	ctDNA Assay	Assay Description	ctDNA Assessment	Baseline ctDNA Detection (%)	Outcomes	References
MARIPOSA (phase III randomized)	672	Amivantamab + lazertinib v osimertinib	Biodesix ddPCR	ddPCR (select mutations in <i>EGFR</i> , <i>ALK</i> , <i>KRAS</i> , <i>BRAF</i> , <i>ROS1</i> , and <i>RET</i>)	Baseline, Week 9	70	<i>Median PFS in baseline ctDNA+</i>: 20.3 months in ami + laz v 14.8 months in osi (HR, 0.68 [95% CI, 0.53 to 0.86]) <i>Median PFS in baseline ctDNA-</i>: 27.7 months in ami + laz v 21.9 months in osi (HR, 0.72 [95% CI, 0.47 to 1.10]) <i>ctDNA clearance at week 9</i>: 81% in osi + chemo v 71% in osi <i>Median PFS in CL+ at week 9</i>: 24.0 months in osi + chemo v 16.5 months in osi (HR, 0.64 [95% CI, 0.48 to 0.87]) <i>Median PFS in CL- at week 9</i>: 16.5 months in osi + chemo v 9.1 months in osi (HR, 0.49 [95% CI, 0.27 to 0.87])	⁹¹
PAPILLON (phase III randomized)	117	Amivantamab + chemo-therapy v chemotherapy	Guardant360 CDx	Hybrid capture NGS (74-gene panel)	Baseline, Week 6	86	<i>Median PFS in baseline ctDNA+</i>: 11.1 months in ami + chemo v 5.8 months in chemo (HR, 0.38 [95% CI, 0.26 to 0.55]) <i>ctDNA clearance at week 6</i>: 69% in ami + chemo v 45% in chemo <i>Median PFS in CL+ at week 6</i>: 12.2 months in ami + chemo v 6.8 months in chemo (HR, 0.26 [95% CI, 0.13 to 0.50]) <i>Median PFS in CL- at week 6</i>: 9.8 months in ami + chemo v 4.8 months in chemo (HR, 0.55 [95% CI, 0.27 to 1.13])	⁹²

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TABLE 2. ctDNA Analyses in Selected Studies of Advanced NSCLC (continued)

Study (phase)	Sample Size ^a	Systemic Therapy	ctDNA Assay	Assay Description	ctDNA Assessment	Baseline ctDNA Detection (%)	Outcomes	References
BR.36 (phase II single-arm)	45	Pembrolizumab	PGDX elio plasma resolve	Hybrid capture NGS (33-gene panel)	Baseline, Week 3, Week 6	78	Median PFS: 5.0 months in MR+ v 2.6 months in mPD+ (HR, 0.55 [95% CI, 0.27 to 1.13]) Median OS: NR in MR+ v 7.2 months in mPD+ (HR, 0.16 [95% CI, 0.05 to 0.50]) ctDNA clearance: 43% ^{d,e}	⁵⁰
IMpower150 (phase III randomized)	240	Atezolizumab + chemo-therapy v bevacizumab + chemo v atezolizumab + bevacizumab + chemotherapy	FoundationOne Liquid CDx	Hybrid capture NGS (324-gene panel)	Baseline, Week 3, Week 9	85	Median OS: 18.8 months in ctDNA+ v 26.6 months in ctDNA– (HR, 1.33 [95% CI, 0.87 to 2.06]) ctDNA clearance at week 3: 30%	^{93,94}

Abbreviations: ami, amivantamab; chemo, chemotherapy; CL, clearance; ctDNA, circulating tumor DNA; ddPCR, digital droplet PCR; EGFR, epidermal growth factor receptor; HR, hazard ratio; laz, lazertinib; mPD, molecular disease progression; MR, molecular response; NGS, next-generation sequencing; NR, not reached; NSCLC, non–small cell lung cancer; OR, odds ratio; OS, overall survival; osi, osimertinib; PCR, polymerase chain reaction; PD, progressive disease; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

^aSample size restricted to patients with evaluable ctDNA levels, if available.

^bMedian time from ctDNA PD to RECIST PD in osi: 2.8 months.

^cMedian time from ctDNA PD to RECIST PD in osi: 3.4 months.

^dMedian time to ctDNA response: 2.1 months.

^ectDNA response is concordant with radiographic response.

overall response and, importantly, was associated with significant improvements in PFS and OS.⁵⁰ IMPower150 similarly found that decreases in ctDNA from baseline to week 9 correlated with radiographic response.^{93,94} Altogether, these studies suggest that ctDNA molecular response may enable early and accurate therapy response assessment and facilitate long-term response monitoring during immunotherapy, especially for the heterogeneous—but sizable—subset of patients with radiographically stable disease.

LIQUID BIOPSY IN THE MANAGEMENT OF EARLY-STAGE AND METASTATIC BREAST CANCER

Detection of Actionable Mutations in Metastatic Breast Cancer for Personalized Therapy

Liquid biopsy-guided treatment has been transforming the evolving landscape of metastatic breast cancer, becoming a routine tool for cancer genotyping and aiding in monitoring treatment response. Liquid biopsy-driven molecular profiling plays a pivotal role in guiding treatment decisions, particularly for patients progressing after cyclin-dependent kinase 4/6 (CDK4/6) inhibitor therapy. Fixed gene panel NGS analyses before and after first-line treatment for metastatic breast cancer with CDK4/6 inhibitors in the MONALEESA trial suggested that acquired mutations in *RB1*, *SPEN*, *TPR*, *PCDH15*, *FGFR2*, and *ESR1* may represent genomic mechanisms of resistance to CDK4/6 inhibitors.¹⁰⁶ In tandem, approximately 40% of estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancers harbor oncogenic *PIK3CA* driver mutations. Current clinical practice reserves the PI3K inhibitor alpelisib¹⁰⁷ and AKT inhibitor capivasertib¹⁰⁸ for second-line treatment after CDK4/6 inhibitor therapy. For *PIK3CA*-mutated, ER-positive, HER2-negative metastatic breast cancer, the combination of inavolisib, fulvestrant, and palbociclib significantly extends PFS, especially in patients with primary resistance to endocrine therapy in the frontline setting.¹⁰⁹ Data from PALOMA-3 using cfDNA whole-exome sequencing analyses suggested that emerging mutations in *ESR1* and *PIK3CA* drive resistance to fulvestrant,¹¹⁰ while mutations in *PTEN* and *AKT1* detected by gene panel NGS may drive resistance to PI3K inhibitors.¹¹¹ Furthermore, *ESR1* mutations, which develop in response to endocrine therapy, can be countered by selective estrogen receptor degraders (SERDs). Elacestrant, an oral SERD, is an effective treatment option for *ESR1*-mutated tumors after CDK4/6 inhibitor therapy.^{112,113} Beyond CDK4/6 inhibitors and targeted therapies for *PI3K/AKT* and *ESR1* mutations, additional actionable genomic alterations, such as *BRCA* mutations and *NTRK* fusions, have broadened the potential targeted therapy options. Determining the optimal sequencing of therapies remains a complex challenge, particularly for patients harboring multiple actionable mutations.

Monitoring Treatment Resistance and Optimizing Subsequent Therapy in Metastatic Breast Cancer

Liquid biopsy-driven *ESR1* mutation detection in ctDNA has demonstrated the potential to inform timely therapeutic

interventions.¹¹⁰ The PADA-1 trial serially tested patients with ctDNA via ddPCR every one to two cycles while on first-line therapy for advanced breast cancer with palbociclib plus aromatase inhibitor. Patients with emerging *ESR1* mutations without radiographic evidence of progression were randomly assigned to either continue current therapy or switch aromatase inhibitor to fulvestrant while maintaining palbociclib. Patients who switched to fulvestrant had a 6-month PFS benefit over those who maintained current therapy.¹¹³ The SERENA-6 trial institutes a similar design as PADA-1, switching aromatase inhibitor to camizestrant, a novel SERD, while maintaining the partner CDK4/6 inhibitor in patients on first-line therapy for advanced breast cancer upon the detection of an *ESR1* mutation by the Guardant 360 CDx assay.¹¹⁴ The aim of this global phase III trial is to treat *ESR1*-mutant clones and extend the duration of control of ER-driven tumor growth ahead of disease progression. However, the impact of therapeutic interventions informed by ctDNA and preceding radiographic and/or clinical progression on OS are currently unknown. Collectively, these studies highlight the role of minimally invasive comprehensive resequencing in informing the sequence and timing of targeted therapies for this patient population.

Liquid Biopsy for MRD in Early-Stage Breast Cancer

In early-stage breast cancer, assessing the clinical utility of ctDNA as a tool for assessing MRD and informing adjuvant and neoadjuvant therapy is under active investigation. Multiple studies of early-stage breast cancer have demonstrated that decreasing levels or clearance of ctDNA during neoadjuvant therapy, predominantly measured by tumor-informed bespoke approaches, is associated with an increased likelihood of pCR and improvement in DFS.^{115–117} On the contrary, patients with detectable ctDNA at the end of neoadjuvant therapy had lower rates of pCR¹¹⁶ and experienced higher rates of relapse.^{115,118–120} Among patients with residual disease, those who were ctDNA-negative had better outcomes than those who were ctDNA-positive.¹¹⁷ Overall, this suggests a role for further monitoring of patients who do not attain pCR for surveillance of relapse and potentially escalation of therapy in the adjuvant setting. Studies incorporating ctDNA MRD testing in the adjuvant setting to date have focused on identifying patients at high risk for recurrent disease. Across trials such as EBLIS, LEADER, and SUCCESS-A, it has been well demonstrated that ctDNA detection during adjuvant treatment is predictive of recurrence, with clinical sensitivity ranging between 93% and 100%, with the highest rates of recurrence in patients who remain ctDNA-positive at multiple time points.^{121–123} In the EBLIS trial, ctDNA sensitivity (utilizing a bespoke multiplex PCR assay used every 6 months after surgery for up to 12 years) for relapse in patients with triple-negative breast cancer (TNBC) and hormone receptor-positive/HER2-negative breast cancer was 100% and 81.8%, respectively.⁵³ In the MonarchE trial of adjuvant abemaciclib and endocrine therapy for high-risk early stage ER-positive/HER2-negative breast cancer, patients were evaluated with a tumor-informed

ctDNA assay before treatment and at 3, 6, and 24 months after treatment. All patients who had positive ctDNA at more than one time point experienced an invasive DFS (IDFS) event. Rates of IDFS events were lower for patients whose adjuvant treatment resulted in clearance of ctDNA (42%) or remained negative throughout the treatment course (15%).¹²⁴ Importantly, median time from ctDNA MRD detection to clinical recurrence across studies was 7–16 months, which highlights the window of opportunity and lead-time with liquid biopsies to timely identify disease recurrence and inform additional therapy interventions.^{121,122,124–126}

Incorporating a ctDNA-informed MRD approach, the ZEST trial enrolled patients with stage I to III disease who had completed adjuvant treatment but closed early after only 7.7% of the 1,901 patients tested were found to be ctDNA MRD-positive, on the basis of a tumor-informed bespoke assay with a LOD of 0.01%.¹²⁷ Two thirds of patients who were ctDNA MRD-positive were identified at the first ctDNA collection, and 51% of those had clinically detectable recurrence at time of ctDNA collection. Patients who were ctDNA MRD-positive were more likely to have positive lymph nodes, have larger tumors, stage III disease, and have residual disease after neoadjuvant therapy (thus collectively harbor known high-risk clinicopathologic features) in comparison with patients with negative ctDNA MRD status. Of note, patients who were treated on the basis of ctDNA MRD experienced a numerically higher RFS (11.4 months v 5.4 months) in comparison with patients who received placebo after MRD detection, suggesting that this approach, when implemented more precisely, may be effective. Although the optimal time point for ctDNA MRD screening is not well established, the ZEST study suggested that earlier ctDNA evaluation in the adjuvant setting may be beneficial.

The ongoing phase II DARE trial (ClinicalTrials.gov identifier: [NCT04567420](#)) is evaluating the impact of changing treatment on the basis of the presence of MRD via a tumor-informed ctDNA assay in the adjuvant setting. Patients who have completed at least 6 months of adjuvant endocrine therapy (and at least 12 months after finishing CDK4/6 inhibitor therapy, if received) for high-risk ER-positive/HER2-negative early-stage breast cancer are enrolled. Patients with ctDNA MRD undergo staging imaging; if staging imaging is negative, then patients are randomly assigned 1:1 to continue standard endocrine therapy or transition to palbociclib plus fulvestrant. In a preliminary feasibility announcement, a total of 37 tests were positive for ctDNA MRD out of 1,120 assays completed, for a 3.3% assay positivity rate.¹²⁸ In response to the admittedly very low ctDNA MRD positivity rate, the protocol has been amended to restrict enrollment of patients with high-risk clinicopathologic features (ClinicalTrials.gov identifier: [NCT04567420](#)).

Taken together, detecting ctDNA MRD may serve as a surrogate endpoint for neoadjuvant therapy and could potentially inform decisions for further adjuvant therapy, guiding therapy escalation to reduce recurrence or de-escalation to

minimize treatment-related toxicity. Nevertheless, as ctDNA MRD detection rates remain low, higher assay analytical sensitivity is required together with prospective validation of the clinical utility of ctDNA MRD for patients with early-stage breast cancer. Furthermore, tumor shedding rates vary across different breast cancer subtypes, with HR+ HER2– subtype exhibiting the lowest shedding, making detection particularly challenging for this patient population. Although patients with ctDNA MRD experience high relapse rates, further studies are needed to assess the clinical benefit of altering treatment strategies on the basis of ctDNA MRD detection. In tandem, ctDNA MRD detection can refine patient selection for adjuvant CDK4/6 inhibitors in addition to endocrine therapy in the adjuvant hormone receptor+ HER2– setting, and as such, alleviate unnecessary toxicities and financial burden. Similarly, for patients with stage I HER2-positive breast cancer or TNBC, assessing the need for adjuvant chemotherapy and HER2-directed therapy is critical, given the excellent survival rates without adjuvant therapy.

POTENTIAL OF LIQUID BIOPSIES TO ADDRESS UNMET CLINICAL NEEDS AND CIRCUMVENT CHALLENGES OF CONVENTIONAL APPROACHES

ctDNA-Informed Therapy in Oligometastatic/Oligoprogressive Disease

Liquid biopsies hold promise in guiding treatment strategies for patients with oligometastatic disease, potentially distinguishing between those who may benefit from curative-intent localized therapies (such as surgery and/or radiation therapy) and those who should continue with standard palliative systemic therapies. Detection of ctDNA before or after locoregional therapy for oligometastatic colorectal cancer has been shown to correlate with inferior outcomes,^{129,130} highlighting the role of ctDNA assessment in risk stratification in this patient population. Similarly, for patients with oligometastatic NSCLC, undetectable ctDNA levels before locally consolidative radiotherapy identified a subset of patients who attained longer PFS and OS.¹³¹ As the value of stereotactic body radiotherapy in targeting oligoprogressive NSCLC and breast cancer has been previously shown,¹³² liquid biopsy approaches can be used to identify candidates for localized ablative therapies as well as to longitudinally assess the treatment effectiveness for patients with oligometastatic disease.^{133,134}

Value of Liquid Biopsies in Interpretation of the Heterogeneity of Therapy Response

Accurate assessment of tumor burden and changes thereof with treatment are integral to inform medical decisions. To this end, ctDNA kinetics can be used to assess tumor burden in various clinical scenarios where conventional imaging can be inaccurate.³⁷ The challenge with radiographic imaging in timely and accurately capturing therapy response is exemplified in the context of radiographically stable disease for

patients receiving immunotherapy.^{37,135} ctDNA molecular responses may be particularly informative for this heterogeneous group, as ctDNA molecular response has been shown to predict PFS and OS in patients receiving immunotherapy-containing regimens and attaining stable disease on imaging.^{49,50} In more granularly evaluating tumor burden kinetics by RECIST, change in sum of longest diameters (SLD) inconsistently captures ctDNA dynamics and clearance and importantly, patients with molecular response but stable RECIST SLD have been reported to attain favorable clinical outcomes.^{49,50} Collectively, these findings highlight the limitations of imaging-based response assessments for accurate evaluation of therapeutic benefit from immunotherapy and the utility of ctDNA molecular response for capturing the magnitude of therapeutic responses in patients with radiographically stable disease. In addition to refining stable disease, longitudinal ctDNA monitoring can help distinguish between pseudoprogression and true disease progression on immunotherapy.¹³⁶ Another area of clinical need where ctDNA analyses can be uniquely informative is that of capturing tumor burden kinetics in patients with bone-predominant or bone-only metastatic disease. As an example, deterioration of skeletal symptoms due to reasons other than progressive disease, such as adverse events from aromatase inhibitors, constitutes a frequent clinical scenario that can be arbitrated with ctDNA analyses. Although ctDNA shedding may be limited in these patients, imaging or skeletal symptoms do not accurately capture the burden of metastatic disease, and more sensitive liquid biopsy assays have the potential to offer a molecular read-out of therapy response.

cfDNA Testing of Proximal Fluids

Plasma ctDNA may not correlate with disease extent in patients with serosal-only metastatic disease¹³⁷; however, pleural and peritoneal fluid tumor DNA analyses, falling under the greater auspices of liquid biopsy, can inform treatment selection,^{138,139} especially when serosal membranes constitute the predominant site of involvement and tumor tissue cannot be otherwise obtained. Similarly, ctDNA analysis in the CSF can improve the sensitivity in diagnosing leptomeningeal disease, inform treatment selection by identifying actionable resistance mutations, and monitor treatment response and emergence of resistance.¹⁴⁰⁻¹⁴⁵ Although CSF acquisition is an invasive procedure, the low cellularity of CSF in comparison with plasma coupled with the proximity of CSF to the CNS primary or metastatic tumor sites¹⁴⁶ leads to a lesser dilution of the ctDNA by nontumor cfDNA resulting in enriched variant allelic frequencies and increased sensitivity in detecting ctDNA compared with plasma.¹⁴⁵ CSF ctDNA can also capture the genomic profile of CNS metastatic disease that is known to diverge and evolve independently from that of systemic disease¹⁴⁷ and consequently, identify actionable alterations not detected in plasma ctDNA. Taken together and contingent on further validation for routine clinical use, ctDNA-informed approaches in these scenarios may address unmet clinical

needs especially where challenges exist with radiographic assessments and/or tissue sampling driven by the nature and progression patterns of the disease.

Integration of ctDNA Approaches With Functional Assessment of Circulating Tumor Cells

Although ctDNA analyses offer a reliable dynamic means to track tumor burden dynamics, CTCs offer another minimally invasive approach to capture the evolving cancer biology. For patients with breast cancer, the presence of CTCs, and especially CTC clusters, has been associated with inferior outcomes, as patients with five or more CTCs per 7.5 mL of blood have been reported to attain worse PFS and OS in comparison with patients with <5 CTCs.^{148,149} Although studies to date have not demonstrated a survival benefit in switching therapies on the basis of rising CTCs,^{150,151} CTCs may provide complementary insights into emerging therapy resistance through single-cell genomic analysis, cell imaging, and HER2 single-cell status assessment. This information is particularly valuable in enhancing our understanding of HER2 heterogeneity and inform potential HER2-targeted therapies, as seen in the DETECT III trial.¹⁵² Given that in the early-stage setting, CTCs are detected in approximately 20% of patients at diagnosis, further studies are needed to evaluate CTCs as a possible adjunct test for MRD. The underlying premise of integrating the cellular component with plasma cfDNA is that combined biomarkers may better address complex pressing clinical questions such as emergence of therapy resistance or development of immune-related adverse events.¹⁵³

Deconvolution of cfDNA Epigenetic Profiles to Infer Lineage Subtyping and Plasticity

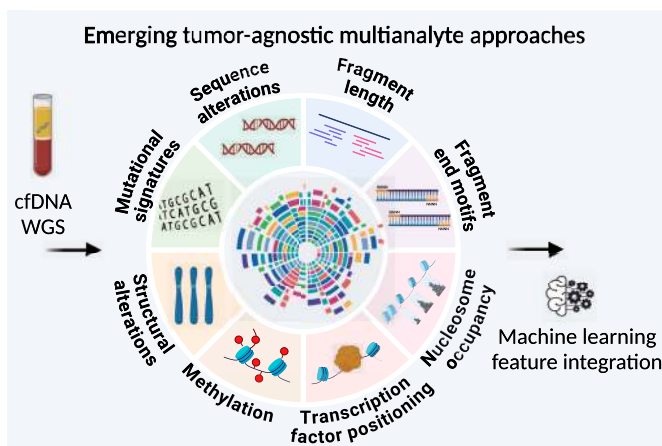
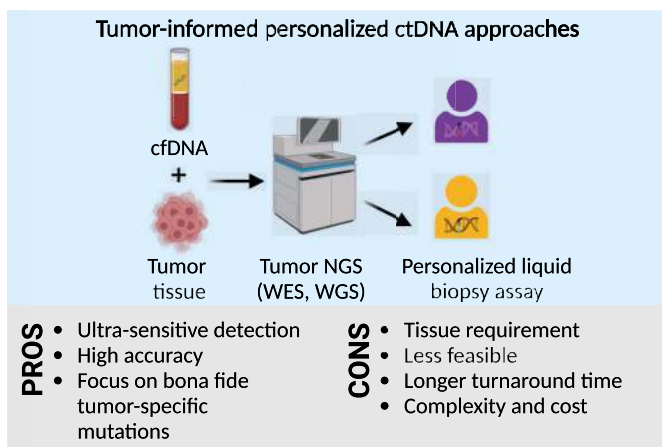
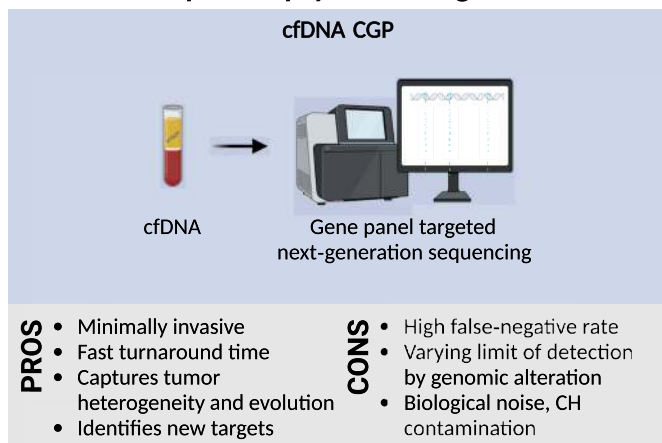
Interrogation of epigenetic profiles, directly via cfDNA methylation or indirectly via nucleosome positioning or cfDNA fragmentation patterns, can be informative in deducing cancer lineage, molecular subtyping, and histologic transformation.²⁷ By inferring differentially methylated loci from cfDNA fragmentation patterns in whole-genome sequence data, computational modeling has been shown to predict tissue-of-origin methylation profiles across human cancers, including triple-negative and HER2+ breast cancers.¹⁵⁴ Similarly, nucleosomal profiling has been shown to be informative in capturing breast cancer estrogen receptor subtyping.¹⁵⁵ Such approaches have the potential to obviate repeat invasive biopsies to determine and redetermine hormone receptor and HER2 status of metastatic breast cancer and optimize the use of HER2-targeting antibodies and antibody-drug conjugates. Although these methods may not replace tissue testing to assess receptor status at diagnosis or confirm metastatic breast cancer, they can be proven extremely useful in capturing the transcriptional changes caused by therapeutic pressure in metastatic hormone receptor-positive breast cancer and guide transition to chemotherapy. cfDNA fragmentation patterns could also be derived from targeted NGS data, routinely used for genotyping in clinical practice. Fragmentation patterns of the first exon can be

TABLE 3. Selected Active ctDNA-Informed Clinical Trials in Breast Cancer

Clinical Trial (phase)	Size	Stage/Subtype	Setting	Liquid Biopsy Assay	Assay Description	Intervention	Primary End Point	Results Expected
B-STRONGER-1 NCT06230185	422	Stage I to III/TNBC	Neoadjuvant	Personalis NeXT Personal CTA	Tumor-informed NGS (approximately 1,800 tumor-specific variants)	Observational	pCR	2025
SERENA-6 NCT04964934 (phase III)	3,000	Hormone receptor+/HER2–	Metastatic with stable disease on AI + CDK4/6 for ≥6 months	Guardant360CDx assay every 8-12 weeks	Hybrid capture NGS (74-gene panel)	If <i>ESR1</i> mutation detected, A: Switch AI to camizestrant, maintain same CDK4/6i B: Continue AI, maintain same CDK4/6i	PFS	2025
HARMONY NCT05433753	60	Stage IIA to IIIC/HER2+	Neoadjuvant and adjuvant	TOP + methylation level of DNA	DNA/RNA hybrid capture NGS (464-gene panel)	Observational	Invasive disease–free survival	2027
AMENDER NCT05345860	300	Stage I to III/Any	Adjuvant	<i>Unknown</i>		Tailor adjuvant therapy on the basis of clinical risk and presence of MRD	3-year disease-free survival	2027
MiRaDoR NCT05708235 (phase II)	1,260	pN2/N3 or pT3/T4N1 or high genomic risk or grade II/III and Ki-67 >20%/hormone receptor+/HER2–	2 years into adjuvant therapy	FoundationOne Tracker	Tumor-informed multiplex PCR NGS (2-16 tumor-specific variants)	If ctDNA+, randomized to A: Control B: Giredestrant C: Giredestrant + abemaciclib D: Giredestrant + inavolisib	ctDNA clearance	2028
EXActDNA-003 NCT06401421	1,800	T2N1 or T2N0 TNBC or T2N0 HER2+ or T2N0 hormone receptor+ with grade III or Ki-67 >20%	Neoadjuvant and adjuvant	Exact Sciences Oncodetect	Tumor-informed hybrid capture NGS (50-200 tumor-specific variants)	Observational	Distant recurrence–free interval	2030
TRAK-ER NCT04985266 (phase II)	1,100	T3 or N+ with T >3 cm, grade III or high genomic risk/ER+/HER2–	Adjuvant	Invitae personalized cancer monitoring	Tumor-informed multiplex PCR NGS (18-50 tumor-specific variants)	If ctDNA+, randomized to A: Endocrine therapy B: Palbociclib + fulvestrant	ctDNA positivity; relapse-free survival	2030
TREAT ctDNA NCT05512364 (phase III)	220	Stage IIB or III hormone receptor+/HER2– or RCB after neoadjuvant therapy	2 years into adjuvant therapy	Signatera ctDNA assay	Tumor-informed multiplex PCR NGS (16 tumor-specific variants)	If ctDNA+, randomized to Arm A: Maintain endocrine therapy Arm B: Switch to elacestrant	Distant metastasis–free survival	2030
SURVIVE NCT05658172 (phase III)	3,500	Neoadjuvant therapy or grade III or T3 or N+/any	Adjuvant	NeoGenomics RaDaR	Tumor-informed multiplex PCR NGS (48 tumor-specific variants)	A: Standard surveillance B: Surveillance with tumor markers, CTCs, and ctDNA	Overall survival; lead-time effect	2035

Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CTA, clinical trial assay; CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MRD, minimal residual disease; NGS, next-generation sequencing; pCR, pathologic complete response; PCR, polymerase chain reaction; PFS, progression-free survival; RCB, residual cancer burden; TNBC, triple–negative breast cancer; TOP, Today OncoPanel.

Liquid Biopsy Technologies



Liquid Biopsy Current and Emerging Applications

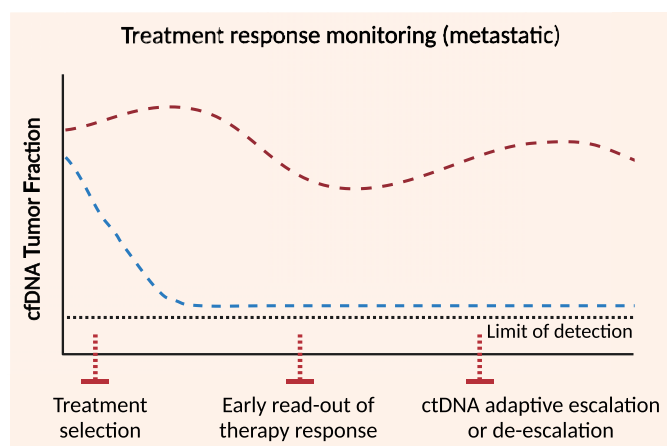
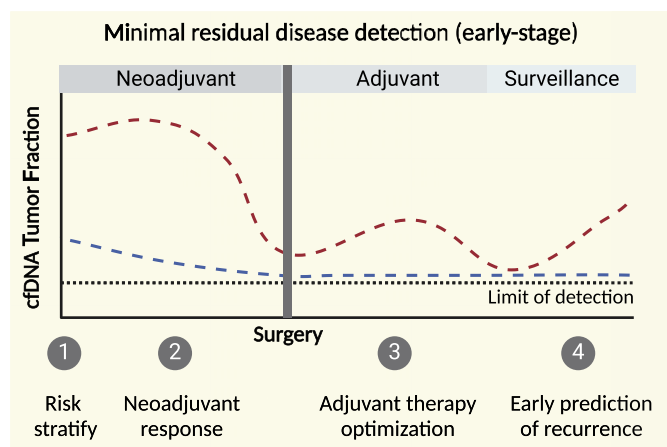
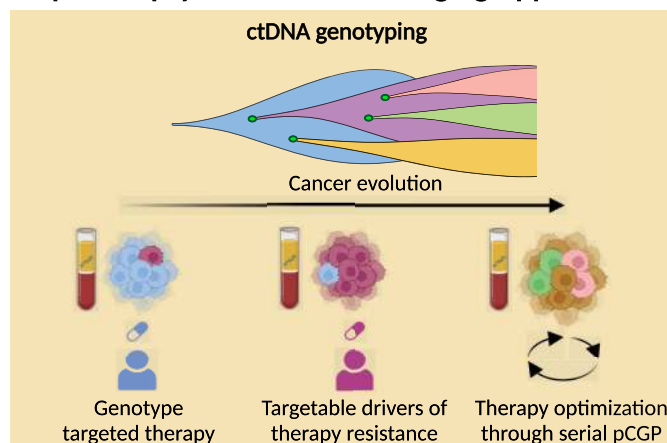


FIG 1. Liquid biopsy current and emerging technologies together with clinical applications and emerging uses in guiding precision oncology decision making. Plasma CGP leveraging targeted NGS enables identification of genotype-matched therapeutic targets, while serial assessments provide insights into the course of tumor evolution and aid in detection of targetable resistance mechanisms. In the context of ctDNA MRD detection in early-stage disease, tumor-informed approaches are used where tumor tissue WGS or WES data are used to design personalized liquid biopsy assays on the basis of the mutational profile of each tumor. Tumor-agnostic multianalyte technologies coupled with machine learning methodologies that incorporate ctDNA methylation, fragmentation, and mutational signature profiles hold promise for feasible, scalable, and sensitive residual disease detection. These approaches can be implemented at critical decision time points that affect the patient's disease trajectory. ctDNA analysis at the time of diagnosis of early-stage cancers allows risk stratification and patient selection for neoadjuvant therapies. Sequential assessments during or after completion of neoadjuvant therapy have the potential to determine treatment response and the need for further intervention after curative-intent surgery. ctDNA evaluation after surgery—within the 4- to 6-week postoperative window—may help select high-risk patients for intensified adjuvant therapy and guide treatment duration and maintenance strategies. During surveillance, ctDNA residual disease tracking offers a means of detecting recurrence earlier than radiologic imaging. In the (continued on following page)

FIG 1. (Continued). metastatic setting, longitudinal ctDNA molecular response monitoring during therapy enables early response assessment and informs therapy optimization on the basis of ctDNA dynamics (created in BioRender. Anagnostou, V (2025) <https://BioRender.com/ofknw5y>). cfDNA, cell-free DNA; CH, clonal hematopoiesis; ctDNA, circulating tumor DNA; CGP, comprehensive genomic profiling; MRD, minimal residual disease; NGS, next-generation sequencing; pCGP, plasma comprehensive genomic profiling; WES, whole-exome sequencing; WGS, whole-genome sequencing.

informative in deducing the transcriptional biology of the tumor of origin and in distinguishing tumor subtypes, including tumors with neuroendocrine differentiation.¹⁵⁶ Epigenomic profiling via capturing histone modifications has also been shown to provide a real-time read-out of transcriptional programs and point to cancer lineage, including in cases of lineage plasticity and neuroendocrine differentiation.¹⁵⁷ Taken together, cfDNA NGS data can be leveraged to infer epigenetic states of cancer cells as these evolve under selective pressure of therapy and may point to additional therapeutic vulnerabilities.

ctDNA-Adaptive Clinical Trials for Treatment Optimization

Importantly, tracking ctDNA residual disease has the exciting potential to both prevent undertreatment and overtreatment of patients in the early-stage, oligometastatic, and metastatic settings. The FDA has acknowledged the potential of liquid biopsy approaches and has issued a draft guidance on the development and implementation of ctDNA as a biomarker for solid tumor clinical trials.¹⁵⁸ Landmark and longitudinal ctDNA analyses can serve as a pivotal tool in guiding treatment escalation strategies in both early and metastatic cancers by enabling the early detection of specific mutations associated with therapeutic resistance. Such an approach facilitates timely intervention before clinical progression becomes apparent during both active treatment and surveillance. As discussed above, the PADA-1 escalation trial showed that liquid biopsy-informed early switch in antiestrogen therapies led to an improved PFS,^{113,114} and additional ongoing clinical trials using ctDNA approaches for early-stage breast cancer are summarized in Table 3. These trials will provide proof of concept to support whether change in management on the basis of ctDNA detection during adjuvant therapy will result in prevention of clinical recurrence. The value of real-time ctDNA monitoring and ctDNA-guided early treatment modification is currently being intensely investigated. The phase II APPLE trial included an arm in which first-line gefitinib was switched for osimertinib on the basis of positive *EGFR* T790M detection via ctDNA before RECIST progression, and this showed a comparable PFS and OS when compared with osimertinib upfront, although with higher rates of CNS progression.^{159,160} A nonrandomized controlled trial showed de-escalation of TKI guided by undetectable ctDNA in patients who attained complete remission after local consolidative therapy was feasible with equivalent outcomes to first-line TKI, potentially minimizing treatment-related toxicities without

compromising efficacy.¹⁶¹ An ongoing phase II study will assess ctDNA persistence after osimertinib monotherapy and randomly assign patients with persistent ctDNA to either continue osimertinib alone or augment with chemotherapy (ClinicalTrials.gov identifier: [NCT04410796](https://clinicaltrials.gov/ct2/show/study?term=NCT04410796)).

In parallel, liquid biopsy-informed treatment de-escalation aims to identify patients who may safely receive less intensive therapy while maintaining effective disease control. Such therapy optimization has the potential to reduce overtreatment, minimize toxicity, and improve quality of life without compromising outcomes, particularly by identifying patients with no detectable ctDNA who might forgo aggressive interventions. As an example, in early-stage colon cancer, the Circulating Tumor DNA Analysis Informing Chemotherapy for Stage II Colon Cancer (DYNAMIC) study evaluated the use of ctDNA MRD to guide adjuvant chemotherapy decisions in patients with stage II colon cancer.¹⁶² In this randomized trial, patients were assigned to either ctDNA-guided management, where chemotherapy was given only if ctDNA was detected postoperatively, or standard management on the basis of clinicopathologic features. The ctDNA-guided approach reduced chemotherapy use (15% v 28% in the standard group) without compromising RFS and similar 5-year OS rates.¹⁶³ These findings suggest that ctDNA can personalize treatment decisions, reducing unnecessary chemotherapy while maintaining effective cancer control. In the context of metastatic NSCLC, adaptive de-escalation strategies guided by ctDNA have been evaluated.

ctDNA molecular response-adaptive trials are underway for patients with advanced/metastatic NSCLC. A phase II study of pembrolizumab will measure ctDNA before cycle 3 and escalate therapy to include concurrent chemotherapy if patients have radiographic progressive or stable disease without plasma response (ClinicalTrials.gov identifier: [NCT04166487](https://clinicaltrials.gov/ct2/show/study?term=NCT04166487)). The second stage of BR36 will randomly assign patients with ctDNA molecular progression after 6 weeks of pembrolizumab to either continue pembrolizumab monotherapy or add chemotherapy with primary end points of PFS for the phase II and OS for the phase III portion of the study (ClinicalTrials.gov identifier: [NCT04093167](https://clinicaltrials.gov/ct2/show/study?term=NCT04093167)). These studies will provide critical insights on the clinical utility of real-time ctDNA monitoring and molecular response in guiding treatment escalation strategies.

CONCLUSIONS

The medical community has embraced liquid biopsies propelled by the insights they provide and the promise they hold

to improve patient outcomes. Over the past decade, significant advances in the development of liquid biopsy technologies have significantly improved the analytical performance and enabled ultra-sensitive ctDNA detection. Although CGP is becoming increasingly established as a critical diagnostic tool, increasing excitement surrounds the potential for liquid biopsy to influence cancer treatment practices through ctDNA-adaptive therapeutic strategies. However, implementing such strategies faces challenges, including the risk of false-negative results leading to undertreatment, variability in ctDNA detection sensitivity

across cancer types, tumor burden, and assay platforms, and potential selection biases because of the exclusion of patients with low ctDNA shedding. Additionally, ctDNA studies can have lead-time bias; therefore, associations with long-term end points such as OS need to be tested before ctDNA-adaptive strategies become common clinical practice. Nonetheless, the promise of liquid biopsy stands strong as it offers a minimally invasive approach to cancer characterization, residual disease detection, and treatment response monitoring, and can extend the promise of precision oncology across the cancer care continuum.

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REFERENCES

- Garcia-Pardo M, Makarem M, Li JJN, et al: Integrating circulating-free DNA (cfDNA) analysis into clinical practice: Opportunities and challenges. *Br J Cancer* 127:592-602, 2022
- Toden S, Goel A: Non-coding RNAs as liquid biopsy biomarkers in cancer. *Br J Cancer* 126:351-360, 2022
- Ring A, Nguyen-Sträuli BD, Wicki A, et al: Biology, vulnerabilities and clinical applications of circulating tumour cells. *Nat Rev Cancer* 23:95-111, 2023
- Kalluri R, McAndrews KM: The role of extracellular vesicles in cancer. *Cell* 186:1610-1626, 2023
- Li S, Lu Z, Wu S, et al: The dynamic role of platelets in cancer progression and their therapeutic implications. *Nat Rev Cancer* 24:72-87, 2024

6. Hu Z, Chen H, Long Y, et al: The main sources of circulating cell-free DNA: Apoptosis, necrosis and active secretion. *Crit Rev Oncol Hematol* 157:103166, 2021
7. Tivey A, Church M, Rothwell D, et al: Circulating tumour DNA—Looking beyond the blood. *Nat Rev Clin Oncol* 19:600-612, 2022
8. Jahr S, Hentze H, Englisch S, et al: DNA fragments in the blood plasma of cancer patients: Quantitations and evidence for their origin from apoptotic and necrotic cells. *Cancer Res* 61:1659-1665, 2001
9. Moss J, Magenheimer J, Neiman D, et al: Comprehensive human cell-type methylation atlas reveals origins of circulating cell-free DNA in health and disease. *Nat Commun* 9:5068, 2018
10. Leon SA, Shapiro B, Sklaroff DM, et al: Free DNA in the serum of cancer patients and the effect of therapy. *Cancer Res* 37:646-650, 1977
11. Bettgeowda C, Sausen M, Leary RJ, et al: Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med* 6:224ra24, 2014
12. Phallen J, Sausen M, Adleff V, et al: Direct detection of early-stage cancers using circulating tumor DNA. *Sci Transl Med* 9:eaan2415, 2017
13. Newman AM, Bratman SV, To J, et al: An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med* 20:548-554, 2014
14. Leary RJ, Sausen M, Kinde I, et al: Detection of chromosomal alterations in the circulation of cancer patients with whole-genome sequencing. *Sci Transl Med* 4:162ra54, 2012
15. Olsson E, Winter C, George A, et al: Serial monitoring of circulating tumor DNA in patients with primary breast cancer for detection of occult metastatic disease. *EMBO Mol Med* 7:1034-1047, 2015
16. Lo YMD, Han DSC, Jiang P, et al: Epigenetics, fragmentomics, and topology of cell-free DNA in liquid biopsies. *Science* 372:eaaw3616, 2021
17. Cristiano S, Leal A, Phallen J, et al: Genome-wide cell-free DNA fragmentation in patients with cancer. *Nature* 570:385-389, 2019
18. Mathios D, Johansen JS, Cristiano S, et al: Detection and characterization of lung cancer using cell-free DNA fragmentomes. *Nat Commun* 12:5060, 2021
19. Foda ZH, Annappagada AV, Boyapati K, et al: Detecting liver cancer using cell-free DNA fragmentomes. *Cancer Discov* 13:616-631, 2023
20. Medina JE, Annappagada AV, Lof P, et al: Early detection of ovarian cancer using cell-free DNA fragmentomes and protein biomarkers. *Cancer Discov* 15:105-118, 2025
21. Snyder MW, Kircher M, Hill AJ, et al: Cell-free DNA comprises an in vivo nucleosome footprint that informs its tissues-of-origin. *Cell* 164:57-68, 2016
22. Bai J, Jiang P, Ji L, et al: Histone modifications of circulating nucleosomes are associated with changes in cell-free DNA fragmentation patterns. *Proc Natl Acad Sci USA* 121:e2404058121, 2024
23. Esfahani MS, Hamilton EG, Mehrmohamadi M, et al: Inferring gene expression from cell-free DNA fragmentation profiles. *Nat Biotechnol* 40:585-597, 2022
24. Ulz P, Thallinger GG, Auer M, et al: Inferring expressed genes by whole-genome sequencing of plasma DNA. *Nat Genet* 48:1273-1278, 2016
25. Annappagada AV, Niknafs N, White JR, et al: Genome-wide repeat landscapes in cancer and cell-free DNA. *Sci Transl Med* 16:eadj9283, 2024
26. Jiang P, Sun K, Tong YK, et al: Preferred end coordinates and somatic variants as signatures of circulating tumor DNA associated with hepatocellular carcinoma. *Proc Natl Acad Sci USA* 115: E10925-E10933, 2018
27. Bruhm DC, Vulpescu NA, Foda ZH, et al: Genomic and fragmentomic landscapes of cell-free DNA for early cancer detection. *Nat Rev Cancer* [epub ahead of print on March 4, 2025]
28. Bruhm DC, Mathios D, Foda ZH, et al: Single-molecule genome-wide mutation profiles of cell-free DNA for non-invasive detection of cancer. *Nat Genet* 55:1301-1310, 2023
29. Esteller M, Sanchez-Cespedes M, Rosell R, et al: Detection of aberrant promoter hypermethylation of tumor suppressor genes in serum DNA from non-small cell lung cancer patients. *Cancer Res* 59:67-70, 1999
30. Shen SY, Singhanian R, Fehringer G, et al: Sensitive tumour detection and classification using plasma cell-free DNA methylomes. *Nature* 563:579-583, 2018
31. Shen SY, Burgener JM, Bratman SV, et al: Preparation of cfMeDIP-seq libraries for methylome profiling of plasma cell-free DNA. *Nat Protoc* 14:2749-2780, 2019
32. Guo S, Diep D, Plongthongkum N, et al: Identification of methylation haplotype blocks aids in deconvolution of heterogeneous tissue samples and tumor tissue-of-origin mapping from plasma DNA. *Nat Genet* 49:635-642, 2017
33. Liu MC, Oxnard GR, Klein EA, et al: CCGA Consortium: Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol* 31:745-759, 2020
34. Diehl F, Li M, He Y, et al: BEAMing: Single-molecule PCR on microparticles in water-in-oil emulsions. *Nat Methods* 3:551-559, 2006
35. Hindson BJ, Ness KD, Masquelier DA, et al: High-throughput droplet digital PCR system for absolute quantitation of DNA copy number. *Anal Chem* 83:8604-8610, 2011
36. Sivapalan L, Iams WT, Belcaid Z, et al: Dynamics of sequence and structural cell-free DNA landscapes in small-cell lung cancer. *Clin Cancer Res* 29:2310-2323, 2023
37. Sivapalan L, Murray JC, Canzoniero JV, et al: Liquid biopsy approaches to capture tumor evolution and clinical outcomes during cancer immunotherapy. *J Immunother Cancer* 11:e005924, 2023
38. Razavi P, Li BT, Brown DN, et al: High-intensity sequencing reveals the sources of plasma circulating cell-free DNA variants. *Nat Med* 25:1928-1937, 2019
39. Newman AM, Lovejoy AF, Klass DM, et al: Integrated digital error suppression for improved detection of circulating tumor DNA. *Nat Biotechnol* 34:547-555, 2016
40. U.S. Food & Drug Administration: List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools), 2025. <https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>
41. Anagnostou V, Forde PM, White JR, et al: Dynamics of tumor and immune responses during immune checkpoint blockade in non-small cell lung cancer. *Cancer Res* 79:1214-1225, 2019
42. Siravegna G, Mussolin B, Buscarino M, et al: Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients. *Nat Med* 21:795-801, 2015
43. Kasi PM, Lee JK, Pasquino LW, et al: Circulating tumor DNA enables sensitive detection of actionable gene fusions and rearrangements across cancer types. *Clin Cancer Res* 30:836-848, 2024
44. Chabon JJ, Hamilton EG, Kurtz DM, et al: Integrating genomic features for non-invasive early lung cancer detection. *Nature* 580:245-251, 2020
45. De Mattos-Arruda L, Mayor R, Ng CKY, et al: Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma. *Nat Commun* 6:8839, 2015
46. Lam VK, Zhang J, Wu CC, et al: Genotype-specific differences in circulating tumor DNA levels in advanced NSCLC. *J Thorac Oncol* 16:601-609, 2021
47. Leal A, van Grieken NCT, Palsgrove DN, et al: White blood cell and cell-free DNA analyses for detection of residual disease in gastric cancer. *Nat Commun* 11:525, 2020
48. Magee D, Domenyuk V, Abraham J, et al: Characterization of plasma cell-free DNA variants as of tumor- or clonal hematopoiesis-origin in 16,812 advanced cancer patients. *Clin Cancer Res* [epub ahead of print on February 26, 2025]
49. Murray JC, Sivapalan L, Hummelink K, et al: Elucidating the heterogeneity of immunotherapy response and immune-related toxicities by longitudinal ctDNA and immune cell compartment tracking in lung cancer. *Clin Cancer Res* 30:389-403, 2024
50. Anagnostou V, Ho C, Nicholas G, et al: ctDNA response after pembrolizumab in non-small cell lung cancer: phase 2 adaptive trial results. *Nat Med* 29:2559-2569, 2023
51. Reinert T, Henriksen TV, Christensen E, et al: Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncol* 5:1124-1131, 2019
52. Christensen E, Birkenkamp-Demtroder K, Sethi H, et al: Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma. *J Clin Oncol* 37:1547-1557, 2019
53. Shaw JA, Page K, Wren E, et al: Serial postoperative circulating tumor DNA assessment has strong prognostic value during long-term follow-up in patients with breast cancer. *JCO Precis Oncol* 10.1200/PO.23.00456
54. Abbosh C, Birkbak NJ, Wilson GA, et al: Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature* 545:446-451, 2017
55. Gale D, Heider K, Ruiz-Valdepenas A, et al: Residual ctDNA after treatment predicts early relapse in patients with early-stage non-small cell lung cancer. *Ann Oncol* 33:500-510, 2022
56. Northcott J, Bartha G, Harris J, et al: Analytical validation of NeXT Personal, an ultra-sensitive personalized circulating tumor DNA assay. *Oncotarget* 15:200-218, 2024
57. Zviran A, Schulman RC, Shah M, et al: Genome-wide cell-free DNA mutational integration enables ultra-sensitive cancer monitoring. *Nat Med* 26:1114-1124, 2020
58. Kurtz DM, Soo J, Co Ting Keh L, et al: Enhanced detection of minimal residual disease by targeted sequencing of phased variants in circulating tumor DNA. *Nat Biotechnol* 39:1537-1547, 2021
59. Nakamura Y, Tsukada Y, Matsushashi N, et al: Colorectal cancer recurrence prediction using a tissue-free epigenomic minimal residual disease assay. *Clin Cancer Res* 30:4377-4387, 2024
60. van 't Erve I, Alipanahi B, Lombard K, et al: Cancer treatment monitoring using cell-free DNA fragmentomes. *Nat Commun* 15:8801, 2024
61. Mazonne PJ, Bach PB, Carey J, et al: Clinical validation of a cell-free DNA fragmentome assay for augmentation of lung cancer early detection. *Cancer Discov* 14:2224-2242, 2024
62. Zhou Q, Kang G, Jiang P, et al: Epigenetic analysis of cell-free DNA by fragmentomic profiling. *Proc Natl Acad Sci USA* 119:e2209852119, 2022
63. Chung DC, Gray DM 2nd, Singh H, et al: A cell-free DNA blood-based test for colorectal cancer screening. *N Engl J Med* 390:973-983, 2024
64. U.S. Food & Drug Administration: Cobas EGFR Mutation Test V2 2016. <https://www.fda.gov/drugs/resources-information-approved-drugs/cobas-egfr-mutation-test-v2>
65. Pascual J, Attard G, Bidard FC, et al: ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: A report from the ESMO precision medicine working group. *Ann Oncol* 33:750-768, 2022
66. Rolfo C, Mack P, Scagliotti GV, et al: Liquid biopsy for advanced NSCLC: A consensus statement from the International Association for the Study of Lung Cancer. *J Thorac Oncol* 16:1647-1662, 2021
67. Minari R, Bordin P, Del Re M, et al: Primary resistance to osimertinib due to SCLC transformation: Issue of T790M determination on liquid re-biopsy. *Lung Cancer* 115:21-27, 2018
68. U.S. Food & Drug Administration: FDA approves osimertinib as adjuvant therapy for non-small cell lung cancer with EGFR mutations. 2020. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-osimertinib-adjuvant-therapy-non-small-cell-lung-cancer-egfr-mutations>
69. U.S. Food & Drug Administration: FDA approves atezolizumab as adjuvant treatment for non-small cell lung cancer. 2021. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-adjuvant-treatment-non-small-cell-lung-cancer>
70. U.S. Food & Drug Administration: FDA approves neoadjuvant nivolumab and platinum-doublet chemotherapy for early-stage non-small cell lung cancer. 2022. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvant-nivolumab-and-platinum-doublet-chemotherapy-early-stage-non-small-cell-lung>

71. U.S. Food & Drug Administration: FDA approves neoadjuvant/adjuvant pembrolizumab for resectable non-small cell lung cancer. 2023. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvant-adjuvant-pembrolizumab-resectable-non-small-cell-lung-cancer>
72. Aggarwal C, West HJ: Molecular marker testing in curable non-small cell lung cancer-practice necessarily precedes data. *JAMA Oncol* 9:758-760, 2023
73. Normanno N, Morabito A, Rachiglio AM, et al: Circulating tumour DNA in early stage and locally advanced NSCLC: Ready for clinical implementation? *Nat Rev Clin Oncol* 22:215-231, 2025
74. Owen DH, Chافت JE, Haura EB, et al: MA15.09 LCMC3: Long-term disease-free and overall survival and their association with ctDNA after neoadjuvant atezolizumab for NSCLC. *J Thorac Oncol* 19: S119, 2024
75. Kris MG, Grindheim JM, Chافت JE, et al: 10 dynamic circulating tumour DNA (ctDNA) response to neoadjuvant (NA) atezolizumab (atezo) and surgery (surg) and association with outcomes in patients (pts) with NSCLC. *Ann Oncol* 32:S1373, 2021
76. Provencio M, Nadal E, Insa A, et al: Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 25:1453-1464, 2024
77. Forde PM, Spicer J, Lu S, et al: Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* 386:1973-1985, 2022
78. Spicer J, Girard N, Provencio M, et al: Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816. *J Clin Oncol* 42, 2024 (suppl 17; abstr LBA8010)
79. Reck M, Gale D, Harpole D, et al: LBA59 associations of ctDNA clearance and pathological response with neoadjuvant treatment in patients with resectable NSCLC from the phase III AEGEAN trial. *Ann Oncol* 34:S1300-S335, 2023
80. Reck M, Gale D, Zhu Z, et al: LBA49 associations of ctDNA clearance (CL) during neoadjuvant Tx with pathological response and event-free survival (EFS) in pts with resectable NSCLC (R-NSCLC): Expanded analyses from AEGEAN. *Ann Oncol* 35:S1239, 2024
81. Zhou C, Thakur MD, Srivastava MK, et al: 20 IMPower010: Biomarkers of disease-free survival (DFS) in a phase III study of atezolizumab (atezo) vs best supportive care (BSC) after adjuvant chemotherapy in stage IB-IIIA NSCLC. *Ann Oncol* 32:S1374, 2021
82. Felip E, Srivastava M, Reck M, et al: 10 IMPower010: ctDNA status in patients (pts) with resected NSCLC who received adjuvant chemotherapy (chemo) followed by atezolizumab (atezo) or best supportive care (BSC). *Immuno-oncol Technol* 16:100106, 2022
83. John T, Grohe C, Goldman J, et al: Molecular residual disease (MRD) analysis from the ADAURA trial of adjuvant (adj) osimertinib in patients (pts) with resected EGFR-mutated (EGFRm) stage IB-IIIA non-small cell lung cancer (NSCLC). *J Clin Oncol* 42, 2024 (suppl 16; abstr 8005)
84. Black JRM, Bartha G, Abbott CW, et al: Ultrasensitive ctDNA detection for preoperative disease stratification in early-stage lung adenocarcinoma. *Nat Med* 31:70-76, 2025
85. Kelly RJ, Landon BV, Zaidi GR, et al: Neoadjuvant nivolumab or nivolumab plus LAG-3 inhibitor relatlimab in resectable esophageal/gastroesophageal junction cancer: A phase Ib trial and ctDNA analyses. *Nat Med* 30:1023-1034, 2024
86. Verschoor N, Bos MK, Oomen-de Hoop E, et al: A review of trials investigating ctDNA-guided adjuvant treatment of solid tumors: The importance of trial design. *Eur J Cancer* 207:114159, 2024
87. Mok TS, Wu YL, Ahn MJ, et al: Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* 376:629-640, 2017
88. Gray JE, Ahn MJ, Oxnard GR, et al: Early clearance of plasma epidermal growth factor receptor mutations as a predictor of outcome on osimertinib in advanced non-small cell lung cancer; exploratory analysis from AURA3 and FLAURA. *Clin Cancer Res* 29:3340-3351, 2023
89. Soria JC, Ohe Y, Vansteenkiste J, et al: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 378:113-125, 2018
90. Janne PA, Kobayashi K, Robichaux J, et al: Abstract CT017: FLAURA2: Exploratory analysis of baseline (BL) and on-treatment plasma EGFRm dynamics in patients (pts) with EGFRm advanced NSCLC treated with first-line (1L) osimertinib (osi) ± platinum-pemetrexed. *Cancer Res* 84:CT017, 2024 (suppl 7)
91. Felip E, Cho BC, Gutierrez V, et al: Amivantamab plus lazertinib vs osimertinib in first-line EGFR-mutant advanced non-small cell lung cancer (NSCLC) with biomarkers of high-risk disease: A secondary analysis from the phase 3 MARIPOSA study. *J Clin Oncol* 42, 2024 (suppl 16; abstr 8504)
92. Goldman J, Cho BC, Cheng S, et al: MA12.06 PAPILLON: TP53 Co-mutations, sites of insertion, and ctDNA clearance among patients with EGFR Ex20ins-mutated advanced NSCLC. *J Thorac Oncol* 19:S102-S103, 2024
93. Assaf ZJF, Zou W, Fine AD, et al: A longitudinal circulating tumor DNA-based model associated with survival in metastatic non-small-cell lung cancer. *Nat Med* 29:859-868, 2023
94. Assaf ZJ, Fine AD, Zou W, et al: MA07.02 evaluating circulating tumour DNA to predict overall survival risk in non-squamous non-small cell lung cancer in IMPower150. *J Thorac Oncol* 16: S905-S6, 2021
95. Cheng ML, Milan MSD, Tamen RM, et al: Plasma cfDNA genotyping in hospitalized patients with suspected metastatic NSCLC. *JCO Precis Oncol* 10.1200/PO.21.00029
96. Besse B, Subbiah V, Drilon A, et al: Detection and clearance of RET variants in plasma cell free DNA (cfDNA) from patients (pts) treated with LOXO-292. *Ann Oncol* 29:viii33, 2018
97. Soo RA, Martini JF, van der Wekken AJ, et al: Early circulating tumor DNA dynamics and efficacy of lorlatinib in patients with treatment-naïve, advanced, ALK-positive NSCLC. *J Thorac Oncol* 18: 1568-1580, 2023
98. Pawletz CP, Heavey GA, Kuang Y, et al: Early changes in circulating cell-free KRAS G12C predict response to adagrasib in KRAS mutant non-small cell lung cancer patients. *Clin Cancer Res* 29: 3074-3080, 2023
99. Paik PK, Veillon R, Felip E, et al: METex14 ctDNA dynamics & resistance mechanisms detected in liquid biopsy (LBx) from patients (pts) with METex14 skipping NSCLC treated with tepotinib. *J Clin Oncol* 39, 2021 (suppl 15; abstr 9012)
100. Planchard D, Jänne PA, Cheng Y, et al: Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC. *N Engl J Med* 389:1935-1948, 2023
101. Cho BC, Lu S, Felip E, et al: Amivantamab plus lazertinib in previously untreated EGFR-mutated advanced NSCLC. *N Engl J Med* 391:1486-1498, 2024
102. Jee J, Lebow ES, Yeh R, et al: Overall survival with circulating tumor DNA-guided therapy in advanced non-small-cell lung cancer. *Nat Med* 28:2353-2363, 2022
103. Vellanki PJ, Ghosh S, Pathak A, et al: Regulatory implications of ctDNA in immuno-oncology for solid tumors. *J Immunother Cancer* 11:e005344, 2023
104. Wang H, Zhou F, Qiao M, et al: The role of circulating tumor DNA in advanced non-small cell lung cancer patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis. *Front Oncol* 11:671874, 2021
105. Vega DM, Nishimura KK, Zariffa N, et al: Changes in circulating tumor DNA reflect clinical benefit across multiple studies of patients with non-small-cell lung cancer treated with immune checkpoint inhibitors. *JCO Precis Oncol* 10.1200/PO.21.00372
106. André F, Solovieff N, Su F, et al: Acquired gene alterations in patients treated with ribociclib plus endocrine therapy or endocrine therapy alone using baseline and end-of-treatment circulating tumor DNA samples in the MONALEESA-2, -3, and -7 trials. *Ann Oncol* 36:54-64, 2025
107. André F, Ciruelos E, Rubovszky G, et al: Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med* 380:1929-1940, 2019
108. Turner NC, Oliveira M, Howell SJ, et al: Capivasertib in hormone receptor-positive advanced breast cancer. *N Engl J Med* 388:2058-2070, 2023
109. Turner NC, Im SA, Saura C, et al: Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. *N Engl J Med* 391:1584-1596, 2024
110. O'Leary B, Cutts RJ, Liu Y, et al: The genetic landscape and clonal evolution of breast cancer resistance to palbociclib plus fulvestrant in the PALOMA-3 trial. *Cancer Discov* 8:1390-1403, 2018
111. Varkaris A, Fece de la Cruz F, Martin EE, et al: Allosteric PI3Kα inhibition overcomes on-target resistance to orthosteric inhibitors mediated by secondary PIK3CA mutations. *Cancer Discov* 14: 227-239, 2024
112. Bidard FC, Klamani VG, Neven P, et al: Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase III EMERALD trial. *J Clin Oncol* 40:3246-3256, 2022
113. Bidard FC, Hardy-Bessard AC, Dalenc F, et al: Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): A randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 23:1367-1377, 2022
114. Turner N, Huang-Bartlett C, Kalinsky K, et al: Design of SERENA-6, a phase III switching trial of camizestrant in ESR1-mutant breast cancer during first-line treatment. *Future Oncol* 19:559-573, 2023
115. Cavallone L, Aguilar-Mahecha A, Lafleur J, et al: Prognostic and predictive value of circulating tumor DNA during neoadjuvant chemotherapy for triple negative breast cancer. *Sci Rep* 10:14704, 2020
116. Chen JH, Addanki S, Roy D, et al: Monitoring response to neoadjuvant chemotherapy in triple negative breast cancer using circulating tumor DNA. *BMC Cancer* 24:1016, 2024
117. Magbanua MJM, Brown Swigart L, Ahmed Z, et al: Clinical significance and biology of circulating tumor DNA in high-risk early-stage HER2-negative breast cancer receiving neoadjuvant chemotherapy. *Cancer Cell* 41:1091-1102.e4, 2023
118. Cailleux F, Agostinetto E, Lambertini M, et al: Circulating tumor DNA after neoadjuvant chemotherapy in breast cancer is associated with disease relapse. *JCO Precis Oncol* 10.1200/PO.22.00148
119. Elliott M, Antras JF, Echelard P, et al: Abstract PS06-08: Longitudinal neoadjuvant and post-operative evaluation of circulating tumor DNA in early breast cancer using a tumor-informed assay: Updated analysis of the TRACER cohort. *Cancer Res* 84:PS06-08, 2024 (suppl 9)
120. Magbanua MJM, Swigart LB, Wu HT, et al: Circulating tumor DNA in neoadjuvant-treated breast cancer reflects response and survival. *Ann Oncol* 32:229-239, 2021
121. Coombes RC, Page K, Salari R, et al: Personalized detection of circulating tumor DNA antedates breast cancer metastatic recurrence. *Clin Cancer Res* 25:4255-4263, 2019

122. Janni W, Friedl T, Rack B, et al: Abstract PS06-06: Analysis of ctDNA for the detection of minimal residual disease (MRD) using a tissue-free, multiomic assay in patients with early-stage breast cancer. *Cancer Res* 84:PS06-06, 2024 (suppl 9)
123. Spring LM, Scarpetti L, Medford AJ, et al: Adjuvant endocrine therapy with cyclin-dependent kinase 4/6 inhibitor, ribociclib, for localized hormone receptor-positive/HER2- breast cancer (LEADER). *NPJ Breast Cancer* 11:2, 2025
124. Loi S, Johnston SRD, Arteaga CL, et al: Prognostic utility of ctDNA detection in the monarchE trial of adjuvant abemaciclib plus endocrine therapy (ET) in HR+, HER2-node-positive, high-risk early breast cancer (EBC). *J Clin Oncol* 42, 2024 (suppl 17; abstr LBA507)
125. Cutts R, Ulrich L, Beaney M, et al: Association of post-operative ctDNA detection with outcomes of patients with early breast cancers. *ESMO Open* 9:103687, 2024
126. Lipsyc-Sharf M, de Bruin EC, Santos K, et al: Circulating tumor DNA and late recurrence in high-risk hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer. *J Clin Oncol* 40:2408-2419, 2022
127. Turner N. GS3-01: Circulating tumor DNA surveillance in ZEST, a randomized, phase 3, double-blind study of niraparib or placebo in patients w/triple-negative breast cancer or HER2+ BRCA-mutated breast cancer with molecular residual disease after definitive therapy. *San Antonio Breast Cancer Symposium*; San Antonio, TX2024
128. Pusztai L, Kalashnikova E, Hobbs E, et al: Abstract PS06-02: Circulating tumor DNA (ctDNA) monitoring of estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) high risk breast cancer during adjuvant endocrine therapy. *Cancer Res* 84:PS06-02, 2024 (suppl 9)
129. Parikh AR, Chee BH, Tsai J, et al: Minimal residual disease using a plasma-only circulating tumor DNA assay to predict recurrence of metastatic colorectal cancer following curative intent treatment. *Clin Cancer Res* 30:2964-2973, 2024
130. O'Donnell CDJ, Naleid N, Siripoon T, et al: Circulating tumor DNA predicts early recurrence following locoregional therapy for oligometastatic colorectal cancer. *Cancers (Basel)* 16:2407, 2024
131. Semenkovich NP, Badiyan SN, Samson PP, et al: Pre-radiotherapy ctDNA liquid biopsy for risk stratification of oligometastatic non-small cell lung cancer. *NPJ Precis Oncol* 7:100, 2023
132. Tsai CJ, Yang JT, Shaverdian N, et al: Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (consolidative use of radiotherapy to block [CURB] oligoprogression): An open-label, randomised, controlled, phase 2 study. *Lancet* 403:171-182, 2024
133. Cortinovis D, Malapelle U, Pagni F, et al: Diagnostic and prognostic biomarkers in oligometastatic non-small cell lung cancer: A literature review. *Transl Lung Cancer Res* 10:3385-3400, 2021
134. Radigan R, Kao CS, Krainovich M, et al: Long-term survival and undetectable circulating tumor DNA following comprehensive involved site radiotherapy for oligometastases. *Sci Rep* 15:6126, 2025
135. Marron TU, Luke JJ, Hoffner B, et al: A SITC vision: Adapting clinical trials to accelerate drug development in cancer immunotherapy. *J Immunother Cancer* 13:e010760, 2025
136. Lee JH, Long GV, Menzies AM, et al: Association between circulating tumor DNA and pseudoprogression in patients with metastatic melanoma treated with anti-programmed cell death 1 antibodies. *JAMA Oncol* 4:717-721, 2018
137. Baumgartner JM, Botta GP: Role of circulating tumor DNA among patients with colorectal peritoneal metastases. *J Gastrointest Cancer* 55:41-46, 2024
138. Siravegna G, Marsoni S, Siena S, et al: Integrating liquid biopsies into the management of cancer. *Nat Rev Clin Oncol* 14:531-548, 2017
139. Wu H, Ji H, Yang W, et al: Liquid biopsy using ascitic fluid and pleural effusion supernatants for genomic profiling in gastrointestinal and lung cancers. *BMC Cancer* 22:1020, 2022
140. Bai K, Chen X, Qi X, et al: Cerebrospinal fluid circulating tumour DNA genotyping and survival analysis in lung adenocarcinoma with leptomeningeal metastases. *J Neurooncol* 165:149-160, 2023
141. Fitzpatrick A, Irvani M, Mills A, et al: Assessing CSF ctDNA to improve diagnostic accuracy and therapeutic monitoring in breast cancer leptomeningeal metastasis. *Clin Cancer Res* 28:1180-1191, 2022
142. Miao Q, Zheng X, Li L, et al: Cerebrospinal fluid circulating tumor DNA contributes to the detection and characterization of leptomeningeal metastasis in non-small cell lung cancer. *J Neurooncol* 165:517-525, 2023
143. van der Wel JWT, Boelens MC, Jebbink M, et al: Osimertinib-induced DNA resistance mutations in cerebrospinal fluid of epidermal growth factor receptor-mutated non-small-cell lung carcinoma patients developing leptomeningeal metastases: Osimertinib resistance analysis-leptomeningeal metastases study. *Neuro Oncol* 26:2316-2327, 2024
144. Zhao Y, He JY, Zou YL, et al: Evaluating the cerebrospinal fluid ctDNA detection by next-generation sequencing in the diagnosis of meningeal carcinomatosis. *BMC Neurol* 19:331, 2019
145. Zhu JW, Shum M, Qazi MA, et al: Cerebral spinal fluid analyses and therapeutic implications for leptomeningeal metastatic disease. *J Neurooncol* 172:31-40, 2025
146. Izhar M, Ahmad Z, Moazzam M, et al: Targeted liquid biopsy for brain tumors. *J Liq Biopsy*. 6:100170, 2024
147. Brastianos PK, Carter SL, Santagata S, et al: Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov* 5:1164-1177, 2015
148. Cristofanilli M, Budd GT, Ellis MJ, et al: Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med* 351:781-791, 2004
149. Zhang Q, Cai Z, Gerrata L, et al: Early evaluation of risk stratification and clinical outcomes for patients with advanced breast cancer through combined monitoring of baseline circulating tumor cells and DNA. *Clin Cancer Res* 30:3470-3480, 2024
150. Giuliano M, Giordano A, Jackson S, et al: Circulating tumor cells as early predictors of metastatic spread in breast cancer patients with limited metastatic dissemination. *Breast Cancer Res* 16:440, 2014
151. Cabel L, Berger F, Cottu P, et al: Clinical utility of circulating tumour cell-based monitoring of late-line chemotherapy for metastatic breast cancer: The randomised CirCe01 trial. *Br J Cancer* 124:1207-1213, 2021
152. Fehm T, Mueller V, Banys-Paluchowski M, et al: Efficacy of lapatinib in patients with HER2-negative metastatic breast cancer and HER2-positive circulating tumor cells-the DETECT III clinical trial. *Clin Chem* 70:307-318, 2024
153. Alix-Panabières C, Pantel K: Liquid biopsy: From discovery to clinical application. *Cancer Discov* 11:858-873, 2021
154. Liu Y, Reed SC, Lo C, et al: FinaleMe: Predicting DNA methylation by the fragmentation patterns of plasma cell-free DNA. *Nat Commun* 15:2790, 2024
155. Doebley AL, Ko M, Liao H, et al: A framework for clinical cancer subtyping from nucleosome profiling of cell-free DNA. *Nat Commun* 13:7475, 2022
156. Helzer KT, Sharifi MN, Sperger JM, et al: Fragmentomic analysis of circulating tumor DNA-targeted cancer panels. *Ann Oncol* 34:813-825, 2023
157. Baca SC, Seo JH, Davidsohn MP, et al: Liquid biopsy epigenomic profiling for cancer subtyping. *Nat Med* 29:2737-2741, 2023
158. U.S. Food & Drug Administration: Use of Circulating Tumor Deoxyribonucleic Acid for Early-Stage Solid Tumor Drug Development; Guidance for Industry; Availability. 2024. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-circulating-tumor-deoxyribonucleic-acid-early-stage-solid-tumor-drug-development-guidance>
159. Remon J, Besse B, Aix SP, et al: Osimertinib treatment based on plasma T790M monitoring in patients with EGFR-mutant non-small-cell lung cancer (NSCLC): EORTC lung cancer group 1613 APPLE phase II randomized clinical trial. *Ann Oncol* 34:468-476, 2023
160. Remon J, Besse B, Aix SP, et al: Overall survival from the EORTC LCG-1613 APPLE trial of osimertinib versus gefitinib followed by osimertinib in advanced EGFR-mutant non-small-cell lung cancer. *J Clin Oncol* 42:1350-1356, 2024
161. Dong S, Wang Z, Zhang JT, et al: Circulating tumor DNA-guided de-escalation targeted therapy for advanced non-small cell lung cancer: A nonrandomized controlled trial. *JAMA Oncol* 10:932-940, 2024
162. Tie J, Cohen JD, Lahouel K, et al: Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. *N Engl J Med* 386:2261-2272, 2022
163. Tie J, Wang Y, Lo SN, et al: Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial. *Nat Med* [epub ahead of print on March 7, 2025]

Treatment Innovations in Pancreatic Cancer: Putting Patient Priorities First

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OVERVIEW

Pancreatic adenocarcinoma remains one of the most aggressive and difficult-to-treat solid tumor malignancies, with a high mortality-to-incidence ratio. Globally, pancreatic cancer ranks 12th in terms of incidence but sixth for mortality signifying its aggressive behavior and limited treatment options. While the mortality rates for many other solid tumors have substantially improved over the past few decades, temporal trends in pancreatic cancer mortality rates are quite sobering. In the United States, from 2000 to 2020, the mortality rates from pancreatic cancer have increased, whereas at the same time, mortality rates from other cancers, such as lung, colorectal, or kidney, have fallen appreciably. Is this for lack of treatment innovation? How do we improve survival for patients with pancreatic cancer? In this chapter, we discuss the recent advances and future directions with targeted therapies and immunotherapies in the treatment of pancreatic cancer, and provide the reasons for both optimism and caution for the future of systemic treatment of pancreatic cancer.

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INTRODUCTION

Until recently, the mainstay of systemic treatment of pancreatic cancer has been chemotherapy.^{1,2} The first treatment to be approved for advanced pancreatic cancer was gemcitabine, which was tested in a 1997 trial against fluorouracil. Gemcitabine led to weight gain and decreased pain, leading to improved quality of life.³ In 2007, a phase III randomized controlled trial showed statistically significant but clinically dubious improvement in overall survival (OS) of a median of 10 days by the addition of erlotinib to gemcitabine.⁴ Since then, two clinical trials from 2011 and 2013 have established the chemotherapy combinations of 5-fluorouracil plus irinotecan plus oxaliplatin (FOLFIRINOX)⁵ and gemcitabine plus nab-paclitaxel⁶ as the standard-of-care first-line therapy on the basis of OS improvements of four and two months, respectively, against gemcitabine monotherapy. These are still the standard-of-care options because no other treatments have shown superiority over these combinations in the past decade.⁷

The median OS for a patient diagnosed with advanced pancreatic cancer at present remains less than a year, in part, because of the lack of efficacy of novel therapeutics such as targeted therapies and immunotherapies in this disease. Indeed, it is telling that the standard first-line treatment of pancreatic cancer at present has remained the same for the past decade. However, this is not for lack of effort,⁷ and recent developments offer reasons for cautious optimism. In this chapter, we discuss targeted drugs and immunotherapy in pancreatic cancer.

PROGRESS AND CHALLENGES OF TARGETED THERAPY IN PANCREATIC CANCER

Over the past decade, research has helped identify several possible actionable targets in pancreatic cancer that could be harnessed for therapeutic efficacy. Most currently targetable variants are only present in a small percentage of patients (**Fig 1**); however, the recent development of pan-KRAS and KRAS G12D targeting compounds has the potential to transform pancreatic cancer to a much more targetable disease. Challenges to this transformation include low cellularity tumor tissue for somatic sequencing, innate and adaptive resistance, and optimization of therapeutic sequencing. Finally, for most rare variants, adequate representation of patients with pancreatic cancer in tumor agnostic trials has limited our ability to draw conclusions regarding efficacy.

Germline and Somatic Testing Guidelines and Challenges

Guidelines now recommend germline panel testing for all patients diagnosed with pancreatic cancer (excluding neuroendocrine tumors), regardless of stage, family or personal history of cancer, and somatic sequencing for all patients with advanced disease. The latter presents a unique challenge: Pancreatic cancer is hypocellular, and primary tumor biopsies are often fine-needle aspirates that provide limited material. Core tissue helps maximize the opportunity for somatic testing. Circulating tumor material assays can be sent as alternatives, although these tests share their own

PRACTICAL APPLICATIONS

- Chemotherapy combinations have remained the mainstay of treating advanced pancreatic cancer for past several decades.
- Several potential targets have now been identified, many of which are actionable with newer targeted therapies.
- Novel vaccination strategies such as personalized mRNA vaccines and lymph node-targeted mKRAS vaccines have shown promise in early clinical trials.
- Targeted approach and immunotherapies hold promise to improve outcomes for patients with advanced pancreatic cancer, but need to be tested in clinical trials.
- Clinical trials should be designed to test for outcomes that matter to patients and report data without bias.

challenges: (1) They are currently not as comprehensive; (2) pancreatic cancer does not shed prolifically into the blood stream, leading to risk that tumoral variants are missed; and (3) some variants identified in blood may be the result of clonal hematopoiesis rather than originating in the tumor.

As the menu of targetable alterations expands, specifications of various testing platforms should be considered. For example, pathogenic fusions can be missed by DNA sequencing and are better identified by RNA sequencing.⁸ Additionally, for human epidermal growth factor receptor 2 (HER2) amplification, immunohistochemistry and reflex in situ hybridization are more appropriate. An understanding of the available therapeutic targets and their expected clinical benefit is required for shared decision making.

Available Targeted Treatments of Pancreatic Cancer

Microsatellite Instability/Tumor Mutational Burden

The anti-PD-1 antibody pembrolizumab was US Food and Drug Administration (FDA) approved in 2017 for the treatment of advanced, microsatellite instability-high (MSI-high) solid tumors (Table 1). Pancreatic cancer is estimated to be MSI-H in only 1% of patients and, as such, was minimally represented in the studies that led to this approval.²⁷ Indeed, the reported response rate of MSI-H pancreatic cancer to single-agent anti-PD-1 ranges from 18%²⁸ to 62%.¹² In 2020, the FDA approved anti-PD-1 therapy for any solid tumor with a high tumor mutational burden (TMB) on the basis of an analysis of the KEYNOTE-158 study that showed an association between

TMB >10 mut/Mb and response to pembrolizumab.¹⁴ There were 63 patients with biliary cancers in this analysis, none of whom had TMB >10 mut/Mb. The activity of anti-PD-1 treatment of TMB-high pancreatic cancer, particularly in the absence of MSI, is likely limited. Two additional immunotherapies are in the National Comprehensive Cancer Network (NCCN) guidelines for patients with MSI-H or TMB-high pancreatic cancer: the combination of nivolumab/ipilimumab for patients with TMB-high cancers¹⁵ and dostarlimab for patients with MSI-H cancers.¹³ Testing immunotherapy in the MSI-H or TMB-high setting for pancreatic cancer is particularly challenging because of the very small number of patients with these findings. As such, they are rolled into tissue agnostic trials that improve feasibility, but ultimately lead to minimal representation of pancreatic cancer in the results.

BRCA/PALB2 Mutations

Approximately 5%–10% of patients with pancreatic cancer have germline or somatic pathogenic variants in *BRCA1*, *BRCA2*, or *PALB2*. Germline variants lead to biallelic loss and subsequent tumoral homologous recombination deficiency (HRD) nearly 90% of the time.²⁹ For somatic variants, this correlation is less robust.

In a 2020 study, patients with newly diagnosed metastatic pancreatic cancer and germline variants in *BRCA* or *PALB2* were randomly assigned to cisplatin plus gemcitabine with or without veliparib. Although veliparib did not add activity, the robust response rate of approximately 70% in both arms supported cisplatin plus gemcitabine as an important therapeutic option for this population.⁹ Retrospective studies suggest that other platinum-containing regimens such as FOLFIRINOX; infusional fluorouracil, leucovorin, and oxaliplatin; and gemcitabine/oxaliplatin are also effective.³⁰ Whenever possible, platinum-based chemotherapies are preferred for patients with *BRCA* or *PALB2*-related pancreatic cancer.

Prolonged durability of response to platinum-based therapy may be observed in patients with *BRCA* or *PALB2*-related pancreatic cancer. Indeed, in the veliparib trial discussed above, the median progression-free survival (mPFS) in both arms was 10 months. The randomized phase III POLO trial tested maintenance olaparib for patients with germline *BRCA* variants¹⁰; however, this trial has been criticized for the use of a placebo control and no improvement in OS or quality of life.^{7,31} A phase II single-arm trial tested rucaparib for patients with either germline or somatic variants in *BRCA* or *PALB2* and showed an encouraging mPFS of 13.1 months and OS of 23.5 months.¹¹

Medians do not tell the whole story for the activity of poly(ADP-ribose) polymerase inhibitors (PARPis) in pancreatic cancer. Indeed, there is wide variability in outcomes: Approximately 25% of patients progress rapidly while another 25% of patients have long-term stable disease for >3 years.³² Explanations for rapid progression include monoallelic loss

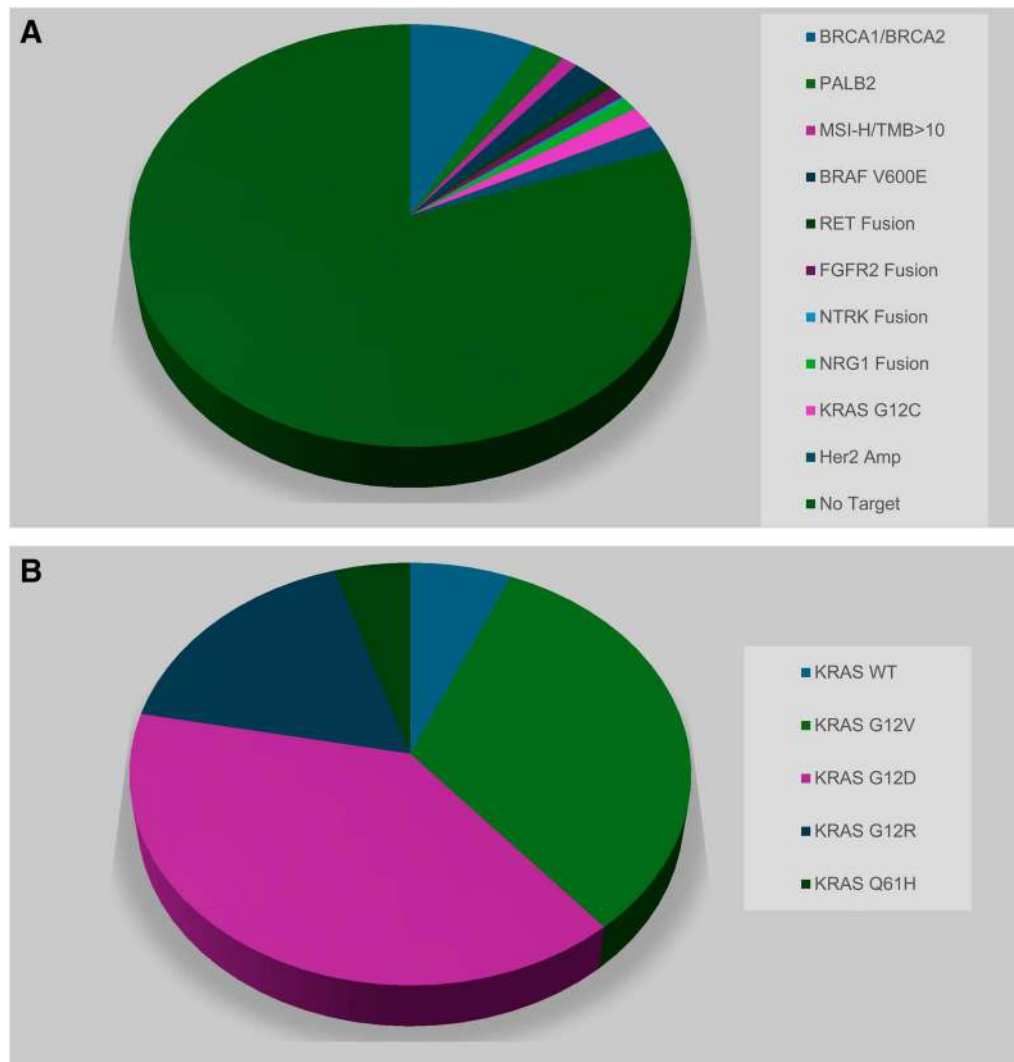


FIG 1. (A) Percentage of pancreatic cancers with currently targetable variants. (B) Percentage of pancreatic cancers with potentially targetable KRAS variants. Pancreatic cancer has recently gone from being an entirely untreatable disease to one that has several druggable germline and somatic variants, albeit rare ones. Our current active targets are shown in this pie chart. It is important to note that the list is actively growing—in particular, the expansion of targetable KRAS variants, specifically KRAS G12D—the first molecule for which recently entered phase I testing—and KRAS G12V—may drastically alter the landscape of precision for pancreatic cancer. Amp, amplification; MSI-H, microsatellite instability-high; TMB, tumor mutational burden; WT, wild type.

(ie, lack of HRD in the tumor) and development of reversion variants,^{32,33} although much remains unknown about additional mechanisms of resistance to PARPi in pancreatic cancer. Multiple active trials are addressing the issue of resistance with up-front combinations as well as post-PARPi progression treatments. These include combinations with immunotherapy, Pol-θ inhibitors, and USP1 inhibitors.

KRAS G12C

Mutations in *KRAS G12C*, present in 1%-2% of patients with pancreatic cancer, were the first of the *KRAS* variants to demonstrate targetability. In 2022, Strickler et al²⁵ published

the partial results of CODEBREAK100, a phase I/II trial studying sotorasib in patients with *KRAS G12C*-mutated solid tumors. As part of this group, they treated 38 patients with advanced pancreatic cancer who had progressed on first-line treatment, of which eight (21%) had an objective response. The PFS and OS were 4.0 months and 6.9 months, respectively. In 2023, Bekaii-Saab et al²⁴ published the results of KRYSTAL-1, which evaluated the activity of adagrasib in patients with *KRAS G12C*-mutated solid tumors. Twenty-one patients with advanced pancreatic cancer enrolled, of whom 22% had an objective response. The PFS and OS of these 21 patients were 5.4 and 8.0 months, respectively.²⁴ As with many monotherapy-targeted treatments, rapid development of resistance is a key challenge. To delay

TABLE 1. Targeted Treatments of Pancreatic Cancer

Target	Agent(s); FDA Approved or NCCN Guidelines	Prevalance, %	Settings	Reference(s)
<i>BRCA1, BRCA2, PALB2</i>	Cisplatin/gemcitabine (germline only) Olaparib (germline only) Rucaparib (germline or somatic)	5%-10%	LAPC (gem/cis) Metastatic/recurrent first line (gem/cis) Metastatic/recurrent second line+ (gem/cis) Maintenance (olaparib or rucaparib)	O'Reilly et al ⁹ Golan et al ¹⁰ Reiss et al ¹¹
MSI-H	Pembrolizumab Dostarlimab	1%	LAPC (pembro) Metastatic/recurrent first line (pembro) Metastatic/recurrent second line+ (pembro) Metastatic/recurrent second line+ (dostarlimab)	Le et al ¹² Marabelle et al ⁵⁷ André et al ¹³
TMB >10 mut/Mb	Pembrolizumab Nivolumab/ipilimumab	1%	LAPC (pembro) Metastatic/recurrent first line (pembro) Metastatic/recurrent second line+ (pembro) Metastatic/recurrent second line+ (nivo/ipi)	Marabelle et al ¹⁴ Schenker et al ¹⁵
<i>BRAF V600E</i>	Dabrafenib/trametinib	2.2%	LAPC Metastatic/recurrent first line Metastatic/recurrent second line+	Salama et al ¹⁶ Subbiah et al ¹⁷
RET fusion	Selpercatinib	0.6%	LAPC Metastatic/recurrent first line Metastatic/recurrent second line+	Subbiah et al ¹⁸
<i>FGFR2</i> fusion	Erdafitinib	1%	Metastatic/recurrent second line+	Pant et al ¹⁹
<i>NTRK</i> fusion	Entrectinib Larotrectinib Repotrectinib	0.22%	Metastatic/recurrent first line Metastatic/recurrent second line+	Drilon et al ²⁰ Doebele et al ²¹ Hong et al ⁵⁸ Solomon et al ²²
<i>NRG1</i> fusion	Zenocutuzumab	1%	Metastatic/recurrent second line+	Schram et al ²³
<i>KRAS G12C</i>	Adagrasib Sotorasib	1.7%	Metastatic/recurrent second line+	Bekaii-Saab et al ²⁴ Strickler et al ²⁵
HER2 amp	Fam-trastuzumab deruxtecant-nxki	2%	Metastatic/recurrent second line+	Meric-Bernstam et al ²⁶

Abbreviations: amp, amplification; cis, cisplatin; FDA, US Food and Drug Administration; gem, gemcitabine; HER2, human epidermal growth factor receptor 2; ipi, ipilimumab; LAPC, locally advanced pancreatic cancer; MSI-H, microsatellite instability–high; mut, mutation; NCCN, National Comprehensive Cancer Network; nivo, nivolumab; pembro, pembrolizumab; TMB, tumor mutational burden.

resistance, trials are combining *KRAS G12C* inhibitors with other agents, such as EGFR antibodies and SHP2 inhibitors. Additionally, a second generation of *KRAS G12C* inhibitors is being tested in patients who have already progressed on prior *KRAS G12C*–targeted therapy.

BRAF V600E

The role of *BRAF*–targeting therapy for pancreatic cancer is largely based on case reports as the rarity of the *BRAF V600E* mutation in pancreatic cancer is prohibitive to generate adequate prospective data. Two prospective clinical trials of solid tumors with *BRAF V600E* variants have been published, although pancreatic cancer was minimally represented: The

2023 ROAR trial¹⁷ included no patients with pancreatic cancer, and the NCI-MATCH trial¹⁶ enrolled two patients with pancreatic cancer, neither of whom had a response to therapy. Nonetheless, the NCCN guidelines recommend dabrafenib plus trametinib for patients with previously treated pancreatic cancer harboring *BRAF V600E* variants.

HER2 Amplification

The phase II DESTINY–PanTumor02 clinical trial demonstrated the efficacy of trastuzumab–deruxtecant (T–Dxd) in patients with advanced solid tumors who had received at least 1 prior systemic therapy.²⁶ A total of 267 patients were treated, of which 25 had pancreatic cancer. One patient had a

partial response and 16 had stable disease, and the mPFS was 3.2 months. Owing to the minimal benefit, the pancreatic cancer cohort was stopped early, although it was noted that only two patients in this group had HER2 3+ disease. T-DXd has a pantumor FDA approval and is in the NCCN guidelines for patients with advanced, previously treated pancreatic cancer.

Fusions

Pancreatic cancers display pathogenic fusions in approximately 1.2% of patients and are highly enriched in KRAS wild-type tumors, highlighting the role of fusion as true cancer drivers. Indeed, pancreatic cancers with pathogenic fusions are also less likely to have other common driver mutations (ie, *TP53*, *SMAD4*, *CDKN2A*).³⁴ Multiple fusions are targetable including those in *NTRK*, *NRG1*, *FGFR2*, and *RET*.

For patients with pancreatic cancer and *NTRK* fusions, there are three potential therapeutic options: entrectinib and larotrectinib for tyrosine kinase inhibitor (TKI)-naïve patients and repotrectinib for patients who are either naïve or resistant to prior TKI. All three drugs received pantumor approvals from the FDA on the basis of several key trials that enrolled previously treated patients with solid tumors harboring *NTRK* fusions.^{20–22} Notably, pancreatic cancer was minimally represented in these studies, highlighting the rarity of the alteration in this population.

Selpercetinib was approved for the treatment of solid tumors with *RET* fusions on the basis of the LIBRETTO-001 trial,¹⁸ which included 11 evaluable patients with pancreatic cancer, six of whom had a partial response to treatment.

Erdafitinib is in the NCCN guidelines for patients with pancreatic cancer and *FGFR* fusions based on the single-arm, phase II RAGNAR trial¹⁹ that included 18 patients with pancreatic cancer of whom 10 (55%) had an objective response to treatment.

Most recently, the FDA granted approval for the use of zenocutuzumab, a HER2/HER3 bispecific antibody, for patients with *NRG1* fusions and either NSCLC or pancreatic cancer. The approval was based on a tumor-agnostic phase II trial that included 29 patients with pancreatic cancer, of whom 13 had an objective response to treatment. The median duration of response in this population was 7.4 months.²³

Pan-KRAS/KRAS G12D

Pathogenic *KRAS* mutations are present in >90% of pancreatic adenocarcinomas⁵⁹ with *KRAS G12D*, *KRAS G12V*, and *KRAS G12R* being the most prevalent. *KRAS* had previously been described as an undruggable therapeutic target because of its smooth protein structure and undesirable polarity, making it difficult to generate inhibitors that could successfully bind to its surface.³⁵ However, the newfound ability to overcome this challenge—spearheaded by the discovery

of a compound that could bind into the small pocket of the *KRAS Gly12Cys* protein—has opened the door for further drug discovery. Multiple compounds are now under active clinical investigation in monotherapy and in combinations (Table 2) including pan-KRAS inhibitors and *KRAS G12D* inhibitors, which will be of highest relevance to patients with pancreatic cancer.

Treatment of Early-Stage Disease

As we make progress in the treatment of patients with targetable, advanced pancreatic cancer, there is hope that some of these agents may ultimately prove beneficial to patients in early-stage disease settings. In general, the rarity of variants makes the study of an even smaller population (ie, the 10%–15% of patients with surgically resectable disease) highly challenging. For example, the ongoing EA2192 (APOLLO) trial is investigating the role of adjuvant olaparib in patients with germline or somatic *BRCA* or *PALB2* variants who have completed all standard curative-intent therapy. This study is open nationally and in Israel. Additionally, multiple adjuvant *KRAS*-targeting vaccine trials are in progress for patients who have undergone curative-intent resection and adjuvant chemotherapy.

Stimulating the Immune System to Treat Pancreatic Cancer

The foundation of cancer immunotherapy is therapeutically unleashing the host's immune system to recognize and kill cancer cells. This can be achieved by disrupting immunosuppressive signals with immune checkpoint inhibitors or augmenting tumor-specific T-cell responses with adoptive T-cell therapy or vaccination. Stimulating the immune system to treat pancreatic cancer has been uniquely challenging with poor response observed to conventional single-agent immune checkpoint inhibitors and only isolated success with adoptive T-cell therapies.^{36–39} The proposed barriers to mounting an effective immune response in pancreatic cancer include its immunosuppressive tumor microenvironment, relatively low mutational burden, and overall oncologic aggressiveness, often presenting at an advanced stage of disease.⁴⁰

Despite these barriers, novel vaccination strategies with personalized mRNA vaccines and lymph node-targeted mutant *KRAS* (mKRAS) vaccines, as well as combinatorial immunotherapy strategies, have shown promise in successfully stimulating antitumor immune responses in patients with pancreatic cancer.^{41–43} Results from these early-phase clinical trials, as well as ongoing phase II trials, have renewed hope in the future of immunotherapy for pancreatic cancer (Table 3). Moving forward, studying novel immunotherapy strategies to treat pancreatic cancer in the setting of adaptive clinical trials will optimize ongoing discovery and improve the efficiency of translating early discovery to improved patient outcomes.

TABLE 2. Ongoing Clinical Trials of Targeted Therapeutics in or Including Pancreatic Cancer

Clinical Trial	Compound (company)	Phase	Target	Population
Phase 1/2 Study of TSN1611 in Subjects With KRAS G12D Mutant Advanced Solid Tumors	TSN1611 (Tyligand Therapeutics)	I/II	KRAS G12D	Phase I: solid tumors Phase II: PDAC, CRC, NSCLC
A Study of the Pan-KRAS Inhibitor LY4066434 in Participants With KRAS Mutant Solid Tumors	LY4066434 (Lilly)	I	Pan-KRAS	Solid tumors
Study of RMC-9805 in Participants With KRAS G12D Mutant Solid Tumors	RMC9805 (Revolution Medicine)	I	KRAS G12D	Solid tumors
A Study of LY3962673 in Participants With KRAS G12D Mutant Solid Tumors	LY3962673 (Lilly)	I	KRAS G12D	Solid tumors
Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS	RMC6236 (Revolution Medicine)	I/Ib	Pan-KRAS	Solid tumors
A First-in-human Study of BGB-53038, a Pan-KRAS Inhibitor, Alone or in Combinations in Participants With Advanced or Metastatic Solid Tumors With KRAS Mutations or Amplification	BGB53038 (Beigene)	Ia/Ib	Pan-KRAS	Solid tumors
Study of RAS(ON) Inhibitors in Patients With Gastrointestinal Solid Tumors	RMC6236 RMC9805	Platform	Pan-KRAS KRAS G12D	Pancreatic cancer Colorectal cancer
A Study to Evaluate INCB161734 in Participants With Advanced or Metastatic Solid Tumors With KRAS G12D Mutation	INCB161734 (Incyte)	I	KRAS G12D	Solid tumors
Phase 3 Study of RMC-6236 in Patients With Previously Treated Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (RASolute 302)	RMC6236	III	Pan-KRAS	Pancreatic cancer
A Phase I/IIa Study of AZD0022 as Monotherapy and in Combination With Anti-cancer Agents in Adult Participants With Tumors Harboring a KRASG12D Mutation (ALA-FOSS-01)	AZD0022 (AstraZeneca)	I/IIa	KRAS G12D	Solid tumors

Abbreviations: CRC, colorectal cancer; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

Personalized mRNA Neoantigen Vaccines

Although pancreatic cancer is considered poorly immunogenic and has a relatively low mutational burden, the immune system still plays an important role in a subset of patients as evident by the positive correlation of intra-tumoral T-cell density with patient outcomes.⁴⁰ By studying long-term survivors of pancreatic cancer, high-quality neoantigens that were unique to individual patients were found to be a biomarker for immunogenic tumors and were associated with improved survival.⁴⁴ The observation of unique high-quality neoantigens in pancreatic cancer, in conjunction with the advancement of mRNA vaccine technology, allowed for the investigation of personalized mRNA vaccination in patients with resected pancreatic cancer. This

personalized strategy was a major deviation from conventional vaccination approaches that target shared neoantigens.^{41,45}

A phase I clinical trial of personalized mRNA neoantigen vaccines (autogene cevumeran) plus atezolizumab, followed by standard-of-care modified FOLFIRINOX, was conducted in 16 patients with surgically resected pancreatic cancer.⁴¹ Vaccination was safe and induced a neoantigen-specific T-cell response in 8 of 16 patients. Vaccine responders, defined as those with vaccine-expanded T cells, had a longer recurrence-free survival than nonresponders. Recently reported long-term follow-up data (median follow-up 3.2 years) has demonstrated the durability of the antigen-specific vaccine T-cell response and promising recurrence

TABLE 3. Completed and Ongoing Vaccine Immunotherapy Trials in Pancreatic Cancer

Trial	Phase	Inclusion	Intervention	Primary Outcome	Secondary Outcomes
Personalized mRNA vaccine	I	R0/R1 resection	Autogene cevumeran Atezolizumab mFOLFIRINOX	Safety	RFS OS Immune response
IMCODE 003 ^a	II	R0/R1 resection Preserved spleen	Autogene cevumeran atezolizumab mFOLFIRINOX v mFOLFIRINOX (control)	RFS	OS Safety
AMPLIFY-201	I	G12D or G12R mutation MRD (ctDNA + or biomarker +)	Amph-Peptides-2P Amph-CpG-7909	Safety RP2D	Biomarker response Immune response RFS
AMPLIFY-7P ^a	I/II	mKRAS/NRAS NED	Amph-Peptides-2P Amph-CpG-7909 v observation (control)	RFS	OS Biomarker response Safety
GVAX trial	Platform	Resectable PDA	A: Cy-GVAX B: Cy-GVAX, nivolumab C: Cy-GVAX, nivolumab, urelumab	Immune response	OS RFS Safety

Abbreviations: Cy, cyclophosphamide; GVAX, allogeneic GM-CSF-transfected pancreatic tumor vaccine; mFOLFIRINOX, 5-FU plus irinotecan plus oxaliplatin; MRD, minimal residual disease; NED, no evidence of disease; OS, overall survival; PDA, pancreatic ductal adenocarcinoma; RFS, recurrence-free survival; RP2D, recommended phase II dosing.

^aTrial ongoing, accrual complete.

free survival (RFS) data with a median RFS not reached in vaccine responders versus 13.4 months in vaccine non-responders.⁴⁶ This therapy is currently in a multicenter phase II clinical trial randomly assigning patients with resected pancreatic cancer to individualized mRNA vaccination plus atezolizumab with standard-of-care chemotherapy versus chemotherapy alone after surgical resection (IMCODE 003; ClinicalTrials.gov identifier: [NCT05968326](https://clinicaltrials.gov/ct2/show/study/NCT05968326)).

Lymph Node–Targeted Mutant KRAS Vaccination

ELI-002 2P is a mutant KRAS (G12D and G12R) and adjuvant Toll-like receptor 9 (TLR9) vaccine (Amph-Peptides-2P and Amph-CpG-7909) that is targeted to lymph nodes to augment the vaccine-induced T-cell response.⁴² Lymph node targeting is achieved through amphiphile modification where the antigen (in this case, mutant KRAS peptide) is linked to an albumin-binding lipid. Albumin binding increases the molecular weight leading to increased lymphatic absorption and transport to draining lymph nodes, which more efficiently coordinate antigen presentation and T-cell priming.^{47,48}

A phase I trial of ELI-002 2P (AMPLIFY-201) was completed in patients with mKRAS pancreatic cancer (20 patients) and colorectal cancer (5 patients) with minimal residual disease after locoregional treatment, defined as an elevated tumor antigen (cancer antigen 19-9 or carcinoembryonic antigen) or elevated circulating DNA. This trial met its primary end point of safety and identification of the maximum tolerated dose. Secondary and exploratory outcomes revealed stimulation of the immune system, with mKRAS-specific T-cell responses being observed in most of the patients (21 of 25 patients). Mutant KRAS-specific T-cell responses correlated with reduction in tumor biomarkers, which occurred in 80% of patients with pancreatic cancer.⁴² Additionally, mKRAS

T-cell response correlated with improved disease-free survival. A seven-peptide (G12D, G12R, G12V, G12A, G12C, G12S, G13D) mutant KRAS/NRAS peptide amphiphile-modified vaccine (ELI-002 7P) is being studied in a multicenter phase I/II clinical trial that aims to enroll 135 patients with pancreatic cancer in the phase II portion (AMPLIFY-7P; ClinicalTrials.gov identifier: [NCT05726864](https://clinicaltrials.gov/ct2/show/study/NCT05726864)). The phase I results recently presented demonstrate ELI-002 7P as safe. Additionally, the median recommended phase II antigen dose T-cell responses exceeded the first-generation vaccine.⁴⁹

“Window of Opportunity” and “Platform” Clinical Trial Designs

Novel clinical trial designs, including window of opportunity and platform trials, will be an important consideration in maximizing the efficiency in which novel immunotherapies can be studied, optimized, and translated to the clinic (Fig 2). Window of opportunity trials capitalize on the window of time between cancer diagnosis and the initiation of standard-of-care treatment.⁵⁰ Immunotherapy for resectable pancreatic cancer offers an ideal context for this trial design as patients can receive an experimental intervention in the window of time before surgical resection, and resected specimens can be analyzed to evaluate immunologic response to treatment. Platform trials are a type of adaptive clinical trial design based on the principle of testing multiple experimental groups and allowing for additional treatment arms as the study progresses. The key benefit of platform trial design is efficiency with the use of a single control arm for multiple experimental arms and its ability to adapt as treatment evolves.⁵¹

These novel trial designs were incorporated into the platform trial of neoadjuvant and adjuvant whole-cell pancreatic

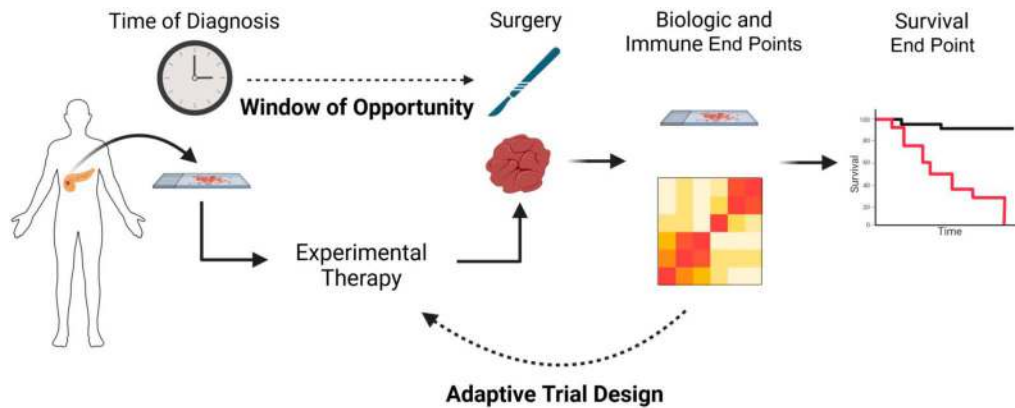


FIG 2. Window of opportunity trial design in resectable pancreatic cancer. Window of opportunity trials capitalize on a window of time in a patient's treatment sequence. For patients with resectable pancreatic cancer, the window of time from diagnosis to surgery offers an opportunity to test experimental therapies with immediate analysis of biologic and immune end points after surgical resection and, subsequently, survival end points. In an adaptive trial design, biologic and immune end points can help guide subsequent experimental arms.

cancer vaccination (allogeneic GM-CSF-transfected pancreatic tumor vaccine [GVAX]) with low-dose cyclophosphamide alone or with a PD-1 antagonist (nivolumab) in patients with resectable pancreatic cancer. In this trial, patients were treated with 1 cycle of the experimental therapy 2 weeks before planned surgical resection, which allowed for comprehensive analysis of immunologic changes in the tumor microenvironment. The experimental treatments were then continued after standard-of-care chemotherapy in the adjuvant setting. The two initial treatment arms of GVAX or GVAX plus nivolumab were subsequently expanded to a third combinatorial treatment arm including a CD137 agonist (urelumab) after correlative studies from the first two experimental arms demonstrated increased intratumoral CD137⁺ activated T cells within tertiary lymphoid aggregates that were associated with improved survival. The combinatorial treatment arm met its primary end point of increasing intratumoral CD8⁺ CD137⁺ T cells.⁴³ The success of this trial highlights the value of window of opportunity and adaptive clinical trial designs in promoting scientific discovery and efficient clinical investigation.

Although historically pancreatic cancer has been poorly responsive to immunotherapy, multiple novel strategies to stimulate the immune system to treat pancreatic cancer have shown promise in early-phase clinical trials. These breakthroughs, as well as more efficient clinical trial design, offer hope for better patient outcomes in the future.

THE TRULY PERSONALIZED THERAPY

Despite lack of progress in the past few decades, the future of pancreatic cancer care looks more promising as we see early signs of success using genomically targeted and immunotherapies. However, in this excitement, we should not forget the essence of our treatment goals and what truly matters at the end. Patients with pancreatic cancer, just like patients

with any other cancer, want to live longer and better. They deserve the treatments that help them achieve these goals. In clinical trials, this will need to be demonstrated as improved OS and quality of life. Unfortunately, no targeted drugs or immunotherapy modalities have yet to definitively demonstrate these improvements, although multiple have been included in treatment guidelines and/or have received FDA approval. Most of these additions are based on response rates from single-arm trials, and many of these studies included only a small number of patients with pancreatic cancer. Thus, while in theory we have several new potential treatment options, we have not yet seen definitive evidence that these treatments result in meaningful benefits for patients.

With the identification of multiple possible molecular targets, including KRAS mutations, we currently have opportunity to better study genomically driven treatments of pancreatic cancer. This can create challenges in running a randomized trial because of inadequate sample size for each subcohort. Thus, parallel to the development of new strategies for treatment, innovations in trial design and implementation are also needed, such as the window of opportunity trials and platform trials discussed above. Multiarm multistage trials, such as the STAMPEDE trial in prostate cancer, offer another example of how a single control arm can be used for comparison against multiple treatment options, thus reducing the need for a larger sample size or multiple separate trials.^{52,53} One can also envision a trial wherein multiple molecular subtypes of pancreatic cancer are included and patients are randomly assigned to receive either the targeted treatment or the standard-of-care chemotherapy.

In recent years, there have been several new FDA-approved treatments for patients with pancreatic cancer including nanoliposomal irinotecan plus 5-FU plus oxaliplatin in the first-line setting based on the NAPOLI-3 study and olaparib

maintenance for patients with germline *BRCA* variants based on the POLO trial. However, the positive results of these studies have been criticized for simply being secondary to trial engineering and not necessarily improving patient outcomes.⁷ Future trials should be designed to ensure that patient outcomes are prioritized and demonstrated in clinical trials, consistent with the clinical trial design checklist published by the Common Sense Oncology initiative.⁵⁴ That all advances in pancreatic cancer since the advent of gemcitabine plus nab-paclitaxel in 2013 have actually not improved patient OS is supported by global and temporal trends in pancreatic cancer mortality rates.^{2,55} It is well known that mortality rates are worse in low- and middle-income countries versus those in high-income countries, for almost every cancer type, explained partly by the differences in accessibility and affordability of new anticancer drugs for

advanced cancers. However, pancreatic cancer is an exception—there is no difference in mortality rates for advanced pancreatic cancer across countries globally.⁵⁵ This implies that not having access to the newer drugs is not leading to worse mortality outcomes, which means those drugs probably do not improve outcomes meaningfully to affect mortality rates at a population level. So, for us involved in the science and treatment of pancreatic cancer, our goal should be to identify and demonstrate treatments that genuinely improve the lives of our patients and then to ensure that these treatments reach patients irrespective of where they live or what they can afford. This is aligned with the principles of Common Sense Oncology that prioritizes treatments that improve patient outcomes and ensures equity in access to those treatments.⁵⁶ The future looks promising, but there are miles to go before we sleep.

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REFERENCES

- Bray F, Laversanne M, Sung H, et al: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74:229-263, 2024
- Siegel RL, Kratzer TB, Giaquinto AN, et al: Cancer statistics, 2025. *CA Cancer J Clin* 75:10-45, 2025
- Burris HA III, Moore MJ, Andersen J, et al: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol* 15:2403-2413, 1997
- Moore MJ, Goldstein D, Hamm J, et al: Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 25:1960-1966, 2007
- Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364:1817-1825, 2011
- Von Hoff DD, Ervin T, Arena FP, et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 369:1691-1703, 2013
- Gyawali B, Booth CM: Treatment of metastatic pancreatic cancer: 25 years of innovation with little progress for patients. *Lancet Oncol* 25:167-170, 2024
- Pang W, Gong L, Shi W, et al: Identification of gene variation feature for targeted therapy of non-small cell lung cancer through combined method of DNA and RNA sequencing. *Discov Oncol* 15:67, 2024
- O'Reilly EM, Lee JW, Zalupski M, et al: Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline *BRCA1*/PALB2 mutation. *J Clin Oncol* 38:1378-1388, 2020
- Golan T, Hammel P, Reni M, et al: Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. *N Engl J Med* 381:317-327, 2019
- Reiss KA, Mick R, O'Hara MH, et al: Phase II study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic variant in *BRCA1*, *BRCA2*, or *PALB2*. *J Clin Oncol* 39:2497-2505, 2021
- Le DT, Durham JN, Smith KN, et al: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 357:409-413, 2017
- André T, Berton D, Curigliano G, et al: Antitumor activity and safety of dostarlimab monotherapy in patients with mismatch repair deficient solid tumors: A nonrandomized controlled trial. *JAMA Netw Open* 6:e2341165, 2023
- Marabelle A, Fakih M, Lopez J, et al: Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: Prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 21:1353-1365, 2020

15. Schenker M, Burotto M, Richardet M, et al: Randomized, open-label, phase 2 study of nivolumab plus ipilimumab or nivolumab monotherapy in patients with advanced or metastatic solid tumors of high tumor mutational burden. *J Immunother Cancer* 12:e008872, 2024
16. Salama AKS, Li S, Macrae ER, et al: Dabrafenib and trametinib in patients with tumors with *BRAF*^{V600E} mutations: Results of the NCI-MATCH trial subprotocol H. *J Clin Oncol* 38:3895-3904, 2020
17. Subbiah V, Kreitman RJ, Wainberg ZA, et al: Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: The phase 2 ROAR trial. *Nat Med* 29:1103-1112, 2023
18. Subbiah V, Wolf J, Konda B, et al: Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): A phase 1/2, open-label, basket trial. *Lancet Oncol* 23:1261-1273, 2022
19. Pant S, Schuler M, Iyer G, et al: Erdafitinib in patients with advanced solid tumours with FGFR alterations (RAGNAR): An international, single-arm, phase 2 study. *Lancet Oncol* 24:925-935, 2023
20. Drilon A, Laetsch TW, Kummar S, et al: Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 378:731-739, 2018
21. Doebele RC, Drilon A, Paz-Ares L, et al: Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. *Lancet Oncol* 21: 271-282, 2020
22. Solomon BJ, Drilon A, Lin JJ, et al: 1372P Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial. *Ann Oncol* 34:S787-S788, 2023
23. Schram AM, Goto K, Kim DW, et al: Efficacy of zenocutuzumab in *NRG1* fusion-positive cancer. *N Engl J Med* 392:566-576, 2025
24. Bekaii-Saab TS, Yaeger R, Spira AI, et al: Adagrasib in advanced solid tumors harboring a KRAS(G12C) mutation. *J Clin Oncol* 41:4097-4106, 2023
25. Strickler JH, Satake H, George TJ, et al: Sotorasib in KRAS p.G12C-mutated advanced pancreatic cancer. *N Engl J Med* 388:33-43, 2023
26. Meric-Bernstam F, Makker V, Oaknin A, et al: Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: Primary results from the DESTINY-PanTumor02 phase II trial. *J Clin Oncol* 42:47-58, 2024
27. Kasi PM, Bucheit LA, Liao J, et al: Pan-cancer prevalence of microsatellite instability-high (MSI-H) identified by circulating tumor DNA and associated real-world clinical outcomes. *JCO Precis Oncol* 10.1200/PO.23.00118
28. Maio M, Ascierto PA, Manzyuk L, et al: Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: Updated analysis from the phase II KEYNOTE-158 study. *Ann Oncol* 33: 929-938, 2022
29. Golani T, O'Kane GM, Denroche RE, et al: Genomic features and classification of homologous recombination deficient pancreatic ductal adenocarcinoma. *Gastroenterology* 160:2119-2132.e2119, 2021
30. Wattenberg MM, Asch D, Yu S, et al: Platinum response characteristics of patients with pancreatic ductal adenocarcinoma and a germline BRCA1, BRCA2 or PALB2 mutation. *Br J Cancer* 122: 333-339, 2020
31. Nishikawa G, Booth C, Prasad V: Olaparib for BRCA mutant pancreas cancer: Should the POLO trial change clinical practice? *Cancer* 126:4087-4088, 2020
32. Stossel C, Raites-Gurevich M, Atias D, et al: Spectrum of response to platinum and PARP inhibitors in germline BRCA-associated pancreatic cancer in the clinical and preclinical setting. *Cancer Discov* 13:1826-1843, 2023
33. Brown TJ, Reiss KA: PARP inhibitors in pancreatic cancer. *Cancer J* 27:465-475, 2021
34. Gkoutakos A, Singhi AD, Westphalen CB, et al: Fusion genes in pancreatic tumors. *Trends Cancer* 10:430-443, 2024
35. Huang L, Guo Z, Wang F, et al: KRAS mutation: From undruggable to druggable in cancer. *Signal Transduct Target Ther* 6:386, 2021
36. Royal RE, Levy C, Turner K, et al: Phase 2 trial of single agent ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother* 33:828-833, 2010
37. Brahmer JR, Tykodi SS, Chow LQ, et al: Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 366:2455-2465, 2012
38. Leidner R, Sanjuan Silva N, Huang H, et al: Neoantigen T-cell receptor gene therapy in pancreatic cancer. *N Engl J Med* 386:2112-2119, 2022
39. Zhong G, Zhang X, Guo Z, et al: Complete remission of advanced pancreatic cancer induced by claudin18.2-targeted CAR-T cell therapy: A case report. *Front Immunol* 15:1325860, 2024
40. Hilmi M, Delaye M, Muzzolini M, et al: The immunological landscape in pancreatic ductal adenocarcinoma and overcoming resistance to immunotherapy. *Lancet Gastroenterol Hepatol* 8: 1129-1142, 2023
41. Rojas LA, Sethna Z, Soares KC, et al: Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. *Nature* 618:144-150, 2023
42. Pant S, Wainberg ZA, Weekes CD, et al: Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: The phase 1 AMPLIFY-201 trial. *Nat Med* 30:531-542, 2024
43. Heumann T, Judkins C, Li K, et al: A platform trial of neoadjuvant and adjuvant antitumor vaccination alone or in combination with PD-1 antagonist and CD137 agonist antibodies in patients with resectable pancreatic adenocarcinoma. *Nat Commun* 14:3650, 2023
44. Balachandran VP, Łuksza M, Zhao JN, et al: Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. *Nature* 551:512-516, 2017
45. Vormehr M, Türeci Ö, Sahin U: Harnessing tumor mutations for truly individualized cancer vaccines. *Annu Rev Med* 70:395-407, 2019
46. Sethna Z, Guasp P, Reiche C, et al: RNA neoantigen vaccines prime long-lived CD8(+) T cells in pancreatic cancer. *Nature* 10.1038/s41586-024-08508-4 [epub ahead of print on February 19, 2025]
47. Supersaxo A, Hein WR, Steffen H: Effect of molecular weight on the lymphatic absorption of water-soluble compounds following subcutaneous administration. *Pharm Res* 7:167-169, 1990
48. Liu H, Moynihan KD, Zheng Y, et al: Structure-based programming of lymph-node targeting in molecular vaccines. *Nature* 507:519-522, 2014
49. Devoe C, Pant S, Wainberg Z, et al: AMPLIFY-7P, a first-in-human safety and efficacy trial of adjuvant mKRAS-specific lymph node targeted amphiphile ELI-002 7P vaccine in patients with minimal residual disease-positive pancreatic and colorectal cancer. *J Clin Oncol* 42, 2024 (suppl 16; abstr 2636)
50. Aroldi F, Lord SR: Window of opportunity clinical trial designs to study cancer metabolism. *Br J Cancer* 122:45-51, 2020
51. Webb SA, Derde LPG: Platform clinical trials for the efficient evaluation of multiple treatments. *JAMA* 10.1001/jama.2024.27688 [epub ahead of print on February 17, 2025]
52. Sydes MR, Parmar MKB, Mason MD, et al: Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: A multi-arm multi-stage randomized controlled trial. *Trials* 13:168, 2012
53. Sydes MR, Parmar MK, James ND, et al: Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: The MRC STAMPEDE trial. *Trials* 10:39, 2009
54. Gyawali B, Eisenhauer EA, van der Graaf W, et al: Common Sense Oncology principles for the design, analysis, and reporting of phase 3 randomised clinical trials. *Lancet Oncol* 26:e80-e89, 2025
55. Pourshams A, Sepanlou SG, Ikuta KS, et al: The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 4:934-947, 2019
56. Booth CM, Sengar M, Goodman A, et al: Common sense oncology: Outcomes that matter. *Lancet Oncol* 24:833-835, 2023
57. Marabelle A, Le DT, Ascierto PA, et al: Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. *J Clin Oncol* 38:1-20, 2020
58. Hong DS, DuBois SG, Kummar S, et al: Larotrectinib in patients with TRK fusion-positive solid tumours: A pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol* 21:531-540, 2020
59. Nusrat F, Khanna A, Jain A, et al: The clinical implications of KRAS mutations and variant allele frequencies in pancreatic ductal adenocarcinoma. *J Clin Med* 13:2103, 2024

Advancing Perioperative Treatment Options for Localized Muscle-Invasive Bladder Cancer: A Step Forward

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OVERVIEW

Muscle-invasive bladder cancer (MIBC) is an aggressive disease, with substantial recurrence risk after radical cystectomy and pelvic lymph node dissection alone. In cisplatin-eligible patients, administration of neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy has been shown to improve overall survival (OS) and has become the standard of care. Nevertheless, approximately 40%–50% of patients will still experience disease recurrence after curative-intent treatment. Moreover, a significant proportion of patients with MIBC are ineligible for cisplatin and represent a challenging clinical scenario. In recent years, different strategies aiming to improve patient outcomes by incorporating immune checkpoint inhibitors in the treatment paradigm were explored. Two key management approaches emerged: neoadjuvant chemotherapy with risk-adapted adjuvant immunotherapy and universal perioperative immunotherapy-based treatment. We review the rationale, current evidence, challenges, and future directions for the perioperative management of muscle-invasive urothelial carcinoma.

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RISK-ADAPTED PERIOPERATIVE THERAPY

Background and Rationale

In the risk-adapted approach, neoadjuvant cisplatin-based chemotherapy is offered to all eligible patients with muscle-invasive disease, followed by adjuvant immunotherapy for patients at high risk.^{1–8} The goals are to improve outcomes in high-risk disease, while safely de-escalate treatment for patients at low risk of recurrence, thus avoiding overtreatment and unnecessary toxicity. Effective execution requires reliable prognostic and predictive biomarkers to stratify patients according to the recurrence risk and potential benefit from the adjuvant treatment.

In the adjuvant setting, two phase III trials showed improved outcomes with single-agent immune checkpoint inhibitors (ICIs) for patients at high risk of disease recurrence. In CheckMate274, 709 patients with high-risk disease, defined as $\geq$ ypT2 or ypN+ with prior neoadjuvant chemotherapy and $\geq$ pT3 or pN+ without prior neoadjuvant chemotherapy, were randomly assigned to receive nivolumab, a PD-1 inhibitor, or placebo for 1 year. Disease-free survival (DFS) was significantly improved with nivolumab in the intention-to-treat (ITT) population (hazard ratio [HR], 0.71; 95% CI, 0.58 to 0.86), with a trend for improved overall survival (OS; HR, 0.76 [95% CI, 0.61 to 0.96]; data immature),^{9,10} leading to approval by the US Food and Drug Administration (FDA).¹¹ The European Medicine Agency (EMA) restricted the approval to

patients with tumor cell PD-L1 expression $\geq$ 1%,¹² as discussed below. The AMBASSADOR trial randomly assigned 702 patients to receive pembrolizumab, a PD-1 inhibitor, for 1 year versus observation, using similar high-risk definition with inclusion of positive surgical margins as a risk factor. Adjuvant pembrolizumab resulted in improved DFS (HR, 0.73 [95% CI, 0.59 to 0.9]; $P = .003$) but not OS at the interim analysis (HR, 0.98; 95% CI, 0.76 to 1.26).¹³ Notably, a third phase III trial, IMvigor010, comparing atezolizumab, a PD-L1 inhibitor, for 1 year to observation in 809 patients at high risk of disease recurrence, did not meet the primary end point of DFS (HR, 0.89 [95% CI, 0.74 to 1.08]; $P = .24$).¹⁴ Table 1 summarizes the reported clinical trials of adjuvant ICI.

Pathologic Risk Stratification

The most established risk stratification strategy in urothelial carcinoma relies on the pathologic staging at radical cystectomy. Pathologic complete response (pCR, defined as pT0N0) and pathologic downstaging (pDS, defined as $\leq$ pT1N0) are reported in 27.5%–36% and 40.6%–50% of patients treated with neoadjuvant cisplatin + gemcitabine^{6,8,15} and in 32%–42% and 55%–63% of patients treated with neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC),^{6,15} respectively.

Patients with pCR have improved outcomes after radical cystectomy, with or without prior neoadjuvant chemotherapy.^{16,17} In the landmark phase III Southwest Oncology Group (SWOG)

PRACTICAL APPLICATIONS

- Perioperative management for muscle invasive bladder cancer (MIBC) includes neoadjuvant cisplatin-based chemotherapy (NAC) followed by radical cystectomy and risk-adapted adjuvant immunotherapy. More recently, neoadjuvant durvalumab plus NAC followed by radical cystectomy and adjuvant durvalumab has become an additional standard option based on the NIAGARA trial demonstrating improved outcomes compared with NAC followed by radical cystectomy alone.
- Circulating tumor DNA (ctDNA) is emerging as a promising biomarker in MIBC, randomized studies evaluating risk-adapted treatment based on ctDNA status are ongoing.
- The management paradigm for MIBC will continue to evolve in the upcoming years. Data from randomized studies of perioperative immunotherapy-based treatment, including the highly anticipated immunotherapy-antibody drug conjugates combination studies, will further inform management. Biomarker-guided strategies for bladder-sparing are currently explored and may offer patients future hope for avoid radical surgery.

8710 trial comparing neoadjuvant MVAC followed by radical cystectomy versus radical cystectomy alone, neoadjuvant chemotherapy was associated with higher rates of pCR at cystectomy (38% v 15% with surgery alone, $P < .001$).³ Patients with pCR in both arms had significantly better outcomes compared with patients with residual disease at cystectomy, with 85% survival at 5 years. Similar association was seen in

multiple subsequent studies,^{16,18–20} and a meta-analysis of 13 studies found that the relative risk of OS in patients with pCR compared with non-pCR was 0.45 (95% CI, 0.36 to 0.56, $P < .00001$).²¹ The prognostic value of pCR was re-enforced with improved outcomes reported in the neoadjuvant subset of the VESPER trial comparing cisplatin-based regimens²² and in the NIAGARA trial, discussed in detail below.^{8,23}

In patients with residual disease at radical cystectomy, downstaging may also be used to stratify recurrence risk. In a retrospective analysis of SWOG 8710, residual muscle-invasive disease ($\geq pT2$) was associated with worse OS compared with pDS (HR, 2.24; 95% CI, 1.34 to 3.67; $P = .0022$).²⁴ In this analysis, there was a nonsignificant trend for worse survival in patients with residual non-muscle-invasive disease (pTa/Tis/T1) compared with pCR (HR, 2.05 [95% CI, 0.99 to 4.24]; $P = .054$). A population-based study from Norway ($n = 575$) reported improved survival in patients with pDS (HR, 0.22 [95% CI, 0.15 to 0.34]; $P = 1.9 \times 10^{-12}$).²⁵ In this cohort, neoadjuvant chemotherapy was associated with increased odds of pDS (odds ratio, 2.51 [95% CI, 1.37 to 4.60]; $P = .003$) but not improved survival (HR, 1.16 [95% CI, 0.81 to 1.68]; $P = .417$), and the authors preformed a mediation analysis suggesting an indirect effect of neoadjuvant chemotherapy on survival through pDS ($P = .026$). While these data suggest similar outcomes when pDS is achieved with or without neoadjuvant chemotherapy, in a post hoc analysis of the randomized prospective Nordic cystectomy trials 1 and 2 ($n = 449$), noninvasive residual disease (defined as pTo/pTa/pTisNo) after neoadjuvant chemotherapy had significantly improved 5-year OS versus noninvasive residual disease in the surgery-only arm (82.9% v 65%, $P = .018$).¹⁸

Circulating Tumor DNA

In recent years, circulating tumor DNA (ctDNA) has emerged as a promising biomarker to identify molecular residual disease and predict outcomes after curative-intent therapy

TABLE 1. Summary of Reported Clinical Trials of Adjuvant Immune Checkpoint Inhibitors for Muscle-Invasive Urothelial Carcinoma

Study	Phase	Study Arms	N	N+, %	NAC, %	UTUC, %	DFS HR (95% CI)	Overall Survival HR (95% CI)	Key Subgroup (DFS)
IMvigor010 NCT02450331	III	Atezolizumab v observation	809	52	48	7	19.4 months v 16.6 months 0.89 (0.74 to 1.08) $P = .24$	0.91 (0.73 to 1.13)	ctDNA positive ^a : HR, 0.58 (0.43-0.79)
CheckMate 274 NCT02632409	III	Nivolumab v placebo	709	47.2	43	21	22.0 months v 10.9 months 0.71 (0.58 to 0.86) $P < .001$	0.76 (0.61 to 0.96)	PD-L1 $\geq 1\%$ ^b : 52.6 months v 8.4 months; HR, 0.52 (0.37-0.72)
AMBASSADOR NCT03244384	III	Pembrolizumab v observation	702	49.9	63.7	21.9	29.6 months v 14.2 months 0.73 (0.59 to 0.9) $P = .003$	0.98 (0.76 to 1.26)	—

Abbreviations: ctDNA, circulating tumor DNA; DFS, disease-free survival; HR, hazard ratio; NAC, neoadjuvant chemotherapy; N+, node positive; UTUC, upper tract urothelial carcinoma.

^aExploratory analysis.

^bMeasured on tumor cells.

in several solid tumors.²⁶ In muscle-invasive urothelial carcinoma, detectable ctDNA after radical cystectomy was significantly associated with worse recurrence-free survival (RFS) in 68 patients treated with neoadjuvant chemotherapy (HR, 37.7 [95% CI, 8.5 to 167.1]; $P < .0001$) and in 102 neoadjuvant chemotherapy-naïve patients (HR, 17.8 [95% CI, 3.9 to 81.2]; $P = .0002$).²⁷ Similar association was seen in a retrospective cohort of 167 patients, reporting inferior DFS in patients with detectable ctDNA after radical cystectomy (HR, 6.93 [95% CI, 2.4 to 20.05]; $P < .001$).²⁸

IMvigor010 mentioned above was a negative phase III trial evaluating adjuvant atezolizumab for high-risk urothelial carcinoma after definitive surgery. While the study did not meet the primary end point, an exploratory analysis was performed on the basis of ctDNA status.^{29,30} Overall, 581 of 809 patients had evaluable ctDNA samples, 37% of them had detectable ctDNA at baseline, measured at the start of adjuvant therapy or observation (C1D1). Detectable ctDNA was associated with higher risk of disease recurrence (HR, 6.3 [95% CI, 4.45 to 8.92]; $P < .0001$) or death (HR, 6.3 [95% CI, 4.3 to 9.3]) compared with undetectable ctDNA. Repeat ctDNA testing after 6 weeks (C3D1) improved the sensitivity for detecting radiographic relapse compared with baseline testing alone in the observation arm. The median lead time to radiographic recurrence was 2.9 months when detectable ctDNA was measured on C1D1 and 3.8 months when detectable ctDNA was measured on either C1D1 or C3D1. Among the patients with detectable ctDNA, adjuvant atezolizumab was associated with improved DFS (HR, 0.58 [95% CI, 0.43 to 0.79]; $P = .0024$) and OS (0.59 [95% CI, 0.42 to 0.83]), while no difference was seen in patients with undetectable ctDNA. The rate of ctDNA clearance at C3D1 was higher with atezolizumab versus observation (18.2% v 3.8%, $P = .0204$) and was associated with superior DFS (HR, 0.26 [95% CI, 0.12 to 0.56]; $P = .0014$).

The prognostic value of ctDNA was further demonstrated in an initial analysis from IMvigor011 (ClinicalTrials.gov identifier: [NCT04660344](#)).³¹ This is an ongoing phase III study comparing adjuvant atezolizumab versus placebo in patients with high-risk urothelial cancer and detectable ctDNA within 12 months after radical cystectomy. Patients with undetectable ctDNA are observed using conventional imaging and serial ctDNA testing. In 171 patients with maintained undetectable ctDNA for >12 months after cystectomy, the 18-month DFS and OS rates were 88% and 98%, respectively. Considering the high-risk patient population, with 21.1% node-positive and 54.5% T3-4 disease, these data suggest that serial ctDNA may augment the traditional pathologic risk stratification and could potentially inform treatment de-escalation in patients who otherwise seem to be at high risk by conventional pathology criteria. In the ongoing nonrandomized phase II TOMBOLA trial (ClinicalTrials.gov identifier: [NCT04138628](#)), patients who underwent neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy are monitored using serial ctDNA testing, and 1 year of adjuvant atezolizumab is initiated upon

ctDNA detection irrespective of radiographic findings. Preliminary results of the first 179 patients have been reported, with ctDNA detected in 56% of patients during follow-up, 75% of whom were <4 months after cystectomy.³² Notably, as patients were enrolled regardless of pathologic stage at cystectomy, 61% of patients had low-risk disease, defined as <ypT2N0. The 1-year RFS among patients with serial undetectable ctDNA was 98.5%. The primary end point, complete response defined as undetectable ctDNA and negative imaging, was achieved in 55% of patients initiating atezolizumab with detectable ctDNA. Risk-adapted adjuvant treatment based on ctDNA is also evaluated in the ongoing MODERN trial (ClinicalTrials.gov identifier: [NCT05987241](#)) where patients with undetectable ctDNA at baseline are randomly assigned to immediate nivolumab versus nivolumab upon ctDNA conversion to detectable, testing whether this strategy results in a similar DFS. Patients with detectable ctDNA at baseline are randomly assigned to standard-of-care nivolumab versus treatment intensification with a combination of nivolumab and relatlimab, a LAG-3 inhibitor. These prospective studies will help inform the use of ctDNA in the perioperative space to risk adapt therapy for patients.

PD-L1 Expression

PD-L1 expression level is a widely explored biomarker for ICI efficacy in solid malignancies, using variable immunohistochemistry assays, scoring techniques, and positivity cutoff definitions,³³ although the predictive value in urothelial carcinoma studies has not been consistent.³⁴ In the positive CheckMate274 study, patients were stratified according to PD-L1 expression level measured on tumor cell, defining 40% of patients as PD-L1 positive using a cutoff of $\geq 1\%$ versus <1%. The study met the dual primary end points demonstrating improved DFS with adjuvant nivolumab in the ITT population (HR, 0.71 [95% CI, 0.58 to 0.86]) and PD-L1 $\geq 1\%$ population (HR, 0.52 [95% CI, 0.37 to 0.72]), with no significant benefit seen in an exploratory subgroup analysis of the PD-L1 <1% population (HR, 0.84 [95% CI, 0.66 to 1.06]).^{9,10} In a post hoc exploratory analysis, outcomes were compared using the prespecified PD-L1 expression on tumor cells (TCs) and Combined Positivity Score (CPS), measured on tumor and immune cells using a cutoff of ≥ 1 versus <1.³⁵ Among patients with TC <1%, 81% had CPS ≥ 1 . In this subpopulation, HR for disease recurrence or death was 0.73 (95% CI, 0.54 to 0.99). No DFS benefit was observed in patients with CPS <1 (HR, 1.22 [95% CI, 0.67 to 2.2]), but the interpretation is limited by the small number of patients, comprising only 11% of the study population.

In the AMBASSADOR trial, PD-L1 expression was evaluated using CPS with a cutoff of ≥ 10 versus <10, 57.5% of patients were defined as PD-L1 positive.¹³ While PD-L1 status was not predictive of benefit with adjuvant pembrolizumab, improved outcomes were observed among patients with CPS ≥ 10 in both arms, suggesting a prognostic value. IMvigor010 reported a similar prognostic but not predictive role for PD-L1 expression measured in immune cells only.¹⁴

Overall, these data highlight the limitations of using PD-L1 status to select patients for adjuvant ICI. From a regulatory standpoint, the FDA approved adjuvant nivolumab regardless of PD-L1 expression,¹¹ while the EMA restricted the approval to patients with tumor cell PD-L1 expression $\geq 1\%$.¹²

UNIVERSAL PERIOPERATIVE IMMUNOTHERAPY-BASED TREATMENT

Insights From the Neoadjuvant Immunotherapy Studies

In recent years, several phase I/II studies evaluated neoadjuvant ICI for muscle-invasive urothelial cancer, especially for patients who are ineligible for cisplatin-based chemotherapy because of impaired renal function and other neurologic or cardiovascular comorbidities. Although some of these studies demonstrated efficacy in this scenario, the absence of a comparator arm restricts the interpretation of their findings and their applicability compared with standard-of-care neoadjuvant chemotherapy. Nevertheless, the neoadjuvant immunotherapy studies provided valuable data that affected the evolving paradigm. Reported clinical trials of single-agent and combination ICIs in the neoadjuvant setting and key outcomes are summarized in [Table 2](#).

In the PURE-01 study, 155 patients received three cycles of neoadjuvant pembrolizumab followed by radical cystectomy, representing the largest of the single-agent neoadjuvant ICI trials published. The study met the primary end point, with a pCR rate of 36.8% and pDS ($\leq$ pT1No) rate of 53.6%.^{36,37} Long-term follow-up reinforced the durability of these responses, with sustained DFS and OS confirmed over 3 years.³⁷ Among patients with divergent histology, responses were seen only in tumors with squamous cell differentiation (pDS in six of seven patients, one of them with pCR) and lymphoepithelioma-like features (pCR in two of three patients), highlighting an underexplored population requiring further investigation.³⁸ Exploratory biomarker analysis suggested enhanced responses with high tumor mutational burden (TMB) and high PD-L1 expression,³⁶ and subsequent studies of gene expression patterns³⁹ and tumor microenvironment⁴⁰ aimed to better define sensitivity and resistance mechanisms.⁴¹

Although the toxicity profile of ICIs has been well described, the potential implications on surgery warrant further investigation. Across the single-agent neoadjuvant ICI studies, the percentage of patients undergoing cystectomy as planned ranges between 73% and 100%. Evaluation of the perioperative outcomes in the PURE-01 trial⁴² reported 32% high-grade complications (defined as Clavien-Dindo $\geq 3a$). In the ABACUS study,⁴³ evaluating two cycles of neoadjuvant atezolizumab with a pCR rate of 31%, over 60% of patients experienced surgical complications, but there were no delays in surgery.

ICI doublet combinations have also been evaluated as neoadjuvant treatment of muscle-invasive bladder cancer (MIBC). Interpretation is limited by small cohort size, but the preliminary results suggests that ICI dose might affect outcomes. In the NABUCCO trial,⁴⁴ two different dose and schedules of nivolumab and ipilimumab were explored and the pCR rate was 43% with high-dose ipilimumab (3 mg/kg) and 7% with low-dose ipilimumab (1 mg/kg). Nevertheless, as novel efficacious combinations emerge, and considering the increased risk of immune-related adverse events with ICI doublet combinations, pure ICI doublet combinations are currently not developed further. Several early-phase studies explored the efficacy and safety of neoadjuvant ICI + chemotherapy, predominantly in cisplatin-eligible populations. While there is considerable variability in the patient population, agents used, and reported outcomes, the proportion of patients proceeding with radical surgery as planned across studies was high, and most studies reported pCR rates of approximately 40%–50%.

As antibody-drug conjugates (ADCs) transformed the management of metastatic urothelial carcinoma, there has been increasing interest in investigating their role in muscle-invasive disease. Enfortumab vedotin (EV), a Nectin-4-targeting ADC with a monomethyl auristatin E (MMAE) payload, was evaluated as monotherapy neoadjuvant treatment in the phase Ib/II study EV-103 cohort H.⁴⁵ All 22 cisplatin-ineligible patients treated with neoadjuvant EV underwent surgery as planned, with pCR and pDS rates of 36.4% and 50%, respectively, and 2-year event-free survival of 62%. Ongoing studies of combination ICIs + ADCs are investigating perioperative approaches and are discussed below.

NIAGARA Trial: Paradigm Shift in Perioperative Therapy

The recently presented positive phase III NIAGARA trial is the first to report results among several large randomized studies evaluating perioperative immunotherapy-based combinations. This treatment strategy is commonly referred to as a sandwich approach. Ongoing and reported perioperative clinical trials are summarized in [Tables 3 and 4](#).

The NIAGARA trial included 1,063 cisplatin-eligible patients with cT2–T4aN0–1M0 urothelial carcinoma of the bladder. Patients were randomly assigned in a 1:1 ratio to either neoadjuvant durvalumab, a PD-L1 inhibitor, + gemcitabine and cisplatin for four cycles followed by radical cystectomy and adjuvant durvalumab for eight cycles, or neoadjuvant gemcitabine and cisplatin for four cycles followed by radical cystectomy alone. The primary end points were pCR and event-free survival (EFS), defined as progression, recurrence, not undergoing radical cystectomy, or death from any cause. Secondary outcomes included OS, metastasis-free survival, disease-specific survival, and safety.⁸

TABLE 2. Summary of Reported Clinical Trials of Neoadjuvant Immune Checkpoint Inhibitors for Muscle-Invasive Urothelial Carcinoma

Study	Phase	Study Arms	N	Clinical Stage (≥T3N0)	Cisplatin Eligibility	Primary Endpoint	Cystectomy Rates, %	pCR, %	pDS, %	Survival
Single-agent ICI										
PURE-1 NCT02736266	II	Pembrolizumab	155	T2-4aN0M0 (51.6%)	Not required	pCR	92	36.8	53.6	3 years OS 83%
PANDORE NCT03212651	II	Pembrolizumab	39	T2-4aN0M0 (NA)	Ineligible	pCR	87.2	29.4	41.2	2 years OS 79%
ABACUS NCT02662309	II	Atezolizumab	95	T2-4aN0M0 (26%)	Ineligible	pCR	92	31	—	2 years OS 77%
NCT02451423	II	Atezolizumab	22	T2-4aN0-1M0 (32%)	Ineligible	pCR	100	14	23	2 years OS 90%
NCT03520491 Cohort 1	II	Nivolumab	15	T2-4aN0M0 (NA)	Ineligible	Feasibility	73	13	26	—
BLASST-2 NCT03773666	I	Durvalumab	10	T2-4aN0M0 (NA)	Ineligible	Feasibility	80	12.5	25	—
AURA NCT03674424	II	Avelumab	29	T2-4aN0-2M0 (NA)	Ineligible	pCR	96.5	36	39	1 year OS 75%
SunRISe-4 cohort 2 NCT04919512	II	Cetrelimab	41	T2-4aN0M0 (14.6%)	Ineligible	pCR	—	23	36	—
Combination: ICI + ICI										
NABUCCO NCT03387761	Ib	Ipilimumab + nivolumab Cohort 1	24	T3-4aN0M0 or T1-4aN1-3M0 (100%)	Ineligible	Feasibility	96	46	58	2 years OS 90%
		Ipi 3 mg/kg + nivo 1 mg/kg Cohort 2A	15			pCR	87	43	57	2 years OS 90%
		Ipi 1 mg/kg + nivo 3 mg/kg Cohort 2B	15					7	29	2 years OS 73%
NCT03520491 Cohort 2	II	Ipilimumab + nivolumab	15	T2-4aN0M0 (NA)	Ineligible	Feasibility	60	7	20	—
DUTRENEO ^a NCT03472274	II	Durvalumab + tremelimumab	23	T2-T4aN0-1M0 (22%)	Eligible	pCR	87	34.8	56.5	—
		Cisplatin-based chemotherapy	22				91	36.4	59.1	
NCT02812420	I	Durvalumab + tremelimumab	28	T1-4aN0M0 ^b (54%)	Ineligible	Safety	86	37.5	58	1 year OS 89%
Combination: ICI + chemotherapy/other										
BLASST-1 NCT03294304	II	Nivolumab + cisplatin + gemcitabine	41	T2-T4aN0-1M0 (10%)	Eligible	pDS	95	49	65.8	—
NCT02989584	II	Atezolizumab + cisplatin + gemcitabine	39	T2-4aN0M0 (20.5%)	Eligible	pDS	92.3	41	69.2	—
LCCC1520 NCT02690558	II	Pembrolizumab + cisplatin + gemcitabine	39	T2-4aN0M0 (28%)	Eligible	pDS	97.4	35	56	1 year OS 91%
HCRN GU 14-188 NCT02365766	Ib/II	Pembrolizumab + cisplatin + gemcitabine	42	T2-4aN0M0 (42.9%)	Eligible	pDS	88.1	41	54	3 years OS 79%
		Pembrolizumab + gemcitabine	39	T2-4aN0M0 (60%)	Ineligible		87.2	41	53	3 years OS 66%
NEMIO NCT03549715	I/II	Durvalumab + dd MVAC	60	T2-T4aN0-1M0 (18%)	Eligible	pCR and safety	91.7	49	71	1 year OS 89%
		Durvalumab + tremelimumab + dd MVAC	59	T2-T4aN0-1M0 (9%)	Eligible		98.3	57	61	1 year OS 97%

(continued on following page)

TABLE 2. Summary of Reported Clinical Trials of Neoadjuvant Immune Checkpoint Inhibitors for Muscle-Invasive Urothelial Carcinoma (continued)

Study	Phase	Study Arms	N	Clinical Stage (≥T3N0)	Cisplatin Eligibility	Primary Endpoint	Cystectomy Rates, %	pCR, %	pDS, %	Survival
AURA NCT03674424	II	Avelumab + dd MVAC	39	T2-4aN0-2M0 (NA)	Eligible	pCR	—	58	—	3 years OS 87%
		Avelumab + cisplatin + gemcitabine	40		Eligible		—	52	—	3 years OS 61%
		Avelumab + paclitaxel + gemcitabine	29		Ineligible		100	18	21	1 year OS 67%
ChiCTR2000032359	II	Camrelizumab + cisplatin + gemcitabine	40	T2-T4aN0-1M0 (57.5%)	Eligible	pCR	75	43.3	53.3	1 year OS 82%
BGB-A317-2002-IIT ChiCTR2000037670	II	Tislelizumab + cisplatin + gemcitabine	65	T2-4aN0M0 (41.5%)	Eligible	pCR	87.7	50.9	75.4	1 year OS 91%
ONO-4538-X41 KCT0003804	II	Nivolumab + cisplatin + gemcitabine	51	T2-4aN0M0 (35.3%)	Eligible	pCR	69	35.3	64.7	—
GZZJU-2021NB NCT04861584	II	Toripalimab + cisplatin + gemcitabine	16	T2-T4aN0-1M0 (75%)	Eligible	pDS	87.5	28.6	85.7	—
SunRISe-4 cohort 1 NCT04919512	II	Cetrelimab + TAR-200 ^c	79	T2-4aN0M0 (21.5%)	Ineligible	pCR	—	42	60	—
Neodurvarib NCT03534492	II	Durvalumab + olaparib	28	T2-4aN0M0 (26.4%)	Not required	pCR	—	44.5 ^d	—	—

Abbreviations: dd MVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; NA, not available; Nivo, nivolumab; OS, overall survival; pCR, pathologic complete response; pDS, pathologic downstaging.

^aPatients with hot tumors based on proinflammatory signature were randomly assigned to receive durvalumab and tremelimumab or chemotherapy; patients with cold tumors received chemotherapy and are not described in the table.

^bRequired high-risk features.

^cIntravesical targeted release system (gemcitabine).

^dPreliminary results.

TABLE 3. Summary of Reported Perioperative Immunotherapy-Based Clinical Trials

Study	Phase	Study Arms	N	Clinical Stage (≥T3N0)	Cisplatin Eligibility	Primary Endpoint	RC Rates, %	pCR, %	EFS	OS
NIAGARA NCT03732677	III	NA: durvalumab + cisplatin + gemcitabine Q3w ×4 cycles A: durvalumab Q4w ×8 cycles	533	T2-T4aN0-1M0 (60%)	Eligible	EFS and pCR	88	37.3	HR, 0.68 (0.56-0.82) P < .001	HR, 0.75 (0.59-0.93) P = .01
		NA: cisplatin + gemcitabine Q3w ×4 cycles A: —	530				83.2	27.5		
SAKK 06/17 NCT03406650	II	NA: durvalumab + cisplatin + gemcitabine Q3w ×4 cycles A: durvalumab Q4w ×10 cycles	61	T2-T4aN0-1M0 (31%)	Eligible	EFS	91	31	2 years EFS 83.5%	2 years OS 87.3%
RC48-C017 NCT05297552	II	NA: toripalimab + disitamab vedotin Q2w ×6 cycles A: toripalimab Q2w ×20 cycles	47	T2-T4aN0-1M0 (59.6%) HER2+	Not required	pCR	70.2	63.6	1 year EFS 89.5%	1 year OS 95.5%

Abbreviations: A, adjuvant; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NA, neoadjuvant; OS, overall survival; pCR, pathologic complete response; Q, every; RC, radical cystectomy; w, week.

Radical cystectomy was performed in 88.0% of patients in the durvalumab group and 83.2% in the comparator group. The median time from the last dose of neoadjuvant therapy to cystectomy was similar between the groups.

In the primary analysis, a pCR occurred in 33.8% of patients in the durvalumab group and 25.8% in the comparator group (risk ratio, 1.30 [95% CI, 1.09 to 1.56]; $P = .004$). In a re-analysis including 59 additional samples, the pCR rate was 37.3% in the durvalumab group and 27.5% in the comparator group (risk ratio, 1.34 [95% CI, 1.13 to 1.60]). At 24 months, the estimated EFS was 67.8% in the durvalumab group compared with 59.8% in the comparator group. The hazard ratio for EFS was 0.68 (95% CI, 0.56 to 0.82; $P < .001$). The EFS benefit was consistent across various subgroups, including age, sex, race, geographic region, histologic type, previous BCG therapy, regional lymph node stage, tumor stage, creatinine clearance, and PD-L1 expression level. The estimated 24-month OS rate was 82.2% in the durvalumab group versus 75.2% in the comparator group. The hazard ratio for death was 0.75 (95% CI, 0.59 to 0.93; $P = .01$). Consistent benefit was recently reported for metastasis-free survival (HR, 0.67 [95% CI, 0.54 to 0.83]; nominal $P < .001$) and disease-specific survival (HR, 0.69 [95% CI, 0.52 to 0.91]; nominal $P = .008$).²³

Treatment-related adverse events of grade 3 or 4 occurred in 40.6% of patients in the durvalumab group and 40.9% in the comparator group. Treatment-related adverse events leading to death occurred in 0.6% of patients in each group. The most common adverse events were nausea, anemia, and constipation. When focusing on the immune-mediated adverse events, 21% of patients in the durvalumab arm

and 3% in the comparator arm reported, most commonly, thyroid abnormalities.

An exploratory post hoc analysis presented at ASCO GU 2025 showed a benefit of durvalumab regardless of the pathologic response.²³ Patients in the durvalumab arm derived greater EFS benefit versus the comparator arm in both pCR (HR, 0.58 [95% CI, 0.33 to 0.99]) and non-pCR (HR, 0.77 [95% CI, 0.63 to 0.95]) groups. Additionally, patients in the durvalumab arm derived greater OS benefit versus the comparator arm in both pCR (HR, 0.72 [95% CI, 0.37 to 1.43]) and non-pCR (HR, 0.84 [95% CI, 0.66 to 1.07]) groups.

On March 28, 2025, the FDA approved neoadjuvant durvalumab with cisplatin and gemcitabine, followed by radical cystectomy and adjuvant single-agent durvalumab for MIBC, on the basis of the positive results of the NIAGARA trial.⁴⁶

Some concerns about the perioperative use of durvalumab may arise considering the potentially overtreated patients, especially those with a complete response. In addition, the comparator arm in NIAGARA did not allow dose-dense MVAC, a standard of care, and patients did not receive adjuvant nivolumab subsequently shown to improve outcomes in noncomplete responders after neoadjuvant treatment as discussed above. Furthermore, NIAGARA has not yet reported results of molecular markers that could help in the selection of the best candidates to receive the adjuvant portion of durvalumab treatment, such as ctDNA.⁴⁷

Multiple large phase III trials with similar designs have enrolled patients but have not reported the results. Two

large phase III trials evaluated perioperative immunotherapy in a similar setting: In Keynote-866 (ClinicalTrials.gov identifier: [NCT03924856](#)), patients were randomly assigned to receive neoadjuvant gemcitabine-cisplatin followed by radical cystectomy with or without perioperative pembrolizumab; in ENERGIZE (ClinicalTrials.gov identifier: [NCT03661320](#)), patients were randomly assigned to the comparator arm, receiving neoadjuvant gemcitabine-cisplatin followed by radical cystectomy, or one of two study arms evaluating the addition of perioperative nivolumab alone or in combination with linrodostat mesylate (a selective oral IDO1 inhibitor) to gemcitabine and cisplatin chemotherapy.

The perioperative approach is also implemented in three highly anticipated phase III studies evaluating combinations of EV and ICIs. In EV-304/KEYNOTE-B15 (ClinicalTrials.gov identifier: [NCT04700124](#)), cisplatin-eligible patients were randomly assigned to receive perioperative EV + pembrolizumab (EV and pembrolizumab given for four cycles before radical cystectomy and five cycles after, with single-agent pembrolizumab continued to complete 1 year) or neoadjuvant gemcitabine-cisplatin followed by radical cystectomy. In EV-303/KEYNOTE-905 (ClinicalTrials.gov identifier: [NCT03924895](#)), cisplatin-ineligible patients were

randomly assigned to receive perioperative single-agent pembrolizumab (three cycles before surgery, complete 1 year after) or perioperative EV + pembrolizumab (EV and pembrolizumab given for three cycles before radical cystectomy and six cycles after, with single-agent pembrolizumab continued to complete 1 year) or undergo upfront radical cystectomy (control arm). The VOLGA trial (ClinicalTrials.gov identifier: [NCT04960709](#)) also enrolled cisplatin-ineligible patients, comparing three cycles for neoadjuvant EV + durvalumab with or without tremelimumab followed by surgery and adjuvant ICI to complete 1 year (durvalumab with or without tremelimumab), compared with surgery alone. All these studies have completed accrual and await data maturation (details summarized in [Table 4](#)).

Additional studies evaluate perioperative treatment using ICIs with different ADCs. Human epidermal growth factor receptor 2 (HER2) has recently emerged as a potent target in urothelial carcinoma, highlighted by the tumor agnostic approval of trastuzumab deruxtecan for HER2 3+ tumors on the basis of the DESTINY PanTumor-02 study.⁴⁸ In MIBC, a phase II study evaluating a combination of disitamab vedotin, a HER2-targeting ADC with MMAE payload, and toripalimab, a PD-1 inhibitor, for HER2-expressing tumors (1+/2+/3+)

TABLE 4. Summary of Ongoing Phase III Clinical Trials of Perioperative Immunotherapy-Based Treatment for Muscle-Invasive Urothelial Carcinoma

Study	Phase		Neoadjuvant Component	Adjuvant Component	N	Cisplatin Eligibility
KEYNOTE-866 NCT03924856	III	Study arm	Pembro + cisplatin + gemcitabine Q3w ×4 cycles	Pembro Q3w ×13 cycles	907	Eligible
		Control	Placebo + cisplatin + gemcitabine Q3w ×4 cycles	Placebo Q3w ×13 cycles		
ENERGIZE NCT03661320	III	Control	Cisplatin + gemcitabine Q3w ×4 cycles	—	861	Eligible
		Arm B	Nivo + placebo ^a + cisplatin + gemcitabine Q3w ×4 cycles	Nivo + placebo Q4w ×9 cycles		
		Arm C	Nivo + linrodostat ^a + cisplatin + gemcitabine Q3w ×4 cycles	Nivo + linrodostat Q4w ×9 cycles		
KEYNOTE-B15/EV-304 NCT04700124	III	Study arm	EV + pembro Q3w ×4 cycles	EV + pembro Q3w ×5 cycles, followed by pembro Q3w ×8 cycles	784	Eligible
		Control	Cisplatin + gemcitabine Q3w ×4 cycles	—		
KEYNOTE-905/EV-303 NCT03924895	III	Arm A	Pembro Q3w ×3 cycles	Pembro Q3w ×14 cycles	857	Ineligible
		Arm B	EV + pembro Q3w ×3 cycles	EV + pembro Q3w ×6 cycles, followed by pembro Q3w ×8 cycles		
		Control	—	—		
VOLGA NCT04960709	III	Arm A	EV + durva + treme Q3w ×3 cycles	Durva + treme Q3w ×1 cycle followed by durva Q4w ×9 cycles	830	Ineligible
		Arm B	EV + durva Q3w ×3 cycles	Durva Q4w ×9 cycles		
		Control	—	—		

Abbreviations: Durva, durvalumab; EV, enfortumab vedotin; Nivo, nivolumab; Pembro, pembrolizumab; Q, every; Treme, tremelimumab; w, week.

^aAdministered daily, oral.

have recently been presented.⁴⁹ Although the interpretation is limited by the small sample size and significant proportion of patients declining surgery, among 33 patients who underwent radical cystectomy, the overall pCR rate was 63.6%, with a striking 84.6% of HER2 3+ tumors achieving pCR. Further studies are needed to explore HER2-directed strategies as well as other targets, such as SURE-01/02 trial (ClinicalTrials.gov identifier: [NCT05535218](#)) exploring sacituzumab govitecan, a TROP-2–targeting ADC with SN-38 payload, with or without pembrolizumab for MIBC.

FUTURE DIRECTIONS

As the perioperative treatment of muscle-invasive urothelial carcinoma evolves, two management approaches emerged: neoadjuvant chemotherapy with risk-adapted adjuvant immunotherapy and universal perioperative immunotherapy-based treatment. In the absence of randomized data, the risks and benefits of each approach guide clinical decisions.

The risk-adapted approach allows 40%–60% of patients treated with cisplatin-based neoadjuvant chemotherapy to avoid immunotherapy and the potential toxicities altogether, but it evidently delays ICI exposure for patients with high-risk disease. Growing evidence suggests that exposure to immunotherapy in the neoadjuvant setting might enhance antitumor activity. In preclinical and clinical models, the use of immunotherapy in the neoadjuvant setting was associated with greater T-cell expansion compared with the adjuvant setting, presumably because of increased exposure to tumor antigens.⁵⁰ Results from early-phase clinical trials support this hypothesis, including a phase II randomized trial in patients with melanoma demonstrating significantly improved EFS when pembrolizumab was given perioperatively compared with adjuvant only for the same total duration.⁵¹ Furthermore, in an exploratory analysis of the NIAGARA study, the addition of perioperative durvalumab to neoadjuvant chemotherapy resulted in improved outcomes even among patients achieving pCR,²³ suggesting benefit in a lower risk population. Overall, these data highlight the rationale for universal neoadjuvant chemoimmunotherapy, especially considering the challenges for accurate risk stratification before neoadjuvant therapy.

A key unanswered question is the relative contribution of the neoadjuvant and adjuvant components of the perioperative treatment with immunotherapy. Given the NIAGARA trial design, no conclusions can be made regarding the benefit of the adjuvant therapy in general and specifically for patients with pCR who otherwise would not have been offered adjuvant immunotherapy.²³ Adjuvant treatment exposes patients to additional adverse events (in the adjuvant phase of NIAGARA, treatment-related adverse events were reported in 40.7% of patients who started adjuvant durvalumab v 6% in the comparison arm), as well as financial and time toxicities. Given the perioperative design of the awaited phase III perioperative studies, this question will remain a challenge. Moreover, the adjuvant component of EV-304/KEYNOTE-B15

and EV-303/KEYNOTE-905 includes 5 of 6 cycles of EV in addition to pembrolizumab, which will likely result in added toxicity compared with prior reports with single-agent ICIs. Similar challenges are arising across solid tumors,⁵² with different strategies explored to address these questions. In melanoma, the NADINA trial reported a striking significantly improved EFS (HR, 0.32) using two cycles of neoadjuvant ipilimumab + nivolumab with adjuvant nivolumab administered only in nonresponders, compared with adjuvant nivolumab alone. The ongoing OptimICE-pCR trial in triple-negative breast cancer is randomly assigning patients with pCR after neoadjuvant chemoimmunotherapy to receive adjuvant pembrolizumab or observation (ClinicalTrials.gov identifier: [NCT05812807](#)). Furthermore, the encouraging outcomes reported in patients with persistent undetectable ctDNA from IMvigor011³¹ and TOMBOLA³² suggest that ctDNA might play a role in optimizing patient selection for treatment de-escalation beyond pathologic response. Data from IMvigor011 and the MODERN trial (ClinicalTrials.gov identifier: [NCT05987241](#)) will hopefully inform future directions in this space. Moreover, while the multiarm MODERN trial is also evaluating treatment escalation for high-risk disease on the basis of ctDNA status, future studies are needed to explore additional strategies in the post-neoadjuvant chemoimmunotherapy population.

It is still largely unknown whether the universal perioperative immunotherapy-based treatments make the radical cystectomy and lymph node dissection more difficult, thus increasing the risk of postoperative complications. Briganti et al⁴² reported the first prospective rigorous assessment of perioperative outcomes after radical cystectomy after neoadjuvant pembrolizumab in the PURE-01 trial. This single-cohort study showed 77%, 69%, and 32% of the patients experienced any-grade complications, grade ≥2 complications, and readmission at 90 days, respectively. High-grade complications (defined as Clavien-Dindo ≥3a) were observed in 34% of the patients. A recent retrospective cohort study analyzed patients who underwent robotic radical cystectomy with intracorporeal urinary diversion and who received an immunotherapy-based neoadjuvant regimen. The study showed the cumulative 90-day complication rate after novel immunotherapy-based neoadjuvant treatment seems higher than those previously reported for robotic cystectomy alone or for a chemotherapy-based neoadjuvant regime.⁵³ Both studies had no comparative groups. One of the authors (A.S.) have seen significant fibrotic changes in the surgical field after immunotherapy-based neoadjuvant treatment, especially among those with clinical nodal disease that had substantial clinical response. Phase III trials should also focus on surgical morbidities in light of the potential cumulative toxicities with combination neoadjuvant therapies, although more resources are needed for collecting detailed surgical complications.

Another consideration of de-escalating the systemic therapy would be offering up-front radical cystectomy and lymph node dissection for patients with localized organ-confined

MIBC (cT2No) and without high-risk features such as lymphovascular invasion, hydronephrosis, or divergent histology. Surgery alone can be curative for a subgroup of patients, and adjuvant systemic therapy (chemotherapy or immunotherapy) can be reserved for patients with high-risk pathology (pT3/4 or pN+) from radical cystectomy.⁵⁴ Risk stratification using ctDNA is a promising potential strategy to inform de-escalation of neoadjuvant systemic therapy before radical cystectomy.^{28,53,55} Exploratory biomarker data from the perioperative trials as well as the ongoing prospective ctDNA-guided adjuvant studies will provide insights regarding the possibility of designing a future trial using ctDNA as a biomarker for a neoadjuvant treatment in MIBC.

Finally, there is growing interest in bladder-sparing strategies or radical cystectomy avoidance, especially with the increasing efficacy of systemic combination treatments (ICI + chemotherapy or ICI + ADCs). Although still the standard of care for MIBC, radical cystectomy is a complex operation with significant perioperative complications and impact on quality of life. Many patients would like to avoid radical cystectomy if safe after planned neoadjuvant therapy. A significant portion of patients will achieve complete response after neoadjuvant therapy, which may make radical cystectomy avoidance possible. In addition, although no randomized controlled trials are available, a multi-institutional study provides the best evidence to date showing similar oncologic outcomes between radical cystectomy and trimodal therapy for select patients with MIBC.⁵⁶ In a single-arm phase II trial, patients with MIBC received four cycles of gemcitabine, cisplatin, and nivolumab followed by clinical restaging.⁵⁷ Among the 76 patients enrolled, 33 (43%) achieved a clinical complete response and 32 (32%) opted to forgo immediate cystectomy. The authors concluded that stringently defined clinical complete response after gemcitabine, cisplatin, and nivolumab facilitated bladder

sparing. Unfortunately, there are currently no standard biomarkers to accurately identify patients with clinical complete response. Imaging techniques, such as multiparametric magnetic resonance imaging, were tested as a noninvasive tool for evaluating tumor response before surgery.⁵⁸ The Vesical Imaging-Reporting and Data System (VI-RADS) and the derived NAC VI-RADS further facilitated response stratification, aiming to identify complete responders who may benefit from active surveillance programs or bladder-sparing modalities rather than radical cystectomies.^{58,59} Again, ctDNA might be a very promising biomarker to identify candidates for a bladder-sparing approach. Ongoing prospective studies have been exploring risk-adapted management on the basis of specific genomic alterations. In RETAIN-1, a single-arm, phase II, noninferiority trial, patients with cT2-T3NoMo MIBC underwent neoadjuvant dose-dense MVAC.⁶⁰ Prechemotherapy transurethral bladder tumor specimens were sequenced to identify mutations in *ATM*, *ERCC2*, *FANCC*, and *RB1*. Patients with ≥ 1 mutation and cT0 after chemotherapy were offered active surveillance. Although the primary end point was not met, 48% of the active surveillance group avoided cystectomy without metastatic disease. Two additional ongoing trials, RETAIN-2 (ClinicalTrials.gov identifier: [NCT04506554](#)), evaluating similar design using dose-dense MVAC + nivolumab, and A031701 (ClinicalTrials.gov identifier: [NCT03609216](#)), evaluating bladder sparing in patients with DNA damage repair alterations and clinical complete response after gemcitabine and cisplatin, will shed light on the viability of this approach.

In summary, as the landscape of perioperative treatment paradigm continues to evolve, new trials exploring novel therapies and incorporating risk-adapted strategies are reshaping the management of this disease and offer hope for a more personalized approach to treating patients with muscle-invasive urothelial cancer in the future.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Stein JP, Lieskovsky G, Cote R, et al: Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. *J Clin Oncol* 19:666-675, 2001
- Madersbacher S, Hochreiter W, Burkhard F, et al: Radical cystectomy for bladder cancer today—A homogeneous series without neoadjuvant therapy. *J Clin Oncol* 21:690-696, 2003
- Grossman HB, Natale RB, Tangen CM, et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 349:859-866, 2003
- International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working Party now the National Cancer Research Institute Bladder Cancer Clinical Studies Group, European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, et al: International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: Long-term results of the BA06 30894 trial. *J Clin Oncol* 29:2171-2177, 2011
- Advanced Bladder Cancer ABC Meta-analysis Collaboration: Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data: Advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol* 48:202-206, 2005
- Pfister C, Gravis G, Flechon A, et al: Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine and cisplatin as perioperative chemotherapy for patients with nonmetastatic muscle-invasive bladder cancer: Results of the GETUG-AFU V05 VESPER trial. *J Clin Oncol* 40:2013-2022, 2022
- Pfister C, Gravis G, Flechon A, et al: Perioperative dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin in muscle-invasive bladder cancer (VESPER): Survival endpoints at 5 years in an open-label, randomised, phase 3 study. *Lancet Oncol* 25:255-264, 2024
- Powles T, Catto JWF, Galsky MD, et al: Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. *N Engl J Med* 391:1773-1786, 2024
- Bajorin DF, Witjes JA, Gschwend JE, et al: Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med* 384:2102-2114, 2021
- Galsky MD, Witjes JA, Gschwend JE, et al: Adjuvant nivolumab in high-risk muscle-invasive urothelial carcinoma: Expanded efficacy from CheckMate 274. *J Clin Oncol* 43:15-21, 2025
- US Food and Drug Administration: FDA Approves Nivolumab for Adjuvant Treatment of Urothelial Carcinoma. FDA, 2024. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-adjuvant-treatment-urothelial-carcinoma>
- European Medicines Agency (EMA): Opdivo. 2015. <https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo>
- Apolo AB, Ballman KV, Sonpavde G, et al: Adjuvant pembrolizumab versus observation in muscle-invasive urothelial carcinoma. *N Engl J Med* 392:45-55, 2025
- Bellmunt J, Hussain M, Gschwend JE, et al: Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 22:525-537, 2021
- Flaig TW, Tangen CM, Daneshmand S, et al: A randomized phase II study of Coexpression Extrapolation (COXEN) with neoadjuvant chemotherapy for bladder cancer (SWOG S1314; NCT02177695). *Clin Cancer Res* 27:2435-2441, 2021
- Kassouf W, Spiess PE, Brown GA, et al: P0 stage at radical cystectomy for bladder cancer is associated with improved outcome independent of traditional clinical risk factors. *Eur Urol* 52:769-774, 2007
- Bhindi B, Frank I, Mason RJ, et al: Oncologic outcomes for patients with residual cancer at cystectomy following neoadjuvant chemotherapy: A pathologic stage-matched analysis. *Eur Urol* 72:660-664, 2017
- Rosenblatt R, Sherif A, Rintala E, et al: Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. *Eur Urol* 61:1229-1238, 2012
- Martini A, Jia R, Ferket BS, et al: Tumor downstaging as an intermediate endpoint to assess the activity of neoadjuvant systemic therapy in patients with muscle-invasive bladder cancer. *Cancer* 125:3155-3163, 2019
- Peyton CC, Tang D, Reich RR, et al: Downstaging and survival outcomes associated with neoadjuvant chemotherapy regimens among patients treated with cystectomy for muscle-invasive bladder cancer. *JAMA Oncol* 4:1535-1542, 2018
- Petrelli F, Coinu A, Cabiddu M, et al: Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: A meta-analysis. *Eur Urol* 65:350-357, 2014
- Culine S, Harter V, Krucker C, et al: Refining the characterization and outcome of pathological complete responders after neoadjuvant chemotherapy for muscle-invasive bladder cancer: Lessons from the randomized phase III VESPER (GETUG-AFU V05) trial. *Cancers* 15:1742, 2023
- Galsky MD, Van Der Heijden MS, Catto JWF, et al: Additional efficacy and safety outcomes and an exploratory analysis of the impact of pathological complete response (pCR) on long-term outcomes from NIAGARA. *J Clin Oncol* 43, 2025 (suppl 5; abstr 659)
- Sonpavde G, Goldman BH, Speights VO, et al: Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. *Cancer* 115:4104-4109, 2009
- Møller CT, Støer NC, Blindheim A, et al: Downstaging and survival after Neoadjuvant chemotherapy for bladder cancer in Norway; a population-based study. *BMC Cancer* 22:1301, 2022
- Zhu L, Xu R, Yang L, et al: Minimal residual disease (MRD) detection in solid tumors using circulating tumor DNA: A systematic review. *Front Genet* 14:1172108, 2023
- Lindskog SV, Birkenkamp-Demtröder K, Nordentoft I, et al: Circulating tumor DNA analysis in advanced urothelial carcinoma: Insights from biological analysis and extended clinical follow-up. *Clin Cancer Res* 29:4797-4807, 2023
- Sfakianos JP, Basu A, Laliotis G, et al: Association of tumor-informed circulating tumor DNA detectability before and after radical cystectomy with disease-free survival in patients with bladder cancer. *Eur Urol Oncol* 8:306-314, 2025
- Powles T, Assaf ZJ, Degaonkar V, et al: Updated overall survival by circulating tumor DNA status from the phase 3 IMvigor010 trial: Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma. *Eur Urol* 85:114-122, 2024
- Powles T, Assaf ZJ, Davaranan N, et al: ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. *Nature* 595:432-437, 2021
- UROONCO: Clinical outcomes in patients with high-risk, post-cystectomy muscle-invasive bladder cancer (MIBC) with persistent circulating tumour DNA-negative (ctDNA-) status on serial testing: Surveillance analysis from the IMvigor011 study. <https://uroonco.uroweb.org/webcast/clinical-outcomes-in-patients-with-high-risk-post-cystectomy-muscle-invasive-bladder-cancer-mibc-with-persistent-circulating-tumour-dna-negative-ctdna-status-on-serial-testing-surveillance-anal/>
- Bjerggaard Jensen J, Birkenkamp-Demtröder K, Nordentoft I, et al: 19600 Identification of bladder cancer patients that could benefit from early post-cystectomy immunotherapy based on serial circulating tumour DNA (ctDNA) testing: Preliminary results from the TOMBOLA trial. *Ann Oncol* 35:S1133, 2024
- Doroshov DB, Bhalla S, Beasley MB, et al: PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol* 18:345-362, 2021
- Parent P, Marcq G, Adeleke S, et al: Predictive biomarkers for immune checkpoint inhibitor response in urothelial cancer. *Ther Adv Med Oncol* 15:17588359231192402, 2023
- Galsky MD, Bajorin DF, Witjes JA, et al: Disease-free survival analysis for patients with high-risk muscle-invasive urothelial carcinoma from the randomized CheckMate 274 trial by PD-L1 combined positive score and tumor cell score. *Eur Urol* 83:432-440, 2023
- Necchi A, Anichini A, Raggi D, et al: Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): An open-label, single-arm, phase II study. *J Clin Oncol* 36:3353-3360, 2018
- Basile G, Bandini M, Gibb EA, et al: Neoadjuvant pembrolizumab and radical cystectomy in patients with muscle-invasive urothelial bladder cancer: 3-Year median follow-up update of PURE-01 trial. *Clin Cancer Res* 28:5107-5114, 2022
- Necchi A, Raggi D, Gallina A, et al: Updated results of PURE-01 with preliminary activity of neoadjuvant pembrolizumab in patients with muscle-invasive bladder carcinoma with variant histologies. *Eur Urol* 77:439-446, 2020
- Reike MJ, Raggi D, Mercinelli C, et al: Distinct gene expression patterns identify patients who relapse after neoadjuvant pembrolizumab and radical cystectomy in the PURE-01 study. *Clin Genitourin Cancer* 22:102214, 2024
- Clinton TN: Defining resistance to immune checkpoint inhibitors in urothelial carcinoma: Insights from PURE-01. *Eur Urol* 80:323-324, 2021
- Iacovino ML, Miceli CC, De Felice M, et al: Novel therapeutic opportunities in neoadjuvant setting in urothelial cancers: A new horizon opened by molecular classification and immune checkpoint inhibitors. *Int J Mol Sci* 23:1133, 2022
- Briganti A, Gandaglia G, Scuderi S, et al: Surgical safety of radical cystectomy and pelvic lymph node dissection following neoadjuvant pembrolizumab in patients with bladder cancer: Prospective assessment of perioperative outcomes from the PURE-01 trial. *Eur Urol* 77:576-580, 2020

43. Szabados B, Kockx M, Assaf ZJ, et al: Final results of neoadjuvant atezolizumab in cisplatin-ineligible patients with muscle-invasive urothelial cancer of the bladder. *Eur Urol* 82:212-222, 2022
44. van Dijk N, Gil-Jimenez A, Silina K, et al: Preoperative ipilimumab plus nivolumab in locoregionally advanced urothelial cancer: The NABUCCO trial. *Nat Med* 26:1839-1844, 2020
45. O'Donnell PH, Hoimes CJ, Rosenberg JE, et al: Study EV-103: Neoadjuvant treatment with enfortumab vedotin monotherapy in cisplatin-ineligible patients with muscle invasive bladder cancer (MIBC)—2-year event-free survival and safety data for Cohort H. *J Clin Oncol* 42, 2024 (suppl 16; abstr 4564)
46. US Food and Drug Administration: FDA approves durvalumab for muscle invasive bladder cancer. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-muscle-invasive-bladder-cancer>
47. Crupi E, de Padua TC, Marandino L, et al: Circulating tumor DNA as a predictive and prognostic biomarker in the perioperative treatment of muscle-invasive bladder cancer: A systematic review. *Eur Urol Oncol* 7:44-52, 2024
48. Meric-Bernstam F, Makker V, Oaknin A, et al: Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: Primary results from the DESTINY-PanTumor02 phase II trial. *J Clin Oncol* 42:47-58, 2024
49. Sheng X, Zhang C, Ji Y, et al: Neoadjuvant treatment with disitamab vedotin plus perioperative toripalimab in patients with muscle-invasive bladder cancer (MIBC) with HER2 expression: Updated efficacy and safety results from the phase II RC48-C017 trial. *J Clin Oncol* 43, 2025 (suppl 5; abstr 665)
50. Versluis JM, Long GV, Blank CU: Learning from clinical trials of neoadjuvant checkpoint blockade. *Nat Med* 26:475-484, 2020
51. Patel SP, Othus M, Chen Y, et al: Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma. *N Engl J Med* 388:813-823, 2023
52. Wakelee H, Liberman M, Kato T, et al: Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med* 389:491-503, 2023
53. Ben-David R, Pellegrino F, Mehrzin R, et al: Immunotherapy-based neoadjuvant treatment and complication rates after radical cystectomy. *BJU Int* 10.1111/bju.16662 [epub ahead of print on January 23, 2025]
54. Yelfimov DA, Frank I, Boorjian SA, et al: Adjuvant chemotherapy is associated with decreased mortality after radical cystectomy for locally advanced bladder cancer. *World J Urol* 32:1463-1468, 2014
55. Ben-David R, Lidagoster S, Geduldig J, et al: Undetectable pre-radical cystectomy circulating tumour DNA status predicts improved oncological outcomes. *BJU Int* 135:473-480, 2025
56. Zlotta AR, Ballas LK, Niemierko A, et al: Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: A multi-institutional propensity score matched and weighted analysis. *Lancet Oncol* 24:669-681, 2023
57. Galsky MD, Daneshmand S, Izadmehr S, et al: Gemcitabine and cisplatin plus nivolumab as organ-sparing treatment for muscle-invasive bladder cancer: A phase 2 trial. *Nat Med* 29:2825-2834, 2023
58. Necchi A, Bandini M, Calareso G, et al: Multiparametric magnetic resonance imaging as a noninvasive assessment of tumor response to neoadjuvant pembrolizumab in muscle-invasive bladder cancer: Preliminary findings from the PURE-01 study. *Eur Urol* 77:636-643, 2020
59. Brembilla G, Basile G, Cosenza M, et al: Neoadjuvant chemotherapy VI-RADS scores for assessing muscle-invasive bladder cancer response to neoadjuvant immunotherapy with multiparametric MRI. *Radiology* 313:e233020, 2024
60. Geynisman DM, Abbosh PH, Ross E, et al: Phase II trial of risk-enabled therapy after neoadjuvant chemotherapy for muscle-invasive bladder cancer (RETAIN 1). *J Clin Oncol* 43:1113-1122, 2025

Emerging Paradigms in Genitourinary Cancers: Integrating Molecular Imaging, Hypoxia-Inducible Factor–Targeted Therapies, and Antibody-Drug Conjugates in Renal Cell and Urothelial Carcinomas

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OVERVIEW

Novel approaches in molecular imaging and targeted therapeutics are transforming the management of renal cell carcinoma (RCC) and urothelial carcinoma (UC). This review focuses on three key areas of innovation: molecular imaging, hypoxia-inducible factor-2 α (HIF-2 α) inhibition, and antibody-drug conjugates (ADCs). In molecular imaging, prostate-specific membrane antigen positron emission tomography/computed tomography has shown promise in RCC, while novel tracers targeting carbonic anhydrase IX and nectin-4 are emerging for RCC and UC, respectively. These approaches may enable better characterization of disease and treatment response monitoring. HIF-2 α inhibition represents a breakthrough in targeting the fundamental pathobiology of clear cell RCC, with belzutifan demonstrating significant clinical benefit in both von Hippel-Lindau disease and sporadic RCC. Next-generation HIF-2 α inhibitors, including casdatifan, show promising early clinical results with distinct pharmacologic properties. ADCs have become a cornerstone of UC treatment, with enfortumab vedotin plus pembrolizumab now approved as first-line therapy. Multiple human epidermal growth factor receptor 2 (HER2)-directed ADCs have shown efficacy in HER2-expressing UC, including trastuzumab deruxtecan, which recently received tumor-agnostic approval. While ADC development in RCC faces unique challenges, novel approaches including immunostimulatory payloads and bispecific antibodies are being explored. The integration of these advances in molecular imaging and therapeutics offers opportunities for more personalized treatment approaches in RCC and UC.

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INTRODUCTION

The management of renal cell carcinoma (RCC) and urothelial carcinoma (UC) continues to evolve with significant advances in both diagnostic imaging and therapeutic approaches. Recent developments in molecular imaging and targeted therapeutics are transforming our ability to characterize and treat these malignancies. This review focuses on three key areas of innovation: novel positron emission tomography (PET) imaging approaches that may mirror the paradigm shift seen in prostate cancer, the emergence of hypoxia-inducible factor-2 α (HIF-2 α) inhibitors that directly target the fundamental pathobiology of clear cell RCC (ccRCC), and the development of antibody-drug conjugates (ADCs) that offer new strategies for direct tumor killing (Table 1). These complementary advances are reshaping the landscape of genitourinary oncology and opening new opportunities for personalized treatment approaches.

NOVEL PET IMAGING APPROACHES

Within genitourinary oncology, there has been a paradigm shift for the management of prostate cancer with new tumor-specific PET/computed tomography (CT) agents that have complemented or replaced conventional modalities including CT, magnetic resonance imaging (MRI), and ultrasound (Table 2). We envisage a similar paradigm shift occurring in RCC and urothelial cancer, which may mirror the transformation occurring in prostate cancer. The advent of prostate-specific membrane antigen (PSMA) PET/CT has become a new standard of care for staging,¹ biochemical recurrence,² and evaluating suitability for radionuclide therapy³ and also has an evolving role for diagnosis.⁴ In the future, it may also replace technetium bone scan for response assessment with metastatic disease, although further work is needed to standardize criteria and reporting.⁵ In RCC and UC, triple-phase CT or MRI remains the standard of care to characterize renal, ureteric, or bladder lesions,⁶ while

PRACTICAL APPLICATIONS

- Novel molecular imaging with positron emission tomography/computed tomography tracers targeting prostate-specific membrane antigen and carbonic anhydrase IX can improve disease characterization in renal cell carcinoma (RCC), potentially changing clinical management decisions and treatment-monitoring approaches.
- Hypoxia-inducible factor-2 α inhibitors represent a new therapeutic class for clear cell RCC with a distinct and manageable safety profile, requiring specific monitoring and management strategies for anemia and hypoxia.
- Enfortumab vedotin plus pembrolizumab has emerged as a new standard first-line therapy option for advanced urothelial carcinoma (UC), affecting treatment sequencing decisions.
- Human epidermal growth factor receptor 2 (HER2)-directed antibody-drug conjugates (ADCs) have demonstrated efficacy in HER2-expressing UC, expanding treatment options and highlighting the importance of HER2 testing in patients with UC.
- Understanding the unique challenges of ADC development in RCC, including resistance to cytotoxic agents, is crucial when considering therapeutic options and clinical trial participation for patients with RCC.

CT is used to exclude metastatic disease in patients at high risk of distant disease. Bone scan, despite limitations, and brain MRI are also recommended in the presence of clinical symptoms suggestive of metastatic disease. PET/CT is not yet routinely recommended by consensus guidelines.

PET for RCC

In addition to its role in prostate cancer, PSMA PET/CT has been explored for the evaluation of metastatic RCC with promising results. Unlike prostate cancer, PSMA expression is in the neovasculature rather than cell surface. Histopathologically, PSMA expression varies and correlates with angiogenic gene expression, increased survival, and a longer duration of tyrosine kinase inhibitor treatment.⁷ In 61 patients of whom 89% had ccRCC, PSMA-positive disease was detected in 84% of patients.⁸ PSMA PET/CT detected additional metastases compared with CT in 25% of patients and in patients who also had fluorodeoxyglucose (FDG) PET/CT; Standardized Uptake Value maximum (SUVmax) was higher for PSMA (SUVmax 15.2 ν 8.0; $P = .02$). A change in management after PSMA PET/CT occurred in 49% (Fig 1). In a small series, the

potential of PSMA PET/CT to evaluate response to radiotherapy was also demonstrated.⁹ Intensity on PSMA PET/CT strongly correlates with immunohistochemistry and conveys a poor prognosis confirming its potential as an aggressiveness biomarker.¹⁰ Although promising, further research is needed to determine whether PSMA PET/CT can be used as a predictive biomarker, to help optimize treatment selection. Given the absence of cell surface expression, however, there does not seem to be a role for lutetium-177 radioligand therapy, as rapid washout of the radiotracer occurs.¹¹

Carbonic anhydrase IX (CA-IX) is overexpressed in ccRCC, with early experience suggesting that it has the potential to revolutionize imaging similar to what PSMA PET/CT has achieved in prostate cancer. Early work explored radiolabeled antibodies labeled with iodine-131,¹² zirconium-89,¹³ or iodine-124¹⁴ for PET/CT imaging. Unlike the high physiologic renal cortical activity of PSMA PET/CT, these radiolabels have no cortical activity, enabling evaluation of primary renal masses (Fig 2). Recently, the accuracy of ⁸⁹Zr-girentuximab PET/CT was evaluated in a phase III study of 300 patients with renal masses 7 cm or smaller (cT1) suspicious for ccRCC scheduled for nephrectomy.¹⁵ The study demonstrated an accuracy of 86% for detecting ccRCC with histopathology as the reference standard, representing a sensitivity and specificity of 86% and 87%, respectively. Accuracy remained high in the subgroup of 20 patients with ≤ 2 cm masses (97%). The mean SUVmax was 56 in 158 patients with ccRCC.

There are also emerging data for radiolabeled peptides, which have favorable pharmacokinetics compared with antibodies targeting CA-IX for PET/CT imaging. The first experience with ⁶⁸Ga-DPI-4452, a cyclic peptide, demonstrated exceptional tumor-to-background ratio in three patients with metastatic ccRCC, with SUVmax in tumor above 100 in all three patients.¹⁶ ⁶⁸Ga-DPI-4452 PET/CT was also able to visualize 17 metastases not seen on conventional imaging (Fig 3); low renal parenchymal uptake enabled identification of renal tumors. Tumor uptake was visualized as early as 15 minutes, with optimal imaging time at 60 minutes. This compares favorably to antibody-based imaging, which is performed 3–7 days after radiotracer administration; at this late time point, scanning time is longer than with early ¹⁸F or ⁶⁸Ga imaging. Furthermore, a phase I trial of ¹⁷⁷Lu-DPI-4452 is currently underway. High physiologic gastric and small bowel activity may limit dose escalation with small molecules, whereas prolonged thrombocytopenia was seen with antibody-based approaches.¹⁷

PET for UC

For UC, there are less mature data for tumor-specific PET/CT ligands. A recent publication of ⁶⁸Ga-N188, a bicyclic peptide targeting nectin-4, demonstrated specific uptake¹⁸ (Fig 4) correlating with immunohistochemistry staining.¹⁹ Given the role of nectin-4-directed ADCs, as discussed further

TABLE 1. Emerging Diagnostic and Therapeutic Approaches in RCC and UC

Therapeutic Approach	RCC	UC	Key Clinical Implications
Molecular imaging	CA-IX PET: 86% accuracy for ccRCC detection PSMA PET: targets neovasculature with 84% detection rate FDG PET: important prognostic value	PSMA PET: limited data FDG PET: prognostic value Nectin-4 PET: emerging	Improved staging accuracy Better characterization of disease Potential to guide therapy selection
HIF-2 α inhibitors	Belzutifan: first-in-class, FDA approved for VHL disease and sporadic ccRCC Casdatifan: early promising results Class effect: anemia and hypoxia as on-target AEs	Not applicable	Novel mechanistic approach targeting RCC pathobiology Expanding options beyond immunotherapy and TKIs Multiple combinations under investigation
ADCs	Limited efficacy to date	EV (nectin-4): standard of care, first-line with pembrolizumab Trop-2 ADCs: SG approval withdrawn; Dato-DXd in early trials HER2-directed: multiple ADCs showing efficacy	Practice changing in UC management

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; CA-IX, carbonic anhydrase IX; ccRCC, clear cell RCC; Dato-DXd, datopotamab deruxtecan; EV, enfortumab vedotin; FDA, US Food and Drug Administration; FDG, fluorodeoxyglucose; HER2, human epidermal growth factor receptor 2; HIF-2 α , hypoxia-inducible factor-2 α ; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RCC, renal cell carcinoma; SG, sacituzumab govitecan; TKI, tyrosine kinase inhibitor; Trop-2, trophoblast cell surface antigen 2; UC, urothelial carcinoma; VHL, von Hippel-Lindau.

below, exploring this target for nuclear medicine applications is encouraging. This might enable selection of patients most likely to benefit from ADC therapy or nectin-4 radionuclide therapy. CA-IX PET/CT is also being explored for UC.^{20,21} Imaging the tumor microenvironment with ⁶⁸Ga-FAPI, a radiolabeled peptide-targeting fibroblast activating protein²² is also emerging, although not tumor specific.

A disadvantage of tumor-specific imaging is that the target may not be expressed on all tumor subtypes. This is particularly true for CA-IX, which is overexpressed in clear cell but not other subtypes of RCCs. Moreover, within a patient, expression may be heterogeneous at different sites of metastases. Conversely, PET/CT provides an opportunity to visualize tumor heterogeneity and overcome some of the limitations of single-tumor biopsy samples (Fig 5). Indeed, tumor heterogeneity presents a major challenge to personalized medicine approaches.²³ This is particularly evident when combining a tumor-specific radiotracer with FDG PET/CT.²⁴ They provide complementary roles owing to differing mechanisms of uptake. This may enable disease characterization to inform treatment change beyond what is achievable with histopathology.

FDG PET in RCC and UC

The role of FDG PET/CT should not be underestimated in both RCC and UC. This is a sensitive modality in patients with high-grade disease for detecting locoregional, nodal, and distant metastatic disease. However, it may not be sensitive in patients with lower grade disease. This differentiation, however, confers a role as a powerful prognostic biomarker. For example, in a 48-patient study, the predictive value of both FDG PET/CT and ⁸⁹Zr-girentuximab PET/CT was

explored.²⁵ Patients with high metabolic activity on FDG PET/CT or high CA-IX expression had shorter time to watchful waiting of 9.0 versus 36.2 months or 9.3 versus 21.3 months, respectively. In multivariate analysis, FDG was the only predictive biomarker surpassing International Metastatic RCC Database Consortium (IMDC) criteria. Other studies have supported the role of FDG as a powerful prognostic biomarker in RCC,²⁶ either visually (positive or

TABLE 2. Potential Advantages and Disadvantages of Emerging Tumor-Targeted PET/CT Agents in Renal and Urogenital Cancers

Advantages
Improved sensitivity with <5 mm lesion characterization
Improved specificity
Better define oligometastatic disease
Replace invasive biopsy in selected patients
Enable early on-treatment response assessment
New prognostic or predictive biomarker
Image tumor heterogeneity
Select patient for radiopharmaceutical therapy
"All in one scan" in combination with contrast-enhanced CT, obviating need for bone scintigraphy
Disadvantages
Potential for stage migration with increased sensitivity
Nonvalidated interpretation compared with CT RECIST
Subtypes may not express target leading to false-negative results
Changes in intensity of uptake can be inaccurate for restaging

Abbreviations: CT, computed tomography; PET, positron emission tomography.

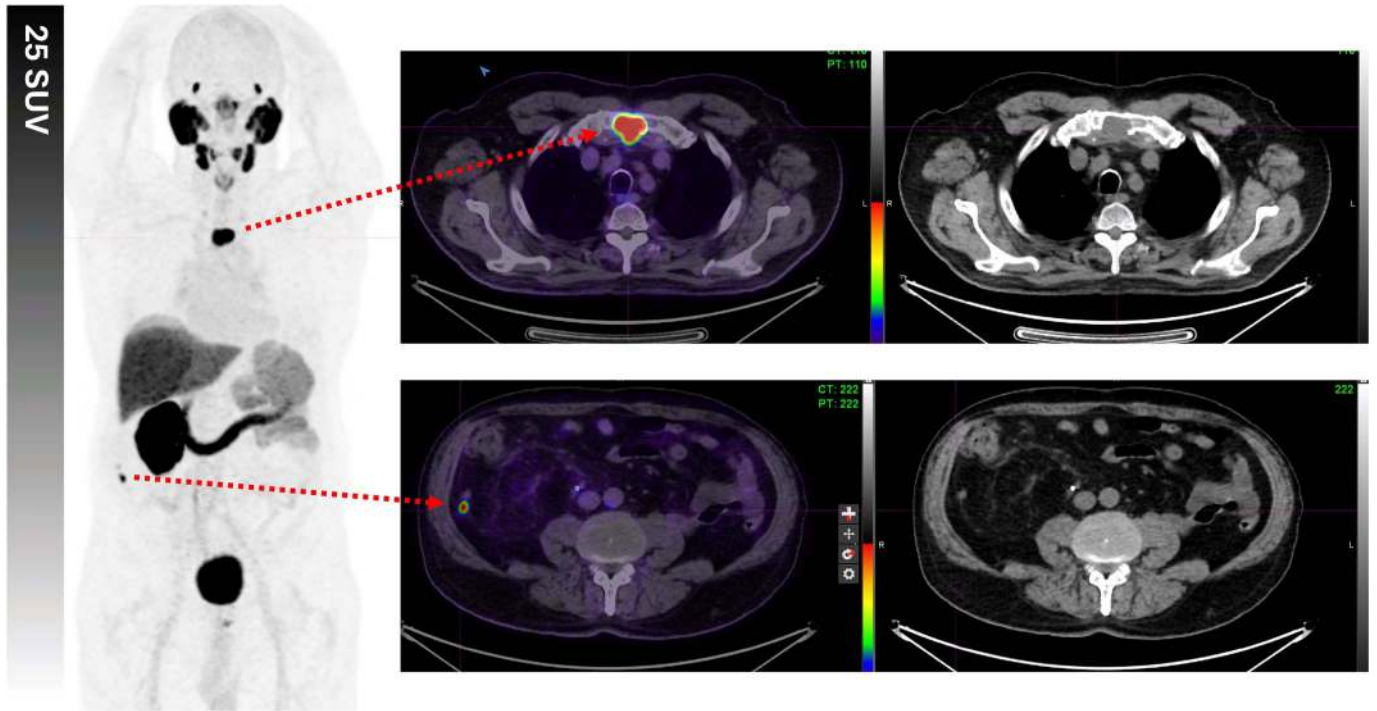


FIG 1. Prior nephrectomy for clear cell renal cell carcinoma. Presented with painful sternal metastasis, with CT confirming a destructive lytic lesion, but other metastases visualized. F-18 DCFPyL PSMA PET/CT demonstrated intense uptake in the sternal metastasis (SUVmax 31) with additional finding of several peritoneal metastases, which were too small to identify or characterize on CT. In addition to radiotherapy to the sternal metastasis for symptomatic relief, immunotherapy was commenced. CT, computed tomography; F-18 DCFPyL, F-18 Piflufolastat; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SUV, Standardized Uptake Value; SUVmax, Standardized Uptake Value maximum.

negative) or using SUVmax.²⁷ FDG PET/CT has also been shown to be prognostic for overall survival (OS) in UC.²⁸

The landscape of molecular imaging in genitourinary oncology continues to evolve rapidly, with emerging modalities showing promise beyond conventional imaging. Just as PSMA PET/CT has revolutionized prostate cancer management, novel tracers such as CA-IX for ccRCC and nectin-4-targeted imaging for urothelial cancer show similar potential. Capacity for radioisotope production is a concern for patient access to novel imaging; however, PSMA theranostics has shown this technology is scalable with ongoing efforts needed to ensure training of health professionals to ensure equitable access.²⁹ Use of novel imaging can decrease use of multiple conventional imaging scans such as CT and bone scanning, which may reduce costs.³⁰ Moreover, the cost of novel imaging remains low compared with the therapeutic costs, so the optimizing selection and sequencing of expensive therapies can reduce costs. Despite challenges with target expression heterogeneity, the integration of tumor-specific imaging may ultimately enable more personalized treatment approaches in genitourinary cancers.

HIF PATHWAY INHIBITION IN RCC

The emergence of HIF-2 α inhibitors marks a transformative advancement in the treatment of ccRCC, introducing a novel therapeutic class that specifically targets the fundamental

pathobiology of this disease. The scientific rationale for targeting HIF-2 α emerges from our deep understanding of ccRCC pathogenesis, where loss of von Hippel-Lindau (VHL) tumor suppressor function represents the earliest and most frequent genetic event.³¹ HIF-2 α functions as a master regulator of cellular adaptation to hypoxia through its role as an oxygen-sensing transcription factor.³² Under normal oxygen conditions, the VHL protein targets HIF-2 α for ubiquitin-mediated proteasomal degradation, maintaining tight regulation of this pathway.³² However, in ccRCC, VHL loss leads to inappropriate HIF-2 α stabilization and accumulation regardless of oxygen levels.³² Upon stabilization, HIF-2 α translocates to the nucleus where it heterodimerizes with HIF-1 β , forming a transcriptional complex that drives the expression of numerous genes involved in angiogenesis, cellular proliferation, and metabolic reprogramming.³² The central role of HIF-2 α in ccRCC progression creates an opportunity for synthetic lethality in VHL-deficient tumors, making it an especially compelling therapeutic target.³²

Clinical Evidence of Belzutifan: Establishing HIF-2 α as a Valid Therapeutic Target

Belzutifan (MK-6482, previously PT2977) emerged as the first-in-class HIF-2 α inhibitor, establishing clinical validation for this therapeutic approach (Table 3). The compound demonstrates favorable pharmacologic properties

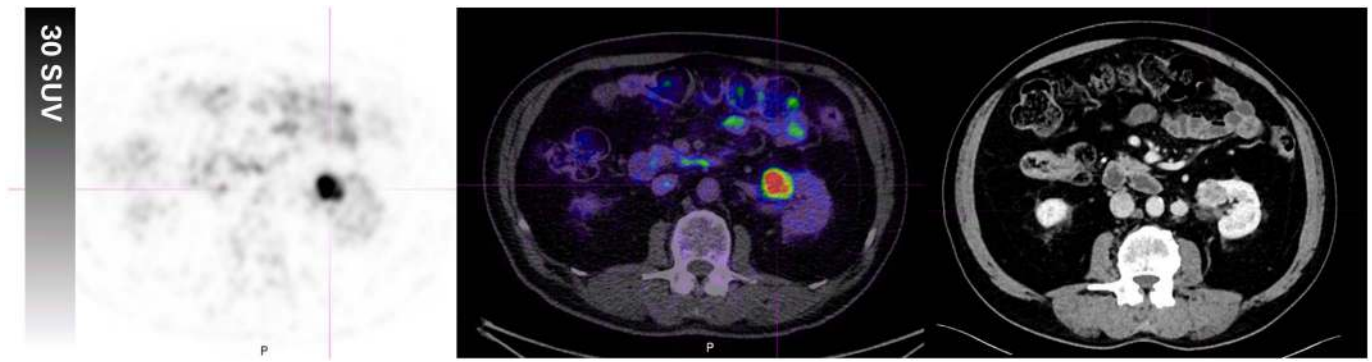


FIG 2. Patient with renal mass on contrast-enhanced CT. Histopathologic confirmation was preferred before surgical intervention, but the location made biopsy challenging. Zr-89 girentuximab PET/CT demonstrates intense uptake in the mass (SUVmax 43) consistent with clear cell renal cell carcinoma. Robotic partial nephrectomy confirmed the pathology. CT, computed tomography; PET, positron emission tomography; SUV, Standardized Uptake Value; SUVmax, Standardized Uptake Value maximum.

with a mean elimination half-life of 14 hours, supporting once-daily oral dosing.³³ Target engagement has been clearly demonstrated through dose-dependent and exposure-dependent reductions in plasma erythropoietin (EPO) levels at dosages up to 120 mg once daily.³³ Maximum EPO suppression, approximately 60% decrease from baseline, is typically achieved after 2 weeks of consecutive dosing, with levels gradually returning to baseline after 12 weeks.³³

The initial validation of belzutifan's mechanism of action came from studies in VHL disease, where constitutive HIF-2 α

activation drives multiple tumor types. In a pivotal phase II study of VHL disease-associated tumors, belzutifan demonstrated remarkable activity with a 49% objective response rate (ORR; 95% CI, 36 to 62) in RCC, with a median time to response of 8.2 months and, notably, no disease progression observed.³⁴ Responses extended beyond RCC to other VHL-associated neoplasms, including pancreatic lesions (77%) and central nervous system hemangioblastomas (30%).³⁴ These results led to belzutifan's first approval for VHL disease-associated tumors and provided strong rationale for its further development in sporadic ccRCC.

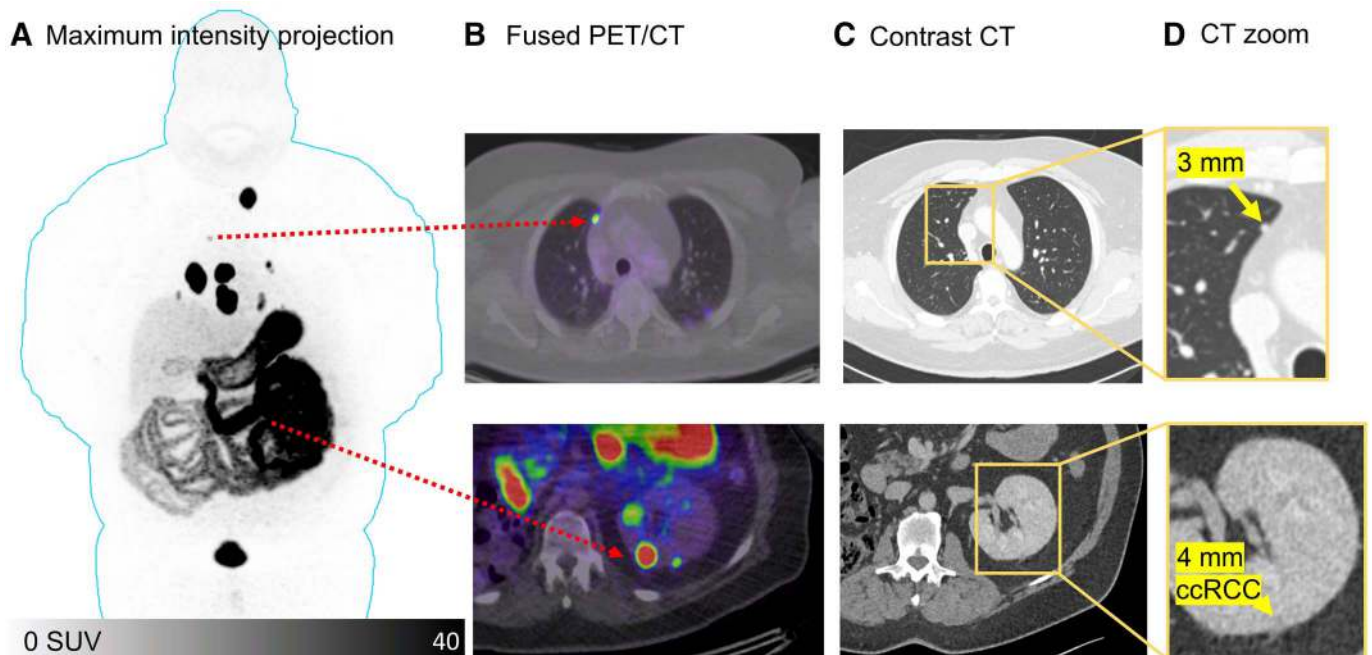


FIG 3. Ga-68 CA-IX (DPI-4452) PET/CT in a patient with prior right nephrectomy for ccRCC. Several presumed primary sites of disease were visualized in the left kidney, with high tumor-to-background contrast. Pulmonary metastases <5 mm were also visualized. Note physiologic high gastric and small bowel activity. CA-IX, carbonic anhydrase IX; ccRCC, clear cell renal cell carcinoma; CT, computed tomography; PET, positron emission tomography; SUV, Standardized Uptake Value.

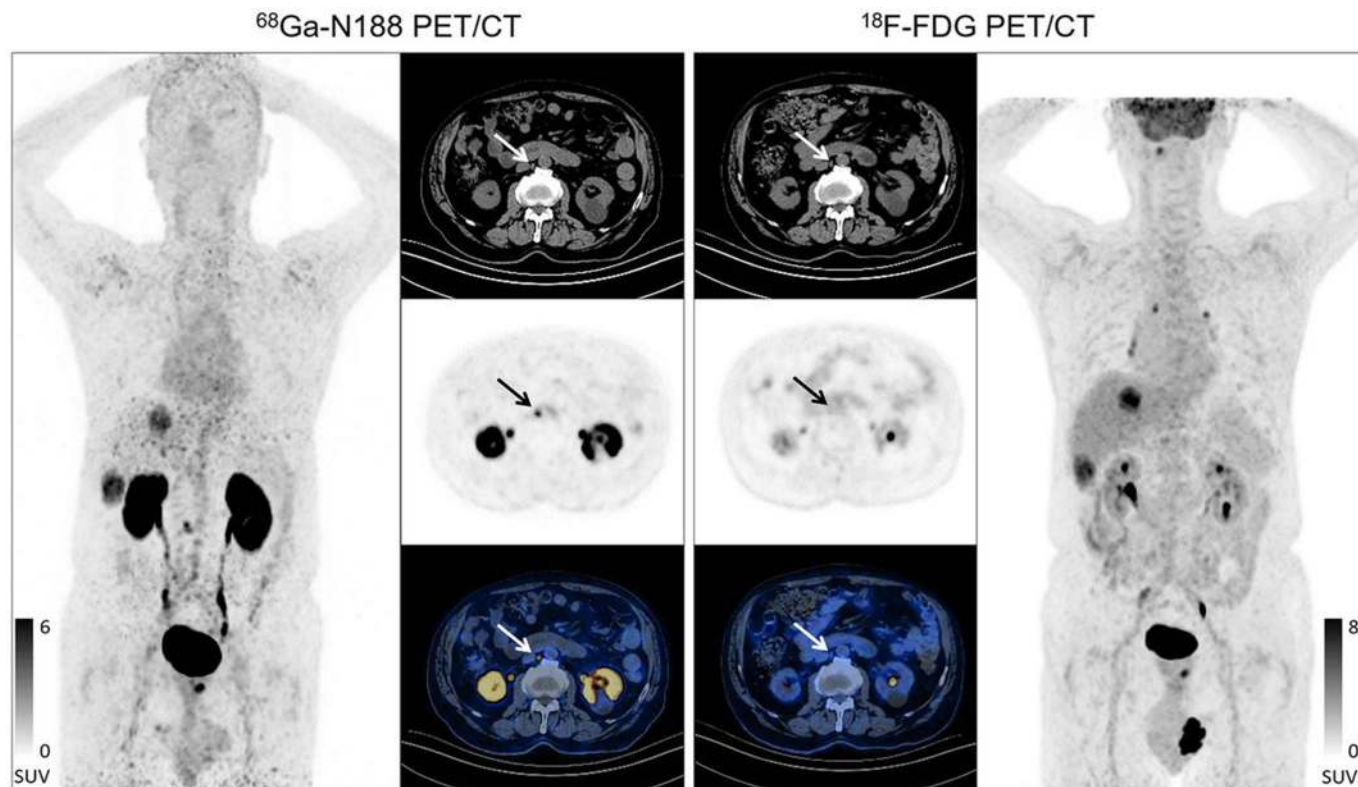


FIG 4. Ga-68 nectin-4 (N188) and FDG PET/CT in a patient with urothelial carcinoma. Liver metastases are visualized on both nectin-4 and FDG PET/CT, whereas a sub-cm para-aortic node is only seen on nectin-4 imaging (SUVmax 4.3). Reproduced with permission from 19. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUV, Standardized Uptake Value; SUVmax, Standardized Uptake Value maximum.

The pivotal LITESPARK-005 phase III trial established the efficacy of belzutifan in previously treated advanced ccRCC.³⁵ With extended follow-up (median, 35.8 months), the trial demonstrated sustained clinical benefit.³⁶ The progression-free survival (PFS) advantage was maintained (hazard ratio [HR], 0.75 [95% CI, 0.63 to 0.88]), with median PFS of 5.6 months in both arms but superior 12-month (33.7% v 17.6%) and 24-month (17.5% v 4.1%) PFS rates favoring belzutifan. The final OS analysis showed a median OS of 21.4 months with belzutifan versus 18.2 months with everolimus (HR, 0.92 [95% CI, 0.77 to 1.10]; $P = .18$). The ORR remained consistent at 22.7% for belzutifan versus 3.5% for everolimus, with a notably longer duration of response (19.3 v 13.7 months); however, the progressive disease (PD) rate was higher with belzutifan (34% v 21.5%).

A comprehensive safety analysis of belzutifan from a pooled analysis of 576 patients across four LITESPARK trials (001, 004, 005, and 013) has provided detailed characterization of its safety profile.³⁷ Treatment-related adverse events (AEs) occurred in 91.3% of patients, with grade 3–5 events in 37.7%. The most common AEs were anemia (84.2%), fatigue (42.7%), and hypoxia (16.3%). These on-target effects typically emerged early in treatment, with a median time to onset of 29 days for anemia and 31 days for hypoxia. Management of anemia included erythropoiesis-stimulating agents alone (22.9%), blood transfusions alone (17.5%), or

both modalities (12.8%). Hypoxia was effectively managed with supplemental oxygen in 70.2% of patients, with a median time to resolution of 11 days. Importantly, only 6.4% of patients discontinued treatment because of AEs, suggesting an overall manageable safety profile.

The optimal dosing of belzutifan was established through the LITESPARK-013 phase II study, in which 154 patients were randomly assigned to receive either 120 mg or 200 mg once daily.³⁸ The study demonstrated comparable efficacy between doses, with ORR of 23.7% and 23.1% for 120 mg and 200 mg, respectively (difference, -0.5% ; 95% CI, -14.0 to 12.9). PFS was also similar between the doses (HR, 0.94 [95% CI, 0.63 to 1.40]), confirming 120 mg once daily as the optimal dose with a favorable benefit-risk profile.

Building on the established single-agent efficacy of belzutifan, rational combinations are being explored, particularly in earlier disease settings. The combination of belzutifan with cabozantinib has shown promising activity in a phase II study of treatment-naïve and immunotherapy-pretreated ccRCC patients.³⁹ Among 52 patients having received prior immunotherapy, with a median follow-up of 24.6 months, the combination demonstrated an ORR of 30.8% (95% CI, 18.7 to 45.1), including one complete response. Responses were durable, with median duration of response not reached at the time of analysis. Among 50 patients who

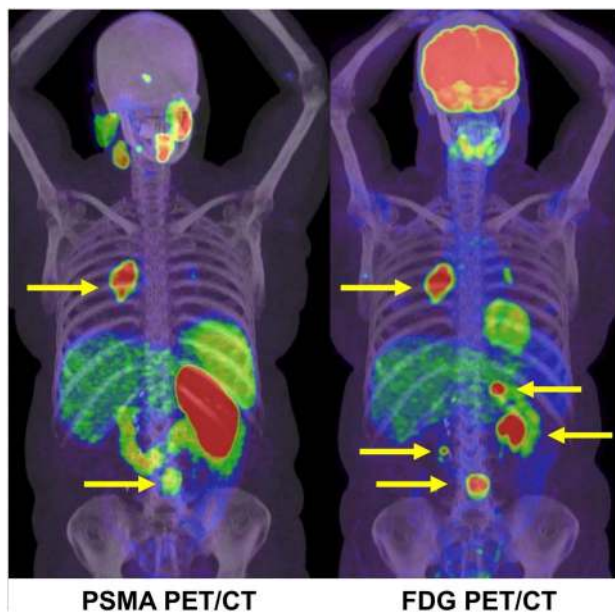


FIG 5. Discordant PSMA and FDG PET/CT findings in a patient with metastatic ccRCC. PSMA PET/CT demonstrated two metastases (central omental nodule, right thoracic hilar lymph node), whereas FDG PET/CT showed five metastases (central omental, right thoracic hilar lymph node, left omental, left anterior diaphragmatic node, peripancreatic nodule). ccRCC, clear cell renal cell carcinoma; CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

were treatment naïve, of whom 56% had IMDC favorable risk disease, with a median follow-up of 24.3 months, the ORR was 70% (95% CI, 55 to 82) with a PD rate of 2% and PFS of 30.3 months (95% CI, 16.6 to not reached).⁴⁰

These results provide rationale for ongoing phase III trials investigating belzutifan across multiple disease settings. MK6482-011 (ClinicalTrials.gov identifier: [NCT04586231](#)) is

evaluating the combination of belzutifan plus lenvatinib versus cabozantinib in patients who have progressed after immunotherapy treatment, while MK6482-012 (ClinicalTrials.gov identifier: [NCT04736706](#)) is investigating belzutifan in the first-line setting for advanced disease. In the adjuvant space, MK6482-022 (ClinicalTrials.gov identifier: [NCT05239728](#)) is studying belzutifan in combination with pembrolizumab in high-risk patients after nephrectomy. Additionally, MK6482-024 (ClinicalTrials.gov identifier: [NCT05468697](#)) is exploring the novel combination of belzutifan with palbociclib targeting cell cycle regulation, and another study is evaluating the combination with HC-7366, a GCN2 activator, in advanced disease (ClinicalTrials.gov identifier: [NCT06234605](#)). There are also plans to evaluate belzutifan in combination with zanzalintinib through a phase I/II trial and two phase III pivotal trials in RCC. These studies will help define the optimal roles for belzutifan from the adjuvant setting through multiple lines of therapy for advanced disease.

Casdatifan (AB521): A Novel Selective HIF-2 α Inhibitor

Casdatifan represents a second-generation HIF-2 α inhibitor with pharmacologic properties that suggest enhanced potency compared with first-generation agents (Table 3). The compound demonstrates linear pharmacokinetics with a terminal half-life of approximately 18–24 hours.⁴¹ Notably, while 20 mg once daily provides comparable EPO suppression to belzutifan 120 mg once daily (approximately 80% reduction from baseline), the selected 100 mg once dose provides 5-fold higher exposure, enabling deeper and more sustained target suppression.⁴¹ On the basis of healthy volunteer studies, the 50 mg twice-daily regimen provides comparable exposure to the 100 mg once-daily regimen, which has been selected for phase III development.⁴¹

In the phase I/Ib ARC-20 trial, with a median follow-up of 15 months, casdatifan (50 mg twice daily) demonstrated an ORR of 25% (95% CI, 11.5 to 43.4) and a low PD rate of 19%.⁴²

TABLE 3. Pharmacologic and Efficacy Characteristics of HIF-2 α Inhibitors in Renal Cell Carcinoma

Agent	t _{1/2}	Dosing	Maximum EPO Suppression	Phase	N	ORR, %	PD, %	Median PFS (months)	Dose for Expansion
Belzutifan (MK-6482)	14 hours	120 mg QD	Approximately 60% at 120 mg QD	III	746	22.7	34	5.6	120 mg QD
Casdatifan (AB521)	18-24 hours	100 mg QD	Approximately 80% at 20 mg QD	I	27	33	7	Not reported	100 mg QD
NKT2152	38 days	Loading: 100-200 mg QD (7-28 days) Maintenance: 50 mg QD or 100-200 mg weekly	Approximately 72% at higher dose levels	I	100	20	28	7.4	Not specified
DFF332	Approximately 85 days	Not established	Variable ^a	I	40	5	Not specified	Not specified	Discontinued

Abbreviations: EPO, erythropoietin; HIF-2 α , hypoxia-inducible factor-2 α ; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; QD, daily; t_{1/2}, half-life.

^aAt dose levels of 50 mg every week, EPO levels increased by day 8. At dose levels of 100 mg every week and 25 mg every day, EPO levels remained relatively stable. At dose levels of 50 mg every day, 100 mg every day, and 150 mg every day, a reduction of 27%–51% in EPO levels was noted by day 8.

In the 100 mg once-daily cohort, with a median follow up of 5 months, the confirmed ORR was 33% (95% CI, 16.5 to 54.0) with PD of 7%. The safety profile at the 100 mg once-daily dose showed grade ≥ 3 drug-related AEs in 28% of patients, primarily anemia (17%) and hypoxia (10%), with no treatment discontinuations because of AEs. On the basis of these promising results, ARC-20 is being expanded to evaluate casdatifan in combination with cabozantinib, and the phase III PEAK-1 trial has been initiated to evaluate this combination versus cabozantinib monotherapy in metastatic ccRCC after anti-PD-1 therapy.

NKT2152: A Novel HIF-2 α Inhibitor With Unique Pharmacologic Properties

NKT2152 presents a distinct pharmacokinetic profile with an unusually long half-life of 38 days for an oral small molecule, necessitating an innovative loading/maintenance dosing approach (Table 3).⁴³ Initial dose finding explored 50–300 mg once daily, but was modified to a loading phase (100–200 mg once daily for 7–28 days) followed by maintenance (50 mg daily or 100–200 mg weekly) to manage drug accumulation while maintaining therapeutic exposure.⁴³ In a phase I/II trial of 100 heavily pretreated patients, NKT2152 demonstrated an ORR of 20% across all doses, with deeper responses (26% ORR) observed in the dose-escalation cohort with longer follow-up. The safety profile showed manageable hypoxia (25% all grades, 2% grade 3) and expected class-effect toxicities, although the extended half-life presents unique considerations for AE management.

DFF332: Development Insights From an Early HIF-2 α Inhibitor

DFF332 provided important insights into HIF-2 α inhibitor development despite its discontinuation (Table 3). The compound showed initial promise with fast oral absorption and dose-proportional exposure, but its exceptionally long half-life (approximately 85 days) presented significant challenges for optimal dosing and toxicity management.⁴⁴ In the phase I study of 40 patients, while clinical activity was observed with a disease control rate of 50% and treatment-related AEs were manageable, the study was halted before an optimal dose could be identified, highlighting the critical importance of pharmacokinetic properties in successful drug development.⁴⁴

Next Steps

HIF-2 α inhibitors represent a targeted therapeutic breakthrough in ccRCC, directly addressing the molecular pathogenesis of the disease. The clinical success of belzutifan and emerging compounds such as casdatifan and NKT2152 demonstrate the potential of this novel approach, with ongoing trials exploring combination strategies and expanding treatment options for patients with advanced RCC. An important limitation of this therapeutic class is that HIF-2 α inhibitors have not been directly tested in non-ccRCC

histologies. Given that the underlying mechanism of HIF-2 α dysregulation through VHL loss is predominantly observed in ccRCC, while non-clear cell subtypes (including papillary, chromophobe, and collecting duct carcinomas) typically exhibit different molecular drivers and pathogenic pathways, there is biological rationale suggesting limited efficacy in these histologies. Looking ahead, further investigation into HIF pathway dependencies across different RCC subtypes may reveal unexpected opportunities for targeted intervention.

ADCs IN RCC AND UC

ADCs have been a highly successful class of systemic therapy, with 13 ADCs approved to date and additional approvals forthcoming. While ADCs have been practice-changing interventions for multiple cancers, including UC where they have become a cornerstone of treatment, there are challenges unique to RCC that contribute to a less straightforward path from bench to bedside for this malignancy.^{45,46}

ADC Principles and Design

ADCs contain three components: (1) a monoclonal antibody (mAb) targeting a cell surface antigen, which is conjugated by a (2) linker molecule to a (3) payload drug. Clinical activity of ADC begins with binding of the mAb to the designated antigen, followed by internalization of the ADC and degradation of the linker, thereby freeing the payload and initiating cell damage and death. While ADCs enable targeted drug delivery and higher intracellular concentrations than conventional therapies, only 1%–2% of ADC payloads typically reach tumor sites.⁴⁷ Most payloads are cytotoxic payloads. The predominant use of cytotoxic payloads presents a distinct challenge for RCC, given the historical resistance of this disease to cytotoxic agents. Despite this, the ongoing development of ADCs with immunostimulatory payloads (eg, toll-like receptor, STING-agonists) represents promising opportunities to expand direct tumor killing treatments.

ADCs for ccRCC

T-Cell Immunoglobulin and Mucin Domain-1 Targeted ADC

One of the earliest ADCs for ccRCC was CDX-014, an ADC directed to T-cell immunoglobulin and mucin domain-1, also called kidney injury molecule-1 and with a Monomethyl Auristatin E (MMAE) payload.⁴⁸ Phase I trial outcomes included 1 partial response (PR) and a clinical benefit rate of 31%.⁴⁹

CD70-Targeted ADCs

CD70 was identified as another possible ADC target in ccRCC because of well-established overexpression in advanced RCC.⁵⁰ More than 1 CD70-directed ADC has been developed, including SGN-CD70A, which uses a pyrrolobenzodiazepine dimer payload and PRO1160, which a topoisomerase

payload.⁵¹ SGN-CD70A was the first to enter into early phase trials but demonstrated only modest clinical benefit: 1 of 18 with PR and 13 of 18 with stable disease.⁵² Ultimately, further clinical development was not pursued. A second CD70-targeting agent, PRO1160, is currently being investigated in a phase I/II trial (ClinicalTrials.gov identifier: [NCT05721222](#)).

Ectonucleotide Pyrophosphate/Phosphodiesterase-3–Targeted ADC

Ectonucleotide pyrophosphate/phosphodiesterase-3, also known as CD203a, is a regulator of purigenic signaling and nucleotide metabolism and is overexpressed in RCC⁵³ and serves as a target for the ADC AGS-16C3F, which uses a Monomethyl Auristatin F payload.⁵⁴ AGS-16C3F demonstrated preliminary efficacy in a phase I trial, with 3 of 15 patients experiencing a PR. However, a follow-up phase II, randomized trial between AGS-16C3F and axitinib failed to demonstrate superior efficacy.⁵⁵

CDH6–Targeted ADC

Additionally, a CDH6-targeted ADC with a topoisomerase 1 payload has been developed. DS-6000a was evaluated in a first-in-human clinical trial, for which the dose-escalation results demonstrated a PR for 1 of 7 patients with ccRCC.⁵⁶ Expansion cohorts in RCC are enrolling (ClinicalTrials.gov identifier: [NCT04707248](#)).

ADCs for UC

ADCs are now established as a mainstay of treatment of advanced UC and are being investigated in novel combinations and disease states.

Nectin-4–Targeting ADC

Nectin-4 is a cell adhesion molecule that is overexpressed on a number of solid tumor malignancies, including UC.⁵⁷ Enfortumab vedotin (EV), a nectin-4-directed ADC containing a MMAE payload, was the first ADC approved for advanced UC. This accelerated approval was granted following the EV-201 trial, a multicenter, single-arm trial investigating EV in cisplatin-ineligible patients with advanced UC.⁴⁶ The phase III EV-301 trial confirmed EV's efficacy versus chemotherapy in patients with advanced UC previously treated with platinum and immune checkpoint inhibitors (ICIs).⁵⁸ In this 608-patient trial, efficacy outcomes demonstrated superiority EV for OS (median OS, 12.9 v 9.0 months; HR, 0.70 [95% CI, 0.56 to 0.89]; $P = .001$) and PFS (median PFS, 5.6 v 3.7 months; HR, 0.62 [95% CI, 0.51 to 0.75]; $P < .001$) and ORR (40.6% v 17.9%; $P < .001$). Skin reactions and peripheral neuropathy were the most frequent AEs of special interest with EV.

Building on its success in later lines, the rationale for combining EV with pembrolizumab in the frontline setting stems from ADC-induced immunogenic cell death,⁵⁹ enhanced

antigen presentation, and MMAE's induction of DAMPs that may increase susceptibility to ICIs.⁶⁰ Early clinical work with this regimen began with the phase Ib/II EV-103 trial, cohort K, investigating EV ± pembrolizumab for patients with advanced UC who were cisplatin ineligible⁶¹ and was followed by the randomized, phase III EV-302 trial investigating first-line EV plus pembrolizumab versus platinum-based chemotherapy.⁶² In 886 participants, EV plus pembrolizumab demonstrated superior efficacy to chemotherapy: with improved PFS (median, 12.5 v 6.3 months; HR, 0.45 [95% CI, 0.38 to 0.54]; $P < .001$), OS (median, 31.5 v 16.5 months; HR, 0.47 [95% CI, 0.38 to 0.58]; $P < .001$), and ORR (67.7% v 44.4%; $P < .001$) with a complete response (CR) rate of 29.1% in the EV plus pembrolizumab group. AEs were aligned with those observed in prior trials; grade 3 peripheral neuropathy was observed in 6.8% of patients, skin eruptions in 15.5%, and pneumonitis in 3.6%. These data led to US Food and Drug Administration (FDA) approval of EV plus pembrolizumab in December 2023 as frontline therapy for advanced UC.

These data have served as clinical and scientific rationale for multiple ongoing clinical trials investigating EV with ICI in the perioperative setting: EV-303/KEYNOTE-905 (ClinicalTrials.gov identifier: [NCT03924895](#)), EV304/KEYNOTE-B15 (ClinicalTrials.gov identifier: [NCT04700124](#)), and VOLGA (ClinicalTrials.gov identifier: [NCT04960709](#)). These trials will provide insights into the benefits of EV plus checkpoint inhibition across different patient populations.

Trophoblast Cell Surface Antigen 2–Targeting ADCs

Sacituzumab govitecan (SG), a trophoblast cell surface antigen 2 (Trop-2)-targeted ADC with a topoisomerase 1 inhibitor payload (SN38), was the second ADC to be approved for advanced UC, although this FDA approval has subsequently been withdrawn. The single-arm phase II TROPHY-U-01 trial investigated SG for patients with metastatic UC who had received prior platinum-based chemotherapy and an ICI agent.⁶³ Efficacy data demonstrated an ORR of 28% (95% CI, 20.3 to 37.6), median PFS of 5.4 months (95% CI, 3.5 to 6.9), and median OS of 10.9 months (95% CI, 8.9 to 13.8 months).⁶⁴ The side effect profile of this agent was noted to be distinct from that of EV. However, the follow-up phase III TROPiCS-04 trial ultimately failed to demonstrate a clinically significant OS benefit.⁶⁵ This led to FDA withdrawal of approval for SG in November 2024. Despite these results, SG is being investigated in the neoadjuvant setting for cisplatin-ineligible patients in the SURE-01 trial (ClinicalTrials.gov identifier: [NCT05226117](#)).

Datopotamab deruxtecan (Dato-DXd) is an emerging Trop-2-targeted ADC with a topoisomerase 1 payload that is early in clinical investigation for advanced UC. Data from the phase I, multicohort TROPIONPanTumor01 trial included 40 patients with advanced UC treated with at least 1 prior systemic therapy (required to include at least 1 ICI therapy). Preliminary efficacy demonstrated an ORR of 25% (95% CI, 12.7 to 41.2),^{66,67} and median PFS was 6.9 months (95% CI,

2.9 to not reached). Follow-up investigation of Dato-DXd in UC will include the phase I/II TROPION-PanTumor02 trial (ClinicalTrials.gov identifier: [NCT05460273](#)) and phase II TROPION-PanTumor03 (ClinicalTrials.gov identifier: [NCT05489211](#)) trial.

Human Epidermal Growth Factor Receptor 2–Targeting ADCs

Human epidermal growth factor receptor 2 (HER2)–directed ADCs have a robust history in the management of HER2–amplified breast cancer and are entering into a period of rapid expansion in HER2 amplified UC. T-DXd, a HER2–targeted ADC with a topoisomerase 1 payload, is being evaluated in HER2–positive UC in the phase II DESTINY-PanTumor02 trial. In the UC cohort, T-DXd achieved an ORR of 39% (95% CI, 24.4 to 55.5) and median PFS and OS of 7.0 months (95% CI, 4.2 to 9.7) and 12.8 months (95% CI, 11.2 to 15.1), respectively. Owing to the results of DESTINY-PanTumor01, DESTINY-Lung01,⁶⁸ and DESTINY-CRC02,⁶⁹ the FDA granted the first tumor-agnostic approval to T-DXd for HER2 3+ advanced solid tumor malignancies on April 5, 2024.

Disitamab vedotin (DV) is another HER2–targeted ADC with a MMAE payload that has been investigated in advanced UC. Two single-arm phase II trials investigated this agent for patients with HER2 2+/3+ advanced UC after at least 1 line of systemic chemotherapy.⁷⁰ The combined analysis of these two trials revealed an ORR of 50.5% (95% CI, 40.6 to 60.3).

Subsequent investigation in DV has moved to the neo-adjuvant space, with the phase II RC-C017 trial investigating DV with perioperative torpalimab (PD-1 inhibitor) for patients with HER2 amplified (1+/2+/3+) muscle-invasive bladder cancer planned for cystectomy.⁷¹ The pathologic CR rate was 63.6% (95% CI, 45.1 to 79.6) in the intention-to-treat population, which rose to 84.6% among patients with tumors expressing HER2 3+ amplification. The 12-month relapse-free survival rate was noted to be 89.5% (95% CI, 69.8 to 96.7) and 12-month OS rate was 95.5% (95% CI, 83.3 to 98.9). Surgical outcomes included 70% of 47 enrolled patients undergoing radical cystectomy and pelvic lymph node dissection.

MGR002 is another HER2–directed ADC with MMAE payload, which has been investigated in MGR002-006, a single-arm phase II trial for patients with HER2 2+/3+ advanced UC status post 1 or more prior systemic therapies.⁷² Among the

41 evaluable participants, ORR was 53% (95% CI, 38.9 to 67.5) and median PFS and OS were 7.0 months (95% CI, 5.4 to not reached) and 14.9 months (95% CI, 11.9 to not reached), respectively.

Future Directions

ADC-ADC Combinations

Strategies to overcome ADC resistance mechanisms, including payload hypermetabolism and drug efflux pumps, are being explored. The DAD/DAD-IO trial (ClinicalTrials.gov identifier: [NCT04724018](#)) is investigating one such approach, combining EV with SG, with early phase I results showing an ORR of 70% (95% CI, 47 to 87) and three CRs among 23 patients, and planned expansion to include pembrolizumab in phase II.⁷³

Bispecific ADCs

Novel bispecific approaches are also being explored to overcome ADC resistance from decreased target expression. BL-B01D1, targeting epidermal growth factor receptor and HER3 with a novel topoisomerase 1 inhibitor payload (Ed-04), has shown preliminary efficacy in second-line UC with 43.5% ORR and 5.5-month median PFS.⁷⁴

ADCs represent a pillar of systemic therapy for advanced UC, and ongoing and future investigations will serve to refine the disease state and stages of greatest benefit from these therapies, as well as the targets, payloads, and combinations that maximize efficacy and quality of life.

CONCLUSION

The field of genitourinary oncology is experiencing rapid advancement through parallel innovations in molecular imaging and targeted therapeutics. Novel PET imaging approaches are poised to transform disease characterization and treatment monitoring, while HIF-2 α inhibitors represent a breakthrough in targeting the fundamental pathobiology of ccRCC. ADCs have already become a cornerstone of UC treatment and show promise in RCC despite unique challenges. The integration of these complementary advances offers the potential for more personalized and effective treatment strategies. Ongoing research will further refine our understanding of optimal patient selection, treatment sequencing, and combination approaches, ultimately improving outcomes for patients with RCC and UC.

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REFERENCES

- Hofman MS, Lawrentschuk N, Francis RJ, et al: Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): A prospective, randomised, multicentre study. *Lancet* 395:1208-1216, 2020
- Perera M, Papa N, Roberts M, et al: Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer—updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: A systematic review and meta-analysis. *Eur Urol* 77:403-417, 2020
- Hofman MS, Emmett L, Sandhu S, et al: [¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): A randomised, open-label, phase 2 trial. *Lancet* 397:797-804, 2021
- Emmett L, Papa N, Buteau J, et al: The PRIMARY score: Using intraprostatic 68Ga-PSMA PET/CT patterns to optimize prostate cancer diagnosis. *J Nucl Med* 63:1644-1650, 2022
- Seifert R, Emmett L, Rowe SP, et al: Second version of the prostate cancer molecular imaging standardized evaluation framework including response evaluation for clinical trials (PROMISE V2). *Eur Urol* 83:405-412, 2023
- Ljungberg B, Albiges L, Abu-Ghanem Y, et al: European Association of Urology Guidelines on renal cell carcinoma: The 2022 update. *Eur Urol* 82:e111-e112, 2022
- Ovruchsky E, Pan E, Guer M, et al: Characterization of FOLH1 expression in renal cell carcinoma. *Cancers* 16:1855, 2024
- Udovitch C, Callahan J, Bressel M, et al: Impact of prostate-specific membrane antigen positron emission tomography/computed tomography in the management of oligometastatic renal cell carcinoma. *Eur Urol Open Sci* 44:60-68, 2022
- Siva S, Callahan J, Pryor D, et al: Utility of 68 Ga prostate specific membrane antigen-positron emission tomography in diagnosis and response assessment of recurrent renal cell carcinoma. *J Med Imaging Radiat Oncol* 61:372-378, 2017
- Gasparro D, Scarlattei M, Silini EM, et al: High prognostic value of 68Ga-PSMA PET/CT in renal cell carcinoma and association with PSMA expression assessed by immunohistochemistry. *Diagnostics (Basel)* 13:3082, 2023
- Zhang J, Schuchardt C, Chen X, et al: Rapid tumor washout of 177 Lu-PSMA radioligand in renal cell carcinoma. *Clin Nucl Med* 48:732-734, 2023
- Steffens MG, Boerman OC, Oosterwijk-Wakka JC, et al: Targeting of renal cell carcinoma with iodine-131-labeled chimeric monoclonal antibody G250. *J Clin Oncol* 15:1529-1537, 1997
- Brouwers A, Verel I, Van Eerd J, et al: PET radioimmunoscintigraphy of renal cell cancer using 89Zr-labeled cG250 monoclonal antibody in nude rats. *Cancer Biother Radiopharm* 19:155-163, 2004
- Divgi CR, Pandit-Taskar N, Jungbluth AA, et al: Preoperative characterisation of clear-cell renal carcinoma using iodine-124-labelled antibody chimeric G250 (124I-cG250) and PET in patients with renal masses: A phase I trial. *Lancet Oncol* 8:304-310, 2007
- Shuch B, Pantuck AJ, Bernhard JC, et al: [89Zr]Zr-girentuximab for PET-CT imaging of clear-cell renal cell carcinoma: A prospective, open-label, multicentre, phase 3 trial. *Lancet Oncol* 25:1277-1287, 2024
- Hofman MS, Tran B, Feldman DR, et al: First-in-human safety, imaging, and dosimetry of a carbonic anhydrase IX-targeting peptide, [68Ga]Ga-DPI-4452, in patients with clear cell renal cell carcinoma. *J Nucl Med* 65:740-743, 2024
- Muselaers CH, Boers-Sonderen MJ, van Oostenbrugge TJ, et al: Phase 2 study of Lutetium 177-labeled anti-carbonic anhydrase IX monoclonal antibody girentuximab in patients with advanced renal cell carcinoma. *Eur Urol* 69:767-770, 2016
- Duan X, Xia L, Zhang Z, et al: First-in-human study of the radioligand 68Ga-N188 targeting nectin-4 for PET/CT imaging of advanced urothelial carcinoma. *Clin Cancer Res* 29:3395-3407, 2023
- Zhang J, Duan X, Chen X, et al: Translational PET imaging of nectin-4 expression in multiple different cancers with 68Ga-N188. *J Nucl Med* 65:38S-45S, 2024 (suppl 1)
- Al-Zubaidi M, Viswambaram P, McCombie S, et al: 89Zirconium-labelled girentuximab (89Zr-TLX250) PET in urothelial cancer patients (ZiPUP): Protocol for a phase I trial of a novel staging modality for urothelial carcinoma. *BMJ Open* 12:e060478, 2022
- Koshkin VS, Kumar V, Kline B, et al: Initial experience with 68Ga-FAP-2286 PET imaging in patients with urothelial cancer. *J Nucl Med* 65:199-205, 2024
- Novruzov E, Dendl K, Ndlovu H, et al: Head-to-head intra-individual comparison of [68Ga]FAPi and [18F]FDG PET/CT in patients with bladder cancer. *Mol Imaging Biol* 24:651-658, 2022
- Gerlinger M, Rowan AJ, Horswell S, et al: Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 366:883-892, 2012
- Buteau JP, Martin AJ, Emmett L, et al: PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [177Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): A biomarker analysis from a randomised, open-label, phase 2 trial. *Lancet Oncol* 23:1389-1397, 2022
- Verhoeff SR, Oosting SF, Elias SG, et al: [89Zr]Zr-DFO-girentuximab and [18F]FDG PET/CT to predict watchful waiting duration in patients with metastatic clear-cell renal cell carcinoma. *Clin Cancer Res* 29:592-601, 2022
- Ferdinandus J, Maric I, Darr C, et al: FDG-PET positivity and overall survival in renal cell carcinoma. *JAMA Netw Open* 5:e2242289, 2022
- Kayani I, Avril N, Bomanji J, et al: Sequential FDG-PET/CT as a biomarker of response to sunitinib in metastatic clear cell renal cancer. *Clin Cancer Res* 17:6021-6028, 2011
- Zattoni F, Incerti E, Dal MF, et al: 18F-FDG PET/CT and urothelial carcinoma: Impact on management and prognosis—A multicenter retrospective study. *Cancers* 11:700, 2019
- Abdel-Wahab M, Giammarile F, Carrara M, et al: Radiotherapy and theranostics: A Lancet Oncology Commission. *Lancet Oncol* 25:e545-e580, 2024
- de Feria Cardet RE, Hofman MS, Segard T, et al: Is prostate-specific membrane antigen positron emission tomography/computed tomography imaging cost-effective in prostate cancer: An analysis informed by the proPSMA trial. *Eur Urol* 79:413-418, 2021
- Kaelin WG Jr: Molecular basis of the VHL hereditary cancer syndrome. *Nat Rev Cancer* 2:673-682, 2002
- Choueiri TK, Kaelin WG Jr: Targeting the HIF2-VEGF axis in renal cell carcinoma. *Nat Med* 26:1519-1530, 2020
- Choueiri TK, Bauer TM, Papadopoulos KP, et al: Inhibition of hypoxia-inducible factor-2alpha in renal cell carcinoma with belzutifan: A phase 1 trial and biomarker analysis. *Nat Med* 27:802-805, 2021

34. Jonasch E, Donskov F, Iliopoulos O, et al: Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. *N Engl J Med* 385:2036-2046, 2021
35. Choueiri TK, Powles T, Peltola K, et al: Belzutifan versus everolimus for advanced renal-cell carcinoma. *N Engl J Med* 391:710-721, 2024
36. Rini BI, Suarez Rodriguez C, Albages L, et al: LBA74 Final analysis of the phase III LITESPARK-005 study of belzutifan versus everolimus in participants (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC). *Ann Oncol* 35:S1262-S1263, 2024
37. Choueiri TK, Ghattalia P, de Velasco G, et al (eds): Safety profile of belzutifan monotherapy in patients with renal cell carcinoma: A pooled analysis of 4 clinical trials. *Kidney Cancer Research Symposium*, Boston, MA, 2024
38. Agarwal N, Brugarolas J, Ghattalia P, et al: Randomized phase II dose comparison LITESPARK-013 study of belzutifan in patients with advanced clear cell renal cell carcinoma. *Ann Oncol* 35:1148-1156, 2024
39. Choueiri TK, McDermott DF, Merchan J, et al: Belzutifan plus cabozantinib for patients with advanced clear cell renal cell carcinoma previously treated with immunotherapy: An open-label, single-arm, phase 2 study. *Lancet Oncol* 24:553-562, 2023
40. Choueiri TK, Merchan JR, Figlin R, et al: Belzutifan plus cabozantinib as first-line treatment for patients with advanced clear-cell renal cell carcinoma (LITESPARK-003): An open-label, single-arm, phase 2 study. *Lancet Oncol* 26:64-73, 2025
41. Ghasemi M, Khosravan R, Kim JY, et al (eds): Clinical pharmacokinetic/pharmacodynamic (PK/PD) relationship for casdatifan (AB521), a small molecule inhibitor of HIF-2 α , confirms best-in-class potential in treatment of renal cell carcinoma. *EORTC-NCI-AACR (ENA) Molecular Targets and Cancer Therapeutics Symposium*, Barcelona, Spain, 2024
42. Choueiri TK, Lee JL, Merchan JR, et al: Casdatifan (Cas) monotherapy in patients (pts) with previously treated clear cell renal cell carcinoma (ccRCC): Safety, efficacy and subgroup analysis across multiple doses from ARC-20, a phase 1 open-label study. *J Clin Oncol* 43, 2025 (suppl 5; abstr 441)
43. Jonasch E, McGregor BA, Msaouel P, et al: 16900 NKT2152, a novel oral HIF-2 α inhibitor, in participants (pts) with previously treated advanced clear cell renal carcinoma (ccRCC): Preliminary results of a phase I/II study. *Ann Oncol* 35:S1011-S1012, 2024
44. Pal SK, Tannir NM, Grell P, et al: Preliminary safety, pharmacokinetics and clinical activity of DFF332, an oral HIF2 α inhibitor, as monotherapy in a phase 1 dose escalation study in patients with advanced clear cell renal cell carcinoma. *J Clin Oncol* 42, 2024 (suppl 16; abstr 4513)
45. Hoimes CJ, Flaig TW, Milowsky MI, et al: Enfortumab vedotin plus pembrolizumab in previously untreated advanced urothelial cancer. *J Clin Oncol* 41:22-31, 2023
46. Yu EY, Petrylak DP, O'Donnell PH, et al: Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): A multicentre, single-arm, phase 2 trial. *Lancet Oncol* 22:872-882, 2021
47. Beck A, Goetsch L, Dumontet C, et al: Strategies and challenges for the next generation of antibody-drug conjugates. *Nat Rev Drug Discov* 16:315-337, 2017
48. Thomas LJ, Vitale L, O'Neill T, et al: Development of a novel antibody-drug conjugate for the potential treatment of ovarian, lung, and renal cell carcinoma expressing TIM-1. *Mol Cancer Ther* 15:2946-2954, 2016
49. McGregor BA, Gordon M, Flippot R, et al: Safety and efficacy of CDX-014, an antibody-drug conjugate directed against T cell immunoglobulin mucin-1 in advanced renal cell carcinoma. *Invest New Drugs* 38:1807-1814, 2020
50. Huang RR, Chen Z, Kroeger N, et al: CD70 is consistently expressed in primary and metastatic clear cell renal cell carcinoma. *Clin Genitourin Cancer* 22:347-353, 2024
51. Jonasch E, Call J, Kambhampati S, et al: Phase 1/2 study of PRO1160, a CD70-directed antibody-drug conjugate, in patients with advanced solid tumors and hematologic malignancies. *Oncologist* 28:S14-S15, 2023 (suppl 1)
52. Pal SK, Forero-Torres A, Thompson JA, et al: A phase 1 trial of SGN-CD70A in patients with CD70-positive, metastatic renal cell carcinoma. *Cancer* 125:1124-1132, 2019
53. Doñate F, Raitano A, Morrison K, et al: AGS16F is a novel antibody drug conjugate directed against ENPP3 for the treatment of renal cell carcinoma. *Clin Cancer Res* 22:1989-1999, 2016
54. Thompson JA, Motzer RJ, Molina AM, et al: Phase I trials of anti-ENPP3 antibody-drug conjugates in advanced refractory renal cell carcinomas. *Clin Cancer Res* 24:4399-4406, 2018
55. Kollmannsberger C, Choueiri TK, Heng DY, et al: A randomized phase II study of AGS-16C3F versus axitinib in previously treated patients with metastatic renal cell carcinoma. *Oncologist* 26:182-e361, 2021
56. Hamilton EP, Jauhari S, Moore KN, et al: Phase I, two-part, multicenter, first-in-human (FIH) study of DS-6000a in subjects with advanced renal cell carcinoma (RCC) and ovarian tumors (OVC). *J Clin Oncol* 40, 2022 (suppl 16; abstr 3002)
57. Heath EI, Rosenberg JE: The biology and rationale of targeting nectin-4 in urothelial carcinoma. *Nat Rev Urol* 18:93-103, 2021
58. Powles T, Rosenberg JE, Sonpavde GP, et al: Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med* 384:1125-1135, 2021
59. Gerber HP, Sapra P, Loganzo F, et al: Combining antibody-drug conjugates and immune-mediated cancer therapy: What to expect? *Biochem Pharmacol* 102:1-6, 2016
60. Heiser RA, Cao AT, Zeng W, et al: Brentuximab vedotin-driven microtubule disruption results in endoplasmic reticulum stress leading to immunogenic cell death and antitumor immunity. *Mol Cancer Ther* 23:68-83, 2024
61. O'Donnell PH, Milowsky MI, Petrylak DP, et al: Enfortumab vedotin with or without pembrolizumab in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer. *J Clin Oncol* 41:4107-4117, 2023
62. Powles T, Valderrama BP, Gupta S, et al: Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med* 390:875-888, 2024
63. Tagawa ST, Balar AV, Petrylak DP, et al: TROPHY-U-01: A phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. *J Clin Oncol* 39:2474-2485, 2021
64. Loriot Y, Petrylak DP, Rezazadeh Kalebasty A, et al: TROPHY-U-01, a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors: Updated safety and efficacy outcomes. *Ann Oncol* 35:392-401, 2024
65. Grivas P, Powles TB, Vulsteke C, et al: LBA9 TROPICS-04, a randomized phase III study of sacituzumab govitecan (SG) vs chemotherapy (CT) in pretreated advanced urothelial carcinoma (aUC): Overall survival (OS) and safety analysis. *Ann Oncol* 35:S1505-S1507, 2024
66. Meric-Bernstam F (ed): Dapotamab deruxtecan (Dato-DXd) in locally advanced/metastatic urothelial cancer: Updated results from the phase 1 TROPIONPanTumor01 study. *American Society of Clinical Oncology Genitourinary Symposium*, San Francisco, CA, 2025
67. Meric-Bernstam F, Makker V, Oaknin A, et al: Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: Primary results from the DESTINY-PanTumor02 phase II trial. *J Clin Oncol* 42:47-58, 2024
68. Smit EF, Felip E, Uprety D, et al: Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): Primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial. *Lancet Oncol* 25:439-454, 2024
69. Raghav K, Siena S, Takashima A, et al: Trastuzumab deruxtecan in patients with HER2-positive advanced colorectal cancer (DESTINY-CRC02): Primary results from a multicentre, randomised, phase 2 trial. *Lancet Oncol* 25:1147-1162, 2024
70. Sheng X, Wang L, He Z, et al: Efficacy and safety of disitamab vedotin in patients with human epidermal growth factor receptor 2-positive locally advanced or metastatic urothelial carcinoma: A combined analysis of two phase II clinical trials. *J Clin Oncol* 42:1391-1402, 2024
71. Sheng X (ed): Neoadjuvant treatment with disitamab vedotin plus perioperative toripalimab in patients with muscle-invasive bladder cancer (MIBC) with HER2 expression: Updated efficacy and safety results from the phase II RC48-C017 trial. *American Society of Clinical Oncology Genitourinary Symposium* 2025, San Francisco, 2025
72. Qu W, Fu C, Han W, et al: A single-arm, multicenter, phase 2 clinical study of recombinant humanized anti-HER2 monoclonal antibody-MMAE conjugate (MRG002) in HER2-positive unresectable locally advanced or metastatic urothelial carcinoma. *Eur J Cancer* 205:114096, 2024
73. McGregor BA, Sonpavde GP, Kwak L, et al: The double antibody drug conjugate (DAD) phase I trial: Sacituzumab govitecan plus enfortumab vedotin for metastatic urothelial carcinoma. *Ann Oncol* 35:91-97, 2024
74. Ye D, Bian X, Yang T, et al: 19590—BL-B01D1, an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic urothelial carcinoma (UC). *Ann Oncol* 35: S1135-S1169, 2021 (suppl 2)

Key Updates in Testicular Cancer: Optimizing Survivorship and Survival

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OVERVIEW

Testicular cancer is a rare but highly curable malignancy, predominantly affecting young men. Advances in multimodal therapy, including cisplatin-based chemotherapy, radiotherapy, and surgical interventions, have resulted in excellent cancer-specific survival. However, with improved survival rates, long-term health consequences and survivorship issues have emerged as critical concerns. Testicular cancer survivors (TCSs) are at risk of adverse health outcomes, including endocrine dysfunction, cardiovascular disease, secondary malignancies, chemotherapy-induced neuropathy, and psychosocial challenges. Endocrine disturbances such as hypogonadism and infertility require careful monitoring, while cardiovascular risks necessitate long-term preventive strategies. Survivors also face an elevated risk of secondary malignancies, necessitating tailored follow-up. Recent advances in the de-escalation of therapy, particularly for stage II seminoma and metastatic germ cell tumors, aim to balance oncologic efficacy with minimizing toxicity. This review discusses the evolving landscape of testicular cancer survivorship, the impact of treatment-related complications, and contemporary management strategies, emphasizing a multidisciplinary approach to optimize long-term outcomes and quality of life.

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INTRODUCTION

Testis cancer (TC) is a relatively rare tumor, representing approximately 1% of male malignancies.¹ However, despite its low incidence, it remains a critical disease because of its prevalence in young men and the primary goal of achieving cure rather than simply prolonging survival. Advances in multimodal therapy have led to excellent cancer-specific survival (CSS) rates. However, as survivorship rates increase, the long-term health consequences of germ cell tumor (GCT) treatment have become an increasing concern. Testicular cancer survivors (TCSs) face significant long-term treatment-related toxicities, affecting quality of life (QoL) and requiring surveillance and management.

This review aims to provide a comprehensive overview of key survivorship considerations in patients with GCT. Contemporary management strategies for stage II seminoma and metastatic GCT are discussed, with an emphasis on balancing oncologic efficacy with long-term toxicity reduction. Given the increasing complexity of survivorship care, a multidisciplinary approach is essential to optimize long-term outcomes and improve patient QoL.

SURVIVORSHIP CONSIDERATIONS IN PATIENTS WITH GERM CELL TUMORS

Overview of Adverse Health Outcomes

Concerns about the long-term effects and adverse health outcomes (AHOs) among TCS have grown in recent decades.^{2,3} While GCT CSS remains excellent in many countries,⁴ reports of increased mortality rates from other causes, particularly secondary malignancies (SMNs), are concerning.^{5,6} Cisplatin-related AHOs, such as chemotherapy-induced peripheral neuropathy (CIPN) and fatigue, put men at risk of prolonged work loss, including sick leave and disability pensions.⁷ Despite AHOs, most survivors experience long-term health-related quality of life (HRQoL) comparable with the general population, although some face persistent health challenges requiring ongoing monitoring and intervention.^{2,8,9}

Endocrine and Reproductive Health

Hypogonadism, Sexuality, and Fertility

Overall, 5%–10% of men treated with orchiectomy alone develop clinical or subclinical hypogonadism during follow-up.¹⁰ The risk increases further in those receiving cisplatin-

PRACTICAL APPLICATIONS

- Testicular cancer survivors require structured long-term follow-up because of risks of cardiovascular disease, secondary malignancies, and endocrine dysfunction.
- Hypogonadism and fertility preservation should be routinely addressed, with testosterone replacement therapy considered when symptomatic.
- Emerging de-escalation strategies, including reduced-intensity chemotherapy, radiation-sparing approaches, and surgical interventions, aim to reduce long-term toxicity while maintaining excellent oncologic outcomes.
- Comprehensive survivorship care should include regular screening for psychosocial challenges, including anxiety, depression, and chronic fatigue.
- Advances in biomarkers and artificial intelligence may improve risk stratification for residual disease, enhancing treatment decision making in metastatic germ cell tumors.

based chemotherapy (CBCT) and/or radiotherapy, with higher treatment intensity and longer observation time associated with greater prevalence.^{11,12} Hypogonadism may present with symptoms such as sexual dysfunction or loss of energy. Testosterone replacement therapy is indicated only when low serum testosterone levels are accompanied by symptoms.⁹ Sexual dysfunction affects 25%–40% of long-term TCS, depending on age, treatment, body image, and pretreatment sexual function.^{12,13}

Fertility Considerations

Fertility is a crucial concern for patients with TC and survivors, given that most men are diagnosed at a young age. Studies show 71%–82% of men attempting conception after treatment successfully achieve fatherhood without the use of cryopreserved sperm.^{14,15} However, fertility outcomes vary depending on treatment intensity, with up to 16% of couples requiring assisted reproductive technology.¹⁵ These findings highlight the importance of preorchietomy sperm cryopreservation as a proactive measure to preserve reproductive potential.⁹

Psychosocial Problems and Fatigue

While endocrine and reproductive health are critical aspects of survivorship, the psychologic and emotional effects of cancer treatment are equally significant. A systematic review

identified anxiety as an important factor for impaired psychologic health among TCSs, with reported rates up to 21%.¹⁶ The risk of depression among TCSs seems to be similar as the general population, with rates at 5%–7%.¹⁶ Additionally, studies suggest that 1 in 3 TCSs experience fear of recurrence, although evidence remains limited.¹⁶

Chronic fatigue is one of the most distressing symptoms in TCSs. A Norwegian survivorship study found that fatigue prevalence increased from 15% after 11 years to 27% after 19 years of follow-up.¹⁷ After 28 years, 44% of men treated with high doses of CBCT had fatigue.² Screening, diagnosis, and management of fatigue are outlined in international practice guidelines, with physical exercise being the most effective intervention.^{18,19}

Cardiovascular Disease

Beyond psychosocial challenges, TCSs face an elevated risk of cardiovascular disease (CVD) after treatment. Several large studies have shown a long-term increased risk of acute coronary syndrome (ACS) after CBCT compared with surgery alone or the general population, with hazard ratios ranging from 1.4 to 3.0, and a median absolute ACS risk of 6% at 19 years after CBCT.^{20–22} Risk factors of ACS after CBCT include smoking, hypertension, obesity, dyslipidemia, in addition to cisplatin exposure and hypogonadism.^{21–23} Notably, current CVD risk prediction models do not account for cisplatin dose or indicators of endothelial dysfunction resulting from cisplatin exposure.²⁰

Data on CVD risk after infradiaphragmatic radiotherapy are mixed, but some studies show increased risk of diabetes years after treatment.^{21,22,24} While a Danish population-based study reported a 60% excess CVD long-term mortality rate among men treated with CBCT,²² a Norwegian study also reported significantly elevated CVD mortality.⁵

Secondary Malignant Neoplasms

TCSs face an increased risk of SMNs. The 25-year cumulative incidence of solid SMNs was reported to be 13%–20% for survivors of seminoma and 10% for survivors of nonseminoma.^{23,25} TCSs have a 1.4–2.4-fold excess risk of developing a non-germ cell SMN after treatment with CBCT and/or radiotherapy, while surgery alone is associated with little to no increased risk.^{23,25,26} After CBCT, elevated SMN risks have been observed in the thyroid, lung, stomach, pancreas, small intestine, colon, bladder, kidney, and soft-tissue sarcoma, particularly due to platinum retention in healthy tissues.²⁷ Infradiaphragmatic radiotherapy is linked to increased risks of cancers in the stomach, small intestine, liver, pancreas, lung, kidney, and bladder. The combination of both CBCT and radiotherapy results in particularly high SMN risks.²⁵

Younger age at TC diagnosis and longer follow-up duration further elevate SMN risk.^{25,26} Given that SMNs are the leading

cause of death among TCSs,⁵ there is a critical need for preventive strategies, including treatment de-escalation where appropriate.

Other Long-Term Effects After Cisplatin-Based Chemotherapy

Chemotherapy-Induced Peripheral Neuropathy

CIPN can emerge during or after cisplatin treatment and persists in 30%–40% of survivors for several years.^{2,28} Symptoms are typically sensory, including numbness, paresthesia, or pain in hands and/or feet.²⁹ Additionally, 19% of TCSs report neuropathic pain at a median of 11 years after treatment.⁸ CIPN negatively affects QoL,^{2,8} and while duloxetine provides moderate clinical benefit for painful CIPN, nonpharmacologic treatment such as exercise may also help.²⁹

Hearing Loss

Cisplatin is one of the most ototoxic agents, and CBCT may result in tinnitus and/or a bilateral sensorineural hearing loss, affecting 23%–74% of TCSs.^{2,30} Risk factors include higher cumulative cisplatin dose, younger age at treatment, and concurrent use of other ototoxic drugs.²⁹

Raynaud Phenomenon

Raynaud phenomenon is another common problem after CBCT, affecting 35% of TCSs median 28 years after treatment.² The prevalence of the Raynaud phenomenon was higher after three cycles of bleomycin, etoposide, and cisplatin (EP) than after four cycles of etoposide plus cisplatin (24% v 12%).³

Implications for Follow-Up

The increasing number of long-term TCSs worldwide necessitates a structured approach to survivorship care.³¹ Prevention, recurrence surveillance, and management of treatment-related complications should be prioritized in follow-up care. In agreement with several international recommendations, we recommend that all TCSs receive a survivorship care plan summarizing their diagnosis, treatment history, follow-up recommendations, and self-management strategies, including exercise programs and smoking cessation efforts.^{9,31}

CONTEMPORARY MANAGEMENT OF STAGE II SEMINOMA

With a survivorship focus, efforts continue to refine Clinical Stage II (CSII) seminoma treatment while minimizing toxicities. For the purposes of this review, CSII seminoma refers to patients with pure seminoma histology on radical orchiectomy with radiographic evidence of metastatic disease confined to the retroperitoneum. This includes patients with retroperitoneal (RP) disease at the time of initial

staging (de novo CSII) along with patients with stage I seminoma who developed RP-only relapse during surveillance. In sum, CSII disease includes the following TNM categories: T_{any}cn1–3cm0s0. Clinically, patients are often categorized as having nonbulky CSII disease (largest node ≤3 cm on the short axis) or bulky CSII disease (largest node >3 cm on the short axis); these terms will also be used. Given that locoregional interventions (radiation therapy and RP lymph node dissection [RPLND]) are management options for patients with CSII seminoma, contemporary and accurate staging is paramount when discussing treatment recommendations.

Standard Treatment Approaches

Historically, management options for CSII seminoma included multicycle chemotherapy or radiotherapy to the retroperitoneum and ipsilateral pelvis. These treatments achieve excellent outcomes, with chemotherapy achieving a 5-year progression-free survival (PFS) and overall survival (OS) rates of 90% and 95%, respectively, for patients with stage IIA/B disease.³² Contemporary radiotherapy data also suggest relapse-free survival >90% for patients with stage IIA/B disease and OS data approaching 100%.³³ Both chemotherapy and radiation therapy are associated with excellent oncologic outcomes and are guideline-directed options in all national and international guidelines.^{34–36} As previously discussed, while chemotherapy and radiation therapy are very effective treatments for patients with stage II seminoma, they come with the potential for short and long-term toxicities that may significantly affect survivorship and survival.

Emerging De-Escalation Strategies

Over the past decade, several prospective studies have investigated novel approaches to manage CSII seminoma with an aim of maintaining oncologic efficacy while reducing toxicity. Safety and efficacy of RPLND for stage II seminoma were studied in three prospective trials (Table 1).^{37–39} Although differences between the trials exist with respect to nodal size inclusion criteria (3 cm v 5 cm), surgical approach (open v robotic), and permitting patients who received previous adjuvant therapy for stage I disease, each demonstrate a safe, chemotherapy-sparing approach in a bulk of patients. However, follow-up duration in these RPLND trials is relatively short, and RPLND should only be considered in high-volume centers with surgical expertise and multidisciplinary support.

Treatment de-escalation strategies on the basis of mid-treatment positron emission tomography (PET) scan results in patients with International Germ Cell Cancer Collaborative Group good-risk seminoma have also been recently reported.³⁵ The SEMITEP trial included 98 such patients who were initiated on EP.⁴⁰ After two cycles, PET scan was performed; those who had resolution of PET avidity were consolidated with 1 cycle of carboplatin while those with

TABLE 1. Comparison of Prospective Trials Evaluating RPLND as a Treatment Strategy for Stage II Seminoma

Trial Name	PRIMETEST ³⁷	SEMS ³⁸	COTRIMS ³⁹
Inclusion criteria	Relapsed or de novo, stage IIA and IIB (<5 cm) seminoma; prior adjuvant therapy allowed	Relapsed or de novo, stage IIA and nonbulky IIB (≤3 cm) seminoma; no prior adjuvant therapy allowed	Relapsed or de novo, stage IIA-B seminoma
Participants	33 (15% postadjuvant carboplatin)	55	30
No. of centers involved	1	12	1
Median follow-up, years (IQR)	2.7 years (1.9-3.8)	33 months (12.0-61.6)	1.8 years (0.7-2.5)
RPLND template	Unilateral modified template resection (nerve sparing when feasible)	Unilateral modified template resection (nerve sparing when feasible) and bilateral template	Modified template resection with nerve sparing
Histology	30/33 seminoma; 3/33 with noncancer	46/55 confirmed cancer (not further specified); 9/55 with noncancer	25/30 seminoma, 2/30 embryonal carcinoma, and 3/30 with noncancer
Relapse	10/33 (30%) relapsed	12/55 (22%) relapsed	3/30 (10%) relapsed
Survival	Two-year progression-free survival 72% OS 100%	Two-year relapse-free survival 81% OS 100%	Relapse-free survival (90%; after a median of 22 months of follow-up) OS 100%
Complications	4 (12%) Clavien-Dindo ≥II complications 6% ejaculatory dysfunction	4 (7%) Clavien-Dindo ≥II complications 5% ejaculatory dysfunction	4 (13%) Clavien-Dindo IIIA complication 10% ejaculatory dysfunction

Abbreviations: OS, overall survival; RPLND, retroperitoneal lymph node dissection.

persistent fluorodeoxyglucose (FDG)-avid lesion continued an additional two cycles of EP. PFS was comparable between the two arms with a toxicity profile favoring those who received single-cycle carboplatin versus EP × 2 after PET scan. Ideally, data comparing EP × 2 versus single-cycle carboplatin in PET responders would be valuable before implementing this strategy.

Another cisplatin-sparing approach involving combined chemoradiotherapy in patients with stage IIA/B seminoma was also recently published.⁴¹ The SAKK 01/10 trial was a multi-institutional, phase II trial of 116 patients with stage IIA/B seminoma who received single-cycle carboplatin (AUC 7), followed by involved-field radiotherapy. This study used a combined modality approach with less intensive chemotherapy and radiotherapy and reported PFS rates of 95% and 93% in patients with stage IIA and stage IIB disease, respectively, along with a favorable toxicity profile. Long-term efficacy data and safety data—particularly given concerns for CVD and SMNs when both chemotherapy and radiation therapy are given using platinum-based regimens—are required before this regimen is widely adopted.

As we have more tools in our toolkit, it remains mandatory that providers treating patients with CSII GCT are aware of and can offer high-quality interventions—whether that be surgery, chemotherapy, radiotherapy, or chemoradiation. A balanced discussion centering on patient preference, oncologic outcomes, and short-term/long-term efficacy is paramount. For the GCT community, it is critical that we monitor long-term cancer control and adverse effects to confirm we are responsibly introducing new interventions.

PITFALLS IN THE TREATMENT OF PATIENTS WITH METASTATIC GERM CELL TUMORS

As GCT management continues to evolve, ensuring accurate decision making remains critical in this highly curable patient population. Despite the availability of effective treatments, there are many potential pitfalls in proper decision making in this young and highly curable patient population. These challenges range from misinterpretation of tumor markers to inappropriate chemotherapy regimens and unnecessary interventions.⁴² Throughout this section, we will describe our recommendation for correct judgments, on the basis of published data as well as the author's 50 years of experience (Lawrence H. Einhorn, MD).

Tumor Markers in GCTs

In this context, proper interpretation of tumor markers is crucial for guiding treatment decisions. Serum human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) have been the quintessential serum biomarkers in cancer.⁴³ Lactic dehydrogenase (LDH) is often included as a tumor marker; however, its levels can be elevated because of nonmalignant causes such as recent surgery (eg, orchiectomy), physical exertion, pulmonary embolism, or the use of granulocyte stimulating growth factors such as pegfilgrastim.⁴³ This false-positive elevation of LDH can mislead clinicians after initial or subsequent courses of cisplatin combination chemotherapy. Given its lack of specificity, LDH should never be used as the sole criterion for risk stratification or decision making regarding treatment response or relapse.

Serum hCG has a half-life of 12–24 hours, primarily applicable to postsurgical clearance, such as after orchiectomy.⁴⁴ For example, in a patient cured by orchiectomy alone, a preorchiectomy serum hCG of 1,000 mIU/mL, would be expected to normalize (< 5 mIU/mL) within a week. By contrast, the half-life for serum AFP is 5 days. However, this short half-life is not relevant for patients with metastatic disease receiving chemotherapy. In curative cisplatin-based combination chemotherapy, serum hCG is generally expected to decrease by 1 logarithmic unit per cycle.⁴⁴ A patient with an initial prechemotherapy hCG of 6,000 mIU/mL should expect levels to drop to approximately 600 mIU/mL or less before the second cycle, approximately 60 mIU/mL before the start of the third, and 6 mIU/mL before the fourth cycle. An important exception occurs in patients with serum hCG levels exceeding 50,000 mIU/mL, where the hCG level drops rapidly during the first two cycles but slow significantly in cycles 3 and 4 for unknown reasons.⁴⁴ Clinicians should be aware of this oddity to avoid prematurely switching to salvage chemotherapy or unnecessarily continuing beyond four cycles. Instead, weekly hCG monitoring is recommended until levels either normalize or begin rising. A rising trend would indicate the need for salvage therapy, whereas persistent declines should prompt evaluation for postchemotherapy surgery or observation.

Marijuana (or perhaps also CBD oil), recent mononucleosis, or crossreaction with luteinizing hormone (LH) can falsely elevate hCG because of the structural homology between LH and hCG in current bioassays.⁴⁵ The pituitary gland detects inadequate testosterone production from the solitary testis and, through normal feedback mechanisms, increases LH secretion to stimulate testosterone production.

Serum AFP levels can be elevated because of hepatic dysfunction, often accompanied by abnormal liver function tests. A lesser known issue among oncologists is that many laboratories report normal AFP values as 0–8 Ng/mL.^{43,46} We have documented and published that any AFP level <25 Ng/mL should be considered normal.⁴⁶ AFP levels in teens should not cause unnecessary patient anxiety, trigger excessive imaging, or lead to premature initiation of salvage chemotherapy.

Emerging Biomarkers: micro-RNA371 and ctDNA

Recent advances in molecular markers have introduced micro-RNA371 and circulating tumor DNA (ctDNA) as promising tools for detecting active disease.^{47,48} However, these advancements also present challenges. For instance, interpreting elevated micro-RNA371 or ctDNA after orchiectomy in clinical stage I disease remains complex. The key dilemma is determining whether such patients should receive 1 or 3 cycles of bleomycin, etoposide, and cisplatin (BEP); undergo RPLND; or continue surveillance. By contrast, elevated hCG or AFP in similar scenarios typically leads to BEP × 3 or EP × 4, whether justified or not, as seen in clinical stage IS.^{44,46}

While micro-RNAs (miRNAs) and ctDNA show promise as biomarkers for Testicular Germ Cell Tumors (TGCTs), current evidence is insufficient to support their routine use in clinical practice. A review highlights that although miRNAs, particularly miR-371a-3p, have demonstrated high sensitivity and specificity in detecting TGCTs, further well-designed clinical trials and long-term data are necessary to validate their clinical utility.⁴⁹ Similarly, studies on ctDNA as a biomarker in testicular cancer are ongoing, and its role in clinical management has yet to be established. Therefore, these modalities should not be used to guide management decisions outside of clinical trials because of the lack of prospective validation.

Chemotherapy and Administration Considerations

Timing and Dose Adjustments

Cisplatin combination chemotherapy should, in most patients, be given every 3 weeks to maintain optimal efficacy. Low WBC counts, unless extremely low or accompanied by clinical deterioration, should not be used as a reason to delay a course of chemotherapy.⁵⁰ This is particularly relevant in patients with poor-risk advanced disease. We recommend adhering to the planned schedule regardless of leukopenia.

Etoposide is the primary myelosuppressive agent in the BEP regimen.^{50–52} In the presence of leukopenia, daily complete blood counts (CBCs) to ensure granulocyte recovery in such patients will almost always demonstrate rapid rise. In the rare case of prolonged leukopenia, we would consider dropping the fifth and final day of etoposide.

Bleomycin Considerations and Pulmonary Toxicity

Bleomycin is a nonmyelosuppressive drug, making routine CBC monitoring unnecessary on days 8 and 15 when it is administered. A transient drop in WBC counts should not deter clinicians from continuing weekly bleomycin doses. However, bleomycin carries a risk of pulmonary fibrosis.^{51,52} It should be avoided in patients older than 50 years, those with extensive pulmonary metastases, or those with primary mediastinal nonseminomatous GCTs (vide infra). Additionally, bleomycin should be avoided in patients with significant renal impairment, as impaired clearance increases systemic exposure and raises the risk of pulmonary toxicity.⁵³ Notably, asthma is not a contraindication for bleomycin. Clinicians should carefully assess patients through history and physical examinations to determine whether bleomycin should be discontinued. Symptoms such as new nonproductive cough, shortness of breath, or findings of basilar inspiratory rales or respiratory lag should not be ignored. Patients with poor-risk advanced disease require four full courses of triple-drug therapy.^{51,52} If bleomycin needs to be discontinued, for example, after the first three courses (9 weeks) of BEP, ifosfamide should be substituted for bleomycin with VP-16 (etoposide) plus ifosfamide plus cisplatin (VIP).⁵²

Primary Mediastinal GCT

Extragonadal GCTs compose 5%–10% of all GCTs. Presentation signs and symptoms include superior vena cava syndrome, facial/neck swelling, chest pain, cough, and dyspnea. Chest x-ray and computed tomography (CT) scans depict a large anterior mediastinal mass. The primary differential diagnosis include lymphoma (most common), thymic malignancy, or primary mediastinal GCT. Mediastinal seminomas have an excellent prognosis, with an expected cure rate of 90% after chemotherapy alone. The preferred treatment regimen includes BEP $\times$ 3 or EP $\times$ 4. There is neither any need nor logic for postchemotherapy surgery or radiation therapy. Given the high cure rates with initial chemotherapy, further interventions offer no additional benefit. An example of such a patient case is depicted in Figure 1. This patient had dramatic radiographic improvement after a single week of BEP.

Primary Mediastinal Nonseminomatous GCTs

By contrast, primary mediastinal nonseminomatous GCTs (PMNSGCTs) are categorized as advanced disease, regardless of tumor size or biomarker levels (AFP/hCG). A diagnosis can be made serologically if there is a significant elevation of serum AFP. PMNSGCTs have a 40%–50% cure rate with initial therapy, which usually requires thoracic surgery expertise in performing postchemotherapy resection of a persistent mediastinal mass. These resections carry serious pulmonary complication risks due to anatomical constraints. Unlike postchemotherapy PRLND, where bleomycin toxicity is less concerning, mediastinal resections have a higher risk of pulmonary complications. Therefore, the preferred initial chemotherapy regimen for PMNSGCT should be VIP rather

than BEP for this category of advanced disease. VIP and BEP offer equivalent long-term survival rates, but VIP is associated with greater toxicity.^{52,54}

In a series of 221 patients with PMNSGCT from Indiana University, the use of bleomycin (BEP) was associated with an increased risk of serious pulmonary complications, compared with VIP, including 11 of 166 versus 0 of 55 patients.⁵⁴ Postoperative mortality was 18% versus 4% with many requiring >48 hours on a ventilator if they received BEP.⁵⁴

Second-line salvage chemotherapy with standard-dose cisplatin chemotherapy has a very low cure rate (<10%). We therefore prefer high-dose carboplatin plus etoposide with peripheral blood stem cell transplant as second-line treatment. Although salvage outcomes remain inferior compared with testicular primary tumors, this approach achieves a notable 20%–30% 2-year PFS rate.⁵⁴ By optimizing first-line treatment strategies and using high-dose salvage therapy when needed, clinicians can maximize survival outcomes for this challenging subset of patients.

Chemotherapy for Intermediate-Risk GCTs

Prognostic Classification and Treatment Guidelines

An international group of investigators convened to establish prognostic variables for first-line chemotherapy in metastatic GCTs. These results were originally published in 1997 and updated in 2021, leading to the widely adopted International Germ Cell Consensus Classification (IGCCCG). This established three separate prognostic groups, namely good, intermediate, and poor prognosis on the basis of 5–

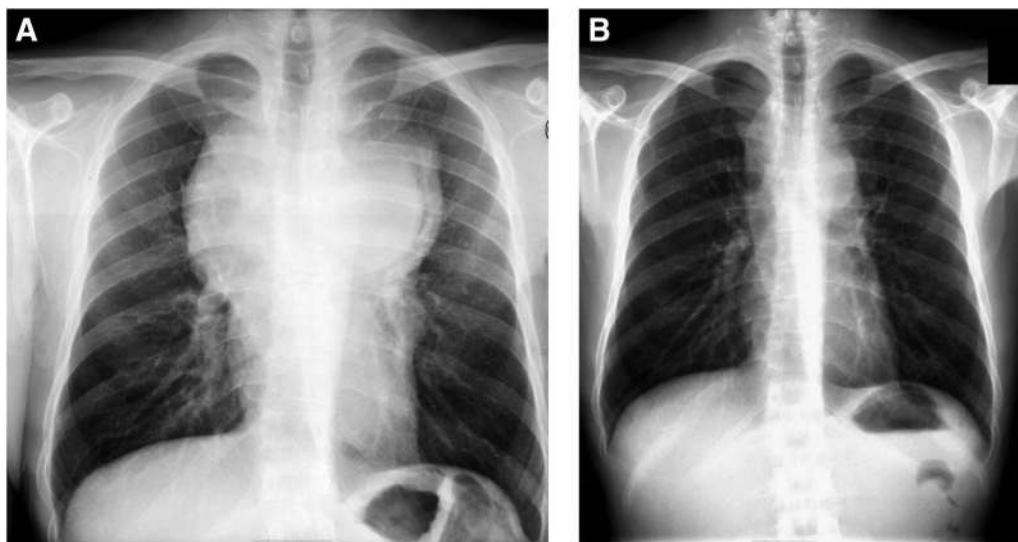


FIG 1. Mediastinal seminoma with significant radiographic improvement after chemotherapy (BEP $\times$ 3 or EP $\times$ 4; A, before chemotherapy; B, after chemotherapy). BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin.

TABLE 2. International Germ Cell Consensus Classification for Intermediate Risk

Biomarker	Intermediate Risk Threshold
AFP	1,000-10,000 Ng/mL
hCG	5,000-50,000 mIU/mL
LDH	2.5-10 times upper limits of normal

NOTE. Any seminoma with nonpulmonary visceral metastases. Abbreviations: AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactic dehydrogenase.

year PFS and OS. Separate treatment recommendations were published by the National Comprehensive Cancer Network (NCCN) and other organizations. Recommended chemotherapy for good prognosis was BEP $\times$ 3 or EP $\times$ 4 and for poor prognosis BEP $\times$ 4 or VIP $\times$ 4.⁵⁴ Although intermediate risk was prognostically between good and poor prognoses, most pathways recommend these patients to be treated as poor prognosis.⁵⁵ The definition for intermediate risk is presented in Table 2. The updated international results for intermediate-risk disease demonstrated a 5-year PFS of 78% and OS of 89%, compared with 54% PFS and 67% OS for poor-risk patients.⁴²

Challenges in Current Treatment Guidelines

Although intermediate-risk patients are often treated as poor risk, this approach is not always appropriate. Table 3 summarizes how current guidelines would recommend BEP $\times$ 4 or VIP $\times$ 4 for all patients, which may not always be necessary. Dr Einhorn believes patient 1 represents clinical stage I disease, which does not require any metastatic chemotherapy. Patient 2 has features more akin to good-risk disease and should receive BEP $\times$ 3 (or EP $\times$ 4 if older than 50 years). Patient 3 has the more typical intermediate presentation. At Indiana University, this patient and similar patient cases would receive BEP $\times$ 3 and a fourth course of EP, avoiding weeks 10–12 of bleomycin. Patient 4 is truly in the poor prognosis category and requires four courses of triple-drug therapy, preferably VIP, because of the innumerable pulmonary metastases. There are no evidence-based data for the preferred chemotherapy for these patients. The NCCN guidelines, which represent consensus statement and not evidence-based medicine lists four courses of triple-drug therapy in their template.

Vascular Access Considerations

A Port-a-Cath or central venous access device (PORT) is commonly used to facilitate the use of intravenous chemotherapy in young patients with metastatic testicular cancer. However, vascular access can be challenging for both patients and nursing staff. Although a PORT provides convenience, most patients with GCT have excellent veins suitable for 9–10 weeks of chemotherapy and may not need a PORT.⁵⁶ These patients are often scheduled for the

TABLE 3. Intermediate-Risk Patients

Patient ID	Description
Patient 1	Serum LDH approximately 3 $\times$ ULN Serum hCG approximately normal Serum AFP approximately normal Scans approximately normal
Patient 2	Serum AFP approximately 1,100 Serum hCG approximately normal 4 cm RPLN Normal chest CT
Patient 3	Serum AFP approximately 2,000 4-cm RPLN and 3 separate 1-2-cm pulmonary metastases
Patient 4	Serum AFP approximately 2,000 Serum hCG approximately 45,000 4-cm RPLN and innumerable pulmonary metastases

Abbreviations: AFP, alpha-fetoprotein; CT, computed tomography; hCG, human chorionic gonadotropin; LDH, lactic dehydrogenase; RPLN, retroperitoneal lymph node; ULN, upper limit of normal.

placement of a PORT before an initial visit with an oncologist. Complications of venous thrombosis or PORT infection can outweigh the convenience benefits.⁵⁷ At Indiana, PORT placement is optional and used only if requested by the patient or nursing staff after discussing risks and benefits.

Late Relapse of GCTs

The goal of initial chemotherapy for patients with metastatic disease should always be cure. Most patients achieve a complete remission, either with chemotherapy alone or with postchemotherapy resection of germ cell cancer or teratoma. Although relapse beyond 2 years is uncommon (2%–3% of patients), it does occur.⁵⁸ Very late relapses can occur beyond 5 years and even rarely beyond 20 years from completion of chemotherapy. Such patients are usually asymptomatic at the time of their late relapse. Diagnosis is often made by elevated serum AFP. Unlike patients who relapse within two years of completing chemotherapy and often achieve high cure rates with salvage treatment, late-relapse patients rarely achieve cure without surgery alone (if anatomically feasible) or postchemotherapy resection.^{59–61}

The retroperitoneum is the most common site for late relapse. Given the risk of late relapse, long-term follow-up is critical. Therefore, we recommend follow-up every 6 months with history and physical examination and serum hCG and AFP during years 2–5 after chemotherapy. This should be continued annually after 5 years. Early detection is essential, as cure rates for late relapse depend on identifying disease while it is still resectable. Late-relapse patients rendered disease free with treatment are prone to subsequent additional early or late relapses.⁶¹ Physical examination is also important given that 2% of cured patients will subsequently develop a second primary in the contralateral testis.^{58,62}

By ensuring appropriate long-term surveillance and individualized treatment strategies, we can improve outcomes

and reduce unnecessary interventions in intermediate-risk GCTs. Many pitfalls can arise initially and subsequently are best addressed by tertiary centers with expertise and experience. This includes coordinated efforts among pathology, radiology, urology, and medical oncology specialists to ensure accurate diagnoses and optimal management strategies.

MANAGEMENT OF POSTCHEMOTHERAPY RESIDUAL MASSES IN METASTATIC GERM CELL TUMORS

While long-term surveillance is crucial for detecting late relapse, another significant challenge in the post-treatment landscape is the management of postchemotherapy residual disease (PCRD). Despite achieving remission with first-line CBCT, approximately 30% of nonseminoma patients and 90% of patients with seminoma present with residual masses.⁶³ Of these patients not everyone requires further interventions; in fact, the management of PCRD spans from conservative approaches (such as active surveillance [AS]) to more invasive and intense treatments (such as surgery and salvage chemotherapy) and is dictated by the initial tumor histology (seminoma v nonseminoma), residual disease size, and serum tumor markers (STMs).⁶⁴

PCRD is defined by the radiographic evidence of any lesion with a long transverse axis measuring ≥ 1 cm. The current diagnostic tools do not allow to discriminate between residual tumor (teratoma or viable GCT [vGCT]) and benign scar tissue creating major issues in identifying patients needing further therapy. The aim of PCRD management is to eradicate any residual teratoma or vGCT that could lead to tumor relapse.⁶⁵ However, thoughtful use of surgery and chemotherapy or radiation therapy should be adopted to reduce long-term toxicity and improve QoL and survival.⁶⁶⁻⁶⁸

Metastatic Seminoma

Although approximately 90% of patients with metastatic seminoma present with PCRD, the presence of vGCT is uncommon. Studies indicated that vGCT is found in approximately 20% of patients with lesions ≥ 3 cm, whereas it is rare (0%-4%) in lesions < 3 cm.⁶⁶⁻⁶⁸ As a result, AS is the preferred approach for PCRD lesions < 3 cm. For patients with PCRD ≥ 3 cm, a multidisciplinary discussion is essential to avoid overtreatment.³⁶

Although FDG-PET is sometimes used in PCRD evaluation, it has significant limitations. The positive predictive values of FDG-PET in this context is approximately 23%, while its sensitivity and negative predictive value are 90%-100% for lesions ≥ 3 cm.^{69,70} Therefore, a negative FDG-PET rules out active seminoma in ≥ 3 cm lesions, while a positive FDG-PET does not accurately identify viable seminoma. In FDG-PET-positive patients, the treatment decision should be informed by further tests, including repeated CT scans (to confirm tumor growth) and eventually a biopsy. In patients with unequivocal vGCT, surgery in high-volume centers is recommended. Experienced surgeons are needed as the

extensive chemotherapy-induced desmoplastic reaction leads to incomplete resection and postsurgical complications, reported in approximately 25%-30% of patients.^{63,71,72} Radiotherapy should be reserved for nonsurgical candidates or in patients for whom surgery is not technically possible.^{36,73}

Metastatic Nonseminoma

The management of nonseminoma PCRD is further complicated by the risk of teratoma, which is less chemosensitive than the other GCT histologies. Surgical resection is necessary to prevent somatic transformation and teratoma growing syndrome, both of which can lead to aggressive disease progression. As a result, surgery is the recommended strategy in any patient with nonseminoma PCRD ≥ 1 cm. Retrospective studies have shown that the following distribution of histologic findings in PCRD ≥ 1 cm include necrosis (40%-45%), teratoma (30%-40%), and vGCT (10%-15%).^{63,74}

Although some data have suggested risk of teratoma or vGCT as high as 30% in PCRD < 1 cm,⁷⁵ data from several institutions have not shown a detrimental effect of AS on long-term survival.⁷⁶⁻⁷⁸ Therefore, in patients with PCRD < 1 cm, the recommended option is AS. FDG-PET scan has no utility in nonseminoma due to teratoma being notoriously FDG-non-avid, having a high false-negative rate, and therefore should not be used to inform clinical decision making in these patients.⁷⁹ Some data suggest benefit in PFS and OS of adjuvant chemotherapy in nonseminoma patients presenting postchemotherapy vGCTs, especially if they had IGCCCG intermediate-poor risk and $> 10\%$ vGCTs.⁸⁰ However, the risks and benefits of adjuvant chemotherapy must be carefully weighed, particularly given the long-term toxicity of additional chemotherapy. Specifically, adjuvant chemotherapy should be avoided in patients with high risk of disseminated disease (extracapsule extension, unresectable, or partially resected tumor) as these patients will most likely need salvage chemotherapy. IGCCCG good-risk patients with complete resection and $< 10\%$ vGCT can be safely managed with AS.^{80,81}

A recent study from the Memorial Sloan Kettering Cancer Center, analyzed over 1,000 patients undergoing post-chemotherapy RPLND and identified both residual mass size and primary tumor histology—particularly the presence of teratoma or yolk sac tumor—as independent predictors of pathology at resection. These data challenge the traditional 1-cm surgical threshold and support more individualized decision making, incorporating initial tumor histology to better stratify patients and guide treatment planning.⁸²

PCRD and STM

Surgery is the recommended curative option for PCRD with negative or declining/steady low positive STM. By contrast, salvage chemotherapy should be considered in patients presenting with persistently rising STM, which indicates

active disease.⁸³⁻⁸⁵ However, in patients with initially very high tumor markers, STM levels may remain elevated after effective chemotherapy. In these patients, weekly assessment of the STM is necessary until normalization to determine whether surgery or salvage chemotherapy is the most appropriate next step.⁴⁴ Moreover, some patients with teratoma may present with mild elevations of AFP or BHCG. If these STMs remain stable in the context of radiographically stable residual disease, surgery can be still considered.⁸⁶ Finally, surgery should be always discussed in patients with PCRD (both seminoma and nonseminoma) after salvage chemotherapy, as the risk of viable, chemoresistant GCT in these patients is around 50%.⁸⁷

Management of Multiple-Site Residual Disease and Extra-RP Residual Disease

For patients with RP and extra-RP lymph node metastases, RPLND is recommended first because the histology of the RP metastases provides critical information to guide further surgery. High concordance (80%) between RP and extra-RP pathology exists in patients with fibrosis. Therefore, surveillance is indicated if RP lesions show necrosis/fibrosis. By contrast, the concordance between teratoma and vGCT in RP and extra-RP lesions is approximately 40%.⁸⁸ Owing to this lower concordance, resection of extra-RP lesions after RPLND is recommended to ensure complete tumor clearance and prevent recurrence. By prioritizing RP histology assessment, clinicians can better stratify patients for subsequent surgical interventions, ensuring that only those requiring additional procedures undergo further resection.

Novel Biomarkers and Tools to Inform PCRD Management

The management of PCRD remains challenging because of the lack of reliable biomarkers to differentiate between

necrosis, teratoma, and vGCT. Although various clinical factors have been evaluated to predict the histology of nonseminoma PCRD, none have shown high accuracy in predicting teratoma.⁸⁸ Recent research has explored the role of miRNAs as potential biomarkers for distinguishing PCRD histology. GCTs express specific clusters of miRNAs, which have been investigated as predictors of PCRD.^{47,89} While elevated serum miR371 levels have been associated with postchemotherapy vGCT (AUC, 0.87 [95% CI, 0.77 to 0.97]), this miRNA does not predict teratoma.⁹⁰ Although the integration of plasma miR375 (overexpressed in teratoma) and miR371 has shown better accuracy in detecting postchemotherapy teratoma (AUC in the validation setting, 0.77 [95% CI, 0.62 to 0.93]), it is still suboptimal to inform clinical management.⁹¹ Artificial intelligence (AI)-driven models integrating radiomics, miR371, and miR375 have shown promising results (AUC, 0.91 [95% CI, 0.80 to 0.99]).⁹² If validated in larger prospective studies, AI-integrated approaches may enhance PCRD management by improving the prediction of teratoma, ultimately informing treatment decisions with greater precision.

CONCLUSION

The long-term impact of GCT treatment extends far beyond initial oncologic control. While survival outcomes for testicular cancer remain outstanding, survivors are at risk of a wide array of treatment-related complications, necessitating structured survivorship care. Future research should prioritize identifying predictive markers for treatment-related toxicities, refining risk-adapted follow-up protocols, and developing evidence-based interventions to mitigate long-term complications. Clinicians must remain vigilant in counseling patients on survivorship risks and implementing proactive strategies to optimize QoL. As the field of GCT management evolves, a balanced approach—prioritizing both cure and survivorship—will be crucial in ensuring the best outcomes for patients.

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REFERENCES

1. National Cancer Institute: Cancer stat facts: Testicular cancer. SEER (surveillance, epidemiology, and end results)
2. Fosså SD, Haugnes HS, Dahl AA, et al: Adverse health outcomes and global quality of life in long-term testicular cancer survivors: A longitudinal 30-year perspective. *Ann Oncol* 34:1165-1174, 2023
3. Fung C, Sesso HD, Williams AM, et al: Multi-institutional assessment of adverse health outcomes among North American testicular cancer survivors after modern cisplatin-based chemotherapy. *J Clin Oncol* 35:1211-1222, 2017
4. Znaor A, Skakkebaek NE, Rajpert-De Meyts E, et al: Global patterns in testicular cancer incidence and mortality in 2020. *Int J Cancer* 151:692-698, 2022
5. Hellesnes R, Myklebust TA, Fosså SD, et al: Testicular cancer in the cisplatin era: Causes of death and mortality rates in a population-based cohort. *J Clin Oncol* 39:3561-3573, 2021
6. Fosså SD, Dahl AA, Thorsen L, et al: Mortality and second cancer incidence after treatment for testicular cancer: Psychosocial health and lifestyle are modifiable prognostic factors. *J Clin Oncol* 40:2588-2599, 2022
7. Kerns SL, Fung C, Fossa SD, et al: Relationship of cisplatin-related adverse health outcomes with disability and unemployment among testicular cancer survivors. *JNCI Cancer Spectr* 4:pkaa022, 2020
8. Dinh PC, Monahan PO, Fosså SD, et al: Impact of pain and adverse health outcomes on long-term US testicular cancer survivors. *J Natl Cancer Inst* 116:455-467, 2024
9. Honecker F, Aparicio J, Berney D, et al: ESMO consensus conference on testicular germ cell cancer: Diagnosis, treatment and follow-up. *Ann Oncol* 29:1658-1686, 2018
10. Bandak M, Jørgensen N, Juul A, et al: Testosterone deficiency in testicular cancer survivors—A systematic review and meta-analysis. *Andrology* 4:382-388, 2016
11. Haugnes HS, Bosl GJ, Boer H, et al: Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. *J Clin Oncol* 30:3752-3763, 2012
12. La Vignera S, Cannarella R, Duca Y, et al: Corrigendum: Hypogonadism and sexual dysfunction in testicular tumor survivors: A systematic review. *Front Endocrinol (Lausanne)* 10:393, 2019
13. Ljungman L, Eriksson LE, Flynn KE, et al: Sexual dysfunction and reproductive concerns in young men diagnosed with testicular cancer: An observational study. *J Sex Med* 16:1049-1059, 2019
14. Brydøy M, Fosså SD, Klepp O, et al: Paternity following treatment for testicular cancer. *J Natl Cancer Inst* 97:1580-1588, 2005
15. Weibring K, Lundberg FE, Cohn-Cedermark G, et al: Parenthood in a Swedish prospective cohort of 1,378 adolescents and young adults banking semen for fertility preservation at time of cancer diagnosis. *Front Endocrinol (Lausanne)* 15:1502479, 2024
16. Rincones O, Smith A, Naher S, et al: An updated systematic review of quantitative studies assessing anxiety, depression, fear of cancer recurrence or psychological distress in testicular cancer survivors. *Cancer Manag Res* 13:3803-3816, 2021
17. Sprauten M, Haugnes HS, Brydøy M, et al: Chronic fatigue in 812 testicular cancer survivors during long-term follow-up: Increasing prevalence and risk factors. *Ann Oncol* 26:2133-2140, 2015
18. Fabi A, Bhargava R, Fatigoni S, et al: Cancer-related fatigue: ESMO clinical practice guidelines for diagnosis and treatment. *Ann Oncol* 31:713-723, 2020
19. Adams SC, DeLorey DS, Davenport MH, et al: Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. *Br J Cancer* 118:1313-1321, 2018
20. Lubberts S, Groot HJ, de Wit R, et al: Cardiovascular disease in testicular cancer survivors: Identification of risk factors and impact on quality of life. *J Clin Oncol* 41:3512-3522, 2023
21. Haugnes HS, Wethal T, Aass N, et al: Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: A 20-year follow-up study. *J Clin Oncol* 28:4649-4657, 2010
22. Lauritsen J, Hansen MK, Bandak M, et al: Cardiovascular risk factors and disease after male germ cell cancer. *J Clin Oncol* 38:584-592, 2020
23. Groot HJ, Lubberts S, de Wit R, et al: Risk of solid cancer after treatment of testicular germ cell cancer in the platinum era. *J Clin Oncol* 36:2504-2513, 2018
24. Groot HJ, Gietema JA, Aleman BMP, et al: Risk of diabetes after para-aortic radiation for testicular cancer. *Br J Cancer* 119:901-907, 2018
25. Hellesnes R, Kvammen Ø, Myklebust TA, et al: Continuing increased risk of second cancer in long-term testicular cancer survivors after treatment in the cisplatin era. *Int J Cancer* 147:21-32, 2020
26. Milano MT, Dinh PC, Yang H, et al: Solid and hematologic neoplasms after testicular cancer: A us population-based study of 24 900 survivors. *JNCI Cancer Spectr* 4:pkaa017, 2020
27. Breekveldt ECH, Ykema BLM, Huitema ADR, et al: Platinum retention in plasma, urine, and normal colonic mucosa in cisplatin-treated testicular cancer survivors. *PLoS One* 19:e0312994, 2024
28. Lauritsen J, Bandak M, Kreiberg M, et al: Long-term neurotoxicity and quality of life in testicular cancer survivors—A Nationwide Cohort Study. *J Cancer Surviv* 15:509-517, 2021
29. Jordan B, Margulies A, Cardoso F, et al: Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO—EONS—EANO clinical practice guidelines for diagnosis, prevention, treatment and follow-up. *Ann Oncol* 31:1306-1319, 2020
30. Sanchez VA, Dinh PC, Monahan PO, et al: Comprehensive audiologic analyses after cisplatin-based chemotherapy. *JAMA Oncol* 10:912-922, 2024
31. Jefford M, Howell D, Li Q, et al: Improved models of care for cancer survivors. *Lancet (London, England)* 399:1551-1560, 2022
32. Garcia-del-Muro X, Maroto P, Gumà J, et al: Chemotherapy as an alternative to radiotherapy in the treatment of stage IIA and IIB testicular seminoma: A Spanish germ cell cancer group study. *J Clin Oncol* 26:5416-5421, 2008
33. Classen J, Schmidberger H, Meisner C, et al: Radiotherapy for stages IIA/B testicular seminoma: Final report of a prospective multicenter clinical trial. *J Clin Oncol* 21:1101-1106, 2003
34. Stephenson A, Eggen SE, Bass EB, et al: Diagnosis and treatment of early stage testicular cancer: AUA guideline. *J Urol* 202:272-281, 2019
35. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer
36. Patrikidou A, Cazzaniga W, Berney D, et al: European association of urology guidelines on testicular cancer: 2023 update. *Eur Urol* 84:289-301, 2023
37. Hieste A, Che Y, Lusch A, et al: Phase 2 single-arm trial of primary retroperitoneal lymph node dissection in patients with seminomatous testicular germ cell tumors with clinical stage IIA/B (PRIMETEST). *Eur Urol* 84:25-31, 2023
38. Daneshmand S, Cary C, Masterson T, et al: Surgery in early metastatic seminoma: A phase II trial of retroperitoneal lymph node dissection for testicular seminoma with limited retroperitoneal lymphadenopathy. *J Clin Oncol* 41:3009-3018, 2023
39. Heidenreich A, Paffenholz P, Hartmann F, et al: Retroperitoneal lymph node dissection in clinical stage IIA/B metastatic seminoma: Results of the COlogne Trial of Retroperitoneal Lymphadenectomy in Metastatic Seminoma (COTRIMS). *Eur Urol Oncol* 7:122-127, 2024
40. Lorient Y, Texier M, Culine S, et al: The GETUG SEMITEP trial: De-escalating chemotherapy in good-prognosis seminoma based on fluorodeoxyglucose positron emission tomography/computed tomography. *Eur Urol* 82:172-179, 2022
41. Alifrangis C, Sharma A, Chowdhury S, et al: Single-agent carboplatin AUC10 in metastatic seminoma: A multi-centre UK study of 216 patients. *Eur J Cancer* 164:105-113, 2022
42. Gillessen S, Sauvè N, Collette L, et al: Predicting outcomes in men with metastatic nonseminomatous germ cell tumors (NSGCT): Results from the IGCCCG update consortium. *J Clin Oncol* 39:1563-1574, 2021
43. Gilligan TD, Seidenfeld J, Basch EM, et al: American Society of Clinical Oncology clinical practice guideline on uses of serum tumor markers in adult males with germ cell tumors. *J Clin Oncol* 28:3388-3404, 2010
44. Zon RT, Nichols C, Einhorn LH: Management strategies and outcomes of germ cell tumor patients with very high human chorionic gonadotropin levels. *J Clin Oncol* 16:1294-1297, 1998

45. Garnick MB: Spurious rise in human chorionic gonadotropin induced by marihuana in patients with testicular cancer. *N Engl J Med* 303:1177, 1980
46. Albany C, Einhorn L: Pitfalls in management of patients with germ cell tumors and slight elevation of serum α -fetoprotein. *J Clin Oncol* 32:2114-2115, 2014
47. Dieckmann KP, Radtke A, Geczi L, et al: Serum levels of MicroRNA-371a-3p (M371 test) as a new biomarker of testicular germ cell tumors: Results of a prospective multicentric study. *J Clin Oncol* 37:1412-1423, 2019
48. Ben-David R, Chehrizi-Raffae A, Laliotis G, et al: Longitudinal tumor-informed ctDNA assay and patient outcomes in testicular cancer. *J Clin Oncol* 42:499, 2024
49. Dittono F, Franco A, Manfredi C, et al: The role of miRNA in testicular cancer: Current insights and future perspectives. *Medicina (Kaunas)* 59:2033, 2023
50. Kesler KA, Stram AR, Timsins LR, et al: Outcomes following surgery for primary mediastinal nonseminomatous germ cell tumors in the cisplatin era. *J Thorac Cardiovasc Surg* 161:1947-1959.e1, 2021
51. Ranganath P, Kesler KA, Einhorn LH: Perioperative morbidity and mortality associated with bleomycin in primary mediastinal nonseminomatous germ cell tumor. *J Clin Oncol* 34:4445-4446, 2016
52. Hinton S, Catalano PJ, Einhorn LH, et al: Cisplatin, etoposide and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumors: Final analysis of an intergroup trial. *Cancer* 97:1869-1875, 2003
53. Watson RA, De La Peña H, Tsakok MT, et al: Development of a best-practice clinical guideline for the use of bleomycin in the treatment of germ cell tumours in the UK. *Br J Cancer* 119:1044-1051, 2018
54. Richardson NH, Taza F, Abonour R, et al: High-dose chemotherapy and peripheral blood stem cell transplantation as salvage therapy in primary mediastinal nonseminomatous germ cell tumors: The Indiana University experience. *Cancer* 130:3115-3122, 2024
55. International Germ Cell Consensus Classification: A prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol* 15:594-603, 1997
56. Mannis D, Brandl A: Efficacy of common decontamination methods for cleaning contaminated wounds. *Health Phys* 108:S5-S12, 2015
57. Haugnes HS, Negaard HF, Jensvoll H, et al: Thromboembolic events during treatment with cisplatin-based chemotherapy in metastatic testicular germ-cell cancer 2000–2014: A population-based cohort study. *Eur Urol Open Sci* 32:19-27, 2021
58. Baniel J, Foster RS, Gonin R, et al: Late relapse of testicular cancer. *J Clin Oncol* 13:1170-1176, 1995
59. Tandstad T, Hellesnes R, Haugnes HS, et al: Late relapses in testicular cancer: Results from a national cohort. *J Clin Oncol* 40:5008, 2022
60. Richardson NH, Althouse SK, Ashkar R, et al: Late relapse of germ cell tumors after prior chemotherapy or surgery-only. *Clin Genitourin Cancer* 21:467-474, 2023
61. Tandstad T, Kollmannsberger CK, Roth BJ, et al: Practice makes perfect: The rest of the story in testicular cancer as a model curable neoplasm. *J Clin Oncol* 35:3525-3528, 2017
62. George DW, Foster RS, Hromas RA, et al: Update on late relapse of germ cell tumor: A clinical and molecular analysis. *J Clin Oncol* 21:113-122, 2003
63. Daneshmand S, Albers P, Fosså SD, et al: Contemporary management of postchemotherapy testis cancer. *Eur Urol* 62:867-876, 2012
64. King J, Adra N, Einhorn LH: Management of residual disease after chemotherapy in germ cell tumors. *Curr Opin Oncol* 32:250-255, 2020
65. Ghodoussipour S, Daneshmand S: Postchemotherapy resection of residual mass in nonseminomatous germ cell tumor. *The Urol Clin North America* 46:389-398, 2019
66. Heidenreich A, Thüer D, Polyakov S: Postchemotherapy retroperitoneal lymph node dissection in advanced germ cell tumours of the testis. *Eur Urol* 53:260-272, 2008
67. Herr HW, Sheinfeld J, Puc HS, et al: Surgery for a post-chemotherapy residual mass in seminoma. *J Urol* 157:860-862, 1997
68. Flechon A, Bompas E, Biron P, et al: Management of post-chemotherapy residual masses in advanced seminoma. *J Urol* 168:1975-1979, 2002
69. De Santis M, Becherer A, Bokemeyer C, et al: 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: An update of the prospective multicentric SEMPET trial. *J Clin Oncol* 22:1034-1039, 2004
70. Cathomas R, Klingbiel D, Bernard B, et al: Questioning the value of fluorodeoxyglucose positron emission tomography for residual lesions after chemotherapy for metastatic seminoma: Results of an international global germ cell cancer group registry. *J Clin Oncol* 36:3381-3387, 2018
71. Pierorazio PM, Biles MJ: Indications for surgery in disseminated seminoma. *Urol Clin North Am* 46:399-407, 2019
72. Mosharaf AA, Foster RS, Leibovich BC, et al: Is post-chemotherapy resection of seminomatous elements associated with higher acute morbidity? *J Urol* 169:2126-2128, 2003
73. Duchesne GM, Stenning SP, Aass N, et al: Radiotherapy after chemotherapy for metastatic seminoma—a diminishing role. MRC Testicular Tumour Working Party. *Eur J Cancer* 33:829-835, 1997
74. Mano R, Di Natale R, Sheinfeld J: Current controversies on the role of retroperitoneal lymphadenectomy for testicular cancer. *Urol Oncol* 37:209-218, 2019
75. Oldenburg J, Alfsen GC, Lien HH, et al: Postchemotherapy retroperitoneal surgery remains necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses. *J Clin Oncol* 21:3310-3317, 2003
76. Daneshmand S, Stephenson AJ, Sheinfeld J, et al: The management of subcentimeter residual mass in NSGCT: pcRPLND vs. observation. *Urol Oncol* 29:842-847, 2011
77. Kollmannsberger C, Daneshmand S, So A, et al: Management of disseminated nonseminomatous germ cell tumors with risk-based chemotherapy followed by response-guided postchemotherapy surgery. *J Clin Oncol* 28:537-542, 2010
78. Ehrlich Y, Brames MJ, Beck SDW, et al: Long-term follow-up of cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: Is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? *J Clin Oncol* 28:531-536, 2010
79. Pfannenberger AC, Oechsle K, Bokemeyer C, et al: The role of [18F] FDG-PET, CT/MRI and tumor marker kinetics in the evaluation of postchemotherapy residual masses in metastatic germ cell tumors—Prospects for management. *World J Urol* 22:132-139, 2004
80. Fizazi K, Oldenburg J, Dunant A, et al: Assessing prognosis and optimizing treatment in patients with postchemotherapy viable nonseminomatous germ-cell tumors (NSGCT): Results of the sCR2 international study. *Ann Oncol* 19:259-264, 2008
81. Fizazi K, Tjulandin S, Salvioni R, et al: Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: Prognostic factors and role of postsurgery chemotherapy—Results from an international study group. *J Clin Oncol* 19:2647-2657, 2001
82. Matulewicz RS, Baky F, Liso N, et al: Oncologic outcomes of retroperitoneal lymph node dissection following first-line chemotherapy for metastatic non-seminomatous germ cell tumors. *Ann Oncol* 2025
83. Beck SDW, Foster RS, Bihler R, et al: Post chemotherapy RPLND in patients with elevated markers: Current concepts and clinical outcome. *Urol Clin North Am* 34:219-225, 2007
84. Lorch A, Bascoul-Mollevi C, Kramar A, et al: Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: Evidence from a large international database. *J Clin Oncol* 29:2178-2184, 2011
85. Einhorn LH, Williams SD, Chamness A, et al: High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med* 357:340-348, 2007
86. Ong TA, Winkler MH, Savage PM, et al: Retroperitoneal lymph node dissection after chemotherapy in patients with elevated tumour markers: Indications, histopathology and outcome. *BJU Int* 102:198-202, 2008
87. Fox EP, Weathers TD, Williams SD, et al: Outcome analysis for patients with persistent nonteratomatous germ cell tumor in postchemotherapy retroperitoneal lymph node dissections. *J Clin Oncol* 11:1294-1299, 1993
88. Masterson TA, Shayegan B, Carver BS, et al: Clinical impact of residual extraretroperitoneal masses in patients with advanced nonseminomatous germ cell testicular cancer. *Urology* 79:156-159, 2012
89. Nappi L, Thi M, Lum A, et al: Developing a highly specific biomarker for germ cell malignancies: Plasma miR371 expression across the germ cell malignancy spectrum. *J Clin Oncol* 37:3090-3098, 2019
90. Leão R, van Agthoven T, Figueiredo A, et al: Serum miRNA predicts viable disease after chemotherapy in patients with testicular nonseminoma germ cell tumor. *J Urol* 200:126-135, 2018
91. Nappi L, Thi M, Adra N, et al: Integrated expression of circulating miR375 and miR371 to identify teratoma and active germ cell malignancy components in malignant germ cell tumors. *Eur Urol* 79:16-19, 2021
92. Li X, Ding R, Liu Z, et al: A predictive system comprising serum microRNAs and radiomics for residual retroperitoneal masses in metastatic nonseminomatous germ cell tumors. *Cell Rep Med* 5:101843, 2024

State of the Art: Personalizing Treatment for Patients With Metastatic Castration-Resistant Prostate Cancer

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OVERVIEW

Until recently, the treatment of metastatic castration-resistant prostate cancer (mCRPC) relied exclusively on hormonal therapies and taxane chemotherapy. The advent of modern molecular profiling methods applied in the clinic, namely, next-generation sequencing and advanced positron emission tomography (PET) imaging, has allowed for the development of biomarker-driven therapeutics including anti-PD-L1 therapy for microsatellite instability-high or tumor mutation burden-high disease, poly(ADP-ribose) polymerase (PARP) inhibitors for patients with DNA damage repair mutations, and lutetium 177 vipivotide tetraxetan (¹⁷⁷Lu-PSMA-617) for patients with prostate-specific membrane antigen (PSMA) PET-avid disease. While these targeted therapies have improved outcomes, there is an opportunity to refine biomarkers to optimize patient selection, understand resistance, and develop novel combination strategies. In addition, studies in the laboratory and in patient-derived samples have shown that a subset of mCRPC tumors lose expression of common prostate cancer markers such as prostate-specific antigen and PSMA because of lineage plasticity and the development of non-androgen receptor (AR)-driven disease. Non-AR-driven prostate cancer has been associated with aggressive behavior and poor prognosis, including in some cases histologic transformation to a poorly differentiated neuroendocrine prostate cancer (NEPC). The clinical management of NEPC typically follows the treatment paradigm for small cell lung cancer and increasingly relies on genomic and phenotypic characterization of disease, including loss of tumor suppressors and expression of cell surface markers such as DLL3. Therefore, both genomic subtyping and phenotypic subtyping are important to consider and can guide the clinical management of patients with advanced prostate cancer.

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INTEGRATING POLY(ADP-RIBOSE) POLYMERASE INHIBITORS IN THE TREATMENT OF PROSTATE CANCER

Poly(ADP-ribose) polymerase (PARP) inhibitors exploit a deficiency in DNA damage repair (DDR) to induce tumor cell death.¹⁻⁴ Inhibition of the PARP enzymes results in the evolution of single-strand breaks into double-strand breaks which are typically repaired via the high-fidelity homologous recombination repair (HRR) pathway. Tumors that are deficient in HRR, such as those that carry loss-of-function alterations in the HRR genes *BRCA1* and *BRCA2*, are unable to repair their DNA, resulting in synthetic lethality. Approximately a decade ago, large genomic studies revealed that up to 20% of patients with metastatic prostate cancer carry germline or somatic loss-of-function alterations in HRR genes (*BRCA2*, *BRCA1*, *PALB2*) and other DNA repair genes that are indirectly implicated in HRR (*ATM*, *CHEK2*, *CDK12*), leading to the investigation of PARP inhibitors in DDR-mutated metastatic castration-resistant prostate cancer (mCRPC).⁵⁻⁸

PARP Inhibitor Monotherapy in DDR-Mutated Prostate Cancer

Several studies have investigated the role of PARP inhibitors delivered as monotherapy in genomically selected mCRPC. TRITON2 was a single-arm phase II study of the PARP inhibitor rucaparib in patients with mCRPC who had previously received at least one androgen receptor pathway inhibitor (ARPI) and one taxane regimen and who carried either a germline or a somatic deleterious alteration in a predefined list of DDR genes. The primary end point was objective radiographic response (ORR) via RECIST1.1 in patients with baseline measurable disease among carriers of deleterious *BRCA2* or *BRCA1* mutations. Secondary end points included prostate-specific antigen (PSA) and radiographic responses in patients with alterations in other genes. The study met its prespecified primary end point with an ORR of 44% (95% CI 31%-57%) among patients with *BRCA2/1* alterations, leading to the first US Food and Drug Administration (FDA) approval of a PARP inhibitor for

PRACTICAL APPLICATIONS

- Molecular phenotyping including next-generation sequencing and advanced positron emission tomography (PET) imaging is now part of the standard of care for patients with metastatic castration-resistant prostate cancer (mCRPC).
- Poly(ADP-ribose) polymerase (PARP) inhibitors are effective therapy for patients with mCRPC and certain homologous recombination repair gene mutations. PARP inhibitors may be given as monotherapy or in combination with an androgen receptor pathway inhibitor.
- Lutetium177-prostate-specific membrane antigen (PSMA) is effective for the treatment of men with mCRPC and PSMA-expressing disease identified on PET imaging.
- A subset of metastatic prostate cancers progress on hormonal therapy to a non-androgen-receptor-dependent phenotype characterized by tumor suppressor loss, neuroendocrine features, and aggressive clinical behavior. The treatment of this disease subtype relies primarily on combination chemotherapy, with targeted therapies currently in development.

BRCA-mutated mCRPC.⁹ Both PSA and radiographic responses were uncommon in patients with alterations in DDR genes that are indirectly implicated in HRR, including *ATM*, *CHEK2*, and *CDK12*, although responses were observed in the smaller subset of patients with alterations in the HRR-related genes *PALB2*, *BRIP1*, and *RAD51*.^{10,11} Two subsequent nonregistrational monotherapy studies of the PARP inhibitors niraparib (GALAHAD)¹² and talazoparib (TALAPRO-1)¹³ had a similar design to TRITON2 and overall similar findings. A confirmatory phase III study, TRITON3, explored the benefit of rucaparib compared with physician's choice therapy of a second-line ARPI or docetaxel chemotherapy in patients with mCRPC carrying an alteration in *BRCA2*, *BRCA1*, or *ATM*. The study found a radiographic progression-free survival (rPFS) benefit for rucaparib (HR, 0.61 [95% CI, 0.47 to 0.80]).¹⁴ In exploratory analysis of the *ATM*-mutated subgroup, there was no significant difference in rPFS for rucaparib versus control therapy (HR, 0.95 [95% CI, 0.59 to 1.52]).

PROFOUND was a randomized phase III study of the PARP inhibitor olaparib versus physician's choice therapy of a second-line ARPI only in patients with mCRPC who carried a deleterious germline or somatic alteration in a prespecified list of 15 DDR genes.¹⁵ The primary end point was rPFS in a cohort of patients with alterations in *BRCA2*, *BRCA1*, and *ATM* (cohort A). The study found an rPFS (HR, 0.34 [95% CI, 0.25

to 0.47]) and overall survival (OS) (HR, 0.69 [95% CI, 0.50 to 0.97]) benefit for olaparib in cohort A, meeting its primary end point.¹⁶ The study also reported an rPFS benefit for olaparib versus the control arm when combining cohort A with exploratory cohort B (HR, 0.49 [95% CI, 0.38 to 0.63]) although benefit might have been driven by patients with *BRCA* mutations.¹⁷ Nonetheless, the FDA approved olaparib for the treatment of men with mCRPC who had previously received an ARPI and who had a germline or somatic alteration in one of 14 DDR genes.

PARP Inhibitor and ARPI Combination Therapy in DDR-Mutated Prostate Cancer

Inhibition of the androgen receptor (AR) axis has been shown in the laboratory to modulate the expression of DNA repair genes including HRR genes,^{18,19} and some data suggest that coinhibition of AR and PARP may synergize to cause tumor cell death.^{20,21} This led to the development of several large studies combining an ARPI and a PARP inhibitor in both DDR-mutated and non-DDR-mutated mCRPCs. PROPEL was a phase III study randomly assigning patients with first-line mCRPC to receive olaparib and abiraterone acetate versus abiraterone acetate alone.²² The study allowed previous treatment with an ARPI in the castration-sensitive setting although fewer than 5% of patients had received one. Patients were not genomically selected for enrollment, and genomic profiling was exploratory and retrospective. The greatest rPFS benefit was observed in patients with *BRCA2/1* mutations (HR, 0.24 [95% CI, 0.12 to 0.45]), leading to the FDA approval of abiraterone acetate with olaparib in patients with first-line mCRPC who carry a mutation in *BRCA2* or *BRCA1* only. MAGNITUDE randomly assigned patients with first-line mCRPC to receive niraparib and abiraterone acetate versus abiraterone acetate alone and also enrolled few patients who had received an ARPI in the castration-sensitive setting.²³ Unlike PROPEL, MAGNITUDE was genomically selected, with prospective enrollment into an HRR-mutated (HRR+) arm and a non-HRR-mutated (HRR-) arm. The greatest rPFS benefit was again observed for patients with *BRCA2/1* mutations (HR, 0.53 [95% CI, 0.36 to 0.79]), leading to FDA approval of the combination of niraparib and abiraterone acetate for men with first-line mCRPC with a *BRCA2* or *BRCA1* mutation. A third study, TALAPRO-2, randomly assigned patients with first-line mCRPC to receive talazoparib and enzalutamide versus enzalutamide alone.²⁴ Few patients (5%) in this study received an ARPI previously. TALAPRO-2 enrolled patients regardless of the genomic profile, but prospective genomic characterization was performed using both tissue and cell-free DNA in most patients. rPFS benefit was observed in patients with a mutation in one of 12 prespecified DDR genes (HR, 0.45 [95% CI, 0.33 to 0.61]), leading to FDA approval of talazoparib plus enzalutamide for men with first-line mCRPC carrying a specified DDR gene mutation. In an exploratory analysis of the TALAPRO-2 results for DDR-mutated patients, the greatest benefit was observed for patients with mutations in *BRCA2* (HR, 0.19 [95% CI, 0.10 to

TABLE 1. Key Studies for FDA-Approved Poly(ADP-ribose) Polymerase Inhibitors and Combinations in mCRPC

Approved Drug/Combination	Key Study	Design	Primary End Point	Result	FDA Approval
Rucaparib	TRITON2 ¹¹	Single-arm phase II post-ARPI post-taxane	ORR in <i>BRCA2/BRCA1</i> patients	ORR, 44%, 95% CI, 31% to 57%	<i>BRCA2, BRCA1</i> after an ARPI and taxane
Olaparib	PROFOUND ¹⁵	Phase III RCT v physician's choice second-line ARPI	rPFS in cohort A (<i>BRCA2, BRCA1, ATM</i>)	HR, 0.34, 95% CI, 0.25 to 0.47 (cohort A only)	14 DDR genes after an ARPI
Olaparib + abiraterone acetate	PROPEL ²⁶	Phase III RCT in first-line mCRPC v abiraterone alone	rPFS in the overall population (unselected, retrospective genomic profiling)	HR, 0.24, 95% CI, 0.12 to 0.45 (<i>BRCA2/1</i>)	<i>BRCA2, BRCA1</i> in first-line mCRPC
Niraparib + abiraterone acetate	MAGNITUDE ²³	Phase III RCT in first-line mCRPC v abiraterone alone	rPFS in patients with DDR gene mutations	HR, 0.53, 95% CI, 0.36 to 0.79 (<i>BRCA2/1</i>)	<i>BRCA2, BRCA1</i> in first-line mCRPC
Talazoparib + enzalutamide	TALAPRO-2 ²⁴	Phase III RCT in first-line mCRPC v enzalutamide alone	rPFS in the overall population, prospective genomic profiling	HR, 0.45, 95% CI, 0.33 to 0.61 (12 DDR genes)	12 DDR genes in first-line mCRPC

Abbreviations: ARPI, androgen receptor pathway inhibitor; DDR, DNA damage repair; FDA, US Food and Drug Administration; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective radiographic response; RCT, randomized controlled trial; rPFS, radiographic progression-free survival.

0.38]), no clear rPFS benefit was observed for patients with mutations in *ATM* and *CHEK2*, and there was a trend toward improved rPFS for patients with *CDK12* mutations (HR, 0.49 [95% CI, 0.23 to 1.02]).²⁵ The key studies that have led to approval of PARP inhibitors as monotherapy or in combination with an ARPI are summarized in Table 1.

One key limitation of the ARPI and PARP inhibitor combination studies is that few patients had received an ARPI in the castration-sensitive state, the current standard of care, and it is therefore unclear whether patients who develop castration-resistant disease on an ARPI would benefit from the combination rather than olaparib or rucaparib alone. It is also unclear whether the combination is superior to sequential use of an ARPI followed by a PARP inhibitor although a small randomized phase II study of olaparib and abiraterone acetate as monotherapy or in combination in patients with mCRPC with a mutation in *BRCA2*, *BRCA1*, or *ATM* showed a significantly higher median rPFS for the combination compared with sequential use of the agents, suggesting that up-front use of the combination may be beneficial.²⁷

PARP Inhibitor and ARPI Combination Therapy in Non-DDR-Mutated Prostate Cancer

The laboratory observation that AR inhibition and PARP inhibition synergize to induce tumor cell death in HRR-proficient cell lines raised the possibility that the combination of an ARPI with a PARP inhibitor may be beneficial in patients without known HRR gene defects.^{20,21} A randomized phase II study explored the benefit of abiraterone acetate plus olaparib versus abiraterone acetate alone in genomically unselected patients with first-line mCRPC and showed an rPFS benefit (HR, 0.66 [95% CI, 0.54 to 0.81]) for the combination.²⁸ This finding led to the development of the phase III study PROPEL which had a randomized design

with a primary end point of rPFS in the overall unselected first-line mCRPC patient population.²² PROPEL met its primary end point of rPFS benefit for abiraterone acetate plus olaparib (HR, 0.66 [95% CI, 0.54 to 0.81]), but a critical limitation was that genomic characterization was retrospective and performed primarily via cell-free DNA testing, such that benefit in the subset of patients without HRR gene mutations could not be proven. MAGNITUDE prospectively enrolled patients without HRR gene mutations in an HRR cohort, where futility was declared early for the abiraterone acetate plus niraparib combination.²³ TALAPRO-2 randomly assigned patients with first-line mCRPC to receive talazoparib and enzalutamide versus enzalutamide alone with prospective genomic profiling performed using both tissue and cell-free DNA.²⁴ The study reported an rPFS benefit for the combination in all patients regardless of HRR status (HR, 0.63 [95% CI, 0.51 to 0.78]) and in patients without a mutation in 12 DDR genes that include *BRCA2* and *BRCA1*, suggesting that benefit from this combination may occur in patients without a detectable HRR gene mutation. Final OS results were reported in abstract form as of the date of writing and showed an OS benefit for the combination in all patients (HR, 0.80 [95% CI, 0.66 to 0.96]), but in pre-specified subgroup analysis, there was no clear OS benefit for patients with nondeficient HRR/unknown HRR status (HR, 0.88 [95% CI, 0.713 to 1.08]).²⁹ At this time, the combination of an ARPI with a PARP inhibitor in men without HRR-mutated prostate cancer remains investigational.

Current and Future Directions in PARP Inhibitor Use

Given the clear efficacy of PARP inhibitors for the treatment of men with HRR-mutated mCRPC, three main avenues are currently being explored for PARP inhibitors in prostate cancer: (1) Early use: several phase III studies are exploring the use of PARP inhibitors as up-front combination therapy with an ARPI and ADT in men with metastatic castration-

sensitive prostate cancer (AMPLITUDE, ClinicalTrials.gov identifier: [NCT04497844](#); TALAPRO-3, ClinicalTrials.gov identifier: [NCT04821622](#); EVOPAR-01, ClinicalTrials.gov identifier: [NCT06120491](#)), and phase II studies are exploring neoadjuvant and adjuvant use of PARP inhibitors with surgery and radiation in high-risk HRR-mutated prostate cancer (eg, Neptune, ClinicalTrials.gov identifier: [NCT05498272](#)); (2) combination with ARPI: final results of the TALAPRO-2 study of enzalutamide and talazoparib in men with first-line mCRPC regardless of HRR gene mutation status are pending, and both TALAPRO-3 and EVOPAR-01 are exploring the combination of an ARPI with a PARP inhibitor in non-HRR-mutated metastatic castration-sensitive prostate cancer; and (3) combination with other DNA-damaging agents: PARP inhibitors were designed to exploit intrinsic HRR deficiency present in some tumors. It is possible that inhibiting parallel repair pathways or inducing DNA damage may synergize with PARP inhibition to cause tumor cell death in the absence of HRR deficiency. Several phase I/II studies are investigating the combination of PARP inhibitors with DNA repair inhibitors (eg, polTheta plus PARP inhibitor combinations ClinicalTrials.gov identifiers: [NCT04991480](#), [NCT06545942](#), [NCT06560632](#)) or radioligand therapies (eg, LuPARP phase I study of olaparib and Lu177 prostate-specific membrane antigen [PSMA]).³⁰

HOW TO GET LUTETIUM-177 PSMA TO THOSE WHO WILL MOST BENEFIT

Evidence for ¹⁷⁷Lu-PSMA-617

PSMA is a cell surface antigen highly expressed by most prostate cancer cells, which has recently emerged as a key target for both diagnostic imaging and therapeutics.³¹ While a number of PSMA targeting therapies are under investigation for systemic treatment of prostate cancer, the radioligand ¹⁷⁷Lu-PSMA-617 is the only agent currently approved by the FDA. ¹⁷⁷Lu-PSMA-617 consists of a small molecule with specificity to PSMA conjugated to radioisotope ¹⁷⁷Lu to selectively deliver DNA-damaging beta-particle radiation to PSMA-expressing cells.^{32,33}

Two key studies, VISION and TheraP, provide evidence for the use of ¹⁷⁷Lu-PSMA-617 in patients with mCRPC. Both enrolled patients previously treated with at least one ARPI and a taxane. The phase III VISION trial demonstrated rPFS and OS benefit of ¹⁷⁷Lu-PSMA-617 compared with protocol-permitted standard of care, leading to FDA approval in March 2022.³⁴ TheraP was a randomized phase II study which compared ¹⁷⁷Lu-PSMA-617 with cabazitaxel.³⁵ Importantly, its design contrasted with VISION, which suboptimally did not allow chemotherapy in the control arm, with most patients receiving an alternate ARPI. Patients randomly assigned to radioligand therapy demonstrated improvement in PSA₅₀ and objective response rates. While these surrogates did not translate into improved OS, ¹⁷⁷Lu-PSMA-617 was associated fewer grade 3/4 adverse events and better quality of life as compared with cabazitaxel.³⁶

The results from these pivotal trials have firmly positioned ¹⁷⁷Lu-PSMA-617 therapy within the standard therapeutic arsenal for mCRPC. However, questions remain regarding identifying which patients are most likely to benefit, the optimal timing within the disease course, and how to best deliver this complex therapy.

Identifying Patients Who Will Benefit Most

PSMA expression can be inferred noninvasively using widely available PSMA positron emission tomography (PET) imaging, and high and homogenous PSMA expression strongly correlates with response to therapy.³⁷⁻³⁹ Consequently, both VISION and TheraP maintained strict, albeit differing, PET imaging criteria for determining eligibility for ¹⁷⁷Lu-PSMA-617.^{34,35} TheraP had more stringent criteria as compared with VISION, including a requirement for baseline FDG PET, which led to more than twice as many patients being excluded (27.4% v 12.6%). It is notable that the PSA response rates were 20% higher in TheraP (66% v 46%). It must also be noted that despite rigorous patient selection, the PFS was still <9 months in VISION and no survival benefit was observed in TheraP as compared with cabazitaxel. Therefore, work to identify characteristics of patients who benefit most from ¹⁷⁷Lu-PSMA-617 is essential.

Subsequent analyses from both studies found that a high PSMA mean standardized uptake value (SUV_{mean}), which provides a global assessment of PSMA expression, was the strongest predictor of outcomes to ¹⁷⁷Lu-PSMA-617.^{39,40} In TheraP, patients with SUV_{mean} >10 had a 91% PSA₅₀ response as compared with 32% in those with SUV_{mean} <10, whereas in VISION, a 1-unit SUV_{mean} increase was associated with a 12% and 10% decrease in risk of an rPFS event and death, respectively. Conversely, a high total tumor volume was associated with inferior outcomes on both studies. Nomograms incorporating PSMA PET parameters and pretreatment clinical and laboratory variables may further improve our understanding of which patients are likely to respond.^{41,42} Incorporation of FDG PET imaging, as was performed in the TheraP trial, may provide additional prognostic information given poor outcomes with ¹⁷⁷Lu-PSMA-617 with discordant (ie, FDG+/PSMA-) lesions.^{39,43,44}

Genomic factors such as alterations in the HRR pathway may also influence response to ¹⁷⁷Lu-PSMA-617, potentially by mediating sensitivity to DNA-damaging radiotherapy. The available evidence is conflicting, with some describing improved outcomes in patients with HRR defects, and others inferior outcomes.⁴⁵⁻⁴⁹ While most patients planning to receive ¹⁷⁷Lu-PSMA-617 have few other standard-of-care options in the current approval environment, improving patient selection will become more crucial as alternative drugs are approved in the postchemotherapeutic space and as ¹⁷⁷Lu-PSMA-617 potentially moves into an earlier disease stage.

Is There a Role for ^{177}Lu -PSMA-617 as an Earlier Line of Therapy?

PSMA expression is dynamic and can potentially be influenced by a number of factors, such as receipt of DNA-damaging therapeutics, emergence of treatment-induced neuroendocrine phenotype, and androgen blockade.^{50–53} Given the importance of PSMA expression to response to therapy, it is conceivable then that a time point may exist where ^{177}Lu -PSMA-617 would provide maximal benefit. Tumor volume is another temporally dynamic variable of importance in considering the optimal timing of ^{177}Lu -PSMA-617 therapy. High tumor volume has been associated with poor outcomes with ^{177}Lu -PSMA-617 therapy, suggesting that earlier treatment might be preferable.^{54,55} However, it is unclear whether high tumor volume is necessarily predictive of inferior outcomes with ^{177}Lu -PSMA-617 or is a signifier of more aggressive disease regardless of the chosen therapy. Furthermore, smaller tumors may not benefit as much from crossfire radiation that is likely necessary for the relatively low-energy beta emission produced from ^{177}Lu -PSMA-617 to result in cell death.^{56,57}

Studies are ongoing to address the question of optimal timing and potential combinatorial strategies. Building on previous observations that AR inhibition may increase PSMA expression and potentially improve response to ^{177}Lu -PSMA-617, the ENZA-p trial randomly assigned patients with mCRPC at high risk for early progression on enzalutamide to enzalutamide versus enzalutamide plus adaptive-dosed ^{177}Lu -PSMA-617 therapy.⁵⁸ Patients were not permitted to have received previous ARPI or docetaxel in the castration-resistant setting. ^{177}Lu -PSMA-617 improved the primary end point of PSA-PFS (HR, 0.43 [95% CI, 0.29 to 0.63]) and more recently demonstrated an OS benefit as well (HR, 0.55 [95% CI, 0.36 to 0.84]).⁵⁹ A key limitation is that only 38% of patients in the control arm received subsequent ^{177}Lu -PSMA-617, and so it remains unclear as to whether an up-front combination is superior to sequential use of these agents. Additional studies are exploring ^{177}Lu -PSMA-617 for patients with oligometastatic prostate cancer (ClinicalTrials.gov identifier: [NCT05939414](#)) and treatment-naïve mHSPC (ClinicalTrials.gov identifier: [NCT04720157](#)).

The phase III PSMAfore trial is the largest study to date to provide data regarding earlier use of ^{177}Lu -PSMA-617. This study randomly assigned taxane-naïve, post-ARPI patients with PSMA-positive mCRPC to ^{177}Lu -PSMA-617 as compared with change of ARPI.⁶⁰ In the most recent analysis, the trial met the primary end point of rPFS and improved time to worsening in quality of life and pain although it did not improve OS. PSMAfore appropriately used a cross-over design with 57% of patients assigned to ARPI change receiving ^{177}Lu -PSMA-617 at the time of progression, which likely influenced OS.

Patients enrolled were from a lower-risk population and were considered to be appropriate candidates for change in

ARPI (ie, rather than chemotherapy). Therefore, while PSMAfore shows that ^{177}Lu -PSMA-617 is certainly active in patients who have not received docetaxel, it remains unclear whether it is a better option compared with chemotherapy, especially in those with inappropriate for ARPI switch disease, limiting the generalizability of this study. Still, many patients would prefer to receive ^{177}Lu -PSMA-617 rather than chemotherapy because of real concerns regarding tolerability, and to ensure access for these patients, regulatory access is currently being sought.

Barriers to ^{177}Lu -PSMA-617 Access

The production of ^{177}Lu -PSMA-617 poses unique challenges.⁶¹ The isotope ^{177}Lu is generated in a select number of nuclear reactors worldwide, which then must be shipped to a manufacturing facility, where conjugation of the PSMA-targeting ligand occurs. ^{177}Lu has a half-life of 6.65 days, and so the final product must then be distributed rapidly to treatment centers to ensure adequate activity at the time of administration; if the delay extends past a 5-day window, the dose must be destroyed.⁶²

The complexity of ^{177}Lu -PSMA-617 production, relatively fragile supply chain, and sudden high demand at the time of approval in March 2022 led to substantial delays with profound costs to patients, with one center reporting a median duration of 96 days between tumor board review and receipt of cycle 1 of ^{177}Lu -PSMA-617.⁶³ In October 2023 after a significant expansion in manufacturing capacity in the United States, the shortage was considered resolved. We must work closely with our industry partners to ensure that supply remains intact, especially given the potential for ^{177}Lu -PSMA-617 indications to expand to earlier disease states.⁶⁴ The introduction of competitive, similar radioligand therapeutics, such as PSMA I&T, may further help improve access and is currently being studied in the ECLIPSE (ClinicalTrials.gov identifier: [NCT05204927](#)) and SPLASH (ClinicalTrials.gov identifier: [NCT04647526](#)) trials.

Administration of ^{177}Lu -PSMA-617 is complex and requires collaboration between medical oncologists, nuclear medicine physicians, medical physicists, and radiation safety officers, representing a range of expertise not available at all centers, including those in the community where most patients receive care.^{65,66} Ensuring equitable access to ^{177}Lu -PSMA-617 must account for socioeconomic and geographic barriers that may limit patients' ability to travel to specialized centers. Academic centers and others with capabilities to administer ^{177}Lu -PSMA-617 may also be overburdened with referrals for consideration of radioligand therapy, which could conceivably lead to unforeseen opportunity costs such as increased wait times for newly diagnosed patients or reduced clinical trial enrollment. Telemedicine consultations and partnerships with regional hospitals may help patients undergo part of their diagnostic workup or follow-up locally, reserving radioligand infusion itself for specialized centers.⁶⁷

NON-ANDROGEN RECEPTOR-DRIVEN PROSTATE CANCER: UPDATES IN BIOLOGY, CLASSIFICATION, AND MANAGEMENT

While most prostate cancers are driven by AR signaling, up to 15%–20% of CRPC tumors evade therapies through loss of AR dependence.⁶⁸ This can manifest as loss of tumor AR expression itself or through downregulation of the AR pathway and AR-regulated genes such as PSA and PSMA. Clinically, non-AR-driven prostate cancer has been associated with aggressive disease and poor prognosis. If patients with CRPC develop rapid progression in setting of a low PSA, or if progressive PSMA-negative disease is seen on PET imaging, a tumor biopsy should be considered to evaluate for histologic transformation to small cell carcinoma (often referred to as neuroendocrine prostate cancer [NEPC]). While NEPC rarely arises *de novo* and represents <1% of new prostate cancer diagnoses, up to 15%–20% of late-stage prostate cancers can develop AR-independent NEPC features.⁶⁸ In its pure form, NEPC looks and acts a lot like other small cell carcinomas like small cell lung cancer (SCLC) and shares similar targets. The National Comprehensive Cancer Network (NCCN) guidelines support treating patients with NEPC like SCLC.⁶⁹

Biology of Non-AR-Driven Disease

Nearly all prostate cancers arise as an AR-driven adenocarcinoma although some have features of AR independence at diagnosis.⁷⁰ The mainstay of systemic therapy for advanced prostate cancer is AR-targeted therapy with androgen deprivation therapy and more potent ARPIs. Resistance to AR therapies most commonly occurs through reactivation of AR signaling through AR gene mutations, amplifications, structural variants, and other mechanisms. Up to 15%–20% of CRPC tumors develop independence from AR signaling and progress through activation of alternative drivers. They retain early prostate cancer genomic aberrations and often acquire tumor suppressor losses (eg, *TP53*, *RB1*) and distinct changes in their epigenetic and transcriptomic landscape.⁷¹ The most readily recognized phenotypic subtype of AR-independent prostate cancer is NEPC, characterized clinically by its histologic features of poorly differentiated neuroendocrine carcinoma and expression of classical neuroendocrine markers such as synaptophysin and INSM1.⁷² Preclinical and clinical studies have supported NEPC developing as the mechanism of treatment resistance through lineage plasticity, where under selective pressures of AR therapy, tumors shut down their luminal prostate program and turn on a neuroendocrine lineage program.⁶⁸ This is mediated through changes in the epigenome, activation of stem-like programs, and changes in the binding of lineage-determining transcription factors such as ASCL1, MYCN, BRN2, and others that drive a distinct transcriptional program.^{73,74} NEPC is not the only subtype of non-AR-driven CRPC. Loss of AR expression can also occur in the absence of NEPC features, often referred to as double-negative prostate cancer

(DNPC). Even within DNPC, there are emerging subtypes including those driven by FGF, WNT, or other pathways.^{75,76} Whether DNPC represents a distinct entity or is on a continuum with NEPC is not fully understood.⁶⁸

Clinical Features of Non-AR-Driven Prostate Cancer

Since PSA is a direct AR-target gene, clinical features of rapid progression in the setting of low or nonrising PSA levels may lead to a suspicion of AR-independent disease, but this relationship is not absolute. Similarly, PSMA is indirectly regulated by the AR, loss of PSMA is often observed in AR-negative CRPC, but this relationship is also not absolute, and some AR-negative prostate cancers retain PSMA expression.⁷⁷ Visceral metastases including liver and brain are commonly seen in NEPC but can also be seen in AR-positive CRPC.

Aparicio, Corn, and colleagues at MD Anderson used a group of clinical features associated with non-AR-driven prostate cancer (referred to as aggressive variant prostate cancer AVPC) in the context of phase II clinical trials investigating platinum-doublet chemotherapy.^{78,79} These clinical features included at least one of the following: (1) exclusive visceral metastases, (2) lytic bone metastases, (3) bulky lymphadenopathy (≥ 5 cm) or bulky high-grade mass (≥ 5 cm, Gleason ≥ 8) in the prostate or pelvis, (4) low PSA (≤ 10 ng/mL) at initial presentation or at the time of symptomatic progression of castrate-resistant disease plus high volume (≥ 20) bone metastases, (5) serum carcinoembryonic antigen (CEA) and/or lactate dehydrogenase twice the upper limit of normal, (6) ≤ 6 months to CRPC after initiation of hormonal therapy, and (7) small cell carcinoma morphology. Notably, tumors from patients with AVPC were evaluated *post hoc* and found to have a high frequency of combined tumor suppressor loss *PTEN*, *TP53*, and *RB1*. In preclinical studies, combined tumor suppressor loss facilitates lineage plasticity, AR independence, and the development of NEPC.⁶⁸ While not specific for the NEPC phenotype and also seen in aggressive prostate adenocarcinomas, co-occurring alterations involving *RB1* and *TP53* are also present in the majority of SCLCs and also enriched in lung adenocarcinomas that later transform to SCLC.⁸⁰

Pathologic Diagnosis of NEPC

While NCCN guidelines support treating patients with pathologically confirmed NEPC like SCLC, the diagnosis of NEPC can be challenging since there can be heterogeneity in morphology seen within and across CRPC lesions. While pure small cell carcinomas are more readily recognized by pathologists, poorly differentiated carcinomas or mixed morphology tumors are harder to classify. The use of immunohistochemistry is often used to aid in the diagnosis, but prioritization of markers is not standardized across centers. In an attempt to better standardize this, a group of expert pathologists and clinicians recently proposed a framework for the pathologic workup of NEPC and to capture the

TABLE 2. Proposed Pathology Workup of Neuroendocrine Prostate Cancer on the Basis of the Study by Haffner et al⁷²

Morphology Classifier (choose one)	IHC Classifier (include the status of each marker)	Proliferation Classifier (choose one)
Small cell carcinoma	AR-positive (on the basis of AR and NKX3.1 IHC)	High (>60% Ki-67+)
Adenocarcinoma	AR-negative (on the basis of AR and NKX3.1 IHC)	Medium (20%-60%)
Poorly differentiated carcinoma	NE-positive (on the basis of SYP and INSM1 IHC)	Low (<20%)
Other	NE-negative (on the basis of SYP and INSM1 IHC)	

Abbreviations: AR, androgen receptor; IHC, immunohistochemistry; NE, neuroendocrine.

spectrum of phenotypes that may be observed in CRPC.⁷² This includes classifying CRPC biopsies on the basis of a combination of morphology, IHC, and Ki-67 (Table 2), which can be implemented using readily available markers. In the future, additional markers (eg, IHC for therapeutic targets like DLL3) or other molecular assays (eg, transcriptomic signaling to look at AR and NEPC signaling scores, liquid biopsies, molecular imaging) may provide added value to complement what exists today.

Treatment of Non-AR-Driven Prostate Cancer

The use of platinum-based chemotherapy for patients with AVPC was investigated in two phase II trials.^{78,79} In the most recent phase II trial of cabazitaxel with or without carboplatin reported by Corn et al,⁷⁹ 160 men with CRPC with or without AVPC clinical features were enrolled. The study reported improved rPFS for cabazitaxel plus carboplatin versus single-agent cabazitaxel in patients with AVPC criteria with an HR of 0.58 (95% CI, 0.37 to 0.89) versus 0.74 (95% CI, 0.46 to 1.21) for those who did not meet AVPC criteria. A post hoc analysis identified that those with combined tumor suppressor loss in their tumor (two of three: *PTEN*, *TP53*, *RB1*) overall had longer median PFS (7.5 v 1.7 months) and median OS (20.2 v 8.5 months) when treated with cabazitaxel plus carboplatin versus cabazitaxel alone. On the basis of these data, there are two ongoing cooperative group trials. A phase III trial through SWOG (ClinicalTrials.gov identifier: [NCT06470243](#)) is randomly assigning patients with metastatic CRPC to cabazitaxel with or without carboplatin, stratified by AVPC molecular features (ie, combined two of three tumors suppressor loss by IHC), and the phase II PREDICT (ClinicalTrials.gov identifier: [NCT06632977](#)) Alliance trial, an umbrella trial, is enrolling patients with CRPC with combined tumor suppressor loss by genomic assays to cabazitaxel plus carboplatin.

For patients with pathologic evidence of NEPC, NCCN guidelines endorse the use of SCLC regimens. This decision often depends on the dominant histology. After platinum chemotherapy, lurbinectedin is one approved chemotherapy option for SCLC. A recent retrospective series of 18 patients with NEPC treated with lurbinectedin after progressing on platinum-based chemotherapy reported a

modest but significant clinical benefit in some patients.⁸¹ The delta-like ligand 3 (DLL3)-targeted T-cell engager tarlatamab was recently approved for SCLC on the basis of the DeLLphi-301 trial.⁸² This may also be an option for NEPC particularly for those with high DLL3 tumor expression. Clinical trials should always be considered for patients with NEPC. There are several trials underway including those targeting DLL3 (eg, ClinicalTrials.gov identifiers: [NCT04471727](#), [NCT05652686](#)), SSTR2 (ClinicalTrials.gov identifier: [NCT06379217](#)), and EZH2 (ClinicalTrials.gov identifier: [NCT06632977](#)).

Monitoring of Non-AR-Driven Prostate Cancer

Patients with CRPC are typically followed on systemic therapy for response and progression by a combination of PSA, imaging, and clinical symptoms. Given that PSA may not fully reflect the spectrum of the disease burden in non-AR-driven CRPC, imaging and symptoms become paramount. Several blood-based biomarkers such as CEA, serum chromogranin, and NSE are available, but there are not a lot of data to support their utility for routine monitoring. Emerging technology such as cell-free DNA (cfDNA) tumor fraction might add value as a response surrogate as seen in other cancer types but is yet to be validated. Plasma cfDNA methylation or evaluation of cfDNA histone marks shows promise in providing more robust molecular readouts that might aid in the diagnosis of NEPC.⁸³⁻⁸⁶ For instance, the targeted cfDNA methylation NEMO panel quantifies tumor content and provides a phenotype evidence score to capture diverse CRPC phenotypes with an AUC of >0.93 for detecting pathology-confirmed NEPC noninvasively.⁸³ Emerging circulating tumor cell technologies may also provide added value to assess the mRNA expression of NEPC and AR-target genes noninvasively.⁸⁷ Furthermore, expanding research on novel molecular imaging to detect non-AR-driven prostate cancer may also help aid in the diagnosis of non-AR-driven disease, detection of heterogeneity, and monitoring on therapies. While non-AR-driven CRPCs are often PSMA-low and FDG-avid, other tracers like DLL3, fluciclovine, DOTATE, and others may complement existing imaging and help identify other distinct tumor and metabolic features of the tumor to guide care. Broader clinical studies investigating these noninvasive platforms are underway.

CONCLUSION

An improved biological understanding of the drivers of advanced prostate cancer and advancements in the molecular profiling of cancer in the clinic including next-generation sequencing methods, advanced imaging, and expression profiling are allowing for the investigation and development of effective molecularly targeted therapies for the treatment of men with the disease. To date,

standard targeted therapies in prostate cancer include PARP inhibitors, anti-PD-L1 therapy, and ¹⁷⁷Lu-PSMA-617, with several promising targeted agents currently under investigation. It is equally important that these developments in testing and targeted therapy will not achieve their full benefit if they are not adopted broadly, including in practices that serve underserved populations, highlighting the need for continuous education and solving barriers to access.

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REFERENCES

- Abida W, Cheng ML, Armenia J, et al: Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. *JAMA Oncol* 5:471-478, 2019
- Lenis AT, Ravichandran V, Brown S, et al: Microsatellite instability, tumor mutational burden, and response to immune checkpoint blockade in patients with prostate cancer. *Clin Cancer Res* 30:3894-3903, 2024
- Barata P, Agarwal N, Nussenzweig R, et al: Clinical activity of pembrolizumab in metastatic prostate cancer with microsatellite instability high (MSI-H) detected by circulating tumor DNA. *J Immunother Cancer* 8:e001065, 2020
- Lord CJ, Ashworth A: PARP inhibitors: Synthetic lethality in the clinic. *Science* 355:1152-1158, 2017
- Robinson D, Van Allen EM, Wu YM, et al: Integrative clinical genomics of advanced prostate cancer. *Cell* 161:1215-1228, 2015
- Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 375:443-453, 2016
- Abida W, Armenia J, Gopalan A, et al: Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. *JCO Precis Oncol* 10.1200/P0.17.00029
- Tukachinsky H, Madison RW, Chung JH, et al: Genomic analysis of circulating tumor DNA in 3,334 patients with advanced prostate cancer identifies targetable BRCA alterations and AR resistance mechanisms. *Clin Cancer Res* 27:3094-3105, 2021
- Abida W, Patnaik A, Campbell D, et al: Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. *J Clin Oncol* 38:3763-3772, 2020
- Abida W, Campbell D, Patnaik A, et al: Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: Analysis from the phase II TRITON2 study. *Clin Cancer Res* 26:2487-2496, 2020
- Abida W, Campbell D, Patnaik A, et al: Rucaparib for the treatment of metastatic castration-resistant prostate cancer associated with a DNA damage repair gene alteration: Final results from the phase 2 TRITON2 study. *Eur Urol* 84:321-330, 2023
- Smith MR, Scher HI, Sandhu S, et al: Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): A multicentre, open-label, phase 2 trial. *Lancet Oncol* 23:362-373, 2022
- de Bono JS, Mehra N, Scagliotti GV, et al: Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): An open-label, phase 2 trial. *Lancet Oncol* 22:1250-1264, 2021
- Fizazi K, Piulats JM, Reaume MN, et al: Rucaparib or physician's choice in metastatic prostate cancer. *N Engl J Med* 388:719-732, 2023
- de Bono J, Mateo J, Fizazi K, et al: Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med* 382:2091-2102, 2020
- Hussain M, Mateo J, Fizazi K, et al: Survival with olaparib in metastatic castration-resistant prostate cancer. *N Engl J Med* 383:2345-2357, 2020
- Stopsack KH: Efficacy of PARP inhibition in metastatic castration-resistant prostate cancer is very different with non-BRCA DNA repair alterations: Reconstructing prespecified endpoints for cohort B from the phase 3 PROfound trial of olaparib. *Eur Urol* 79:442-445, 2021
- Goodwin JF, Schiewer MJ, Dean JL, et al: A hormone-DNA repair circuit governs the response to genotoxic insult. *Cancer Discov* 3:1254-1271, 2013
- Polkinghorn WR, Parker JS, Lee MX, et al: Androgen receptor signaling regulates DNA repair in prostate cancers. *Cancer Discov* 3:1245-1253, 2013
- Asim M, Tarish F, Zecchini HI, et al: Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. *Nat Commun* 8:374, 2017
- Li L, Karanika S, Yang G, et al: Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. *Sci Signal* 10:eam7479, 2017

22. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al: Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid 1:EVID0a2200043*, 2022
23. Chi KN, Rathkopf D, Smith MR, et al: Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. *J Clin Oncol* 41:3339-3351, 2023
24. Agarwal N, Azad AA, Carles J, et al: Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): A randomised, placebo-controlled, phase 3 trial. *Lancet* 402:291-303, 2023
25. Fizazi K, Azad AA, Matsubara N, et al: First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: The phase 3 TALAPRO-2 trial. *Nat Med* 30:257-264, 2024
26. Saad F, Clarke NW, Oya M, et al: Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): Final prespecified overall survival results of a randomised, double-blind, phase 3 trial. *Lancet Oncol* 24:1094-1108, 2023
27. Hussain M, Kocherginsky M, Agarwal N, et al: Abiraterone, olaparib, or abiraterone + olaparib in first-line metastatic castration-resistant prostate cancer with DNA repair defects (BRCAway). *Clin Cancer Res* 30:4318-4328, 2024
28. Clarke N, Wiechno P, Alekseev B, et al: Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: A randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 19:975-986, 2018
29. Agarwal N, Azad A, Carles J, et al: Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as first-line treatment in unselected patients with metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 TALAPRO-2 trial. *J Clin Oncol* 43, 2025 (suppl 5; abstr LBA18)
30. Sandhu S, Joshua AM, Emmett L, et al: LuPARP: Phase 1 trial of ¹⁷⁷Lu-PSMA-617 and olaparib in patients with metastatic castration resistant prostate cancer (mCRPC). *J Clin Oncol* 41, 2023 (suppl 16; abstr 5005)
31. Silver DA, Pellicer I, Fair WR, et al: Prostate-specific membrane antigen expression in normal and malignant human tissues. *Clin Cancer Res* 3:81-85, 1997
32. Hillier SM, Maresca KP, Femia FJ, et al: Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. *Cancer Res* 69:6932-6940, 2009
33. Ahmadzadehfar H, Rahbar K, Kürpig S, et al: Early side effects and first results of radioligand therapy with ¹⁷⁷Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: A two-centre study. *EJNMMI Res* 5:114, 2015
34. Sartor O, de Bono J, Chi KN, et al: Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med* 385:1091-1103, 2021
35. Hofman MS, Emmett L, Sandhu S, et al: [¹⁷⁷Lu] Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): A randomised, open-label, phase 2 trial. *Lancet* 397:797-804, 2021
36. Hofman MS, Emmett L, Sandhu S, et al: Overall survival with [¹⁷⁷Lu] Lu-PSMA-617 versus cabazitaxel in metastatic castration-resistant prostate cancer (TheraP): Secondary outcomes of a randomised, open-label, phase 2 trial. *Lancet Oncol* 25:99-107, 2024
37. Current K, Meyer C, Magyar CE, et al: Investigating PSMA-targeted radioligand therapy efficacy as a function of cellular PSMA levels and intratumoral PSMA heterogeneity. *Clin Cancer Res* 26: 2946-2955, 2020
38. Seifert R, Seitzer K, Herrmann K, et al: Analysis of PSMA expression and outcome in patients with advanced Prostate Cancer receiving ¹⁷⁷Lu-PSMA-617 Radioligand Therapy. *Theranostics* 10: 7812-7820, 2020
39. Buteau JP, Martin AJ, Emmett L, et al: PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [¹⁷⁷Lu] Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): A biomarker analysis from a randomised, open-label, phase 2 trial. *Lancet Oncol* 23:1389-1397, 2022
40. Kuo PH, Morris MJ, Hesterman J, et al: Quantitative ⁶⁸Ga-PSMA-11 PET and clinical outcomes in metastatic castration-resistant prostate cancer following ¹⁷⁷Lu-PSMA-617 (VISION trial). *Radiology* 312:e233460, 2024
41. Herrmann K, Gafita A, de Bono JS, et al: Multivariable models of outcomes with [¹⁷⁷Lu] Lu-PSMA-617: Analysis of the phase 3 VISION trial. *EClinicalMedicine* 77:102862, 2024
42. Gafita A, Calais J, Grogan TR, et al: Nomograms to predict outcomes after ¹⁷⁷Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: An international, multicentre, retrospective study. *Lancet Oncol* 22:1115-1125, 2021
43. Michalski K, Ruf J, Goetz C, et al: Prognostic implications of dual tracer PET/CT: PSMA ligand and [¹⁸F] FDG PET/CT in patients undergoing [¹⁷⁷Lu] PSMA radioligand therapy. *Eur J Nucl Med Mol Imaging* 48:2024-2030, 2021
44. Chen R, Wang Y, Zhu Y, et al: The added value of ¹⁸F-FDG PET/CT compared with ⁶⁸Ga-PSMA PET/CT in patients with castration-resistant prostate cancer. *J Nucl Med* 63:69-75, 2022
45. Raychaudhuri R, Mo G, Tsuchiya AM, et al: Genomic correlates of prostate-specific membrane antigen expression and response to ¹⁷⁷Lu-PSMA-617: A retrospective multicenter cohort study. *JCO Precis Oncol* 10.1200/P0.23.00634
46. Privé BM, Slootbeek PHJ, Laarhuis BI, et al: Impact of DNA damage repair defects on response to PSMA radioligand therapy in metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis* 25:71-78, 2022
47. Crumbaker M, Emmett L, Horvath LG, et al: Exceptional response to ¹⁷⁷Lutetium prostate-specific membrane antigen in prostate cancer harboring DNA repair defects. *JCO Precis Oncol* 10.1200/P0.18.00237
48. Rami A, Rashid NS, Zhong C, et al: Association between DNA damage repair alterations and outcomes to ¹⁷⁷Lu-PSMA-617 in advanced prostate cancer. *ESMO Open* 10:104131, 2025
49. Wenzel M, Koll F, Hoeh B, et al: Cancer-control outcomes of patients with metastatic castration-resistant prostate cancer with *BRCA* gene or tumor suppressor mutations undergoing ¹⁷⁷lutetium prostate-specific membrane antigen radioligand therapy. *JCO Precis Oncol* 10.1200/P0-24-00545
50. Emmett L, Yin C, Crumbaker M, et al: Rapid modulation of PSMA expression by androgen deprivation: Serial ⁶⁸Ga-PSMA-11 PET in men with hormone-sensitive and castrate-resistant prostate cancer commencing androgen blockade. *J Nucl Med* 60:950-954, 2019
51. Bakht MK, Dereichei I, Li Y, et al: Neuroendocrine differentiation of prostate cancer leads to PSMA suppression. *Endocr Relat Cancer* 26:131-146, 2018
52. Bakht MK, Beltran H: Biological determinants of PSMA expression, regulation and heterogeneity in prostate cancer. *Nat Rev Urol* 22:26-45, 2025
53. Paschalis A, Sheehan B, Riisnaes R, et al: Prostate-specific membrane antigen heterogeneity and DNA repair defects in prostate cancer. *Eur Urol* 76:469-478, 2019
54. Seifert R, Herrmann K, Kleesiek J, et al: Semiautomatically quantified tumor volume using ⁶⁸Ga-PSMA-11 PET as a biomarker for survival in patients with advanced prostate cancer. *J Nucl Med* 61: 1786-1792, 2020
55. Kostos L, Buteau JP, Hofman MS, et al: Determinants of outcome following PSMA-based radioligand therapy and mechanisms of resistance in patients with metastatic castration-resistant prostate cancer. *Ther Adv Med Oncol* 15:17588359231179309, 2023
56. Enger SA, Hartman T, Carlsson J, et al: Cross-fire doses from beta-emitting radionuclides in targeted radiotherapy. A theoretical study based on experimentally measured tumor characteristics. *Phys Med Biol* 53:1909-1920, 2008
57. Alcocer-Ávila ME, Ferreira A, Quinto MA, et al: Radiation doses from ¹⁶¹Tb and ¹⁷⁷Lu in single tumour cells and micrometastases. *EJNMMI Phys* 7:33-39, 2020
58. Emmett L, Subramaniam S, Crumbaker M, et al: [¹⁷⁷Lu] Lu-PSMA-617 plus enzalutamide in patients with metastatic castration-resistant prostate cancer (ENZA-p): An open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* 25:563-571, 2024
59. Emmett L, Subramaniam S, Crumbaker M, et al: Overall survival and quality of life with [¹⁷⁷Lu] Lu-PSMA-617 plus enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer (ENZA-p): Secondary outcomes from a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 26:291-299, 2025
60. Morris MJ, Castellano D, Herrmann K, et al: ¹⁷⁷Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naïve patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): A phase 3, randomised, controlled trial. *Lancet* 404:1227-1239, 2024
61. Vogel W, Van Der Marck S, Versleijen M: Challenges and future options for the production of lutetium-177. *Eur J Nucl Med Mol Imaging* 48:2329-2335, 2021
62. Iravani A, Violet J, Azad A, et al: Lutetium-177 prostate-specific membrane antigen (PSMA) theranostics: Practical nuances and intricacies. *Prostate Cancer Prostatic Dis* 23:38-52, 2020
63. Ravi P, Whelpley B, Kelly E, et al: Clinical implementation of ¹⁷⁷Lu-PSMA-617 in the United States: Lessons learned and ongoing challenges. *J Nucl Med* 64:349-350, 2023
64. Czernin J, Calais J: How many theranostics centers will we need in the United States? *J Nucl Med* 63:805-806, 2022
65. Calais J, Morris MJ, Kendi AT, et al: Best patient care practices for administering PSMA-targeted radiopharmaceutical therapy. *J Nucl Med* 65:1666-1671, 2024
66. Kirkwood MK, Hanley A, Bruinooge SS, et al: The state of oncology practice in America, 2018: Results of the ASCO practice census survey. *J Oncol Pract* 14:e412-e420, 2018
67. Bosserman LD, Cianfrocca M, Yuh B, et al: Integrating academic and community cancer care and research through multidisciplinary oncology pathways for value-based care: A review and the city of hope experience. *J Clin Med* 10:188, 2021
68. Beltran H, Hruszkewycz A, Scher HI, et al: The role of lineage plasticity in prostate cancer therapy resistance. *Clin Cancer Res* 25:6916-6924, 2019
69. Schaeffer EM, Srinivas S, Adra N, et al: NCCN Guidelines® Insights: Prostate cancer, version 3.2024. *J Natl Compr Canc Netw* 22:140-150, 2024
70. Mahal BA, Yang DD, Wang NQ, et al: Clinical and genomic characterization of low-prostate-specific antigen, high-grade prostate cancer. *Eur Urol* 74:146-154, 2018
71. Beltran H, Prandi D, Mosquera JM, et al: Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. *Nat Med* 22:298-305, 2016
72. Haffner MC, Morris MJ, Ding KC, et al: Framework for the pathology workup of metastatic castration-resistant prostate cancer biopsies. *Clin Cancer Res* 31:466-478, 2025
73. Yamada Y, Beltran H: Clinical and biological features of neuroendocrine prostate cancer. *Curr Oncol Rep* 23:15-10, 2021

74. Davies A, Zoubeidi A, Beltran H, et al: The transcriptional and epigenetic landscape of cancer cell lineage plasticity. *Cancer Discov* 13:1771-1788, 2023
 75. Bluemn EG, Coleman IM, Lucas JM, et al: Androgen receptor pathway-independent prostate cancer is sustained through FGF signaling. *Cancer cell* 32:474-489.e6, 2017
 76. Tang F, Xu D, Wang S, et al: Chromatin profiles classify castration-resistant prostate cancers suggesting therapeutic targets. *Science* 376:eabe1505, 2022
 77. Bakht MK, Yamada Y, Ku SY, et al: Landscape of prostate-specific membrane antigen heterogeneity and regulation in AR-positive and AR-negative metastatic prostate cancer. *Nat Cancer* 4:699-715, 2023
 78. Aparicio AM, Harzstark AL, Corn PG, et al: Platinum-based chemotherapy for variant castrate-resistant prostate cancer. *Clin Cancer Res* 19:3621-3630, 2013
 79. Corn PG, Heath EI, Zurita A, et al: Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: A randomised, open-label, phase 1–2 trial. *Lancet Oncol* 20:1432-1443, 2019
 80. Lee J-K, Lee J, Kim S, et al: Clonal history and genetic predictors of transformation into small-cell carcinomas from lung adenocarcinomas. *J Clin Oncol* 35:3065-3074, 2017
 81. Meyer H, Sunkara R, Rothmann E, et al: The use of lurbinectedin for the treatment of small cell and neuroendocrine carcinoma of the prostate. *Clin Genitourin Cancer* 22:102172, 2024
 82. Ahn M-J, Cho BC, Felip E, et al: Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med* 389:2063-2075, 2023
 83. Franceschini GM, Quaini O, Mizuno K, et al: Noninvasive detection of neuroendocrine prostate cancer through targeted cell-free DNA methylation. *Cancer Discov* 14:424-445, 2024
 84. Berchuck JE, Baca SC, McClure HM, et al: Detecting neuroendocrine prostate cancer through tissue-informed cell-free DNA methylation analysis. *Clin Cancer Res* 28:928-938, 2022
 85. Baca SC, Seo JH, Davidsohn MP, et al: Liquid biopsy epigenomic profiling for cancer subtyping. *Nat Med* 29:2737-2741, 2023
 86. Sipola J, Munzur AD, Kwan EM, et al: Plasma cell-free DNA chromatin immunoprecipitation profiling depicts phenotypic and clinical heterogeneity in advanced prostate cancer. *Cancer Res* 85:791-807, 2025
 87. Zhao SG, Sperger JM, Schehr JL, et al: A clinical-grade liquid biomarker detects neuroendocrine differentiation in prostate cancer. *J Clin Invest* 132:e161858, 2022
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Is Less More? Maximizing Outcomes by Tailoring Treatments to Patients: Oncofertility and Oncomenopause

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OVERVIEW

Notable advances have been made in improving survival outcomes in various cancers, but some have incurred undesirable costs and effects to patients with respect to fertility and menopause. Patients are living longer with cancer, and patient reported outcomes are influencing decision-making by individuals and their health care providers. It is essential to evaluate existing standards of care on an ongoing basis and prioritize quality of life and long-term survivorship, particularly for interventions in early-stage cancers and risk-reducing strategies that often yield long-term life expectancy.

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A CUT ABOVE: BETTER SURGERY, BETTER OUTCOMES

Transforming Cervical Cancer Surgery

Historically, treatment of gynecologic cancers in young individuals would almost always result in immediate loss of fertility and instantaneous menopause. This was true for most endometrial and ovarian cancers for which standard treatment included hysterectomy and bilateral salpingo-oophorectomy. For cervical cancer, radical hysterectomy was the standard of care for early-stage disease, and chemoradiotherapy was offered for locally advanced disease, both of which would end any chance of future fertility. Although radical hysterectomy cured many patients of cervical cancer, recently we have learned some humbling lessons about the radicality and subsequent aftermath of this intervention. Radical hysterectomy involves resection of the surrounding connective tissue around the cervix called the parametrium, and the upper portion of the vagina, to achieve a wide margin around the primary tumor.¹ Resection of parametrium and upper vagina requires dissection of the ureters, bladder, and bowel. There is greater risk of bleeding and injury to these structures. In addition, resecting the parametrium can cause denervation of the parasympathetics through the uterosacral ligaments. This results in bladder atony, which translates clinically into urinary retention.²⁻⁴ For some patients, this can be long term or even permanent. Removing the upper portion of the vagina shortens the length, and this can be associated with sexual dysfunction.^{5,6}

The Canadian Cancer Trials Group (CCTG) conducted an international Phase III randomized trial comparing simple hysterectomy with radical hysterectomy, both with lymph node assessment, for individuals with early-stage cervical cancer (CCTG CX.5, “SHAPE” for Simple Hysterectomy And Pelvic nodal Evaluation).⁷ The major difference between the

two surgical procedures is that the simple hysterectomy does not require resection of any parametrium or upper vagina. The rationale for this trial evolved after several retrospective reports demonstrated extremely low rates of parametrial invasion in patients with early-stage low-risk cervical cancer (<2 cm and <50% stromal invasion).⁸⁻¹³ Pelvic nodal assessment by sentinel node biopsy or full lymphadenectomy was still mandatory, as there is still a risk of nodal involvement even with small primary tumors. The primary outcome of the SHAPE trial was pelvic recurrence rate at 3 years, and the hypothesis was that simple hysterectomy was noninferior to radical hysterectomy with respect to this outcome. The study demonstrated that simple hysterectomy was indeed noninferior to radical hysterectomy in relation to the primary outcome (3-year recurrence rates of 2.52% and 2.17% for simple hysterectomy and radical hysterectomy, respectively).⁷ There was no difference in overall survival. However, there was a significant difference between simple hysterectomy and radical hysterectomy in regard to post-operative adverse events, notably urinary dysfunction. Urinary incontinence and retention rates persisting beyond 4 weeks in the simple hysterectomy and radical hysterectomy groups were 4.7% and 11.0% ($P = .003$), respectively, and 0.6% and 9.9% ($P < .0001$), respectively. Median ages in the SHAPE trial were 42 and 45 years for simple hysterectomy and radical hysterectomy, respectively. Oophorectomy is generally not required for cervical cancer in premenopausal individuals. There was no difference between the two surgical groups with respect to onset of menopause. In addition, there were lower rates of sexual dysfunction in those having simple hysterectomy compared with radical hysterectomy, with prolonged dysfunction up to 6 months associated with the latter ($P = .02$). Finally, global health status was significantly higher at 3 years in those having simple hysterectomy ($P = .025$).¹⁴ A cost-effectiveness analysis also demonstrated that simple hysterectomy is

PRACTICAL APPLICATIONS

- For early-stage low-risk cervical cancer, simple hysterectomy is noninferior to radical hysterectomy in terms of pelvic recurrence. Simple hysterectomy is associated with better sexual health and quality of life, and is less costly and more effective when quality of life is taken into consideration.
- Because there is no effective screening test for ovarian cancer, those at highest risk are advised to undergo risk-reducing bilateral salpingo-oophorectomy, which renders them menopausal at an early age. There are ongoing clinical trials evaluating a two-stage procedure in which salpingectomy is done first, followed by oophorectomy at a later age to delay onset of menopause.
- Effective management of menopausal symptoms after gynecologic cancer treatment can improve quality of life and reduce long-term adverse effects; however, menopausal hormone therapy (MHT) is underutilized in this patient population. There are many options for estrogen replacement, which should be tailored to the individual. If MHT is contraindicated, nonhormonal options are available, including nonpharmacologic approaches.
- Optimizing fertility in individuals with gynecologic cancer requires a multidisciplinary effort. Future directions include refining fertility preservation techniques such as cryopreservation of oocytes, embryos, and ovarian tissue, enhancing assisted reproductive technologies including earlier timing of protocols, third-party reproduction, gestational surrogacy, and adoption.

less costly and more effective in terms of quality-adjusted life expectancy gained, compared with radical hysterectomy.¹⁵ This landmark trial has transformed surgical treatment of early-stage cervical cancer. Simple hysterectomy is now being offered for early-stage disease that would have been previously treated by radical hysterectomy.

Revolutionizing Risk-Reducing Surgery for Hereditary Ovarian Cancer

For hereditary ovarian cancer attributed to a germline pathogenic variant in *BRCA1* or 2, or *RAD51C/D*, *BRIP1*, *PALB2*, the only intervention known to reduce the incidence and mortality from ovarian cancer is surgery to remove both ovaries and fallopian tubes (risk-reducing bilateral salpingo-oophorectomy [RRBSO]).^{16,17} However, this surgery is generally recommended to individuals between the age of 35 and 40 years for *BRCA1*, and 40–45 years for

BRCA2,¹⁸ and as a result they become prematurely menopausal. There are significant adverse health consequences of premature surgical menopause, such as vasomotor symptoms, urogenital atrophy, mood and sleep disorders, and long-term health risks including osteoporosis, coronary artery disease, and potential early cognitive decline.^{19,20} These effects can be mitigated by hormone replacement therapy (HRT), but the reality is that only a proportion of these individuals use HRT. There is still fear and misinformation that precludes routine use of HRT.²¹ Furthermore, HRT does not fully mitigate vasomotor symptoms.²⁰

Some occult cancers are diagnosed at the time of RRBSO. However, the majority of these occult cancers, which are high-grade serous carcinomas (HGSC), arise in the fallopian tube, not the ovary.^{22–25} A hypothesis evolved as a result of this observation. Because the fallopian tube is the site of origin of the majority of *BRCA*-associated HGSC, it is plausible that removing these organs at greatest risk (fallopian tubes) at an early age could prevent the majority of HGSC, without inducing instant premature surgical menopause by removing the ovaries. There is still benefit to removing the ovaries at some point closer to the age of natural menopause (around age 50 years) for two reasons: (1) there is still a risk of cancer arising primarily in the ovaries,^{22,26–28} and (2) removing the ovaries before natural menopause is associated with a decrease in breast cancer risk, likely attributed to a decrease in endogenous estrogen.^{29,30}

To our knowledge, there are no published data yet to date on the effectiveness of risk-reducing salpingectomy with delayed oophorectomy (two-stage procedure) compared with standard RRBSO for individuals with a *BRCA1/2* germline pathogenic variant. However, there are published studies that have modeled this comparison, as well as prospective trials evaluating the quality of life of these two risk-reducing strategies. A comparison of these two risk-reducing strategies was first modeled in a cost-effectiveness analysis in 2013, which demonstrated that the two-stage procedure was a cost-effective alternative to standard RRBSO when quality of life was taken into consideration.³¹ Although this was conducted in the context of the Canadian health care system, the conclusion was the same when American costs were applied. Similar results were subsequently published in the Netherlands,³² in which the absolute difference in ovarian cancer risk between the two risk-reducing strategies was estimated to be very small. These results prompted the development of two clinical trials. The first was the TUBA study (early salpingectomy [tubectomy] with delayed oophorectomy in *BRCA1/2* gene mutation carriers, ClinicalTrials.gov identifier: [NCT02321228](https://clinicaltrials.gov/ct2/show/study/NCT02321228)), which started accruing in 2015, and the second was the WISP trial: Women choosing Surgical Prevention, which started accruing in 2016 (ClinicalTrials.gov identifier: [NCT02760849](https://clinicaltrials.gov/ct2/show/study/NCT02760849)). Both studies were prospective nonrandomized trials that allowed participants to choose their risk-reducing intervention. Initial results of the TUBA trial demonstrated that patients have better quality of life after the two-stage

procedure, even if they use HRT after RRBSO.³³ Initial results of the WISP trial also demonstrated better sexual function and less menopausal symptoms associated with the two-stage procedure.³⁴ Similarly, those who had RRBSO but used HRT still had greater detriment in sexual function compared with those undergoing the two-stage surgical procedure.³⁵ The two trials are now combined into the TUBA WISP2 trial, which is designed to evaluate the incidence of tubal/ovarian cancer associated with the two risk-reducing strategies (ClinicalTrials.gov identifier: [NCT04294927](#)). The hypothesis is that the two-stage procedure is noninferior to standard RRBSO. It is anticipated that participant recruitment will be complete near the end of 2026, with primary outcomes available in 2036.

There are other prospective trials comparing the two-stage procedure to standard RRBSO. The SOROCK trial (comparing Salpingectomy to Salpingo-Oophorectomy to Reduce the risk of Ovarian Cancer) through NRG (NSABP, RTOG, and GOG) Oncology (ClinicalTrials.gov identifier: [NCT02451052](#)) allows individuals between the age of 35 and 50 years with a *BRCA1* germline pathogenic variant to choose between the two risk-reducing surgical procedures. This is also expected to be complete in 2036. The PROTECTOR trial (Preventing Ovarian Cancer through early Excision of Tubes and late Ovarian Removal) is a 3-arm prospective trial coordinated by Barts Cancer Institute and Queen Mary University of London. It allows participants to choose one of the following: (1) RRBSO; (2) two-stage procedure; or (3) no surgery (control). The targeted recruitment is 1,250 participants, with initial results expected in 2027.³⁶ The primary end point is sexual function according to validated questionnaires. The hypothesis is that the two-stage procedure is noninferior to control, and superior in terms of sexual and endocrine function compared with RRBSO.

Conclusion

In summary, a landmark trial called SHAPE has transformed surgical care for cervical cancer. For those with early-stage low-risk cervical cancer, de-escalation of surgery with simple hysterectomy is noninferior to radical hysterectomy in terms of pelvic recurrence. However, simple hysterectomy is associated with better sexual health and quality of life, and is less costly and more effective than radical hysterectomy when quality of life is taken into consideration. The WHO estimates over 600,000 new cases of cervical cancer annually worldwide.³⁷ Approximately half of those cases will be early stage, with a higher proportion of surgically resectable early-stage cancers in mid- to high-income countries where there is greater access to human papillomavirus vaccination, screening, and treatment.^{38–41} Therefore, thousands of individuals will benefit from less radical surgery for cervical cancer. For those with a hereditary predisposition to ovarian cancer, such as those with a *BRCA1/2* germline pathogenic variant, de-escalation of risk-reducing surgery accomplished by a two-stage strategy (salpingectomy and delayed oophorectomy) appears to be associated with improved

sexual health and quality of life compared with standard RRBSO. The effectiveness (incidence of cancer) of the two-stage strategy is being tested in the context of at least three prospective clinical trials. Individuals and their health care providers are strongly encouraged to consider enrollment in these clinical trials, in which eligibility criteria are standardized and data are collected systematically at specific time points. These clinical trials are pragmatic trials that evaluate real-life preferences and decisions made by participants, and they are the only way to prove that the two-stage strategy is safe for these individuals. Better surgery is not necessarily more surgery. If the hypothesis is correct and de-escalation of surgery can be routinely offered without compromising risk reduction, this will represent another milestone event in the history of cancer treatment and prevention.

MANAGING MENOPAUSE AFTER GYNECOLOGIC CANCER

Introduction

The burden of gynecologic cancers continues to rise, with more than 1.4 million new diagnoses and over 680,000 deaths worldwide in 2022.⁴² Around 40% of those with gynecologic cancers are premenopausal or perimenopausal at the time of diagnosis.⁴³ Combined multimodal therapy including surgery, chemotherapy, and/or radiation commonly induces menopause. Antiestrogen use in selected gynecologic cancers may lead to menopausal symptoms.⁴⁴ Greater access to genetic testing means that more women are identified with pathogenic variants that increase gynecologic cancer risk (such as *BRCA1/2* or Lynch syndrome). In *BRCA1/2* pathogenic variant carriers, National Comprehensive Cancer Network (NCCN) recommends RRBSO at age 35–45 years.⁴⁵ Although these interventions reduce cancer-related and overall mortality, surgical menopause commonly causes troublesome symptoms and may affect long-term bone, cardiovascular, and brain health.⁴⁶

Treatment advances in gynecologic cancer have resulted in longer survival but an increasing burden of treatment-associated outcomes such as early menopause, bone and cardiovascular disease, and reduced quality of life. These women are also at elevated risk of mental health problems,⁴⁷ which may be exacerbated by menopausal symptoms such as sleep disturbance to increase the risk of depression.⁴⁸

Many patients with gynecologic cancer are eligible to take estrogen-containing menopausal hormone therapy (MHT), benefiting from symptom relief and potentially long-term health benefits such as reduced fracture risk (Fig 1).⁴⁶

In women older than 40 years, MHT is primarily for the treatment of symptoms such as hot flashes and night sweats.⁴⁹ For those younger than 40 years, recent ESHRE guidelines advise routine use of MHT in those without contraindications.⁵⁰

In patients with breast cancer, vasomotor symptoms are the leading patient priority for symptom treatment.⁵¹ Symptoms may be more severe after cancer but most published research is in breast cancer, and the prevalence, nature, and severity of menopause symptoms after gynecologic cancer is poorly understood.⁵² In women at elevated risk of gynecologic cancer after RRBSO, rates of vasomotor symptoms, sexual dysfunction, disturbed mood, and disturbed sleep are common, and MHT reduces but does not resolve these symptoms.^{20,53-55}

Genitourinary symptoms such as vulvovaginal dryness and discomfort, pain with sex, irritation, and pain or discomfort when urinating are common after natural menopause.⁵⁶ A 2016 systematic review reported that 78% of patients with gynecologic cancer report sexual dysfunction.⁵⁷ The causes are often multifactorial and may include biological factors (menopause and pelvic radiation), psychological factors (depression and body image), interpersonal factors (relationship and communication issues), or sociocultural factors (religion or cultural).⁴⁶ ASCO recommends that health care providers should initiate a discussion about sexual problems with all patients with cancer and offer counseling and treatment as indicated.⁵⁸ Relatively little information is available about sexual function after gynecologic cancers, but pelvic radiation for cervical cancer may impair sexual function and cause pain during sexual activity.⁵⁹ Vaginal dilators are often recommended but evidence to support their efficacy is scant,⁶⁰ and many patients do not use them.⁵⁹ A 2024 meta-analysis indicated that around 40% of young adults report vaginal toxicity after chemoradiation, including up to 60% with vaginal stenosis.⁶¹ More information is needed about engaging patients to discuss sexual function after gynecologic cancer, prevention of treatment adverse effects such as vaginal stenosis, and effective treatments to manage these adverse effects.

Treatment for Menopausal Symptoms After Gynecologic Cancer

Effective management of menopausal symptoms after gynecologic cancer can improve quality of life and function, and potentially reduce long-term adverse effects of treatment and from induced menopause.⁴⁶ MHT may be underutilized in this population despite potential benefits for short-term and long-term health.⁴³

Menopausal Hormone Therapy

MHT is the most effective treatment for hot flashes and night sweats (vasomotor symptoms).⁶² Treating vasomotor symptoms can also improve mood and quality of life.⁶³ Less is known about the efficacy of MHT after cancer treatment, but may be contraindicated or avoided in some patients with gynecologic cancer (Fig 1). Available systemic estrogen treatments include oral or transdermal preparations. Since patients with cancer are at elevated risk of venous thromboembolic events (VTE), transdermal MHT may be safer.⁶⁴ Those with a uterus are still recommended to use combined

MHT despite pelvic radiation because of a theoretical risk of endometrial hyperplasia. Younger post-menopausal patients may prefer use of the combined oral contraceptive pill for their estrogen replacement. The optimum dose of estrogen after premature/early menopause is uncertain, but younger women may potentially require higher estrogen doses (100 µg transdermal/day) to optimize bone health.⁵⁰

The safety of hormonal treatments after gynecologic cancers depends significantly on the cancer type and histologic subtype (Table 1). MHT should be considered after epithelial ovarian cancer, early-stage endometrial cancer, and cervical cancer.⁴³ Cervical cancers are not considered hormone-dependent. Bodner et al⁶⁵ demonstrated that 39% of cervical adenocarcinomas are ER-positive, but hormone receptor status has not been linked to recurrence or prognosis. MHT may reduce symptoms and improve quality of life after cervical cancer.⁶⁶ MHT is not recommended in low-grade serous ovarian cancer, and certain advanced endometrial cancer, uterine sarcoma, and endometrioid carcinoma.⁴³ After RRBSO for *BRCA1/2* or Lynch syndrome in those without a personal history of breast cancer, MHT use for up to 7 years appears not to increase breast cancer risk in those with *BRCA1/2* pathogenic variants, although data are very limited.⁶⁷

A Cochrane review concluded there was insufficient evidence to conclude whether MHT is safe after endometrial cancer.⁶⁸ Decisions should be made in a multidisciplinary context balancing symptom burden and risk of recurrence. Uterine sarcomas may be hormone-dependent and may be managed with antiestrogen therapy, so MHT should be avoided in those cases. Use of MHT after ovarian cancer depends on histologic subtype (Table 1). In most cases, these recommendations are based on low-quality or moderate-quality evidence. Factors to be considered include symptom impact, hormone receptor status, optimizing use of endocrine therapy, and quality of evidence base.

Vaginal estrogen improves genitourinary symptoms associated with menopause, including vaginal dryness. A large range of products are available and there is a lack of comparative data demonstrating superiority of one product over another. Its efficacy in improving genitourinary symptoms of menopause in the gynecologic cancer population has not been established. Vaginal estrogen therapy is also an important consideration for patients who have undergone pelvic radiation or vault brachytherapy, where, along with vaginal dilators, its use is aimed at preventing vaginal stenosis. However, evidence demonstrating the efficacy of dilators in this context is lacking. Similarly, although vaginal estrogen is commonly recommended, there is little evidence to support efficacy.

Nonhormonal Treatments

When MHT is contraindicated, nonhormonal options are available for troublesome vasomotor symptoms. A recent Cochrane review found that oxybutynin was the most effective

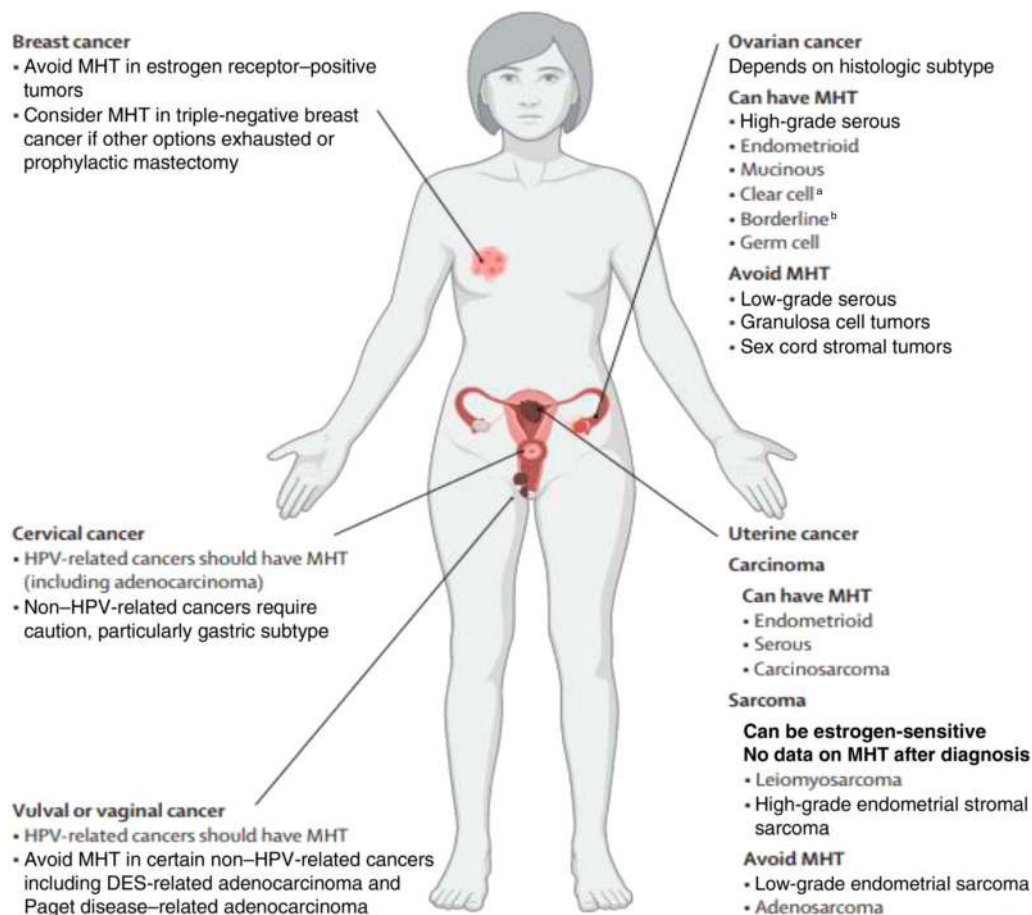


FIG 1. Use of MHT after female-specific cancers. ^aConsider transdermal due to increased venous thromboembolism risk. ^bFully resected, no invasive implants. DES, diethylstilbestrol; HPV, human papillomavirus; MHT, menopausal hormone therapy.

nonhormonal treatment, reducing both frequency and severity of hot flashes (−3.96 hot flashes per day). The neurokinin B antagonists were slightly less effective, mainly reducing frequency. Selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors and gabapentin had small effects, reducing the frequency of hot flashes by around −1.3 per day. Side effects were common with all preparations.

Nonpharmacologic approaches are also effective. Cognitive behavior therapy has the strongest evidence base for vasomotor, sleep disturbance, and depressive symptoms.⁶⁹ Acupuncture is of uncertain benefit but may improve fatigue and joint pains.⁷⁰ Yoga, relaxation, and mindfulness-based stress reduction can improve sleep and reduce stress after breast cancer.⁷¹

Multidisciplinary Care for Menopause After Cancer

Optimal cancer care includes a multidisciplinary team, evidence-based practice, and optimal models for service delivery. Tertiary-based care is unlikely to meet the needs of the growing number of cancer survivors. In Australia, the multidisciplinary menopausal service after cancer (MSAC) is

delivered by specialists (gynecology, endocrinology) and primary providers, together with allied health professionals.⁷² The service manages vasomotor, genitourinary, sleep and mood disturbances, and sexual dysfunction across cancer types and in one place. A 2021 study showed significant improvements in the four most troublesome menopausal symptoms for patients with cancer (hot flashes, fatigue, sleep difficulties, and low libido) in patients managed through MSAC versus usual care.⁷³ After breast cancer, patients managed by MSAC were more likely to adhere to endocrine therapy.⁷⁴ Clear guidelines have been developed to manage menopausal symptoms after different cancers. For *BRCA1/2* patients undergoing RRBSO, information resources about surgical menopause have been developed based on unmet information needs.⁷⁵ To make MSAC services accessible and reduce the burden of hospital appointments, video telehealth services are available and popular with patients and health care providers.⁷⁶

Conclusion

The growing global burden of gynecologic cancers is increasing the impact of treatment-induced menopause and

TABLE 1. Summary of MHT Recommendations in Ovarian Cancer by Histologic Subtype

Cancer Type	Histologic Subtype	MHT Recommendation	Level of Evidence
Ovarian cancer	High-grade serous	Appropriate if indicated	Meta-analyses; epithelial ovarian cancers
	Low-grade serous	Avoid; hormone receptor expression and maintenance antineoplastic therapy	Observational data
	Endometrioid	Consider if indicated	Retrospective cohort data
	Clear cell	Avoid systemic MHT because of increased risk of VTE. Local MHT unclear	RCT, but not specifically in cancer population
	Mucinous	Appropriate if indicated	Meta-analyses; epithelial ovarian cancers
	Germ cell	Appropriate if indicated	No clinical evidence of harm
	Sex cord stromal	Not advised; hormone-dependent, indolent course, late recurrence	No targeted clinical evidence
	Borderline	Appropriate if completely resected disease, that is, no invasive implants	No targeted clinical evidence
Cervical cancer		Appropriate if indicated	Retrospective cohort data
Endometrial cancer		Consider in early-stage disease if indicated	Largely observational in early-stage disease only
Uterine sarcoma		Avoid if hormone receptor expression	No targeted clinical evidence
Vaginal and vulvar cancer		Appropriate if indicated	No clinical evidence of harm

Abbreviations: MHT, menopausal hormone therapy; RCT, randomized controlled trial; VTE, venous thromboembolic events.

troublesome menopausal symptoms. To optimize quality of life, and prognosis where severe symptoms threaten early cessation of endocrine therapy, individualized and patient-focused decision making should occur in a multidisciplinary context. Management should be tailored to the individual, taking into account age, cancer type, time since diagnosis, quality of life, comorbidities (eg, VTE), risk factors for chronic disease (eg, osteoporosis), views, and preferences⁴⁶. Health disparities make cervical cancer a leading cause of morbidity and mortality in low- and middle-income countries (LMIC). Prospective studies report that young age and late cancer stage at diagnosis, low education and health literacy, financial hardship, and inadequate availability of supportive care lead to greater distress in LMIC survivors.⁷⁷

NAVIGATING FERTILITY IN WOMEN WITH GYNECOLOGIC CANCER

Introduction

Gynecologic cancers, including cervical, ovarian, and endometrial cancers, affect thousands of reproductive-age women globally each year.⁷⁸ Advances in early detection and treatment have transformed gynecologic cancer from a terminal diagnosis to a survivable condition.⁷⁹ However, standard treatment approaches—surgery, chemotherapy, and radiation—often compromise fertility, causing emotional and psychological burdens for women desiring

biological children.⁸⁰ Oncologists face difficult decisions on how to balance desire for future fertility with optimal cancer outcomes.^{81,82} Viable fertility preservation (FP) strategies exist, including fertility-sparing surgery and assisted reproductive technology (ART), which can be considered without compromising oncologic outcomes.⁸⁰ This section offers a concise overview highlighting critical topics in reproductive health and FP faced by women with gynecologic cancer.

Addressing Fertility in Women With Gynecologic Cancer

Fertility is a priority concern for many women with gynecologic cancer, and the emotional toll of infertility—including grief, depression, and lower quality of life—is well documented.^{83,84} This highlights the need for FP to be addressed as part of comprehensive, patient-centered cancer care. Organizations including the American Society of Reproductive Medicine and ASCO encourage oncologists to communicate the risks of gonadotoxic therapy, discuss options for FP, and refer patients to reproductive specialists early in the course of treatment planning.⁸⁵ Unfortunately, studies suggest that many patients are uninformed about their options, leading to regret and dissatisfaction.^{86–88}

Socioeconomic and racial disparities also limit access to FP services, highlighting the need for interventions ensuring equitable access to care.⁸⁹ Women living far from gynecologic oncology or fertility clinics have been found to have

decreased odds of undergoing fertility-sparing treatment (FST).⁹⁰ Additionally, 5.7% of reproductive-age women in the United States lack geographic access to oncofertility centers, especially in the Mountain West and West North Central regions.⁹¹ This is further compounded by the absence of FP insurance mandates in certain states.⁹¹

The REI Physician's Role in Fertility Optimization

Reproductive endocrinology and infertility (REI) specialists play a pivotal role in optimizing fertility for women with gynecologic cancer through planning and coordinating multidisciplinary care. REI specialists offer procedures to preserve gametes, oocytes, or gonadal tissue before treatment and can also assist cancer survivors with using preserved gametes or tissue after treatment.⁹² Counseling and comprehensive evaluation help determine reproductive potential, the feasibility of FP, and strategies for family building (Table 2).

FP Options for Women With Gynecologic Cancer

In addition to fertility-sparing therapies for early gynecologic cancers (see Table 3), other FP strategies include

- **Oocyte cryopreservation:** Controlled ovarian stimulation and oocyte retrieval are followed by cryopreservation of harvested oocytes. Frozen oocytes can later be thawed and fertilized to create embryos. This method suits individuals who do not have a male partner, do not wish to cryopreserve embryos, and prioritize reproductive autonomy.
- **Embryo cryopreservation:** Ovarian stimulation and oocyte retrieval are followed by in vitro fertilization (IVF) of retrieved oocytes using sperm to create embryos, which are cryopreserved for future use.
- **Ovarian tissue cryopreservation:** Ovarian tissue, containing immature oocytes, is surgically removed and cryopreserved, then potentially reimplanted later to restore hormonal function. There is potential concern that this method could reintroduce malignancy during transplantation.⁹⁸ This is the only option appropriate for prepubertal females.
- **Ovarian suppression:** The use of gonadotropin-releasing hormone (GnRH) agonists during chemotherapy may offer protective benefits against treatment-induced ovarian damage, although their efficacy remains debated.^{99,100}
- **Ovarian transposition:** The ovaries are surgically repositioned away from the field of radiation with the goal of preserving fertility and hormonal function in patients undergoing pelvic radiotherapy.

ART-Specific Considerations

FP requires tailored strategies that align with oncologic timelines. REI specialists can preserve fertility without interfering with life-saving oncologic treatments, ensuring safety while optimizing outcomes.

TABLE 2. REI Physician's Workup and Role in Fertility Optimization

Evaluation Domain	Details/Considerations
Ovarian reserve testing	AMH, FSH, and antral follicle count via ultrasound estimate ovarian reserve and reproductive potential
Pelvic ultrasound	Confirm ovarian accessibility and rule out obstructive pathology before proceeding with transvaginal or abdominal aspiration. Uterine anatomy assessment is also important if the patient intends to carry the pregnancy
Genetic evaluation	Refer to genetic counseling if hereditary syndrome present and consider PGT-M to inform family planning while minimizing hereditary risks ⁹²
Fertility risk assessment	Identify issues such as endometriosis, ovulatory dysfunction, or diminished ovarian reserve
Individualized counseling	Review realistic chances of success based on age, diagnosis, and ovarian reserve
Expectation setting	Clarify that FP does not guarantee success, and explain risks, benefits, and timeline
Post-treatment planning	Coordinate with MFM for pregnancy planning, especially after trachelectomy
Multidisciplinary care	Ensure communication among oncologists, REI specialists, and supportive care teams to address fertility, hormonal health, and survivorship planning

Abbreviations: AMH, anti-Müllerian hormone; FP, fertility preservation; FSH, follicle-stimulating hormone; MFM, maternal-fetal medicine; PGT-M, preimplantation genetic testing for monogenic conditions; REI, reproductive endocrinology and infertility.

- **Hormone-sensitive cancers:** Aromatase inhibitors can be used during stimulation to suppress estrogen levels, lowering exposure for hormone-sensitive tumors without compromising ART outcomes.^{101,102}
- **Random start IVF:** Unlike conventional IVF protocols, random start IVF begins at any point in the menstrual cycle, avoiding treatment delays. Outcomes are comparable with traditional IVF.^{103,104}
- **Back-to-back stimulation (DuoStim):** Double ovarian stimulation within one menstrual cycle, during the follicular and luteal phases, maximizes oocyte yield in a shortened period for patients needing urgent treatment.¹⁰⁵
- **Trigger selection:** GnRH agonist triggers reduce the risk of ovarian hyperstimulation syndrome, a potentially life-threatening complication of ART that could delay cancer treatment. GnRH agonist triggers are associated with increased mature oocytes and embryos in patients with cancer undergoing FP.¹⁰⁶

TABLE 3. Comparison of Standard Versus Fertility-Sparing Treatment Options in Gynecologic Cancers

Cancer Type	Standard-of-Care Treatment	Fertility-Sparing Treatment Options	NCCN Recommendations	Special Considerations
Cervical	Radical or simple hysterectomy with pelvic nodal assessment ^{7,93} Chemoradiotherapy for advanced-stage disease	Cervical conization Trachelectomy Neoadjuvant chemotherapy	FST considered for early-stage disease ⁹³	FST often not feasible in advanced stages because of need for chemoradiotherapy causing ovarian failure and uterine damage
Ovarian	Bilateral salpingo-oophorectomy with hysterectomy for advanced-stage disease	Preservation of uterus and one ovary for unilateral lesions Uterine preservation for bilateral lesions	FST considered in stage I epithelial ovarian carcinoma with low-risk histologic subtypes (eg, serous, mucinous) ⁹⁴	FST typically limited to low-risk stage I cases No compromise in survival with FST ^{95,96}
Uterine	Hysterectomy with or without bilateral salpingo-oophorectomy, depending on stage and grade	Progestin-based therapy for grade 1, stage IA (noninvasive) endometrioid adenocarcinoma	Progestin-based therapy for early-stage, low-grade cases only FST not recommended for high-risk histologic types	High response rates (82.8% complete remission) for early-stage cases treated with progestins FST supported by ACOG for atypical hyperplasia ⁹⁷

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; FST, fertility-sparing treatment; NCCN, National Comprehensive Cancer Network.

Family-Building Strategies

- **Natural conception:** Survivors with retained reproductive function may conceive naturally. Success depends on cancer type, treatment, age, and ovarian reserve.
- **Use of preserved oocytes or embryos:** Cryopreserved oocytes can be warmed and fertilized via IVF. Frozen embryos can be warmed and transferred into the uterus, offering high success rates depending on maternal age and embryo quality.
- **Third-party reproduction:** Eggs, sperm, or embryos can be obtained from a known or unknown donor.
- **Gestational surrogacy:** Some patients are unable to carry a pregnancy because of uterine pathology or other health concerns. Embryos can be created via IVF using the intended parent's (or donor's) gametes and implanted into a gestational carrier, offering a path to parenthood without the associated pregnancy risks.
- **Adoption:** Survivors can achieve parenthood without relying on their fertility or reproductive health.

Emerging FP strategies include in vitro activation, in vitro maturation, artificial ovary development, uterine transposition, and uterine transplantation.¹⁰⁷ Among these, uterine transplantation has become increasingly accessible, although is still offered at only a few centers worldwide. A recent review suggests that individuals with a history of gynecologic cancer may be considered candidates for transplantation.¹⁰⁸ However, challenges persist, including the need for immunosuppression, increased likelihood of vascular and anastomotic complications after previous surgeries, and the presence of irradiated or fibrotic pelvic tissues.¹⁰⁹

Fertility and Obstetrical Outcomes in Women With Gynecologic Cancer

Chemotherapy and radiation negatively affect reproductive function, leading to depletion of primordial follicles, menstrual irregularities, anatomic or vascular changes to pelvic

organs, abnormal development of secondary sexual characteristics, premature menopause, and infertility.¹¹⁰ Obstetrical outcomes after FP depend on cancer stage, treatment, and preservation strategy.

Cervical Cancer

- Radical trachelectomy may cause cervical stenosis (approximately 10.5% incidence¹¹¹), and approximately 15% of women attempting conception after radical trachelectomy require cervical dilation,¹¹² although this procedure may become less common, given the SHAPE trial and the evidence for less radical therapy.⁷
- Reported reproductive outcomes after FST vary widely across studies. One study found a pregnancy rate of 62.5%, with 61.9% of pregnancies conceived naturally, and a live birth rate of 75%.¹¹³
- Pregnancy complications include high rates of preterm delivery (29%–32%) and second-trimester loss (5.8%).¹⁰⁹
- Patients with advanced disease may require ART and gestational surrogacy.¹¹³

Ovarian Cancer

- Data on post-FST fertility for early-stage epithelial ovarian cancer or low-risk histologies remain limited. Most studies are small case series, often focusing on patients who achieved spontaneous conception, overlooking those who may have required ART.
- One study found no increase in adverse neonatal outcomes among patients who conceived ≥ 3 months after FST compared with matched controls.¹¹⁴
- Patients who undergo unilateral salpingo-oophorectomy and defer FP until after treatment may still be eligible for FP after treatment, depending on exposure to gonadotoxic chemotherapy and ovarian reserve.
- Patients who preserved their uterus after bilateral salpingo-oophorectomy require donor oocytes unless

autologous oocytes were cryopreserved. If autologous oocytes were cryopreserved, they may carry the pregnancy themselves.

- Many patients achieve pregnancy through ART, likely because of comorbidities such as obesity, which is closely linked with infertility.^{116,117} ART has not been shown to increase risk of cancer recurrence.¹¹⁷

Uterine Cancer and Atypical Hyperplasia

- Successful pregnancies are possible after FST but are associated with higher obstetric risks.
- NCCN recommends pregnancy only after achieving and maintaining remission, with endometrial sampling every 3–6 months.¹¹⁵
- Live birth rate after progestin therapy is approximately 62%, although it is associated with higher rates of labor induction, cesarean delivery, and maternal complications such as gestational diabetes and postpartum hemorrhage compared with the general population.¹¹⁶

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REFERENCES

1. Drouin E, Classe JM, Hautecoeur P: 125 years of the Wertheim operation. What next? *J Med Life* 16:341-343, 2023
2. Zullo MA, Mancini N, Angioli R, et al: Vesical dysfunctions after radical hysterectomy for cervical cancer: A critical review. *Crit Rev Oncol Hematol* 48:287-293, 2003
3. Kadar N, Saliba N, Nelson JH: The frequency, causes and prevention of severe urinary dysfunction after radical hysterectomy. *Br J Obstet Gynaecol* 90:858-863, 1983
4. Low JA, Mauger GM, Carmichael JA: The effect of Wertheim hysterectomy upon bladder and urethral function. *Am J Obstet Gynecol* 139:826-834, 1981
5. Jensen PT, Groenvold M, Klee MC, et al: Early-stage cervical carcinoma, radical hysterectomy, and sexual function. A longitudinal study. *Cancer* 100:97-106, 2004
6. Vrzackova P, Weiss P, Cibula D: Sexual morbidity following radical hysterectomy for cervical cancer. *Expert Rev Anticancer Ther* 10:1037-1042, 2010
7. Plante M, Kwon JS, Ferguson S, et al: Simple versus radical hysterectomy in women with low-risk cervical cancer. *N Engl J Med* 390:819-829, 2024
8. Wright JD, Grigsby PW, Brooks R, et al: Utility of parametrectomy for early stage cervical cancer treated with radical hysterectomy. *Cancer* 110:1281-1286, 2007
9. Stegeman M, Louwen M, van der Velden J, et al: The incidence of parametrial tumor involvement in select patients with early cervix cancer is too low to justify parametrectomy. *Gynecol Oncol* 105:475-480, 2007
10. Steed H, Capstick V, Schepansky A, et al: Early cervical cancer and parametrial involvement: Is it significant? *Gynecol Oncol* 103:53-57, 2006
11. Kinney WK, Hodge DO, Egorshin EV, et al: Identification of a low-risk subset of patients with stage IB invasive squamous cancer of the cervix possibly suited to less radical surgical treatment. *Gynecol Oncol* 57:3-6, 1995
12. Frumovitz M, Sun CC, Schmeler KM, et al: Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. *Obstet Gynecol* 114:93-99, 2009
13. Covens A, Rosen B, Murphy J, et al: How important is removal of the parametrium at surgery for carcinoma of the cervix? *Gynecol Oncol* 84:145-149, 2002
14. Ferguson SE, Brotto LA, Kwon J, et al: Sexual health and quality of life in patients with low-risk early-stage cervical cancer: Results from GCIG/CCTG CX.5/SHAPE trial comparing simple versus radical hysterectomy. *J Clin Oncol* 43:167-179, 2025
15. Kwon JS, McTaggart-Cowan H, Ferguson SE, et al: Cost-effectiveness analysis of simple hysterectomy compared to radical hysterectomy for early cervical cancer: Analysis from the GCIG/CCTG CX.5/SHAPE trial. *J Gynecol Oncol* 35:e117, 2024
16. Kauff ND, Satagopan JM, Robson ME, et al: Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 346:1609-1615, 2002
17. Rebbeck TR, Lynch HT, Neuhausen SL, et al: Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med* 346:1616-1622, 2002
18. NCCN.org: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. 2025. Version 2.2025. <https://www.nccn.org>
19. Parker WH, Feskanich D, Broder MS, et al: Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. *Obstet Gynecol* 121:709-716, 2013
20. Hickey M, Moss KM, Krejany EO, et al: What happens after menopause? (WHAM): A prospective controlled study of sleep quality up to 12 months after premenopausal risk-reducing salpingo-oophorectomy. *Gynecol Oncol* 162:447-453, 2021
21. Armon S, Miron-Shatz T, Mor P, et al: BRCA carriers after risk-reducing bilateral salpingo-oophorectomy: Menopausal hormone therapy knowledge gaps, and the impact of physicians' recommendations. *Climacteric* 26:154-160, 2023
22. Powell CB, Chen LM, McLennan J, et al: Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: Experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. *Int J Gynecol Cancer* 21:846-851, 2011
23. Reitsma W, de Bock GH, Oosterwijk JC, et al: Support of the 'fallopian tube hypothesis' in a prospective series of risk-reducing salpingo-oophorectomy specimens. *Eur J Cancer* 49:132-141, 2013

Conclusion

Improved cancer detection and treatment have increased survivorship in reproductive-age patients, making fertility an increasingly important component of comprehensive cancer care. Integrating fertility counseling and services into cancer care improves survivors' quality of life and broadens their family-building options. Continued research, advocacy, and education are essential to overcome barriers and ensure equitable access to these services for all patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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24. Stewart ME, Knisely AT, Sullivan MW, et al: Evaluation of screening and risk-reducing surgery for women followed in a high-risk breast/ovarian cancer clinic: It is all about the tubes in BRCA mutation carriers. *Gynecol Oncol Rep* 28:18-22, 2019
25. Piedimonte S, Frank C, Laprise C, et al: Occult tubal carcinoma after risk-reducing salpingo-oophorectomy: A systematic review. *Obstet Gynecol* 135:498-508, 2020
26. Manchanda R, Abdelrahim A, Johnson M, et al: Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. *BJOG* 118:814-824, 2011
27. Finch A, Beiner M, Lubinski J, et al: Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. *JAMA* 296:185-192, 2006
28. Domchek SM, Friebel TM, Garber JE, et al: Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. *Breast Cancer Res Treat* 124:195-203, 2010
29. Choi YH, Terry MB, Daly MB, et al: Association of risk-reducing salpingo-oophorectomy with breast cancer risk in women with BRCA1 and BRCA2 pathogenic variants. *JAMA Oncol* 7:585-592, 2021
30. Domchek SM, Friebel TM, Singer CF, et al: Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 304:967-975, 2010
31. Kwon JS, Tinker A, Pansegrau G, et al: Prophylactic salpingectomy and delayed oophorectomy as an alternative for BRCA mutation carriers. *Obstet Gynecol* 121:14-24, 2013
32. Harmsen MG, Int'Hout J, Arts-de Jong M, et al: Salpingectomy with delayed oophorectomy in BRCA1/2 mutation carriers: Estimating ovarian cancer risk. *Obstet Gynecol* 127:1054-1063, 2016
33. Steenbeek MP, Harmsen MG, Hoogerbrugge N, et al: Association of salpingectomy with delayed oophorectomy versus salpingo-oophorectomy with quality of life in BRCA1/2 pathogenic variant carriers: A nonrandomized controlled trial. *JAMA Oncol* 7:1203-1212, 2021
34. Lu KH, Nebgen DR, Norquist B, et al: WISP: A prospective multi-center trial of salpingectomy with delayed oophorectomy versus risk reducing salpingo-oophorectomy in women at increased risk for hereditary ovarian cancer. *Gynecol Oncol* 154:22, 2019. Society of Gynecologic Oncology 50th Annual Meeting; Honolulu, HI
35. Norquist B, Nebgen DR, Roche KL, et al: Sexual function and menopausal symptoms among patients at high risk of ovarian carcinoma undergoing interval salpingectomy or risk-reducing salpingo-oophorectomy in the prospective multicenter WISP trial. *Gynecol Oncol* 190:S25-S26, 2024
36. Gaba F, Robbani S, Singh N, et al: Preventing ovarian cancer through early excision of tubes and late ovarian removal (PROTECTOR): Protocol for a prospective non-randomised multi-center trial. *Int J Gynecol Cancer* 31:286-291, 2021
37. Singh D, Vignat J, Lorenzoni V, et al: Global estimates of incidence and mortality of cervical cancer in 2020: A baseline analysis of the WHO global cervical cancer elimination initiative. *Lancet Glob Health* 11:e197-e206, 2023
38. Cervical cancer statistics. 2024. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer#heading-Zero>
39. Society CC: Canadian Cancer Statistics. 2023
40. NHS Cervical Screening Programme Audit of invasive cervical cancer: National report 1 April 2016 to 31 March 2019. 2023. <https://www.gov.uk/government/publications/cervical-screening-invasive-cervical-cancer-audit-2016-to-2019/nhs-cervical-screening-programme-audit-of-invasive-cervical-cancer-national-report-1-april-2016-to-31-march-2019#figo-stage-of-invasive-cervical-cancers>
41. Stage Distribution (%) of New Cancer Cases, All Ages, All Races and Ethnicities, Cervix, United States, 2016-2020. 2024. <https://gis.cdc.gov/Cancer/USCS/#/StageatDiagnosis/>
42. Zhu B, Gu H, Mao Z, et al: Global burden of gynaecological cancers in 2022 and projections to 2050. *J Glob Health* 14:04155, 2024
43. Sinno AK, Pinkerton J, Febraro T, et al: Hormone therapy (HT) in women with gynecologic cancers and in women at high risk for developing a gynecologic cancer: A Society of Gynecologic Oncology (SGO) clinical practice statement: This practice statement has been endorsed by the North American menopause Society. *Gynecol Oncol* 157:303-306, 2020
44. Bell SG, Dalton L, McNeish BL, et al: Aromatase inhibitor use, side effects and discontinuation rates in gynecologic oncology patients. *Gynecol Oncol* 159:509-514, 2020
45. Daly MB, Pal T, Berry MP, et al: Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 19:77-102, 2021
46. Hickey M, Basu P, Sassarini J, et al: Managing menopause after cancer. *Lancet (London, England)* 403:984-996, 2024
47. Shang HX, Ning WT, Sun JF, et al: Investigation of the quality of life, mental status in patients with gynecological cancer and its influencing factors. *World J Psychiatry* 14:1053-1061, 2024
48. Chung HF, Pandeya N, Dobson AJ, et al: The role of sleep difficulties in the vasomotor menopausal symptoms and depressed mood relationships: An international pooled analysis of eight studies in the InterLACE consortium. *Psychol Med* 48:2550-2561, 2018
49. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel: The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause* 24:728-753, 2017
50. Panay N, Anderson RA, Bennie A, et al: Evidence-based guideline: Premature ovarian insufficiency. *Hum Reprod Open* 2024:hoae065, 2024
51. Lan Q, Hickey M, Peate M, et al: Priorities for alleviating menopausal symptoms after cancer. *Menopause* 30:136-142, 2023
52. Brennan A, Brennan D, Rees M, et al: Management of menopausal symptoms and ovarian function preservation in women with gynecological cancer. *Int J Gynecol Cancer* 31:352-359, 2021
53. Islam RM, Davis SR, Bell RJ, et al: A prospective controlled study of sexual function and sexually related personal distress up to 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy. *Menopause* 28:748-755, 2021
54. Hickey M, Trainer AH, Krejany EO, et al: What happens after menopause? (WHAM): A prospective controlled study of vasomotor symptoms and menopause-related quality of life 24 months after premenopausal risk-reducing salpingo-oophorectomy (RRSO). *Gynecol Oncol* 191:201-211, 2024
55. Hickey M, Moss KM, Brand A, et al: What happens after menopause? (WHAM): A prospective controlled study of depression and anxiety up to 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy. *Gynecol Oncol* 161:527-534, 2021
56. Lensen S, Bell RJ, Carpenter JS, et al: A core outcome set for genitourinary symptoms associated with menopause: The COMMA (core outcomes in menopause) global initiative. *Menopause* 28:859-866, 2021
57. Maiorino MI, Chiodini P, Bellastella G, et al: Sexual dysfunction in women with cancer: A systematic review with meta-analysis of studies using the female sexual function index. *Endocrine* 54:329-341, 2016
58. Carter J, Laccchetti C, Andersen BL, et al: Interventions to address sexual problems in people with cancer: American Society of Clinical Oncology clinical practice guideline adaptation of Cancer Care Ontario Guideline. *J Clin Oncol* 36:492-511, 2018
59. Suvaal I, Hummel SB, Mens JWM, et al: A sexual rehabilitation intervention for women with gynaecological cancer receiving radiotherapy (SPARC study): Design of a multicentre randomized controlled trial. *BMC Cancer* 21:1295, 2021
60. Miles T, Johnson N: Vaginal dilator therapy for women receiving pelvic radiotherapy. *Cochrane Database Syst Rev* 2014:Cd007291, 2014
61. Raj S, Prasad RR, Ranjan A: Incidence of vaginal toxicities following definitive chemoradiation in intact cervical cancer: A meta-analysis. *J Contemp Brachytherapy* 16:241-256, 2024
62. Sarri G, Davies M, Lumsden MA, et al: Diagnosis and management of menopause: Summary of NICE guidance. *BMJ* 351:h5746, 2015
63. Savolainen-Peltonen H, Hautamäki H, Tuomikoski P, et al: Health-related quality of life in women with or without hot flashes: A randomized placebo-controlled trial with hormone therapy. *Menopause* 21:732-739, 2014
64. Rovinski D, Ramos RB, Figuera TM, et al: Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: A systematic review and meta-analysis. *Thromb Res* 168:83-95, 2018
65. Bodner K, Laubichler P, Kimberger O, et al: Oestrogen and progesterone receptor expression in patients with adenocarcinoma of the uterine cervix and correlation with various clinicopathological parameters. *Anticancer Res* 30:1341-1345, 2010
66. Ploch E: Hormonal replacement therapy in patients after cervical cancer treatment. *Gynecol Oncol* 26:169-177, 1987
67. Nebgen DR, Domchek SM, Kotsopoulos J, et al: Care after premenopausal risk-reducing salpingo-oophorectomy in high-risk women: Scoping review and international consensus recommendations. *BJOG* 130:1437-1450, 2023
68. Edey KA, Rundle S, Hickey M: Hormone replacement therapy for women previously treated for endometrial cancer. *Cochrane Database Syst Rev* 5:Cd008830, 2018
69. Hunter MS: Cognitive behavioral therapy for menopausal symptoms. *Climacteric* 24:51-56, 2021
70. Mao JJ, Farrar JT, Bruner D, et al: Electroacupuncture for fatigue, sleep, and psychological distress in breast cancer patients with aromatase inhibitor-related arthralgia: A randomized trial. *Cancer* 120:3744-3751, 2014
71. Würtzen H, Dalton SO, Elsass P, et al: Mindfulness significantly reduces self-reported levels of anxiety and depression: Results of a randomised controlled trial among 336 Danish women treated for stage I-III breast cancer. *Eur J Cancer* 49:1365-1373, 2013
72. Hickey M, Emery LI, Gregson J, et al: The multidisciplinary management of menopausal symptoms after breast cancer: A unique model of care. *Menopause* 17:727-733, 2010
73. Hollingworth J, Walsh L, Tran S, et al: Does a multidisciplinary menopausal symptoms after cancer clinic reduce symptoms? *Support Care Cancer* 30:2245-2252, 2022
74. Martin H, Saunders C, Redfern A, et al: A dedicated menopausal after cancer clinic may improve adherence to endocrine therapy for breast cancer: A population based study. *Clin Breast Cancer* 24:e731-e736, 2024
75. Hickey M, Rio I: Considering Surgery to Reduce Your Risk of Ovarian Cancer: A Guide for Patients. The Royal Women's Hospital, 2019. <https://www.thewomens.org.au/health-information/womens-cancers-pre-cancers/ovarian-cancer>
76. Rachagan N, Szabo RA, Rio I, et al: Video telehealth to manage menopausal symptoms after cancer: A prospective study of clinicians and patient satisfaction. *Menopause* 30:143-148, 2023

77. ACTION Study Group, Jan S, Peters SAE, et al: Health-related quality of life and psychological distress among cancer survivors in Southeast Asia: Results from a longitudinal study in eight low- and middle-income countries. *BMC Med* 15:10, 2017
78. Liang Y, Dai X, Chen J, et al: Global burden and trends in pre- and post-menopausal gynecological cancer from 1990 to 2019, with projections to 2040: A cross-sectional study. *Int J Surg (London, England)* 111:891-903, 2025
79. Bodriagova O, Previs RA, Gaba L, et al: Recent advances in gynecological malignancies: Focus on ASCO 2023. *Oncol Ther* 11:397-409, 2023
80. Chan JL, Wang ET: Oncofertility for women with gynecologic malignancies. *Gynecol Oncol* 144:631-636, 2017
81. Aviki EM, Abu-Rustum NR: A call to standardize our approach to fertility-sparing surgery in patients with gynecologic cancers. *Gynecol Oncol* 147:491-492, 2017
82. Zhao Y, Zhang X, Zubizarreta ME, et al: A survey study reveals the positive impact of oncofertility knowledge and attitude on oncofertility practice among oncologists in China. *J Adolesc Young Adult Oncol* 10:606-613, 2021
83. Gorman JR, Su H, Roberts SC, et al: Experiencing reproductive concerns as a female cancer survivor is associated with depression. *Cancer* 121:935-942, 2015
84. Wenzel L, Dogan-Ates A, Habbal R, et al: Defining and measuring reproductive concerns of female cancer survivors. *J Natl Cancer Inst Monogr* 2005:94-98, 2005
85. Su H, Lacchetti C, Letourneau J, et al: Erratum: Fertility preservation in people with cancer: ASCO guideline update. *J Clin Oncol* 10.1200/JCO-25-00662 [epub ahead of print on April 16, 2025]
86. Glazer TS, Schulte F: Barriers to oncofertility care among female adolescent cancer patients in Canada. *Curr Oncol* 29:1583-1593, 2022
87. Grossman Becht LC, Forman EJ: Navigating the complex challenges of fertility preservation. *Fertil Steril* 109:252-253, 2018
88. Shnorhavorian M, Harlan LC, Smith AW, et al: Fertility preservation knowledge, counseling, and actions among adolescent and young adult patients with cancer: A population-based study. *Cancer* 121:3499-3506, 2015
89. Letourneau JM, Smith JF, Ebbel EE, et al: Racial, socioeconomic, and demographic disparities in access to fertility preservation in young women diagnosed with cancer. *Cancer* 118:4579-4588, 2012
90. Kanbergs A, Jorgensen K, Agusti N, et al: Patient location and disparities in access to fertility preservation for women with gynecologic or breast cancer. *Obstet Gynecol* 143:824-834, 2024
91. Peipert BJ, Potapragada NR, Lantos PM, et al: A geospatial analysis of disparities in access to oncofertility services. *JAMA Oncol* 9:1364-1370, 2023
92. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org: Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: A committee opinion. *Fertil Steril* 112:1022-1033, 2019
93. Cohen PA, Jhingran A, Oaknin A, et al: Cervical cancer. *Lancet (London, England)* 393:169-182, 2019
94. Song BB, Anderson ZS, Masjedi AD, et al: Fertility-sparing surgery for stage I epithelial ovarian cancer. *Obstet Gynecol* 144:68-78, 2024
95. Armstrong DK, Alvarez RD, Bakkum-Gomez JN, et al: Ovarian cancer, version 2.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 19:191-226, 2021
96. Bercow A, Nitecki R, Brady PC, et al: Outcomes after fertility-sparing surgery for women with ovarian cancer: A systematic review of the literature. *J Minim Invasive Gynecol* 28:527-536.e1, 2021
97. Management of Endometrial Intraepithelial Neoplasia or Atypical Endometrial Hyperplasia: ACOG clinical consensus No. 5. *Obstet Gynecol* 142:735-744, 2023
98. Bastings L, Beerendonk CC, Westphal JR, et al: Autotransplantation of cryopreserved ovarian tissue in cancer survivors and the risk of reintroducing malignancy: A systematic review. *Hum Reprod Update* 19:483-506, 2013
99. Bildik G, Akin N, Senbabaoglu F, et al: GnRH agonist leuprolide acetate does not confer any protection against ovarian damage induced by chemotherapy and radiation in vitro. *Hum Reprod* 30:2912-2925, 2015
100. Lamberti M, Ceppi M, Poggio F, et al: Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: A meta-analysis of randomized studies. *Ann Oncol* 26:2408-2419, 2015
101. Azim A, Oktay K: Letrozole for ovulation induction and fertility preservation by embryo cryopreservation in young women with endometrial carcinoma. *Fertil Steril* 88:657-664, 2007
102. Bonardi B, Massarotti C, Bruzzone M, et al: Efficacy and safety of controlled ovarian stimulation with or without letrozole co-administration for fertility preservation: A systematic review and meta-analysis. *Front Oncol* 10:574669, 2020
103. Danis RB, Pereira N, Elias RT: Random start ovarian stimulation for oocyte or embryo cryopreservation in women desiring fertility preservation prior to gonadotoxic cancer therapy. *Curr Pharm Biotechnol* 18:609-613, 2017
104. Esmaeilian Y, Hela F, Bildik G, et al: IVF characteristics and the molecular luteal features of random start IVF cycles are not different from conventional cycles in cancer patients. *Hum Reprod* 38:113-124, 2023
105. Puthur SJ, Tracey S, Gould D, et al: DuoStim protocol—A novel fertility preservation strategy for female oncology patients. *Hum Fertil* 26:1361-1367, 2023
106. Pereira N, Kelly AG, Stone LD, et al: Gonadotropin-releasing hormone agonist trigger increases the number of oocytes and embryos available for cryopreservation in cancer patients undergoing ovarian stimulation for fertility preservation. *Fertil Steril* 108:532-538, 2017
107. Vo KCT, Kawamura K: Female oncofertility: Current understandings, therapeutic approaches, controversies, and future perspectives. *J Clin Med* 10:5690, 2021
108. Dahm-Kähler P, Kvarnström N, Alfonzo Rodriguez E, et al: Uterus transplantation for fertility preservation in patients with gynecologic cancer. *Int J Gynecol Cancer* 31:371-378, 2021
109. Marklund A, Jiang Y, Röjlar H, et al: The complexity and challenges of fertility preservation in women with cervix cancer-A prospective cohort study reporting on reproductive outcome and overall survival. *Acta Obstet Gynecol Scand* 104:86-94, 2025
110. Lee SJ, Schover LR, Partridge AH, et al: American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 24:2917-2931, 2006
111. Li X, Li J, Wu X: Incidence, risk factors and treatment of cervical stenosis after radical trachelectomy: A systematic review. *Eur J Cancer* 51:1751-1759, 2015
112. Boss EA, van Golde RJ, Beerendonk CC, et al: Pregnancy after radical trachelectomy: A real option? *Gynecol Oncol* 99:S152-S156, 2005 (3 suppl 1)
113. van der Plas RCJ, Bos AME, Jürgenliemk-Schulz IM, et al: Fertility-sparing surgery and fertility preservation in cervical cancer: The desire for parenthood, reproductive and obstetric outcomes. *Gynecol Oncol* 163:538-544, 2021
114. Nitecki R, Clapp MA, Fu S, et al: Outcomes of the first pregnancy after fertility-sparing surgery for early-stage ovarian cancer. *Obstet Gynecol* 137:1109-1118, 2021
115. Abu-Rustum N, Yashar C, Arend R, et al: Uterine neoplasms, version 1.2023, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 21:181-209, 2023
116. Vasileva R, Wohrer H, Gaultier V, et al: Pregnancy and obstetric outcomes after fertility-sparing management of endometrial cancer and atypical hyperplasia: A multicentre cohort study. *Hum Reprod* 39:1231-1238, 2024
117. Park JY, Seong SJ, Kim TJ, et al: Pregnancy outcomes after fertility-sparing management in young women with early endometrial cancer. *Obstet Gynecol* 121:136-142, 2013

Rare Uterine Tumors: What to Do?

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OVERVIEW

Rare uterine malignancies present treatment challenges because of their clinical and biological heterogeneity. Among the rarest of the uterine cancers are leiomyosarcomas, uterine stromal tumors, and the mesonephric-like and serous carcinomas. In this article, we review recent advancements in diagnostic precision, risk stratification, and identification of biomarker-guided therapeutic options for these rare subtypes of uterine tumors. The improved understanding of the molecular profile of these tumors has led to the development of targeted treatment approaches. Further progress will depend on a coordinated, global effort to further characterize these diseases and enroll patients on biomarker-driven clinical trials.

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INTRODUCTION

Cancers of the uterine corpus were diagnosed in 66,200 women in the United States in 2023 and accounted for 13,030 deaths.¹ They are the fourth most common cancer in women and the sixth most common cause of death. Uterine cancers comprise a highly heterogeneous group of cancers that vary in histology, biological behavior, and therapeutic strategies. Among the rarest of the uterine cancers are leiomyosarcomas, uterine stromal tumors, and the mesonephric-like and serous carcinomas. We review recent advancements in diagnostic precision, risk stratification, and identification of more precise therapeutic options for these rare subtypes of uterine tumors. Although clinical research in these ultrarare tumors is challenging, this work is critical to improve and prolong the lives of the women who have them.

MAKING PROGRESS IN THE TREATMENT OF UTERINE LEIOMYOSARCOMA

Uterine leiomyosarcomas are rare, high-risk tumors. Women with uterine-confined, high-grade leiomyosarcomas have a 50%–70% risk of developing recurrent disease. Patients with metastatic leiomyosarcoma have a poor prognosis with median survival of about 18 months. However, there is significant biological variability in the presentation and behavior of metastatic disease. Some patients may present with an isolated metastatic site after a long disease-free interval and undergo successful resection; others may have multisite but small-volume, indolently paced asymptomatic metastatic disease; and others may have aggressive, large-volume metastatic disease that may or may not be sensitive to systemic cytotoxic therapy. Some key areas of need for investigation include adjuvant therapies to prevent recurrence, improved systemic treatments for metastatic disease, better understanding of the biologic variability in behavior, and incorporation of molecular

testing for diagnostic precision, disease prognosis, and potentially actionable molecular findings. We review some recent advances in these areas.

Leiomyosarcoma is surgically staged using the 2017 International Federation of Gynecology and Obstetrics (FIGO)/TNM classification system. For patients with uterus-confined disease, surgery includes total hysterectomy ± bilateral salpingo-oophorectomy (BSO). It is not clear if BSO influences survival, but is frequently performed for perimenopausal or menopausal patients. It is not recommended for premenopausal patients unless ovarian involvement is identified. Routine lymphadenectomy is not performed for clinically normal lymph nodes but may be performed if adenopathy is present. Surgical resection of extrauterine disease may be considered on the basis of symptoms, extent of disease, and resectability. Chest/abdomen/pelvis computed tomography (CT) and other imaging can assist in identifying potential extrauterine disease.

Adjuvant Therapy in Uterine-Confined Leiomyosarcoma

The current standard management approach for women with uterine-confined, nonmorcellated leiomyosarcoma is surveillance. Although the recurrence risk is high, to our knowledge, to date, no adjuvant intervention has been shown to improve survival outcomes. A prospective, randomized phase III trial was conducted in patients who were randomly assigned to receive treatment with agents with known activity in metastatic disease (gemcitabine plus docetaxel for four cycles, followed by doxorubicin for four cycles) or observation.² Although this trial closed early because of a slow pace of accrual, there was no difference in recurrence rates or survival between the two arms. The restricted mean survival time for overall survival was 34 months in the chemotherapy arm and 46 months in the

PRACTICAL APPLICATIONS

- Doxorubicin plus trabectedin followed by trabectedin maintenance showed a survival advantage over doxorubicin alone for first-line treatment of leiomyosarcoma and is a good first-line treatment option for fit patients whose disease burden merits cytotoxic chemotherapy.
- Endometrial stromal sarcoma (ESS) and related tumors are a subset of mesenchymal neoplasms accounting for <10% of uterine sarcomas. Low-grade ESSs typically have an indolent course and in the metastatic setting can be treated with endocrine therapy. High-grade ESS and undifferentiated uterine sarcomas are highly aggressive and warrant treatment with chemotherapy in the advanced, recurrent, or metastatic setting.
- Uterine serous carcinomas are high-grade aggressive tumors for which chemotherapy with carboplatin and paclitaxel remain standard of care. In certain clinical situations, the addition of immunotherapy, human epidermal growth factor receptor 2–directed therapy, and other targeted therapies can improve prognosis and are under continued investigation.
- Next-generation sequencing has an evolving role in diagnostic precision, identification of therapeutic options, and risk stratification in rare uterine tumors.

observation arm. The recurrence rates were the same (44% observation; 47% chemotherapy) as was the recurrence-free survival. Similarly, a retrospective study of 111 women, of whom 33 received adjuvant gemcitabine plus docetaxel and 77 of whom were observed, showed no benefit from adjuvant chemotherapy.³ Prospective studies of adjuvant therapy are challenging to conduct, given the rarity of these tumors and the accrual challenges for studies in which the standard arm is observation, but nevertheless are needed.

Systemic Treatments for Metastatic Disease

Among the cytotoxic agents with efficacy in metastatic leiomyosarcoma are doxorubicin, gemcitabine, gemcitabine plus docetaxel, trabectedin, dacarbazine, ifosfamide, and pazopanib.⁴ A recent randomized trial was conducted comparing doxorubicin plus trabectedin followed by trabectedin maintenance to doxorubicin alone as first-line treatment for patients with metastatic leiomyosarcoma.⁵ Both progression-free survival and overall survival were superior in the doxorubicin-trabectedin arm. The median overall survival with doxorubicin-trabectedin was 33 months compared with 24 months with doxorubicin alone. Progression-free survival

with doxorubicin-trabectedin was 12 months versus 6 months with doxorubicin. These data provide a compelling rationale for considering doxorubicin-trabectedin followed by trabectedin maintenance as first-line therapy for patients with metastatic uterine leiomyosarcoma whose disease burden merits cytotoxic therapy and whose performance status and organ function can support this regimen. Other regimens such as gemcitabine plus docetaxel remain important options for second and later lines of treatment as no regimen, to our knowledge, to date is curative. The need to identify new agents for high-grade leiomyosarcoma remains high.

Role of Molecular Diagnostics in Uterine Leiomyosarcoma

Uterine leiomyosarcomas do not harbor a pathognomonic chromosomal translocation or gene mutation. Instead, these tumors commonly have multiple chromosomal abnormalities associated with chromothripsis. A majority of uterine leiomyosarcomas have mutations or deletions of *TP53* and/or *RB1*, which are not considered currently actionable. Most leiomyosarcomas have a low tumor mutational burden and are microsatellite stable. Multiple clinical trials have shown a lack of efficacy of immune checkpoint inhibitors in leiomyosarcoma.^{6,7}

It is likely that trials of pathway-specific/targeted agents in patients selected solely by leiomyosarcoma histology may not yield positive results. For example, the combination of lenvatinib plus pembrolizumab (which has activity in advanced endometrial carcinoma) was not effective for leiomyosarcoma.⁸ A phase II trial of olaparib plus temozolomide in uterine leiomyosarcoma showed promise with an objective response rate of 27%; however, the phase II/III trial comparing this combination to physician choice of trabectedin or pazopanib was closed to further accrual at the interim analysis.⁹

A significant challenge is that our current understanding of biomarkers of response is limited in leiomyosarcomas. For example, it was hoped that selecting patients with leiomyosarcoma whose tumors had intact Rb function might yield a biomarker-selected subset of patients whose tumors would respond to CDK4/6 inhibition. Yet, a phase II trial of ribociclib plus everolimus in patients with leiomyosarcoma with intact Rb did not meet its efficacy end point for the leiomyosarcoma cohort.¹⁰ By contrast, a biomarker that likely already has clinical utility for the treatment of uterine leiomyosarcoma is somatic *BRCA* alteration. Several studies have shown that approximately 5%–8% of uterine leiomyosarcomas may have *BRCA* alterations (most commonly homozygous *BRCA2* deletions). PolyADP-ribose polymerase (PARP) inhibitors have been reported to have activity in patients with *BRCA2* deletion leiomyosarcomas.¹¹ A recent retrospective study showed a response rate of 46% and progression-free survival of 13 months.¹²

Emerging data suggest that genomic profiling may have a future role in prognosis/risk stratification for patients with uterine leiomyosarcoma. In a study that included 238 uterine leiomyosarcomas, a genomic risk stratification model yielded three tiers for progression-free survival: high risk for tumors with concurrent TP53 mutation and chromosome 20q amplification/ATRX mutations, intermediate risk for TP53 mutation or ATRX mutation or amplification 20q, and low risk for tumors lacking any of those three alterations.¹³ Another study of 211 patients with leiomyosarcoma showed that those with non-*BRCA* homologous recombination pathway gene alterations had poorer overall survival, although the homologous recombination deficiency score did not correlate with progression-free survival or overall survival outcomes.¹⁴ More research is needed to determine whether and how genomic risk profiling can be integrated with clinicopathologic models for uterine leiomyosarcoma outcomes.

MAKING SENSE OF ENDOMETRIAL STROMAL TUMORS

Endometrial stromal tumors (ESTs) represent a subset of uterine mesenchymal tumors that originate from the smooth muscle of the myometrium and endometrial stroma. They are rare tumors that account for approximately 1% of all uterine malignant neoplasms and 10%–25% of uterine mesenchymal tumors.^{15,16} The terminology and classification system for EST has evolved several times leading to a shift in nomenclature, which makes interpreting studies performed at different times challenging.¹⁶ The 2020 WHO classification system recognizes four EST subgroups: endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS).¹⁷

Advances in understanding the immunohistochemical profile and molecular alterations present in each subset have facilitated more precise classification (Table 1).

ESNs and LG-ESS

ESNs are benign lesions with proliferation of bland, uniform cells resembling endometrial stromal cells in the proliferative phase of the menstrual cycle. ESNs show immunohistochemical positivity for CD10, estrogen receptor (ER), CD 56, smooth muscle actin (SMA), and vimentin, and commonly exhibit characteristic gene rearrangements (Table 1). They are histologically identical to LG-ESS but instead are described as having a pushing border and do not exhibit any evidence of myometrial or vascular invasion. The diagnosis of ESN cannot be made based solely on a biopsy as it requires confirmation of a circumscribed, noninfiltrating border.

Similarly, LG-ESSs are composed of uniform cells that mimic proliferative endometrial stroma with minimal cellular pleomorphism, mild nuclear atypia, and variable mitotic figures; however, they exhibit myometrial and/or

vascular invasion and have metastatic potential. They are classically characterized as having distinctive finger-like projections (sometimes described as tongue-like or worm-like) that invade the myometrium, veins, and lymphatics. They are typically strongly immunoreactive for ER, CD10, and SMA, and negative for h-caldesmon and histone deacetylase 8.

Characteristic chromosomal translocations have been identified in ESN and LG-ESS, commonly involving chromosome arms 6p, 7p, and 17q. The most common translocation t(7;17) results in the *JAZF1/SUZ12* gene fusion, which is found in 70% of ESNs and 30%–50% of LG-ESS. This disrupts the function of SUZ12, a subunit of the polycomb repressive complex 2 (PRC2). Other chromosomal translocations frequently identified in low-grade ESS include t(6;7), t(6;10), and t(1;6) rearrangements, which result in the production of the *JAZF1/PHF1*, *EPC1/PHF1*, and *MEAF6/PHF1* fusion proteins, respectively, which also involve polycomb family genes, suggesting a common pathogenic pathway. PRC2 functions to repress the expression of beta-catenin and Wnt signaling. Elevated expression of beta-catenin and its interacting protein LEF1 has been shown in the majority of low-grade EST, suggesting the Wnt signaling pathway is activated in these cells and may represent a therapeutic target.^{18,19}

LG-ESS can also exhibit atypical differentiation, such as fibrous/myxoid changes, smooth muscle or glandular differentiation, and sex cord-like elements, which can cause additional diagnostic challenges.

HG-ESS

In contrast to LG-ESS, HG-ESS refers to malignant neoplasms with endometrial stromal differentiation that exhibit high-grade nuclear atypia and high mitotic activity.^{17,20}

HG-ESSs do not typically exhibit the characteristic fingerlike invasive projections of LG-ESS and instead show a more destructive growth pattern with extensive myometrial/lymphovascular invasion and necrosis. A low-grade spindle cell component may be present but is not required. Unlike LG-ESS, most HG-ESSs are not immunoreactive for CD10; however, they exhibit strong diffuse staining for cyclin D1 and BCOR.²¹ ER/progesterone receptor (PR) expression may be low or absent. RNA expression analyses showed a majority of HG-ESSs exhibited high expression of *NTRK3* and sonic hedgehog pathway genes (*FGFR3*, *RET*, *BCOR*, *GLI1*, and *PTCH1*).²² Upregulation of these genes was associated with gene rearrangements frequently identified in these tumors, although *NTRK* fusions were not identified. Common gene rearrangements include *YWHAE-NUTM2* fusion, *ZC3H7B-BCOR* fusion, and *BCOR* internal tandem duplications, which have also been identified in nongynecologic sarcomas. HG-ESS with *ZC3H7B-BCOR* fusions can exhibit CD10 positivity as well as increased cyclin D1 staining.

TABLE 1. Characteristics of Endometrial Stromal Tumors

Histologic Type	Tumor and Histologic Appearance	Genetic Alterations	Immunohistochemistry	Primary Therapy
Endometrial stromal nodule	Well-demarcated nodule consisting of a uniform population of cells with round to oval nuclei, scanty cytoplasm, and low mitotic activity, resembles proliferative phase endometrial stromal cells, expansive margins and pushing borders, no lymphovascular space invasion, exhibits ≤three finger-like projections <3 mm from the margin	t(7;17) translocations, most commonly t(7;17) (p21;q15) resulting in <i>JAZF1-SUZ12</i> fusions	Positive for CD10, ER, CD 56, SMA, and vimentin	Hysterectomy
LG-ESS	Poorly defined nodules composed of uniform cells resembling proliferative endometrial stroma with minimal cellular pleomorphism, overt tongue-like projections into the myometrium, LVSI often present, variable mitotic activity	Translocations involving polycomb family genes commonly including t(7;17) translocations, most commonly t(7;17) (p21;q15) resulting in <i>JAZF1-SUZ12</i> fusions; may also exhibit t(6;7) (<i>JAZF1/PHF1</i>), t(6;10) (<i>EPC1/PHF1</i>), and t(1;6) (<i>MEAF6/PHF1</i>) rearrangements	Positive for ER, PR, CD10, AR, SMA, and desmin; generally negative for h-caldesmon and histone deacetylase 8, cyclin D1, and BCOR	Early stage: total hysterectomy without morcellation and BSO ^a Advanced stage: surgical cytoreduction ± endocrine therapy
HG-ESS	Poorly defined masses often with hemorrhage and necrosis, uniform high-grade round or spindle cell histology, with brisk mitotic activity, extensive myometrial invasion, and LVSI, sometimes associated with a low-grade component	Two main subtypes: those with t(10;17) (q23;p13) translocation = <i>YWHAE-NUTM2A/B</i> fusion and those with <i>BCOR</i> gene abnormalities	Diffuse strong staining for cyclin D1 and BCOR, <i>YWHAE-NUTM2A/B</i> fusion tumors are negative for CD10, while <i>BCOR</i> fusion tumors are positive for CD10; ER and PR generally low or absent; negative for desmin, SMA, and caldesmon	Early stage: total hysterectomy without morcellation with BSO ^b Advanced stage: surgical cytoreduction if feasible and chemotherapy
UUS	No clear histologic differentiation, heteromorphic features, high-grade cellular atypia, destructive myometrial invasion, necrosis and hemorrhage, extensive LVSI	No specific genetic abnormalities, <i>YWHAE</i> and <i>JAZF1</i> gene fusions are exclusionary	Positive for p53 and p16, may stain for CD10, lack smooth muscle differentiation	Early stage: total hysterectomy without morcellation with BSO ^b Advanced stage: surgical cytoreduction if feasible and chemotherapy

Abbreviations: AR, androgen receptor; BCOR, BCL6 corepressor; BSO, bilateral salpingo-oophorectomy; ER, estrogen receptor; HG-ESS, high-grade endometrial stromal sarcoma; LG-ESS, low-grade endometrial stromal sarcoma; LVSI, lymphovascular space invasion; PR, progesterone receptor; SMA, smooth muscle actin; UUS, undifferentiated uterine sarcoma.

^aOvarian preservation, fertility-sparing treatment, and adjuvant hormonal therapy ± radiotherapy may be an option in selected cases.

^bOvarian preservation and adjuvant chemotherapy ± radiotherapy may be an option.

UUS

UUSs lack features of normal endometrial stromal differentiation and are characterized by marked cytologic atypia, nuclear pleomorphism, high mitotic activity, and extensive invasion, hemorrhage, and necrosis.^{17,20}

Like HG-ESS, UUSs show destructive myometrial invasion. This is a heterogeneous group of tumors and thus a diagnosis of exclusion. Some UUSs may arise from LG-ESS, representing a dedifferentiated LG-ESS.

UUS can show variable immunohistochemical staining of CD10, ER, PR, SMA, desmin, epithelial membrane antigen, and keratin. Unlike HG-ESS with *YWHAE-NUTM2AB* fusions, which are cyclin D1-positive/CD10-negative, when UUSs stain positive for cyclin D1, CD10 is also typically positive, and this difference can help to differentiate UUS from *YWHAE-NUTM2AB* HG-ESS. UUSs frequently show complex chromosomal abnormalities, although no specific recurring gene rearrangements have been identified. Finding *YWHAE*, *JAZF1*, or *NTRK* rearrangements excludes the diagnosis of UUS.

Clinical Course of ESTs

Few prospective studies have been performed for ESTs specifically, thus treatment approaches are generally based on consensus expert recommendations and case series.

ESNs are benign entities, and surgical intervention is curative. LG-ESS, HG-ESS, and UUS all have malignant potential and exist on a continuum of aggressiveness, with LG-ESS being the least aggressive and UUS the most. The FIGO/American Joint Committee on Cancer uterine sarcoma staging system is used for staging all uterine sarcoma, including ESTs.^{22–24} LG-ESSs commonly present as early-stage disease, while HG-ESSs and UUSs more typically have an advanced-stage presentation.

Similar to leiomyosarcoma, ESTs are surgically staged using the 2017 FIGO/TNM classification system. Chest/abdomen/pelvis CT and other imaging can assist in identifying potential extrauterine disease.

LG-ESSs have an indolent course even in the setting of recurrent disease and are generally hormone-responsive. For stage I disease, surgical resection plus BSO is preferred, although if incidentally diagnosed on hysterectomy, a second surgery for BSO may be avoided in menopausal patients. In premenopausal patients, ovarian conservation and fertility preservation (using myomectomy instead of hysterectomy) are controversial as studies suggest there are higher rates of relapse in these settings, although overall survival may not be affected likely because of response to secondary treatment. For stage II–IV disease, BSO is recommended. Antiestrogen therapy (ie, an aromatase inhibitor) can be considered as adjuvant therapy. Radiation may reduce local

recurrence but it is unclear whether it improves overall survival. Given the indolent course of LG-ESS, the likelihood of response to secondary therapy, and the potential risks of radiation, the decision for adjuvant radiation should be individualized, carefully weighing risks and benefits.

The PARAGON trial, the first prospective study for LG-ESS, evaluated the efficacy of anastrozole in patients with ER- and/or PR-positive LG-ESS with measurable disease.²⁵ Previous endocrine therapy was an exclusion criterion. The 3-month clinical benefit rate (defined as the proportion of patients who had response or stable disease by RECIST1.1 criteria) was the primary end point of the study and was 73% for the 15 patients enrolled. Although the objective response rate was only 26.7%; the progression free survival (PFS) was 73.3%, 73.3%, and 66% at 6, 12, and 18 months, respectively.

In recurrent LG-ESS, surgical resection can be considered in patients with oligometastatic disease, especially for those who have had a long progression-free interval. Endocrine therapy should be offered if not previously used. Aromatase inhibitors are the preferred primary endocrine therapy. Second-line endocrine therapy (eg, fulvestrant) can be beneficial with reports of prolonged stable disease. *ESR1* mutations may develop after exposure to endocrine therapy and may result in resistance to aromatase inhibitors²⁶; in this setting, selective estrogen receptor disruptors (SERDs), such as fulvestrant, and other novel SERDs may be beneficial. Emerging data on Wnt pathway activation in LG-ESS warrant trials of Wnt inhibitors for patients with metastatic recurrent disease who have progressed on previous endocrine therapy.

HG-ESSs more commonly present at an advanced stage. They tend to be highly aggressive, exhibiting a propensity for metastatic recurrence and poorer survival. Prognosis with HG-ESS is poorer than with LG-ESS, but better than with UUS. The optimal approach to treatment of HG-ESS has not been defined, although the more aggressive nature of the disease has led to recommendations to follow treatment algorithms for soft tissue sarcomas. On the basis of case reports, HG-ESS with *YWHAE* rearrangements may benefit from anthracycline-based therapy.²⁷ Although ER expression may be present, the utility of endocrine therapy for this disease has been called into question.²²

Of the ESTs, UUS has the worst prognosis with overall survival usually <2 years.²⁸ The mitotic rate of the tumor influences prognosis with mitotic rate of ≥ 25 mitotic figure count/10 high-power field associating with a significantly worse prognosis.²⁹ The recommended treatment approach is similar to the approach to soft tissue sarcomas with anthracycline-based therapy preferred as first line. Elevated expression of several tyrosine kinases in HG-ESS and UUS suggest tyrosine kinase inhibitors may have therapeutic potential and case reports of benefit have been published.²⁸ Further study is warranted; however, the rarity of these

tumors makes conducting prospective clinical trials challenging.

UNDERSTANDING MESONEPHRIC-LIKE AND UTERINE SEROUS CARCINOMAS

Uterine Serous Carcinomas

Uterine serous carcinomas (USCs) comprise approximately 10% of endometrial carcinomas but account for 40% of endometrial cancer deaths.³⁰ Patients with USC more commonly present with advanced-stage disease, and even in early-stage disease, adjuvant therapy is recommended to reduce the risk of recurrence. In the United States, USCs disproportionately affect Black women, who are at a higher risk of death due to disease.³¹ With the wide adoption of molecular characterization in endometrial cancer (EC), biomarkers such as TP53 and human epidermal growth factor receptor 2 (HER2) guide adjuvant therapy and drug development more so than histology. Other aberrations frequently observed in USCs include *CCNE1*, *MYC*, *PPP2R1A*, *PIKCA*, *FBXW7*, and *CDKN2A*.³²

Surgical Management

Standard of care for apparent early-stage disease consists of complete hysterectomy with BSO and staging. Studies have demonstrated the safety of both a minimally invasive approach, as well as replacement of full pelvic and para-aortic lymphadenectomy with sentinel lymph node mapping.³³ In advanced-stage disease, complete surgical resection offers a survival advantage if complete macroscopic cytoreduction is feasible, and may be completed after neoadjuvant chemotherapy.³⁴ USCs are surgically staged similar to other endometrial cancers. FIGO updated the staging system in 2023 to incorporate molecular characteristics. Chest/abdomen/pelvis CT and other imaging can assist in identifying potential extrauterine disease.

Early-Stage Disease

The five-year survival rate for stage I-II USC approaches 74%, and prognosis depends upon the presence of myometrial invasion.³⁵ However, there are limited prospective data on management. On the basis of the propensity for systemic recurrence, adjuvant chemotherapy with a platinum and taxane is generally pursued with or without vaginal brachytherapy. Large retrospective reviews have consistently demonstrated a benefit favoring chemotherapy over radiation or observation.³⁶ The prospective trials PORTEC-3 and GOG-249 included small numbers of patients with USC and similarly supported the use of chemotherapy in early-stage disease.^{37,38} Vaginal brachytherapy may be incorporated in stage I disease, whereas external-beam radiotherapy is typically included in patients with stage II disease. Patients without residual disease at the time of hysterectomy (ie, entirety of tumor was removed at the time of biopsy and surgical staging is negative) can be safely observed.

Advanced Stage/Recurrent Disease

Patients with stage III/IV USC have a survival of 33% at 5 years.³⁵ For these patients, platinum- and taxane-based chemotherapy remains standard of care. Concomitant radiation may reduce the risk of recurrence but does not significantly affect survival.

With the advent of the Cancer Genome Atlas and later the ProMisE algorithm, which, respectively, classified USC as copy-number high and p53-mutant (p53abn), molecular classification of endometrial cancers has become standard of care. These models predict clinical behavior, guide management, and direct clinical trials development.³⁹⁻⁴¹ For example, a retrospective analysis of PORTEC-3 noted improved outcomes for patients with p53abn endometrial cancers treated with chemoradiation versus radiation alone.³⁷ In analysis of PORTEC-1 and PORTEC-2, patients with p53abn tumors had a higher locoregional recurrence-free survival if they received external-beam radiation (97%) compared with vaginal brachytherapy (64%).⁴² Similarly, in GOG-258, patients with p53abn tumors had an improved recurrence-free survival when randomly assigned to chemoradiation (77%) versus chemotherapy alone (60%); however, overall survival did not differ.⁴³

Approximately 20%-40% of USCs overexpress HER2, and HER2 overexpression portends a worse prognosis in USC.⁴⁴ In 2020, Fader et al presented updated survival results from a cohort of 61 patients with HER2-overexpressing stage III/IV advanced or recurrent USCs, who were randomly assigned to carboplatin and paclitaxel, versus carboplatin, paclitaxel, and trastuzumab followed by trastuzumab maintenance.⁴⁵ Patients assigned to the trastuzumab arm had an improved overall survival of 29.6 versus 24.4 months, most notably in the advanced-stage cohort where median overall survival (OS) was not reached, versus 24.4 months in the control arm.

With the results of both NRG-GY018 and RUBY trials, immunotherapy has become a cornerstone of adjuvant treatment for patients with advanced endometrial cancer.^{46,47} These trials, which randomly assigned patients with advanced or recurrent endometrial cancer to carboplatin and paclitaxel with or without immunotherapy, demonstrated an improvement in both PFS and OS, which was most profound in mismatch repair deficient (MMRd) populations but also extended to mismatch repair proficient histology. This is reflected in the National Comprehensive Cancer Network (NCCN) guidelines, which recommend the addition of immunotherapy to chemotherapy in advanced-stage disease.⁴⁸ These trials both included patients with USC, and subgroup analyses of RUBY revealed a significant benefit in patients with p53abn tumors (hazard ratio [HR], 0.41). However, the recent KEYNOTE-B21 trial, which randomly assigned 1,095 patients with newly diagnosed high-risk endometrial cancer to chemotherapy with pembrolizumab versus placebo with or without radiation, did not substantiate the benefit of

immunotherapy outside of patients with MMRd tumors.⁴⁹ The reason for the discrepancy between the trials is not fully understood; however, there were significant differences in inclusion criteria. For example, patients in the B21 trial had newly diagnosed EC with no previous radiotherapy or systemic treatment, whereas the patients in GY0-18 and RUBY allowed patients with recurrent disease and previous systemic treatment. Similarly, patients in the B21 trial had undergone complete resection with no measurable disease, while both GY-018 and RUBY required the presence of measurable disease in certain subgroups. Finally, outcomes according to molecular classification have not yet been reported.

In recurrent USC, the combination of pembrolizumab plus lenvatinib has become standard of care. Makker et al⁵⁰ demonstrated the benefit of lenvatinib and pembrolizumab in 108 patients with recurrent endometrial cancer, regardless of MSI status. Response rates in patients with USC approached an unprecedented 50%. In KEYNOTE-775, the combination of lenvatinib and pembrolizumab improved both progression-free survival and overall survival in patients with advanced or recurrent disease who were randomly assigned to lenvatinib and pembrolizumab versus physician's choice chemotherapy.⁵¹ The combination of lenvatinib and pembrolizumab showed benefit in OS (HR, 0.65) regardless of MMR status, and the trial included over 200 patients with USC. These studies were completed before the results of GY018 or RUBY were known, thus before the addition of immunotherapy (pembrolizumab or dostarlimab) to paclitaxel-carboplatin in first-line treatment of advanced endometrial cancer. The activity of lenvatinib plus pembrolizumab in patients who have progressed on immunotherapy maintenance is therefore not known.

GOG-86P was a prospective phase II study in 349 patients with advanced EC, which randomly assigned patients to one of three treatment arms: paclitaxel, carboplatin, and bevacizumab; paclitaxel, carboplatin, and temsirolimus; or ixabepilone, carboplatin, and bevacizumab. Although there was no PFS benefit observed in any of the three arms, and the study used historical controls for comparison, patients in the bevacizumab study arm did experience an OS benefit (HR, 0.71).⁵² In a subsequent analysis, it was shown that patients with p53abn tumors derived the most benefit from the addition of bevacizumab, with an improvement in median OS of 15.6 months (HR, 0.28).⁵³ Trials examining the addition of immunotherapy and bevacizumab to chemotherapy in p53abn endometrial cancers are under development.

WEE1, a cell cycle protein, is recognized as a potential treatment target for USC. A phase II trial with the WEE1 inhibitor adavosertib showed a response rate of 30% among 27 patients with recurrent USC.⁵⁴ GOG-3065, an ongoing phase II trial examining azenosertib in patients with recurrent or persistent USC, is nearing completion as well.⁵⁵

TABLE 2. Ongoing Trials in Uterine Serous Carcinomas

NCT Number	Phase	Target	Agent	Reference
NCT06476808	I/IB	Nondisclosed	BMS-986463	61
NCT05902988	I/II	KIF18A	VLS-1488	62
NCT04814108	II	WEE1	Azenosertib	56
NCT03668340	II	WEE1	Adavosertib	63
NCT06126276	II	HER2	Neratinib Palbociclib	64
NCT05554328	II	RAS	Selumetinib Olaparib	65
NCT04080284	II	PARP	Niraparib	66
NCT05870761	II	PARP PD-1	Niraparib Dostarlimab	67
NCT02491099	II	HER2	Afatinib	68
NCT03660826	II	PD-L1 PARP VEGF AKT	Durvalumab Olaparib Cediranib Capivasertib	69
NCT05256225	II/III	HER2	Trastuzumab Pertuzumab	57
NCT03469674	III	P53abn	Radiotherapy	58
NCT05255653-1	III	P53abn	Olaparib	60

Abbreviations: HER2, human epidermal growth factor receptor 2; PARP, polyADP-ribose polymerase.

Biomarker-Driven Trials

Biomarkers such as p53 aberration and HER2 overexpression have recently driven clinical trial development rather than specific histology. For example, in NRG-GY026, patients with HER2-positive stage IA-IVB endometrial cancers are randomly assigned to paclitaxel and carboplatin alone, or to paclitaxel-carboplatin plus trastuzumab followed by trastuzumab maintenance, or to paclitaxel-carboplatin with trastuzumab/pertuzumab followed by trastuzumab/pertuzumab maintenance.⁵⁶ In PORTEC-4a, patients with newly diagnosed high-risk endometrial cancer are divided into radiotherapy cohorts on the basis of biomarkers; patients with p53 mutations and other high-risk profiles receive external-beam therapy,⁵⁷ whereas patients with intermediate-risk profiles receive vaginal brachytherapy, and those with a favorable profile undergo observation. Defects in homologous recombination have been reported in USC, thereby making them potential targets for PARP inhibition.⁵⁸ Accordingly, in the RAINBO ENGOT-en14 biomarker trial, patients with newly diagnosed, early-stage, high-risk endometrial cancer and p53abn tumors receive adjuvant chemoradiation with or without olaparib maintenance.⁵⁹

Similarly, newer classes of antibody-drug conjugates targeting HER2, for example trastuzumab deruxtecan, may yield even higher response rates. The DESTINY-PanTumor02 phase II trial enrolled previously treated patients with HER2-expressing advanced solid tumors, including 40 patients with recurrent endometrial cancer. The EC subgroup

experienced a 57.5% objective response rate (ORR), with a median OS of 26 months; patients with the highest HER2 expression had the highest ORR (84.6%).⁶⁰ These results led to accelerated US Food and Drug Administration approval for patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] 3+) solid tumors. NCCN guidelines support use in IHC 2+ or 3+ scoring.⁴⁸ Notably, HER2 scoring in this trial was performed according to gastric cancer scoring guidelines.

There are several other interesting ongoing trials incorporating targeted therapy in USC, listed in [Table 2](#).

Mesonephric-Like Endometrial Cancers

Mesonephric-like endometrial cancers (MLECs) are extremely rare, accounting for 1% of endometrial cancers, thus case reports and small case series inform diagnosis and management. Histologically, MLECs appear high-grade and display variable architecture with mesonephric features, often posing a diagnostic dilemma. Immunohistochemistry demonstrates overexpression of CD10, GATA3, and TTF1, absent ER/PR expression, and wild-type p53.^{70,71} Molecular analysis of MLEC yields aberrations in *KRAS* (80%), *PTEN*, *ARID1A*, and *PIK3CA*.^{72,73} Clinically, MLECs display aggressive behavior and often present at an advanced stage with a propensity for lung metastases. In one single-institution report of 23 cases of uterine MLEC, 48% of patients presented with stage III or IV disease, 87% had deep myoinvasion, and 70% had lymphovascular space invasion.⁷³ Of the 20 patients who received adjuvant treatment, seven received radiation alone, while 13 received combination chemotherapy and radiation. Median PFS and OS were 18 and 71 months, respectively, and when compared with USC, patients with MLEC had a worse prognosis. Twenty-one patients had

follow-up, and 15 of 21 (71%) developed recurrence, most commonly in the lung. In another multi-institutional study of 44 patients with MLEC, 58% presented at an advanced stage, 32% of whom exhibited lymph node metastases.⁷⁰ Recurrence was common (59%), and most commonly affected the lungs (64%), with a 5-year OS of 72%. Given the rarity of MLEC, the optimal regimen for these entities remains unknown. They are treated similarly to other high-grade EC, with a combination of surgery, radiation, and chemotherapy. Nodal assessment is indicated, given their high-grade nature, and in disease confined to the uterus, both chemotherapy and radiation are used. In metastatic or recurrent disease, chemotherapy is recommended. Molecular profiling may help guide management in patients with recurrent disease. Brambs et al performed a molecular analysis on eight cases of genital tract MLEC with *KRAS* mutations, and suggested consideration of sotorasib in patients with the specific p.G12C-*KRAS* hotspot mutation.⁷⁴ The research by Grisham (ClinicalTrials.gov identifier: [NCT05787561](#)) is a clinical trial studying avutometinib and defactinib in patients with mesonephric-like gynecologic cancers.⁷⁵

CONCLUSION

Given the rarity of these tumors, developing therapies for leiomyosarcomas, ESTs, and the mesonephric-like and serous carcinomas is challenging; however, recent advances in the biological and molecular understanding of these diseases have expanded therapeutic options for patients. To improve outcomes for patients, continued coordinated molecular and genetic characterization to identify precise therapeutic options, increased investment in the development of pre-clinical models, and global participation in prospective clinical trials are required.

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REFERENCES

1. Siegel RL, Miller KD, Wagle NS, et al: Cancer statistics, 2023. *CA Cancer J Clin* 73:17-48, 2023
2. Hensley ML, Enserro D, Hatcher H, et al: Adjuvant gemcitabine plus docetaxel followed by doxorubicin versus observation for high-grade uterine leiomyosarcoma: A phase III NRG Oncology/Gynecologic Oncology Group Study. *J Clin Oncol* 36:3324-3330, 2018
3. Littell RD, Tucker LY, Raine-Bennett T, et al: Adjuvant gemcitabine-docetaxel chemotherapy for stage I uterine leiomyosarcoma: Trends and survival outcomes. *Gynecol Oncol* 147:11-17, 2017
4. George S, Serrano C, Hensley ML, et al: Soft tissue and uterine leiomyosarcoma. *J Clin Oncol* 36:144-150, 2018
5. Pautier P, Italiano A, Piperno-Neumann S, et al: Doxorubicin-trabectedin with trabectedin maintenance in leiomyosarcoma. *N Engl J Med* 391:789-799, 2024
6. Ben-Ami E, Barysauks CM, Solomon S, et al: Immunotherapy with single agent nivolumab for advanced leiomyosarcoma of the uterus: Results of a phase 2 study. *Cancer* 123:3285-3290, 2017
7. Tawbi HA, Burgess M, Bolejack V, et al: Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): A multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol* 18:1493-1501, 2017
8. Movva S, Seier K, Avutu V, et al: Histology-specific clinical trial of lenvatinib and pembrolizumab in patients with sarcoma. *Clin Cancer Res* 30:5612-5619, 2024
9. Ingham M, Allred JB, Chen L, et al: Phase II study of olaparib and temozolomide for advanced uterine leiomyosarcoma (NCI protocol 10250). *J Clin Oncol* 41:4154-4163, 2023
10. Movva S, Matloob S, Handorf EA, et al: SAR-096: Phase II clinical trial of ribociclib in combination with everolimus in advanced dedifferentiated liposarcoma (DDL) and leiomyosarcoma (LMS). *Clin Cancer Res* 30:315-322, 2024
11. Hensley ML, Chavan SS, Solit DB, et al: Genomic landscape of uterine sarcomas defined through prospective clinical sequencing. *Clin Cancer Res* 26:3881-3888, 2020
12. Rao M, Merrill M, Troxel M, et al: A retrospective analysis of BRCA-altered uterine sarcoma treated with PARP inhibitors. *Clin Cancer Res* 9:e2400765, 2025
13. Dermawan JK, Chiang S, Singer S, et al: Developing novel genomic risk stratification models in soft tissue and uterine leiomyosarcoma. *Clin Cancer Res* 30:2260-2271, 2024
14. Rosenbaum E, Jonsson P, Steier K, et al: Clinical outcome of leiomyosarcomas with somatic alteration in homologous recombination pathway genes. *JCO Precis Oncol* 10.1200/PO.20.00122
15. Rauh-Hain JA, del Carmen MG: Endometrial stromal sarcoma: A systematic review. *Obstet Gynecol* 122:676-683, 2013
16. Hoang L, Chiang S, Lee CH: Endometrial stromal sarcomas and related neoplasms: New developments and diagnostic considerations. *Pathology* 50:162-177, 2018
17. Organisation mondiale de la santé Cidrcs (ed): Female Genital Tumours (ed 5). International Agency for Research on Cancer, 2020
18. Niu S, Lu H, Li W, et al: Immunohistochemical expression of lymphoid enhancer-binding factor 1 in low-grade endometrial stromal tumors. *Int J Gynecol Pathol* 43:487-493, 2024
19. Przybyl J, Kidzinski L, Hastie T, et al: Gene expression profiling of low-grade endometrial stromal sarcoma indicates fusion protein-mediated activation of the Wnt signaling pathway. *Gynecol Oncol* 149:388-393, 2018
20. Clement PB, Stall J, Young RH: Atlas of Gynecologic Surgical Pathology (ed 4). Edinburgh, Scotland, Elsevier, 2020
21. Abouelkhair MB, Shakweer MM, Faisal MM, et al: Diagnostic value of combined BCOR, cyclin D1, and CD10 in differentiating endometrial stromal sarcoma from other uterine spindle cell lesions. *Appl Immunohistochem Mol Morphol* 32:326-335, 2024
22. Momeni-Boroujeni A, Mohammad N, Wolber R, et al: Targeted RNA expression profiling identifies high-grade endometrial stromal sarcoma as a clinically relevant molecular subtype of uterine sarcoma. *Mod Pathol* 34:1008-1016, 2021
23. Prat J: FIGO staging for uterine sarcomas. *Int J Gynaecol Obstet* 104:177-178, 2009
24. American Joint Committee on Cancer: AJCC Cancer Staging Manual (ed 8). Chicago, IL, AJCC, American Joint Committee on Cancer, 2017
25. Friedlander M, Benson C, O'Connell RL, et al: Phase 2 study of anastrozole in patients with estrogen receptor/progesterone receptor positive recurrent low-grade endometrial stromal sarcomas: The PARAGON trial (ANZGOG 0903). *Gynecol Oncol* 161:160-165, 2021
26. Gaillard SL, Andreano KJ, Gay LM, et al: Constitutively active ESR1 mutations in gynecologic malignancies and clinical response to estrogen-receptor directed therapies. *Gynecol Oncol* 154:199-206, 2019
27. Hemming ML, Wagner AJ, Nucci MR, et al: YWHAE-rearranged high-grade endometrial stromal sarcoma: Two-center case series and response to chemotherapy. *Gynecol Oncol* 145:531-535, 2017
28. Gadducci A, Multinu F, De Vitis LA, et al: Endometrial stromal tumors of the uterus: Epidemiology, pathological and biological features, treatment options and clinical outcomes. *Gynecol Oncol* 171:95-105, 2023
29. Hardell E, Josefson S, Ghaderi M, et al: Validation of a mitotic index cutoff as a prognostic marker in undifferentiated uterine sarcomas. *Am J Surg Pathol* 41:1231-1237, 2017
30. Bogani G, Ray-Coquard I, Concin N, et al: Uterine serous carcinoma. *Gynecol Oncol* 162:226-234, 2021
31. Whelan K, Dillon M, Strickland KC, et al: TP53 mutation and abnormal p53 expression in endometrial cancer: Associations with race and outcomes. *Gynecol Oncol* 178:44-53, 2023
32. Kuhn E, Wu RC, Guan B, et al: Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses. *J Natl Cancer Inst* 104:1503-1513, 2012
33. Marchocki Z, Cusimano MC, Clarfield L, et al: Sentinel lymph node biopsy in high-grade endometrial cancer: A systematic review and meta-analysis of performance characteristics. *Am J Obstet Gynecol* 225:367.e1-367.e39, 2021
34. Tobias CJ, Chen L, Melamed A, et al: Association of neoadjuvant chemotherapy with overall survival in women with metastatic endometrial cancer. *JAMA Netw Open* 3:e2028612, 2020
35. Hamilton CA, Cheung MK, Osann K, et al: Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. *Br J Cancer* 94:642-646, 2006
36. Cham S, Huang Y, Tergas AI, et al: Utility of radiation therapy for early-stage uterine papillary serous carcinoma. *Gynecol Oncol* 145:269-276, 2017
37. León-Castillo A, de Boer SM, Powell ME, et al: Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: Impact on prognosis and benefit from adjuvant therapy. *J Clin Oncol* 38:3388-3397, 2020
38. Tatebe K, Hasan Y, Son CH: Adjuvant vaginal brachytherapy and chemotherapy versus pelvic radiotherapy in early-stage endometrial cancer: Outcomes by risk factors. *Gynecol Oncol* 155:429-435, 2019
39. Cancer Genome Atlas Research Network; Kandoth C, Schultz N, et al: Integrated genomic characterization of endometrial carcinoma. *Nature* 497:67-73, 2013
40. Talhouk A, McConchy MK, Leung S, et al: Confirmation of ProMIS: A simple, genomics-based clinical classifier for endometrial cancer. *Cancer* 123:802-813, 2017
41. Walsh CS, Hacker KE, Secord AA, et al: Molecular testing for endometrial cancer: An SGO clinical practice statement. *Gynecol Oncol* 168:48-55, 2023
42. Horeweg N, Nout RA, Jürgenliemk-Schulz IM, et al: Molecular classification predicts response to radiotherapy in the randomized PORTEC-1 and PORTEC-2 trials for early-stage endometrioid endometrial cancer. *J Clin Oncol* 41:4369-4380, 2023
43. Clements A, Enserro D, Strickland KC, et al: Molecular classification of endometrial cancers (EC) and association with relapse-free survival (RFS) and overall survival (OS) outcomes: Ancillary analysis of GOG-0258. *Gynecol Oncol* 193:119-129, 2025
44. Erickson BK, Najjar O, Damast S, et al: Human epidermal growth factor 2 (HER2) in early stage uterine serous carcinoma: A multi-institutional cohort study. *Gynecol Oncol* 159:17-22, 2020
45. Fader AN, Roque DM, Siegel E, et al: Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): Updated overall survival analysis. *Clin Cancer Res* 26:3928-3935, 2020
46. Mirza MR, Chase DM, Slomovitz BM, et al: Dostarlimab for primary advanced or recurrent endometrial cancer. *N Engl J Med* 388:2145-2158, 2023
47. Eskander RN, Sill MW, Beffa L, et al: Pembrolizumab plus chemotherapy in advanced endometrial cancer. *N Engl J Med* 388:2159-2170, 2023
48. NCCN guidelines version 3.2025. Endometrial carcinoma. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf
49. Van Gorp T, Cibula D, Lv W, et al: ENGOT-en11/GOG-3053/KEYNOTE-B21: A randomised, double-blind, phase III study of pembrolizumab or placebo plus adjuvant chemotherapy with or without radiotherapy in patients with newly diagnosed, high-risk endometrial cancer. *Ann Oncol* 35:968-980, 2024
50. Makker V, Rasco D, Vogelzang NJ, et al: Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: An interim analysis of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 20:711-718, 2019
51. Makker V, Colombo N, Casado Herráez A, et al: Lenvatinib plus pembrolizumab for advanced endometrial cancer. *N Engl J Med* 386:437-448, 2022
52. Aghajanian C, Filiazi V, Dizon DS, et al: A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. *Gynecol Oncol* 150:274-281, 2018
53. Thiel KW, Devor EJ, Filiazi VL, et al: TP53 sequencing and p53 immunohistochemistry predict outcomes when bevacizumab is added to frontline chemotherapy in endometrial cancer: An NRG Oncology/Gynecologic Oncology Group Study. *J Clin Oncol* 40:3289-3300, 2022
54. Liu JF, Xiong N, Campos SM, et al: Phase II study of the WEE1 inhibitor adavosertib in recurrent uterine serous carcinoma. *J Clin Oncol* 39:1531-1539, 2021
55. A phase 2 open-label, multicenter study to evaluate efficacy and safety of ZN-c3 in adult women with recurrent or persistent uterine serous carcinoma. NCI. <https://clinicaltrials.gov/study/NCT04814108>
56. Erickson B: Testing the addition of trastuzumab or trastuzumab/pertuzumab to the usual chemotherapy for HER2 positive endometrial cancer. NCI. <https://clinicaltrials.gov/study/NCT05256225>
57. Nout RA: PORTEC-4a: Molecular profile-based versus standard adjuvant radiotherapy in endometrial cancer (PORTEC-4a). NCI. <https://clinicaltrials.gov/study/NCT03469674>

58. Wallbillich JJ, Morris RT, Ali-Fehmi R: Comparing mutation frequencies for homologous recombination genes in uterine serous and high-grade serous ovarian carcinomas: A case for homologous recombination deficiency testing in uterine serous carcinoma. *Gynecol Oncol* 159:381-386, 2020
 59. Leary A: Refining adjuvant treatment in endometrial cancer based on molecular features (RAINBO). NCI. <https://clinicaltrials.gov/study/NCT05255653>
 60. Meric-Bernstam F, Makker V, Oaknin A, et al: Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: Primary results from the DESTINY-PanTumor02 phase II trial. *J Clin Oncol* 42:47-58, 2024
 61. A study to evaluate the safety, tolerability, and efficacy of escalating doses of BMS-986463 in participants with select advanced malignant tumors. NCI. <https://clinicaltrials.gov/study/NCT06476808>
 62. A phase I/II study of VLS-1488 in subjects with advanced cancer. NCI. <https://clinicaltrials.gov/study/NCT05902988>
 63. Liu J: AZD1775 in women with recurrent or persistent uterine serous carcinoma or uterine carcinosarcoma. NCI. <https://clinicaltrials.gov/study/NCT03668340>
 64. Mahdi H: Testing the use of neratinib or the combination of neratinib and palbociclib targeted treatment for HER2+ solid tumors (a ComboMATCH treatment trial). NCI. <https://clinicaltrials.gov/study/NCT06126276>
 65. Westin S: Testing the use of the combination of selumetinib and olaparib or selumetinib alone targeted treatment for RAS pathway mutant recurrent or persistent ovarian and endometrial cancers, a ComboMATCH treatment trial. NCI. <https://clinicaltrials.gov/study/NCT05554328>
 66. Frimer M: Trial of maintenance with niraparib-uterine serous carcinoma. NCI. <https://clinicaltrials.gov/study/NCT04080284>
 67. Cosgrove C: Combination niraparib and dostarlimab therapy for recurrent or persistent uterine serous carcinoma. NCI. <https://clinicaltrials.gov/study/NCT05870761>
 68. Santin A: A phase II evaluation of afatinib in patients with persistent or recurrent HER2-positive uterine serous carcinoma (afatinib). NCI. <https://clinicaltrials.gov/study/NCT02491099>
 69. MacKay H: Testing the combination of olaparib and durvalumab, cediranib and durvalumab, olaparib and capivasertib, and cediranib alone in recurrent or refractory endometrial cancer following the earlier phase of the study that tested olaparib and cediranib in comparison to cediranib alone, and olaparib alone. NCI. <https://clinicaltrials.gov/study/NCT03660826>
 70. Pors J, Segura S, Chiu DS, et al: Clinicopathologic characteristics of mesonephric adenocarcinomas and mesonephric-like adenocarcinomas in the gynecologic tract: A multi-institutional study. *Am J Surg Pathol* 45:498-506, 2021
 71. McFarland M, Quick CM, McCluggage WG: Hormone receptor-negative, thyroid transcription factor 1-positive uterine and ovarian adenocarcinomas: Report of a series of mesonephric-like adenocarcinomas. *Histopathology* 68:1013-1020, 2016
 72. Arslanian E, Singh K, Sung CJ, et al: Somatic mutation analysis of mesonephric-like adenocarcinoma and associated putative precursor lesions: Insight into pathogenesis and potential molecular treatment targets. *Gynecol Oncol Rep* 42:101049, 2022
 73. Euscher ED, Bassett R, Duose DY, et al: Mesonephric-like carcinoma of the endometrium: A subset of endometrial carcinoma with an aggressive behavior. *Am J Surg Pathol* 44:429-443, 2020
 74. Brambs CE, Horn LC, Hiller R, et al: Mesonephric-like adenocarcinoma of the female genital tract: Possible role of KRAS-targeted treatment-detailed molecular analysis of a case series and review of the literature for targetable somatic KRAS-mutations. *J Cancer Res Clin Oncol* 149:15727-15736, 2023
 75. Grisham R: A study of avutemetinib (VS-6766) and defactinib in people with mesonephric gynecologic cancer. NCI. <https://clinicaltrials.gov/study/NCT05787561>
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Updates on Treatments and Management of Nasopharyngeal Carcinoma

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OVERVIEW

Nasopharyngeal carcinoma (NPC) is a unique head and neck cancer, where the endemic subtype is strongly associated with Epstein–Barr virus (EBV) infection, whereas emerging data suggest that a subset of nonendemic NPC may be associated with human papillomavirus (HPV) infection. Nonetheless, treatment advances have been driven by clinical trials conducted in endemic NPC, investigating optimal sequencing of chemotherapy and immune checkpoint inhibitors with radiotherapy for locoregionally advanced disease. The preference for induction chemotherapy (IC) in these patients has also led to evolution in the concept of radiotherapy target delineation. Because of its association with EBV, plasma EBV DNA is an archetypal biomarker for endemic NPC, and it is being explored for precise stratification and treatment individualization in several ongoing trials. In the space of recurrent or metastatic–NPC, with the advent of platinum–doublet chemotherapy and anti–PD–1 antibody as the new standard of care, several trials are investigating new immunotherapeutic combinations, bispecific antibodies, and antibody–drug conjugates that have demonstrated promise in early phase trials. An important advance for NPC in 2025 is the update of the 9th version of the TNM staging system, which has introduced several key changes, including downgrading of the TNM stage groupings for localized disease, and splitting of metastatic NPC into IVA and IVB based on the number of metastatic lesions. These revisions would have implications for the treatment and design of future trials. These advances are also relevant to nonendemic NPC, where evidence is inconclusive whether this disease responds differently to current treatments compared with endemic NPC.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a unique head and neck cancer that is endemic in Southern China, South–East Asia, and North Africa.¹ The nonkeratinizing subtype, which predominates in the endemic region, is invariably associated with previous Epstein–Barr virus (EBV) infection.² This subtype generally exhibits a favorable prognosis, characterized by good responsiveness to both radiotherapy and chemotherapy. By contrast, the keratinizing subtype, primarily found in the West, is associated with human papillomavirus (HPV) infection.³

Radiotherapy remains the cornerstone of NPC treatment because of its anatomic location and radiosensitivity. Over the years, advancements in radiotherapy techniques have enhanced tumor control and reduced normal tissue toxicity. Concurrent chemoradiotherapy (CCRT) has been established as the treatment backbone for patients with locoregionally advanced NPC (LA–NPC), primarily as a radiosensitizer and to target occult distant metastases.⁴ However, for this subset of patients, some remain at high risk of distant metastatic

relapse, and thus, the combination of induction chemotherapy (IC) and adjuvant chemotherapy (AC) regimens with CCRT has significantly improved survival rates.⁵ More recently, preliminary evidence suggests that further intensification with immunotherapy, specifically anti–PD–1 antibody, could improve disease-free survival (DFS) for patients with LA–NPC albeit the optimal sequencing remains unclear.^{6,7} Ultimately, it is recognized that NPC is a clinically heterogeneous disease, and treatment recommendations can be individualized based on baseline clinical stratification and on-treatment responses after IC or midway through radiotherapy or CCRT.⁸

In the same vein, patients with recurrent or metastatic NPC (R/M–NPC) can be stratified by the volume of disease (number of metastatic lesions and/or involved organs) and anatomic site of involvement (lung v bone v liver), which can be matched to the aggressiveness of treatments.^{9,10} As a case in point, for patients with oligometastatic de novo metastatic NPC, most physicians would recommend the combination of platinum–doublet chemotherapy followed by consolidation radiotherapy to the primary with or without

PRACTICAL APPLICATIONS

- Induction chemotherapy (IC) followed by chemoradiotherapy is the preferred first-line treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC), and response to IC (by RECIST and/or plasma Epstein-Barr virus DNA) is a strong predictor for survival and can be applied to adapt radiotherapy and systemic treatment.
- Immune checkpoint inhibitors combined with platinum-based chemotherapy prolonged disease control in NPC, but long-term data are required to ascertain its benefit on overall survival in LA-NPC.
- New TNM-9 staging system for NPC added advanced extranodal extension as a criterion for N3 classification and classifies localized NPC into stage IA, IB, II, and III and metastatic NPC into stage IVA (≤ 3 lesions) and IVB (> 3 lesions).
- Chemoradiotherapy is recommended for all patients (if fit) with TNM-9 stage II and III NPC, and some patients with TNM stage IB harboring high-risk features; patients with TNM stage IVA NPC should receive systemic therapy combined with radiotherapy to the primary and/or metastatic site(s), in contrast to patients with TNM stage IVB NPC for whom systemic therapy intensification should be prioritized.
- Treatment of nonendemic NPC should follow treatment guidelines for endemic NPC since evidence is inconclusive regarding whether they harbor inferior prognosis.

metastasis-directed therapy since these patients have a significantly longer survival compared with those with polymetastatic disease.¹¹ In the latter scenario, the new standard of care in 2025 is the combination of platinum-doublet chemotherapy with anti-PD-1 antibody based on the results of three randomized controlled phase III trials.¹²⁻¹⁴ Novel therapeutic combinations beyond chemotherapy and anti-PD-1 antibody are currently being investigated in clinical trials, such as antibody-drug conjugates (ADCs).¹⁵

This review thus aims to outline the latest advances in the treatment strategies of NPC. For LA-NPC, we will focus on new concepts on biomarker-driven personalization of systemic therapy intensification with radiotherapy and delineation of radiotherapy target volumes. For the management of R/M-NPC, we will focus on novel immunotherapeutic combinations and new classes of investigational agents. We

will also discuss the implications of the American Joint Classification of Cancer (AJCC)/Union of International Cancer Control (UICC) 9th version of the TNM stage classification in the treatments of LA-NPC and R/M-NPC. Finally, we will review the application of the data to the treatment of nonendemic NPC, including molecular profiling studies comparing endemic and nonendemic variants that inform on differential biology that may underpin treatment responses.

CURRENT STATE OF TREATMENT IN LA-NPC

Chemoradiotherapy Trials in LA-NPC

To our knowledge, the landmark trial INT-0099 was the first phase III trial to demonstrate the benefits of CCRT and AC in patients with LA-NPC for improving both locoregional and distant disease control, leading to an improvement in overall survival (OS).⁴ This established CCRT as the cornerstone of treatment for LA-NPC, supported by similar results of other chemoradiotherapy trials conducted in the Asia-Pacific region, albeit with variations in chemotherapy sequencing regimens.¹⁶⁻¹⁸ Between IC and AC, while the updated meta-analysis in 2024 indicated that either one in addition to a CCRT backbone was superior to CCRT alone,⁵ globally, there has been a shift toward the preference of platinum-doublet IC as it is better tolerated than platinum-doublet AC. To our knowledge, a randomized phase II trial in Hong Kong was the first to show an OS benefit from induction docetaxel-cisplatin chemotherapy followed by CCRT compared with CCRT alone.¹⁹ This finding was confirmed by two landmark, multicenter phase III trials investigating induction triplet docetaxel, cisplatin, and 5-fluorouracil (5-FU; TPF) and doublet gemcitabine and cisplatin (GP). Both trials reported an improvement of 10%-14% in DFS and 6%-10% in OS at 5 years with long-term follow-up.^{20,21} However, it was the later induction GP trial that convinced the field to pivot to IC as high incidence of grade 3 to 4 toxicities was observed with TPF.

Intuitively, the role of AC in NPC would be like IC, which is to target occult metastases, although in the era of 2- and 3-dimensional radiotherapy, the addition of AC also led to improvement in local control. However, AC in the form of platinum-doublet is poorly tolerated, averaging about 50%-70% compliance rates across studies.^{22,23} Recently, capecitabine has emerged as an alternative option for AC in high-risk LA-NPC, as demonstrated by two randomized phase III trials. Metronomic capecitabine (650 mg/m² twice daily for 1 year) after definitive CCRT with or without IC significantly improved 3-year failure-free survival (FFS; 85.3% v 75.7%) and 3-year OS (93.3% v 88.6%).²⁴ Full-dose adjuvant capecitabine for 6 months (1,000 mg/m² twice daily for 14 days every 21 days) after CCRT also achieved FFS benefit (3-year: 83.3% v 72.2%; 5-year: 78.5% v 65.9%).²⁵ In both studies, compliance rates of above 70% were higher than those of historical platinum-doublet AC.

Current Trials in the Era of Immunotherapy

Despite the intensification with GP in the induction phase or capecitabine in the adjuvant phase, approximately 20% of patients still experience disease recurrences, underscoring the need for more efficacious treatment combinations.²¹ In this context, recent trials have reported promising results regarding the efficacy of adding an anti-PD-1 antibody to a chemoradiotherapy backbone. Liu et al⁷ showed that adding sintilimab to IC and CCRT improved 3-year event-free survival (EFS; 86% v 76%) although results are not mature to reveal an OS benefit. Interestingly, a randomized phase II trial by Liu et al,⁶ using a sandwich approach with toripalimab administered during the IC and AC phases, demonstrated a significant improvement in 2-year DFS of 92% versus 74%. Building on this concept, the same investigators proceeded to conduct a larger phase III trial (ClinicalTrials.gov identifier: [NCT05211232](#)) investigating a similar sandwich approach using tislelizumab, with coprimary end points of EFS and complete response (CR) rates post-IC. Preliminary results suggest that combining tislelizumab and GP yielded higher rates of CR than GP alone (30.5% v 16.7%).²⁶ Finally, Ma et al²⁷ reported that adjuvant camrelizumab after IC and CCRT also led to an improvement of 3-year EFS rates (86.9% v 77.4%). These early results suggest the efficacy of anti-PD-1 antibody when added to a backbone of IC and CCRT, but questions remain regarding (1) optimal sequencing, (2) patient selection, and (3) novel combinations to rescue poor immune responders with primary resistance to GP and anti-PD-1 treatment.

Current Dogma of Radiotherapy Target Delineation

NPC presents challenges in radiotherapy because of its infiltrative nature and frequent skull base invasion, with several neural foramina serving as pathways for tumor spread. The 2018 international guideline defines two clinical target volumes (CTVs) for primary tumor delineation: a high-dose CTV with a uniform 5-mm expansion from gross tumor volume (GTV) and intermediate-dose CTV with a 10-mm expansion, including consideration of adjacent high-risk anatomic structures that are at risk of microscopic disease involvement.²⁸ By contrast, the Chinese guideline does not incorporate a margin to the GTV for constructing the high-dose CTV, and this Chinese protocol was used in most of the landmark trials reporting high tumor control rates.^{20,21} It is also recommended to include high-risk anatomic subsites for prophylactic irradiation, but recent studies have challenged this conventional dogma. Miao et al²⁹ demonstrated that avoiding anatomic regions like the cavernous and maxillary sinuses in 103 patients with early-stage NPC did not compromise on 10-year locoregional control. Sanford et al³⁰ retrospectively evaluated the treatment outcomes using CTV delineation based on an orderly stepwise pattern of tumor spread, reporting a 5-year local control rate of 94%. These contouring guidelines will be updated in 2025 by an International expert panel.

De-escalation strategies are also being explored for managing the neck. Historically, whole-neck irradiation has been standard because of the high frequency of occult nodal metastases, but this approach results in late toxicities like neck fibrosis, dysphagia, and radiation-induced hypothyroidism. A landmark trial by Tang et al confirmed that upper neck irradiation (cervical nodal levels II, III, and Va) only for the uninvolved neck yielded noninferior 5-year regional relapse-free rates and OS with reduced toxicities compared with whole-neck irradiation (cervical nodal levels II, III, IV, Va, and Vb).^{31,32} A randomized, noninferiority trial by Mao et al³³ supported sparing of the medial retropharyngeal nodal region in all patients with NPC who do not harbor retropharyngeal lymph node metastasis, thus reducing rates of dysphagia.

NOVEL TREATMENT CONCEPTS FOR LA-NPC

Plasma EBV DNA as a Biomarker With Broad Clinical Utility in NPC

Circulating cell-free EBV DNA consists of tumorigenic naked small viral DNA fragments (shorter than 181 bp) resulting from tumor necrosis or apoptosis.³⁴ Notably, EBV DNA can be quantified in peripheral blood using an ultrasensitive quantitative polymerase chain reaction–based assay.³⁵ These properties, combined with its ability to provide a real-time reflection of tumor burden in vivo, have led to the widespread adoption of EBV DNA in various aspects of NPC management, including population screening for early detection,³⁶ evaluation of treatment response,^{37–39} and disease surveillance.^{40,41}

After definitive treatment, approximately 10%–30% of patients continue to harbor residual plasma EBV DNA.^{42–44} Persistent EBV DNA post-treatment, whether observed at the completion of radiotherapy or at specific follow-up time points, was shown to be a strong predictor of disease relapse.^{43,45,46} This biomarker could predate clinical recurrence by 3–7 months, highlighting its potential to detect subclinical residual/recurrent disease.⁴⁷ However, its utility in guiding treatment selection is yet to be realized in clinical trials.

Plasma EBV DNA-Directed Precision Trials and Individualized Treatment

Several studies have reported the association between pretreatment EBV DNA levels and risk of disease relapse in NPC.^{48,49} Subsequent studies proposed optimal EBV DNA cutoffs for risk stratification, with Chen et al⁴⁸ suggesting >2,000 copies/mL and Tang et al⁵⁰ identifying ≥4,000 copies/mL. At present, two prospective trials indicate the feasibility of using pretreatment plasma EBV DNA to individualize treatment. One showed that two cycles of concurrent cisplatin with intensity-modulated radiotherapy were noninferior to three cycles in patients with low-risk LA-NPC defined by pretreatment EBV DNA levels of <4,000 copies/mL.⁵¹ Another trial found that omission of

concurrent chemotherapy did not compromise the 3-year DFS rates of patients with TNM-7 stage II and T3N0 NPC who lacked specific poor prognostic features, including pretreatment plasma EBV DNA level of $\geq 4,000$ copies/mL.⁵² In terms of treatment escalation, Liu et al⁶ enrolled patients with high-risk LA-NPC defined by pretreatment EBV DNA levels of $\geq 1,500$ copies/mL to receive neoadjuvant and adjuvant toripalimab and reported promising DFS outcomes. Still, several unresolved issues, particularly the lack of a consensus on the optimal cutoff and widespread assay standardization, preclude the broad adoption of pretreatment EBV DNA for treatment personalization in the clinic.

Given that patients with detectable plasma EBV DNA post-treatment harbor a poor prognosis,^{53,54} this has prompted the investigation on the role of AC in eliminating residual tumor clones postchemoradiotherapy. However, the first biomarker-driven randomized controlled trial—Hong Kong NPC-0502 study, failed to show that six cycles of adjuvant GP improve 5-year OS compared with observation among patients with a detectable EBV DNA 6–8 weeks post-radiotherapy.⁵⁵ First, the lack of benefit might be attributed to poor tolerability of adjuvant GP. Second, it was unexpected that EBV DNA spontaneously cleared in 72.4% of patients within six months post-treatment, which rendered the initial strategy for selecting high-risk candidates ineffective.⁵⁶ This observation concurred with another retrospective analyses by Neo et al,⁵⁷ where they showed that patients who manifested transient clearance between end of radiotherapy and 8–12 weeks post-treatment had low risks of relapse comparable with patients who had an undetectable EBV DNA at both time points. Third, it is plausible that residual subclinical disease is platinum-resistant, suggesting that non-platinum-based AC to avoid cross-resistance might be a better strategy. The ongoing clinical trial NRG-HN001 (ClinicalTrials.gov identifier: [NCT02135042](#)) aims to determine whether adjuvant gemcitabine and paclitaxel are superior to cisplatin and 5-FU for patients with detectable EBV DNA postradiotherapy and whether adjuvant PF can be omitted in patients with undetectable EBV DNA. Other adjuvant strategies investigating immunotherapeutic or targeted drugs are ongoing (ClinicalTrials.gov identifiers: [NCT03544099](#), [NCT02874651](#)). However, further research is needed to determine the optimal EBV assay and cutoff level, assessment time point, therapeutic window, and choice of AC.⁵⁸

From another perspective, rapid EBV DNA clearance during IC has been reported to indicate a favorable prognosis.^{38,59} A retrospective study of 673 patients with NPC identified four distinct EBV DNA response phenotypes during the course of IC and CCRT that were associated with divergent clinical outcomes.³⁸ These phenotypes included early responders (30%), who achieved complete biological response after one cycle of IC; intermediate responders (49%), who achieved complete biological response after three to four cycles of IC or midway through CCRT; late responders (11%), who

achieved complete biological response at the end of CCRT; and treatment-resistant patients (10%), who demonstrated persistent EBV DNA post-treatment. These response phenotypes were validated in another larger prospective study—EP-SEASON (ClinicalTrials.gov identifier: [NCT03855020](#)) that systematically profiled on-treatment EBV DNA patterns across the entire treatment course of 1,000 patients with EBV-positive NPC receiving sequential chemoradiotherapy. This study revealed how on-treatment EBV DNA kinetics could serve as a biomarker for real-time risk determination and facilitate risk-adapted clinical decision making.⁸

To test this concept, two prospective umbrella trials, namely, EP-STAR (ClinicalTrials.gov identifier: [NCT04072107](#)) and RIBBON-UM (ClinicalTrials.gov identifier: [NCT05517135](#)), are investigating whether monitoring longitudinal EBV DNA during IC could enable timely therapeutic adaptation of administering either adjuvant capecitabine or implementing a more intensive regimen in the high-risk group with a persistent EBV DNA post-IC consisting of radiotherapy with concurrent and adjuvant sintilimab for EP-STAR or adjuvant tislelizumab and metronomic capecitabine for RIBBON-LA-01 (ClinicalTrials.gov identifier: [NCT06093061](#)). Other ongoing trials are exploring various combination strategies for poor responders to IC, including anti-PD-1 antibodies and targeted therapies (ClinicalTrials.gov identifiers: [NCT05772208](#), [NCT05628922](#), [NCT04223024](#), and [NCT05201859](#)). For de-escalation, two randomized phase III trials (ClinicalTrials.gov identifiers: [NCT04456322](#), [NCT05674305](#)) are currently investigating whether radiotherapy alone is noninferior to CCRT for good responders (defined by undetectable EBV DNA) to IC. [Table 1](#) provides a summary of the clinical trials investigating plasma EBV DNA-directed treatment selection.

Induction Combinations to Enhance CR Rates Before CCRT in High-Risk LA-NPC

After IC, only 2%–10% of patients achieved a CR, whereas about 80% will have a partial response (PR).^{20,60,61} The depth of tumor response to IC serves as a strong predictor for risk of recurrence in LA-NPC.⁶² From the final analyses of the induction GP trial, 5-year OS rates for CR, PR, and stable/progressive disease post-IC were 100%, 88.4%, and 61.5%, respectively.²¹ These findings support the investigation of intensifying therapies in combination with GP to improve the CR rates to induction treatment. Incorporating anti-PD-1 and antiangiogenesis therapies represents potential approaches. As aforementioned, Mai et al²⁶ showed that the addition of tislelizumab to GP resulted in higher CR rates than GP alone. Another single-arm, phase II trial showed that this combination yielded a CR rate of 41.3%.⁶³ Interestingly, a phase II clinical trial enrolled patients with N3 disease who were at high risk of distant metastasis to receive a combination of camrelizumab and apatinib added to three cycles of IC.⁶⁴ They reported a CR rate of 26.5% post-induction, and the trial met the primary end point of 1-year

TABLE 1. Biomarker-Directed Precision Trials in Nasopharyngeal Carcinoma

Trial No.	Phase	Design	Patient Population ^a	Treatment Arm	Agent(s)	Intervention Period	Enrollment	Primary End Point
Deintensification trials								
NCT06239727	III	Open-label, noninferiority, multicenter, randomized study	Stage III with undetectable EBV DNA after the second cycle of CCRT	Experimental: Reduced-dose RT Control: Conventional-dose RT Treatment sequence: 1. IC with GP + camrelizumab 2. IMRT + 2 cycles of concurrent CT 3. Random assignment to reduced v conventional RT 4. Adjuvant camrelizumab for 9 cycles	Camrelizumab (anti-PD-1) and GP	Induction, concurrent, and adjuvant	593	3-year LRFFS
NCT04456322	III	Randomized, two-arm study	Stage II to IVA with undetectable EBV DNA after IC	Experimental: Definitive radiotherapy + nimotuzumab Control: CCRT with cisplatin	Nimotuzumab (anti-EGFR)	Concurrent radiotherapy	326	2-year PFS
Intensification trials								
NCT03925090	II	Placebo-controlled, two-arm study	Stage III to IVA with baseline EBV DNA $\geq 1,500$ copies/mL	Experimental: Toripalimab (induction and adjuvant) + CCRT Control: Placebo (induction and adjuvant) + CCRT	Toripalimab (anti-PD-1)	Induction and adjuvant	150	2-year PFS
NCT04223024	II	Randomized, two-arm study	Stage II to IVA with detectable EBV DNA after IC	Experimental: CCRT + nimotuzumab Control: CCRT	Nimotuzumab (anti-EGFR)	Concurrent radiotherapy	246	2-year PFS
NCT02874651 ^b	Ila	Randomized, double-blinded, placebo-controlled study	Stage I-II (AJCC 7th ed) with detectable EBV DNA at the end of RT/CCRT	Experimental: Adjuvant apatinib Control: Placebo	Apatinib (anti-VEGFR-2)	Adjuvant	78	3-year DFS
NCT04072107	II	Adaptive, biomarker-driven study	Stage III to IVA (except T3N0)	Intermediate-risk: Adjuvant metronomic capecitabine High-risk: Concurrent and adjuvant anti-PD-1 therapy	Metronomic capecitabine Sintilimab (anti-PD-1)	Adjuvant (intermediate-risk) Concurrent and adjuvant (high-risk)	110	2-year FFS
NCT06093061	II	Adaptive, biomarker-driven study	Stage III to IVA (except T3N0) with detectable EBV DNA after IC	High-risk: Adjuvant metronomic capecitabine and anti-PD-1 therapy	Metronomic capecitabine Tislelizumab (anti-PD-1)	Adjuvant (high-risk)	69	2-year DFS
(continued on following page)								

TABLE 1. Biomarker-Directed Precision Trials in Nasopharyngeal Carcinoma (continued)

Trial No.	Phase	Design	Patient Population ^a	Treatment Arm	Agent(s)	Intervention Period	Enrollment	Primary End Point
NCT02363400	III	Randomized, two-arm study	Stage II to IVB (AJCC 7th ed.) with detectable EBV DNA at 1 ± 1 week post-RT Finished RT ≥66 Gy (with or without IC and/or CCRT)	Experimental: MEP followed by oral Tegafur-uracil Control: Observation with delayed salvage CT	MEP Tegafur-uracil	Adjuvant	147	5-year TTP
NCT04453826	III	Randomized, two-arm study	Stage IVA with detectable EBV DNA after 3 cycles of GP IC	Experimental: Camrelizumab (concurrent and adjuvant) + CCRT Control: CCRT	Camrelizumab (anti-PD-1)	Concurrent and adjuvant	388	3-year PFS
Risk-adapted treatment intensification trial								
NCT04072107	II	Adaptive, biomarker-driven study	Stage III to IVA (except T3N0)	Intermediate-risk: Adjuvant metronomic capecitabine High-risk: Concurrent and adjuvant anti-PD-1 therapy	Metronomic capecitabine Sintilimab (anti-PD-1)	Adjuvant (intermediate-risk) Concurrent and adjuvant (high-risk)	110	2-year FFS
NCT05517135	II	Adaptive, biomarker-driven study	Stage III to IVA (except T3N0)	Low-risk: Up-front CCRT with or without adjuvant chemotherapy Intermediate-risk: IC + CCRT with or without metronomic capecitabine High-risk: IC + CCRT + adjuvant metronomic capecitabine and anti-PD-1 therapy	Metronomic capecitabine Tislelizumab (anti-PD-1)	Induction (intermediate-risk) Adjuvant (high-risk)	142	2-year DFS

NOTE. Ongoing phase II and III clinical trials investigating EBV DNA-guided treatment strategies.

Abbreviations: AJCC, American Joint Classification of Cancer; CCRT, radiotherapy plus concurrent cisplatin; DFS, disease-free survival; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; ed, edition; FFS, failure-free survival; GP, gemcitabine plus cisplatin; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; LRRFS, locoregional failure-free survival; MEP, mitomycin C, epirubicin, and cisplatin; PFS, progression-free survival; RT, radiotherapy; TTP, time to progression; VEGF, vascular endothelial growth factor.

^aStaging according to the 8th AJCC edition, unless otherwise specified.

^bTrial terminated because of unacceptable toxicity (nasopharynx necrosis and massive hemorrhage).

distant metastasis-free survival rate of 98%. However, challenges remain in accurately assessing treatment response at the skull base, paranasal sinuses, and intracranial regions as it is difficult to distinguish between residual and treated tumors on postinduction MRI. Pathologic response evaluated through biopsy would likely overestimate the magnitude of response because of limitations of sampling. Biological response assessed by plasma EBV DNA is a potential assessment tool, except that it is not widely available.

Radiotherapy Dose and Volume Adaptation Based on IC Response

Apart from systemic therapy, radiotherapy approaches could also be individualized based on treatment response. Contouring the GTV based on pre-IC tumor volumes was recommended by the 2018 international consensus,²⁸ but recent evidence has prompted a reconsideration of this approach. A trial from Sichuan, involving 212 patients, demonstrated that using post-IC GTV as CTVp_High resulted in comparable 5-year locoregional relapse-free survival (93.5% v 90.2%) and fewer side effects, such as xerostomia and cognitive impairment.⁶⁵ This was reinforced by a larger phase III noninferiority trial with 445 patients (ClinicalTrials.gov identifier: [NCT04384627](#)), showing comparable survival outcomes between the two contouring methods.⁶⁶

In the same vein, good responders to IC are likely to harbor sensitive tumor clones, thereby questioning the need for high doses of radiotherapy. A phase II study exploring de-escalating radiotherapy doses from 70 to 60 Gy for good responders after 2 cycles of IC showed comparable 3-year DFS rates (85.9% v 84.8%).⁶⁷ An ongoing trial (ClinicalTrials.gov identifier: [NCT04448522](#)) is assessing reduced-dose radiotherapy (63.6 Gy in 30 fractions) in patients with IC-sensitive TNM-8 stage II to III NPC. Conversely, for poor responders, higher radiotherapy doses may be required to overcome resistant clones.

SYSTEMIC THERAPIES AND ANTI-PD-1 ANTIBODIES IN R/M-NPC

Anti-PD-1 Antibody With Platinum-Based Chemotherapy in First-Line Treatment of R/M-NPC

The results of CAPTAIN-1st, JUPITER-02, and RATIONALE-309 have been practice-changing for the first-line treatment of endemic R/M-NPC (Table 2).¹²⁻¹⁴ In these randomized placebo-controlled trials, the addition of anti-PD-1 antibody to GP followed by maintenance with anti-PD-1 antibody alone yielded superior progression-free survival (PFS) compared with chemotherapy-placebo, with similar hazard ratios (HRs) of around 0.51-0.53 across these studies. Objective response (ORR) and disease control rates were also higher, independent of PD-L1 expression status of the tumor and location and number of metastases. Although these studies were not powered to detect an OS difference,

the 5-year OS rates in the JUPITER-02 study were 52% versus 33.9%, in favor of the GP-toripalimab group.⁶⁸ In the RATIONALE-309 study, 49.2% of patients in the GP-placebo group crossed over to receive tislelizumab at progression, which might have accounted for the absence of an OS efficacy signal.¹² The investigators did observe that the use of up-front tislelizumab resulted in a longer PFS2 than the control group that received tislelizumab as second-line treatment (HR of 0.38 [95% CI, 0.2 to 0.58]).¹² Thus, the National Comprehensive Cancer Network 2025 (version 2) guidelines recommended platinum-gemcitabine and toripalimab as the preferred first-line treatment for R/M NPC, whereas other regimens may include the combination of platinum-gemcitabine with other anti-PD-1 antibodies.

Despite the impressive results of these trials, over 40% of patients progressed during the maintenance phase, likely because of acquired resistance. Currently, there is no single standard maintenance regimen after response to chemotherapy with or without anti-PD-1 antibody, and options such as anti-PD-1 antibody or capecitabine may be considered.^{12-14,69} Another potential approach is the dual targeting of immune-checkpoint proteins (ICPs), given the role of other ICPs, such as LAG-3, CTLA-4, and TIM-3, in contributing to T-cell exhaustion as suggested in some single-cell sequencing studies of NPC.⁷⁰⁻⁷³ Therefore, dual targeting of different ICPs is currently under investigation both in the setting of first-line maintenance or subsequent lines of treatment. The REMAIN study (NRG-HN011, ClinicalTrials.gov identifier: [NCT06029270](#)) is a randomized phase II study that is investigating the efficacy of adding relatlimab to nivolumab as maintenance after response to first-line GP-nivolumab in patients with R/M-NPC.

New Combinations With Anti-PD-1 Antibodies Under Investigation

The result of the KEYNOTE122 study in multiply pretreated patients with platinum-refractory R/M-NPC showed that pembrolizumab monotherapy had better tolerability, but was not superior to chemotherapy in terms of OS and ORR, independent of PD-L1 expression.⁷⁴ Subsequent trials have thus turned their focus on combining anti-PD-1 antibody with chemotherapy, antivascular drugs, other ICP inhibitors, or novel targeted therapies. The most mature of these clinical trials, which have led to their incorporation into the Chinese Society of Clinical Oncology practice guidelines, investigated the combination of anti-PD-1 antibody with antivascular endothelial growth factor receptor tyrosine kinase inhibitor.⁷⁵ In a phase II trial, the combination of camrelizumab and apatinib yielded the ORR of 65% in 40 patients who were platinum-refractory and 34.3% in those who had progressed on anti-PD-1 antibody.⁷⁵ However, caution needs to be exercised in patients with previous irradiation and disease invading vascular structures. Severe nasopharyngeal necrosis occurred in nine patients (12.5%), and one patient manifested grade 4 hemorrhage. Zhang et al⁷⁶ who investigated toripalimab and anlotinib also reported similar results. A study

TABLE 2. Summary of Results of Three Landmark Trials Investigating Platinum-Doublet and Anti-PD-1 Antibody for First-Line Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma

RCT Name	JUPITER-02 ¹⁴	CAPTAIN-1st ¹³	RATIONALE-309 ^{12,a}
Trial identifier	NCT03581786	NCT03707509	NCT03924986
Anti-PD-1 antibody	Toripalimab	Camrelizumab	Tislelizumab
Sites	Mainland China, Singapore, Taiwan	Mainland China	Mainland China, Taiwan, Thailand
Sample size	289	263	263
PD-L1 positivity	82.9% ($\geq 1\%$ of TC/ $\geq 1\%$ of IC)	Not screened	79.8% ($\geq 1\%$ of TC)
Median follow-up (months)	36.0	15.6	27.5
Median PFS (months, for anti-PD-1 arm); HR (95% CI)	21.4; 0.52 (0.37 to 0.73)	9.7; 0.54 (0.39 to 0.76)	9.6; 0.53 (0.39 to 0.71)
Median OS (months, for anti-PD-1 arm); HR (95% CI)	Not reached; 0.63 (0.45 to 0.89)	Not reached; 0.67 (0.41 to 1.11)	45.3; 0.73 (0.51 to 1.05)
ORR (IRC)			
Experimental arm, %	78.8	87.3	69.5
Control arm, %	67.1	80.6	55.3

Abbreviations: HR, hazard ratio; IC, induction chemotherapy; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TC, tumor cells.

^aRATIONALE-309: 49.2%-52% of patients in the chemo-placebo arm crossed over to tislelizumab.

conducted in Singapore investigated 48 patients with platinum-refractory R/M-NPC who were randomly assigned to pembrolizumab alone or in combination with bevacizumab.⁷⁷ The study met its primary end point of ORR (58.3% [combination] v 12.5%). Grade 3 to 4 bleeding was reported in 17% of patients from the combination group.

The combination of ICP inhibitors has also shown promise in phase II studies targeting platinum-refractory R/M-NPC. A phase II study of 40 patients involving investigators from Singapore and Taiwan reported that nivolumab-ipilimumab yielded an ORR of 38%, with <5% rates of grade 3 to 4 adverse events.⁷⁸ Building on this concept, the Alliance for Clinical Trial in Oncology group is currently conducting a randomized phase II study of nivolumab and ipilimumab with or without cabozantinib in patients who had failed previous platinum-chemotherapy and immunotherapy (ClinicalTrials.gov identifier: [NCT05904080](#)).

Using a different approach, Chen et al⁷⁹ reported a phase I/II trial of toripalimab and an anti-LAG-3 antibody (LBL-007) in 80 patients with solid tumors, 30 of whom patients had multiply pretreated R/M-NPC. The ORR and 1-year PFS rates were 33.3% and 40% in the anti-PD-1-naïve group, respectively, and 11.8% and 21.2% in the anti-PD-1-exposed group, respectively. The combination of anti-TIM-3 and anti-PD-1 antibodies is under clinical investigation, and preliminary results of TQB2618 and penpulimab suggest that this approach is feasible in NPC (ClinicalTrials.gov identifier: [NCT05563480](#)).⁸⁰

New Therapeutic Classes on the Horizon

Candonilimab is a bispecific antibody targeting both PD-1 and CTLA-4, and its Fc-null design may enhance antitumor

activity while mitigating immune-related adverse events.⁸¹ In the phase II, single-arm AK104-204 study, candonilimab was given to immunotherapy-naïve patients with R/M-NPC who had failed ≥ 2 lines of chemotherapy.⁸² The ORR was 30% in the 20 efficacy-evaluable patients and 57.1% in those who had PD-L1-positive tumors. In the AK104-IIT trial, a phase II single-arm study, candonilimab was combined with 4-6 cycles of chemotherapy in patients with anti-PD-1-refractory R/M-NPC and yielded the ORR of 60% and a 26.7% rate of grade ≥ 3 treatment-related adverse events.⁸³

Another therapeutic class that has shown promise is ADCs, which have rapidly advanced recently and are being investigated across different cancers. MRG003 is a novel ADC with a humanized antiepidermal growth factor receptor antibody that is conjugated to monomethyl auristatin E.⁸⁴ In a phase IIa study in patients with heavily pretreated R/M-NPC, MRG003 was evaluated at two dose levels, with the ORR of 39.3% and 55.2% for the 2.0 and 2.3 mg/kg every 3 weeks dose levels, respectively.

IMPLICATIONS OF THE NEW AJCC/UICC TNM STAGE CLASSIFICATION 9TH VERSION (TNM-9)

Rationale and Concepts Underpinning TNM-9 for Mo and M1 Diseases

With the substantial progress in diagnosis and therapeutics, the prognosis of patients with NPC has significantly improved over time.⁸⁵ To address this, the AJCC/UICC committees reviewed and updated the TNM stage classification from the 8th edition to the 9th version in January 2025.⁸⁶ This revision was based on a retrospective review of 4,914 consecutive patients from eight participating centers who were treated from 2014 to 2015; OS was the primary end

point, and adjusted HRs of different subgroups were analyzed to ascertain the optimal TNM stage grouping. An independent study from China was conducted to provide external validation.⁸⁷ For T classification, there were minimal changes, apart from clarifications on the annotation of skull base and orbit involvement. For N classification, the notable change was the inclusion of advanced extranodal extension (ENE), defined as unequivocal involvement of adjacent muscle, skin, and/or neurovascular structures, under the N3 category.

For patients with M1 disease, Pan et al⁸⁶ found that the number of metastatic lesions was the only independent prognostic factor on multivariable analyses. Thus, in TNM-9, M1 is subclassified as M1a and M1b for patients with ≤ 3 and >3 metastatic lesions, respectively; this was associated with a significant difference in OS between the two groups (5-year OS rates of 60.7% v 44.2%, respectively).⁸⁶

For TNM stage grouping, there was an overall downstaging for TNM-9 (Table 3). T2N0 and T1-2N1 are now classified as stages IA and IB, respectively. It is worth noting that the subdivision of stage I into IA and IB was felt to be necessary despite similar OS, because of the preferential use of chemotherapy and an inferior adjusted HR in patients with stage IB disease. TNM-8 stages III and IVA have been reclassified as TNM-9 stages II and III, respectively. Stage IV is now limited to patients with M1 disease and subdivided into IVA and IVB according to the number of metastatic lesions.

Impact of TNM-9 on Treatment Strategies and Design of New Trials

Despite the overall downstaging in TNM-9, clinicians should not de-escalate treatments until prospective data are

TABLE 3. Comparison of American Joint Classification of Cancer/Union of International Cancer Control 8th Edition and 9th Version of TNM Stage Groupings for Nasopharyngeal Carcinoma

TNM-8					
		T1	T2	T3	T4
M0	N0	I	II	III	IVA
	N1	II	II	III	IVA
	N2	III	III	III	IVA
	N3	IVA	IVA	IVA	IVA
M1	Any N	IVB			

TNM-9					
		T1	T2	T3	T4
M0	N0	IA	IA	II	III
	N1	IB	IB	II	III
	N2	II	II	II	III
	N3	III	III	III	III
M1a	Any N	IVA			
M1b		IVB			

available. For instance, CCRT should still be considered for stage IB disease, especially for T2N1 patients.⁸⁸ On the other hand, treatment intensification with IC should be considered for patients who are now classified as N3 because of the presence of advanced ENE.^{85,88}

For patients with stage IVA disease with good responses to upfront chemotherapy with or without immunotherapy, metastasis-directed therapies (eg, stereotactic body radiation therapy, surgery, or radiofrequency ablation) could be considered because of the better prognosis of these patients. For instance, Yang et al⁸⁹ reported excellent 3-year local control rates of 89.1% with metastasis-directed therapy in patients with M1 NPC. Defining a truly oligo-metastatic subgroup may require factors beyond lesion count, particularly tumor growth kinetics, with local ablative strategies favored in patients with low-tempo argometastatic disease.⁹⁰ The benefit of locoregional radiotherapy in patients with de novo M1 disease who have at least a PR to up-front chemotherapy may be more pronounced in those with M1a than M1b disease although 70% of patients had ≥ 3 metastatic lesions at random assignment in the study by You et al,¹¹ which demonstrated an improvement in OS with locoregional radiotherapy in this patient population.

Further studies are warranted with the advent of TNM-9. The role of concurrent chemotherapy in TNM-9 stage IB NPC and patients with TNM-9 stage II NPC who had a good response to IC deserves investigation. EBV DNA is potentially a useful predictive biomarker for such patients, where concurrent chemotherapy may be omitted for low-risk disease (eg, low pretreatment EBV DNA levels for stage IB NPC and rapid EBV DNA clearance for the latter). The role of IC in patients with N3 disease because of advanced ENE should also be prospectively studied. Trials targeting TNM-9 stage IVA and IVB patients separately should be designed, where for the former, the role of locoregional radiotherapy and/or metastasis-directed therapy when added to a chemotherapy-anti-PD-1 antibody backbone should be investigated, whereas priority ought to be accorded to trials on systemic therapy intensification for patients with stage IVB disease.

APPLICABILITY OF EVIDENCE TO NONENDEMIC NPC

Nonendemic NPC Geographic, Racial, and Ethnic Variation and Natural History

In North America and Europe, NPC represents a rare entity with annual incidence rates of one case per 100,000.^{91,92} However, intermediate rates of incidence have been observed in the Arctic, indigenous populations of Alaska, and Northwest territories of Canada, where eight and nine NPC cases per 100,000 person-years, respectively, have been reported. In Western countries, approximately 40%-50% of NPC cases are of the keratinizing squamous cell carcinoma histologic subtype,⁹³

TABLE 4. Outcomes of Viral-Related and Unrelated Nonendemic Nasopharyngeal Carcinomas

Studies	Timeline Period (years)	No.	Subtypes (%)	Outcomes	Races	Conclusions
Stenmark et al ¹³	26	61	26 (43%) EBV+/HPV–	5-year OS: 72% PFS: 63% LRC: 87% DM: 77%	74% White 15% African American 11% Asian/Middle Eastern	Best OS: EBV+ Worst OS: double-negative HPV+ worse OS than EBV+
			18 (30%) EBV–/HPV+	5-year OS: 48% PFS: 34% LRC: 48% DM: 100%		
			17 (28%) EBV/HPV–	5-year OS: 18% PFS: 12% LRC: 26% DM: 60%		
Dogan et al ¹⁰¹	31	63	38 (60%) EBV+/HPV unknown	3-year FU Median OS: EBV+: 12 years	100% White	Worst OS: double-negative No significant difference between EBV+ and HPV+
			6 (10%) EBV–/HPV+	EBV–: 4 years HPV+: 7 years		
			19 (30%) EBV–/HPV–	OS: 3.8 years		
Wu et al ¹⁰²	19	78	43 (55%) EBV+	3-year OS: 90%		No significant difference in OS between groups
			12 (15%) HPV+	3-year OS: 70%		
			23 (30%) EBV–/HPV–	3-year OS: 52%		
Robinson et al ¹⁰³	12	67	47 (70%) EBV+/HPV–	Mean OS: 5.6 years	51% White 25% Far Eastern Asia 21% Black 3% North Africa	No significant difference in OS between groups
			11 (16%) EBV–/HPV+	Mean OS: 4.5 years		
			9 (13%) EBV–/HPV–	Mean OS: 3.9 years		
Verma et al ¹⁰⁴	19	343	205 (60%) EBV+	Median FU 4.9 years	47% White 37% Asian 16% Other	No significant difference in OS, LRC, and DM between groups
			21 (6%) HPV+	NR by subgroup		
			12 (3.5%) EBV–/HPV–			
			105 (31%) viral unknown			
Huang et al ⁹⁹	15	451	422 (94%) EBV+	3-year OS: 89%	20% White 72% Asian 8% Other	No significant difference in OS between groups
			29 (6%) HPV+	3-year OS: 83%		
Kano et al ¹⁰⁵	19	59	49 (83%) EBV+/HPV–	3-years OS: 57%	NR	No significant difference in OS between groups
			2 (3%) EBV+/HPV+	3-year OS: 50%		
			8 (16%) EBV–/HPV–	3-year OS: 80%		

NOTE. Italics indicate studies displaying no differences in outcome according to subgroups.

Abbreviations: DM, distant metastasis; EBV, Epstein-Barr virus; FU, fluorouracil; HPV, human papillomavirus; LRC, locoregional control; NR, not reported; OS, overall survival; PFS, progression-free survival.

and the racial and ethnic patterns are nonuniform, with higher rates of NPC in Chinese, Filipino, Japanese, Black, and Hispanic Americans compared with White patients.^{94,95} Overall, historical data suggest that non-endemic NPC harbors a poorer prognosis compared with the endemic subtype.⁹⁶ Implicated factors may include genetic factors, environmental characteristics, and the association of EBV infection with the latter.⁹⁷ Molecular profiling studies have also identified higher frequencies of somatic mutations like *BRCA1* in nonendemic than endemic NPC, which may confer a poorer prognosis.⁹⁸

Emergence of HPV-Positive Subtype of Nonendemic NPC

The association of previous HPV infection and NPC was first reported in a population-based study of over 16,000 individuals, of whom 2,747 diagnosed with NPC had a significantly higher previous HPV infection compared with controls, irrespective of sex.⁹⁹ A recent systematic review and meta-analysis reported an 18% global prevalence of HPV-positive NPC, with substantial discrepancy across geographical regions (25% in North America and 13% in

Asia); EBV/HPV co-infection was rare (3%). This is in line with the rising trend of HPV-driven oropharyngeal cancer, suggesting similar risk factors that could be linked to the development of HPV-positive NPC.¹⁰⁰ The authors also identified a higher prevalence of HPV positivity in the keratinizing histologic subtype of NPC than the non-keratinizing subtypes (39% v 16%), supporting the distinct tumorigenesis between EBV-positive and HPV-positive NPCs. Unlike HPV-driven oropharyngeal cancer that is almost exclusively linked to HPV16, HPV-positive NPC is characterized by both HPV16 and 18 genotypes although the implications of non-16 genotypes are unknown.¹⁰⁰

Distinct Treatment Responses and Clinical Outcomes in Nonendemic NPC

While HPV-positive NPC represents a distinct clinical entity, it remains controversial whether the clinical outcomes of this entity differ from EBV-positive NPC (Table 4).^{3,99,101–105} Of note, the studies reporting a significant difference in OS between EBV-positive and HPV-positive NPCs included mostly White patients, and patients with viral-negative disease harbored the worst prognosis.^{3,101} A variety of factors, including small sample size and imbalance between subgroups, as well as ethnicity, geography, variations in follow-up duration, inconsistency between EBV and HPV testing among studies, and disparate treatments, might have driven the differences in survival rates. To date, no prospective data have compared treatment responses according to EBV and HPV status in NPC, and overall, the treatment landscapes for LA- and R/M-nonendemic NPC have been adapted based on the data and practice for endemic NPC. In the R/M setting, RTOG 3521 (ClinicalTrials.gov identifier: [NCT06457503](#)) is a single-arm, multicenter, phase IV trial to prospectively evaluate the efficacy of GP and toripalimab in patients with both EBV-positive and EBV-negative R/M-NPCs. In addition to prospectively determining the efficacy of combination of GP and toripalimab in a North America patient population, this study offers a unique opportunity to explore biomarkers specific to non-EBV-driven NPC.

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Endemic and Nonendemic NPC Molecular Phenotypes and Treatment Implications

The molecular landscape knowledge in nonendemic NPC is limited by paucity of data compared with endemic NPC, which has been characterized by extensive molecular profiling studies including single-cell profiling.^{106,107} To address this knowledge gap, Lenoci et al¹⁰⁸ performed a meta-analysis using six endemic NPC transcriptomic data sets and compared against a nonendemic NPC data set. They identified coherent molecular patterns, segregated in four phenotypic clusters (Cl1: immune-active, Cl2: defense response, Cl3: proliferation, Cl4: perineural interaction/EBV exhaustion) that were differentially associated with prognosis. Among them, the Cl3 cluster harbored high proliferative activity and had the worst prognosis. The authors also evaluated the predictive impact of the clusters, testing their chemosensitivity based on gene expression data, and unveiled Cl3 to be the most chemosensitive, whereas Cl1 and Cl2 were most sensitive to radiation and immune checkpoint inhibition, respectively. Impressively, three of the four phenotypic clusters were recapitulated in an independent cohort of 50 nonendemic tumors from Italy, except for Cl3. This study highlights the importance of developing a deeper understanding of NPC biology, so that treatment of nonendemic NPC can be modified accordingly.

CONCLUSION

Herein, we shared on the advances of treatment of NPC that had been driven by new therapeutic agents, including anti-PD-1 antibody, and novel concepts of precise stratification for treatment individualization. With several ongoing trials investigating these ideas, we expect that the treatment landscape of NPC will continue to evolve rapidly, along with improvement of survival outcomes of patients. It is important to consider the applicability of this evidence to the less frequent nonendemic subtype especially with the adoption of the new TNM-9 for both endemic and nonendemic NPCs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Chua MLK, Wee JTS, Hui EP, et al: Nasopharyngeal carcinoma. *Lancet* 387:1012-1024, 2016
- Chua ML, Sun Y, Supiot S: Advances in nasopharyngeal carcinoma-"West meets East". *Br J Radiol* 92:2019004, 2019
- Stenmark MH, McHugh JB, Schipper M, et al: Nonendemic HPV-positive nasopharyngeal carcinoma: Association with poor prognosis. *Int J Radiat Oncol Biol Phys* 88:580-588, 2014
- Al-Sarraf M, LeBlanc M, Giri PG, et al: Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized intergroup study 0099. *J Clin Oncol* 16:1310-1317, 1998
- Petit C, Lee A, Ma J, et al: Role of chemotherapy in patients with nasopharynx carcinoma treated with radiotherapy (MAC-NPC): An updated individual patient data network meta-analysis. *Lancet Oncol* 24:611-623, 2023
- Liu SL, Li XY, Yang JH, et al: Neoadjuvant and adjuvant toripalimab for locoregionally advanced nasopharyngeal carcinoma: A randomised, single-centre, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 25:1563-1575, 2024
- Liu X, Zhang Y, Yang KY, et al: Induction-concurrent chemoradiotherapy with or without sintilimab in patients with locoregionally advanced nasopharyngeal carcinoma in China (CONTINUUM): A multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial. *Lancet* 403:2720-2731, 2024
- Lv J, Xu LX, Li ZX, et al: Longitudinal on-treatment circulating tumor DNA as a biomarker for real-time dynamic risk monitoring in cancer patients: The EP-SEASON study. *Cancer Cell* 42:1401-1414.e4, 2024
- Zou X, You R, Liu H, et al: Establishment and validation of M1 stage subdivisions for de novo metastatic nasopharyngeal carcinoma to better predict prognosis and guide treatment. *Eur J Cancer* 77:117-126, 2017
- Liu Y, Zuo ZC, Zeng XY, et al: Establishing subdivisions of M1 stage nasopharyngeal carcinoma based on decision tree classification: A multicenter retrospective study. *Oral Oncol* 153:106834, 2024
- You R, Liu YP, Huang PY, et al: Efficacy and safety of locoregional radiotherapy with chemotherapy vs chemotherapy alone in de novo metastatic nasopharyngeal carcinoma: A multicenter phase 3 randomized clinical trial. *JAMA Oncol* 6:1345-1352, 2020
- Yang Y, Pan J, Wang H, et al: Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: A multicenter phase 3 trial (RATIONALE-309). *Cancer Cell* 41:1061-1072.e4, 2023
- Yang Y, Qu S, Li J, et al: Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): A multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 22:1162-1174, 2021
- Mai HQ, Chen QY, Chen D, et al: Toripalimab plus chemotherapy for recurrent or metastatic nasopharyngeal carcinoma: The JUPITER-02 randomized clinical trial. *JAMA* 330:1961-1970, 2023
- Jiménez-Labaig P, Rullan A, Hernando-Calvo A, et al: A systematic review of antibody-drug conjugates and bispecific antibodies in head and neck squamous cell carcinoma and nasopharyngeal carcinoma: Charting the course of future therapies. *Cancer Treat Rev* 128:102772, 2024
- Lee AWM, Tung SY, Ng WT, et al: A multicenter, phase 3, randomized trial of concurrent chemoradiotherapy plus adjuvant chemotherapy versus radiotherapy alone in patients with regionally advanced nasopharyngeal carcinoma: 10-year outcomes for efficacy and toxicity. *Cancer* 123:4147-4157, 2017
- Lin JC, Jan JS, Hsu CY, et al: Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: Positive effect on overall and progression-free survival. *J Clin Oncol* 21:631-637, 2003
- Wee J, Tan EH, Tai BC, et al: Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol* 23:6730-6738, 2005
- Hui EP, Ma BB, Leung SF, et al: Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol* 27:242-249, 2009
- Sun Y, Li WF, Chen NY, et al: Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: A phase 3, multicentre, randomised controlled trial. *Lancet Oncol* 17:1509-1520, 2016
- Zhang Y, Chen L, Hu GQ, et al: Final overall survival analysis of gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma: A multicenter, randomized phase III trial. *J Clin Oncol* 40:2420-2425, 2022
- Chen L, Hu CS, Chen XZ, et al: Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: A phase 3 multicentre randomised controlled trial. *Lancet Oncol* 13:163-171, 2012
- Chen L, Hu CS, Chen XZ, et al: Adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: Long-term results of a phase 3 multicentre randomised controlled trial. *Eur J Cancer* 75:150-158, 2017
- Chen YP, Liu X, Zhou Q, et al: Metronomic capecitabine as adjuvant therapy in locoregionally advanced nasopharyngeal carcinoma: A multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial. *Lancet* 398:303-313, 2021
- Miao J, Wang L, Tan SH, et al: Adjuvant capecitabine following concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: A randomized clinical trial. *JAMA Oncol* 8:1776-1785, 2022

26. Mai H-Q, Liu SL, Chen Q-Y, et al: Tislelizumab versus placebo combined with induction chemotherapy followed by concurrent chemoradiotherapy and adjuvant tislelizumab or placebo for locoregionally advanced nasopharyngeal carcinoma: Interim analysis of a multicenter, randomized, placebo-controlled, double-blind, phase 3 trial. *J Clin Oncol* 42, 2024 (suppl 16; abstr 6001)
27. Ma J, Sun Y, Liang Y-L, et al: Adjuvant PD-1 blockade with camrelizumab in high-risk locoregionally advanced nasopharyngeal carcinoma (DIPPER): A multicenter, open-label, phase 3, randomized controlled trial. *J Clin Oncol* 42, 2024 (suppl 17; abstr LBA6000)
28. Lee AW, Ng WT, Pan JJ, et al: International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma. *Radiother Oncol* 126:25-36, 2018
29. Miao J, Di M, Chen B, et al: A prospective 10-year observational study of reduction of radiation therapy clinical target volume and dose in early-stage nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 107:672-682, 2020
30. Sanford NN, Lau J, Lam MB, et al: Individualization of clinical target volume delineation based on stepwise spread of nasopharyngeal carcinoma: Outcome of more than a decade of clinical experience. *Int J Radiat Oncol Biol Phys* 103:654-668, 2019
31. Tang LL, Huang CL, Zhang N, et al: Elective upper-neck versus whole-neck irradiation of the uninvolved neck in patients with nasopharyngeal carcinoma: An open-label, non-inferiority, multicentre, randomised phase 3 trial. *Lancet Oncol* 23:479-490, 2022
32. Huang CL, Zhang N, Jiang W, et al: Reduced-volume irradiation of uninvolved neck in patients with nasopharyngeal cancer: Updated results from an open-label, noninferiority, multicenter, randomized phase III trial. *J Clin Oncol* 42:2021-2025, 2024
33. Mao YP, Wang SX, Gao TS, et al: Medial retropharyngeal nodal region sparing radiotherapy versus standard radiotherapy in patients with nasopharyngeal carcinoma: Open label, non-inferiority, multicentre, randomised, phase 3 trial. *BMJ* 380:e072133, 2023
34. Shotelersuk K, Khorprasert C, Sakdikul S, et al: Epstein-Barr virus DNA in serum/plasma as a tumor marker for nasopharyngeal cancer. *Clin Cancer Res* 6:1046-1051, 2000
35. Lam WKJ, Jiang P, Chan KCA, et al: Sequencing-based counting and size profiling of plasma Epstein-Barr virus DNA enhance population screening of nasopharyngeal carcinoma. *Proc Natl Acad Sci U S A* 115:E5115-E5124, 2018
36. Chan KCA, Woo JKS, King A, et al: Analysis of plasma Epstein-Barr virus DNA to screen for nasopharyngeal cancer. *N Engl J Med* 377:513-522, 2017
37. Wang WY, Twu CW, Chen HH, et al: Plasma EBV DNA clearance rate as a novel prognostic marker for metastatic/recurrent nasopharyngeal carcinoma. *Clin Cancer Res* 16:1016-1024, 2010
38. Lv J, Chen Y, Zhou G, et al: Liquid biopsy tracking during sequential chemo-radiotherapy identifies distinct prognostic phenotypes in nasopharyngeal carcinoma. *Nat Commun* 10:3941, 2019
39. Xu JY, Wei XL, Ren C, et al: Association of plasma Epstein-Barr virus DNA with outcomes for patients with recurrent or metastatic nasopharyngeal carcinoma receiving anti-programmed cell death 1 immunotherapy. *JAMA Netw Open* 5:e220587, 2022
40. Lo YM, Chan AT, Chan LY, et al: Molecular prognostication of nasopharyngeal carcinoma by quantitative analysis of circulating Epstein-Barr virus DNA. *Cancer Res* 60:6878-6881, 2000
41. Lo YM, Chan LY, Lo KW, et al: Quantitative analysis of cell-free Epstein-Barr virus DNA in plasma of patients with nasopharyngeal carcinoma. *Cancer Res* 59:1188-1191, 1999
42. Chan AT, Lo YM, Zee B, et al: Plasma Epstein-Barr virus DNA and residual disease after radiotherapy for undifferentiated nasopharyngeal carcinoma. *J Natl Cancer Inst* 94:1614-1619, 2002
43. Lin JC, Wang WY, Chen KY, et al: Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med* 350:2461-2470, 2004
44. Le QT, Jones CD, Yau TK, et al: A comparison study of different PCR assays in measuring circulating plasma Epstein-Barr virus DNA levels in patients with nasopharyngeal carcinoma. *Clin Cancer Res* 11:5700-5707, 2005
45. Lee VH, Kwong DL, Leung TW, et al: Prognostication of serial post-intensity-modulated radiation therapy undetectable plasma EBV DNA for nasopharyngeal carcinoma. *Oncotarget* 8:5292-5308, 2017
46. Ghibid A, Benzeid R, Faouzi A, et al: The dynamic change in plasma Epstein-Barr virus DNA load over a long-term follow-up period predicts prognosis in nasopharyngeal carcinoma. *Viruses* 15:66, 2022
47. Chan AT, Ma BB, Lo YM, et al: Phase II study of neoadjuvant carboplatin and paclitaxel followed by radiotherapy and concurrent cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: Therapeutic monitoring with plasma Epstein-Barr virus DNA. *J Clin Oncol* 22:3053-3060, 2004
48. Chen FP, Lin L, Liang JH, et al: Development of a risk classification system combining TN-categories and circulating EBV DNA for non-metastatic NPC in 10,149 endemic cases. *Ther Adv Med Oncol* 13:17588359211052417, 2021
49. Li WZ, Wu HJ, Lv SH, et al: Assessment of survival model performance following inclusion of Epstein-Barr virus DNA status in conventional TNM staging groups in Epstein-Barr virus-related nasopharyngeal carcinoma. *JAMA Netw Open* 4:e2124721, 2021
50. Tang SQ, Chen L, Li WF, et al: Identifying optimal clinical trial candidates for locoregionally advanced nasopharyngeal carcinoma: Analysis of 9468 real-world cases and validation by two phase 3 multicentre, randomised controlled trial. *Radiother Oncol* 167:179-186, 2022
51. Li XY, Luo DH, Guo L, et al: Deintensified chemoradiotherapy for pretreatment Epstein-Barr virus DNA-selected low-risk locoregionally advanced nasopharyngeal carcinoma: A phase II randomized noninferiority trial. *J Clin Oncol* 40:1163-1173, 2022
52. Tang LL, Guo R, Zhang N, et al: Effect of radiotherapy alone vs radiotherapy with concurrent chemoradiotherapy on survival without disease relapse in patients with low-risk nasopharyngeal carcinoma: A randomized clinical trial. *JAMA* 328:728-736, 2022
53. Lin JC, Wang WY, Liang WM, et al: Long-term prognostic effects of plasma Epstein-Barr virus DNA by minor groove binder-probe real-time quantitative PCR on nasopharyngeal carcinoma patients receiving concurrent chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 68:1342-1348, 2007
54. Hui EP, Li WF, Ma BB, et al: Integrating postradiotherapy plasma Epstein-Barr virus DNA and TNM stage for risk stratification of nasopharyngeal carcinoma to adjuvant therapy. *Ann Oncol* 31:769-779, 2020
55. Chan ATC, Hui EP, Ngan RKC, et al: Analysis of plasma Epstein-Barr virus DNA in nasopharyngeal cancer after chemoradiation to identify high-risk patients for adjuvant chemotherapy: A randomized controlled trial. *J Clin Oncol* 10.1200/JCO.2018.77.7847 [epub ahead of print on July 10, 2018]
56. Hui EP, Ma BBY, Lam WKJ, et al: Dynamic changes of post-radiotherapy plasma Epstein-Barr virus DNA in a randomized trial of adjuvant chemotherapy versus observation in nasopharyngeal cancer. *Clin Cancer Res* 27:2827-2836, 2021
57. Neo J, Yip PL, Ong EHW, et al: Longitudinal post-radiotherapy plasma Epstein-Barr virus DNA trends inform on optimal risk stratification in endemic nasopharyngeal carcinoma. *Oral Oncol* 148:106655, 2024
58. Yip PL, Lee AWM, Chua MLK: Adjuvant chemotherapy in nasopharyngeal carcinoma. *Lancet Oncol* 24:713-715, 2023
59. Huang CL, Sun ZQ, Guo R, et al: Plasma Epstein-Barr virus DNA load after induction chemotherapy predicts outcome in locoregionally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 104:355-361, 2019
60. Li WZ, Lv X, Hu D, et al: Effect of induction chemotherapy with paclitaxel, cisplatin, and capecitabine vs cisplatin and fluorouracil on failure-free survival for patients with stage IVA to IVB nasopharyngeal carcinoma: A multicenter phase 3 randomized clinical trial. *JAMA Oncol* 8:706-714, 2022
61. Zhang Y, Chen L, Hu GQ, et al: Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *N Engl J Med* 381:1124-1135, 2019
62. Peng H, Chen L, Li WF, et al: Tumor response to neoadjuvant chemotherapy predicts long-term survival outcomes in patients with locoregionally advanced nasopharyngeal carcinoma: A secondary analysis of a randomized phase 3 clinical trial. *Cancer* 123:1643-1652, 2017
63. Chen Q-Y, Mai H-Q, Tang L-Q, et al: Neoadjuvant chemotherapy plus tislelizumab followed by concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: A single-arm, phase II trial. *J Clin Oncol* 40, 2022 (suppl 16; abstr 6068)
64. Liang H, Jiang YF, Liu GY, et al: Camrelizumab and apatinib plus induction chemotherapy and concurrent chemoradiotherapy in stage N3 nasopharyngeal carcinoma: A phase 2 clinical trial. *Nat Commun* 15:1029, 2024
65. Xiang L, Rong JF, Xin C, et al: Reducing target volumes of intensity modulated radiation therapy after induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: Long-term results of a prospective, multicenter, randomized trial. *Int J Radiat Oncol Biol Phys* 117:914-924, 2023
66. Tang LL, Chen L, Xu GQ, et al: Reduced-volume radiotherapy versus conventional-volume radiotherapy after induction chemotherapy in nasopharyngeal carcinoma: An open-label, noninferiority, multicenter, randomized phase 3 trial. *CA Cancer J Clin* 10.3322/caac.21881 [epub ahead of print on February 19, 2025]
67. Guo SS, Yang JH, Sun XS, et al: Reduced-dose radiotherapy for Epstein-Barr virus DNA selected staged III nasopharyngeal carcinoma: A single-arm, phase 2 trial. *Eur J Cancer* 194:113336, 2023
68. Chen Q-Y, Mai H-Q, Chen D-P, et al: Four-year overall survival follow-up and dynamic EBV titer analysis of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC). *J Clin Oncol* 42, 2024 (suppl 16; abstr 6039)
69. Liu GY, Li WZ, Wang DS, et al: Effect of capecitabine maintenance therapy plus best supportive care vs best supportive care alone on progression-free survival among patients with newly diagnosed metastatic nasopharyngeal carcinoma who had received induction chemotherapy: A phase 3 randomized clinical trial. *JAMA Oncol* 8:553-561, 2022
70. Liu Y, He S, Wang XL, et al: Tumour heterogeneity and intercellular networks of nasopharyngeal carcinoma at single cell resolution. *Nat Commun* 12:741, 2021
71. Jin S, Li R, Chen MY, et al: Single-cell transcriptomic analysis defines the interplay between tumor cells, viral infection, and the microenvironment in nasopharyngeal carcinoma. *Cell Res* 30:950-965, 2020
72. Gong L, Kwong DL, Dai W, et al: Comprehensive single-cell sequencing reveals the stromal dynamics and tumor-specific characteristics in the microenvironment of nasopharyngeal carcinoma. *Nat Commun* 12:1540, 2021

73. Chen YP, Yin JH, Li WF, et al: Single-cell transcriptomics reveals regulators underlying immune cell diversity and immune subtypes associated with prognosis in nasopharyngeal carcinoma. *Cell Res* 30:1024-1042, 2020
74. Chan ATC, Lee VHF, Hong RL, et al: Pembrolizumab monotherapy versus chemotherapy in platinum-pretreated, recurrent or metastatic nasopharyngeal cancer (KEYNOTE-122): An open-label, randomized, phase III trial. *Ann Oncol* 34:251-261, 2023
75. Yuan L, Jia GD, Lv XF, et al: Camrelizumab combined with apatinib in patients with first-line platinum-resistant or PD-1 inhibitor resistant recurrent/metastatic nasopharyngeal carcinoma: A single-arm, phase 2 trial. *Nat Commun* 14:4893, 2023
76. Zhang Y, Zou Q, Zhao B, et al: Toripalimab plus anlotinib in patients with recurrent or metastatic nasopharyngeal carcinoma: A multicenter, single-arm phase 2 trial (TORAL). *Cell Rep Med* 5:101833, 2024
77. Chong WQ, Low JL, Tay JK, et al: Pembrolizumab with or without bevacizumab in platinum-resistant recurrent or metastatic nasopharyngeal carcinoma: A randomised, open-label, phase 2 trial. *Lancet Oncol* 26:175-186, 2025
78. Lim DW, Kao HF, Suteja L, et al: Clinical efficacy and biomarker analysis of dual PD-1/CTLA-4 blockade in recurrent/metastatic EBV-associated nasopharyngeal carcinoma. *Nat Commun* 14:2781, 2023
79. Chen G, Sun DC, Ba Y, et al: Anti-LAG-3 antibody LBL-007 plus anti-PD-1 antibody toripalimab in advanced nasopharyngeal carcinoma and other solid tumors: An open-label, multicenter, phase Ib/II trial. *J Hematol Oncol* 18:15, 2025
80. Xu C, Xia Y, Wang S, et al: 153P combination of Tim-3 blockade TQB2618 with PD-1 blockade for patients with immunotherapy-resistant recurrent/metastatic nasopharyngeal carcinoma (R/M NPC): Preliminary results from a phase II study. *Immunooncol Technol* 24:100782, 2024
81. Pang X, Huang Z, Zhong T, et al: Cadonilimab, a tetravalent PD-1/CTLA-4 bispecific antibody with trans-binding and enhanced target binding avidity. *MAbs* 15:2180794, 2023
82. Mai H, Lin S, Chen D, et al: 436 A phase II study of AK104, a bispecific antibody targeting PD-1 and CTLA-4, in patients with metastatic nasopharyngeal carcinoma (NPC) who had progressed after two or more lines of chemotherapy. *Regular Young Investigator Award Abstr* 9:A466, 2021
83. Wen L, Zhang Z, Huang J, et al: 416P A study of AK104 (an anti-PD1 and anti-CTLA4 bispecific antibody) combined with chemotherapy for the treatment of anti-PD-1 resistant, recurrent, or metastatic nasopharyngeal carcinoma (R/M NPC). *Ann Oncol* 35:S1559, 2024
84. Han F, Wang F, Shi Y-R: 860MO MRG003: A novel EGFR-targeted antibody-drug conjugate (ADC) for recurrent/metastatic nasopharyngeal carcinoma. *Ann Oncol* 34:S559, 2023
85. Wong KCW, Hui EP, Lo KW, et al: Nasopharyngeal carcinoma: An evolving paradigm. *Nat Rev Clin Oncol* 18:679-695, 2021
86. Pan JJ, Mai HQ, Ng WT, et al: Ninth version of the AJCC and UICC nasopharyngeal cancer TNM staging classification. *JAMA Oncol* 10:1627-1635, 2024
87. Du XJ, Wang GY, Zhu XD, et al: Refining the 8th edition TNM classification for EBV related nasopharyngeal carcinoma. *Cancer Cell* 42:464-473.e3, 2024
88. Chen YP, Ismaila N, Chua MLK, et al: Chemotherapy in combination with radiotherapy for definitive-intent treatment of stage II-IVA nasopharyngeal carcinoma: CSCO and ASCO guideline. *J Clin Oncol* 39:840-859, 2021
89. Yang J, Liao W, Su S, et al: Long-term outcomes of metastasis-directed stereotactic body radiation therapy in metastatic nasopharyngeal carcinoma. *Cancer Med* 13:e6764, 2024
90. Szturz P, Vermorken JB: Steering decision making by terminology: Oligometastatic versus argometastatic. *Br J Cancer* 127:587-591, 2022
91. Chang ET, Adami HO: The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 15:1765-1777, 2006
92. van Velsen JS, van der Veegt B, Plaat BEC, et al: Nasopharyngeal carcinoma: Nationwide trends in subtype-specific incidence and survival over 3 decades in a non-endemic area. *J Cancer Res Clin Oncol* 150:49, 2024
93. Wang Q, Xie H, Li Y, et al: Racial and ethnic disparities in nasopharyngeal cancer with an emphasis among Asian Americans. *Int J Cancer* 151:1291-1303, 2022
94. Burt RD, Vaughan TL, McKnight B: Descriptive epidemiology and survival analysis of nasopharyngeal carcinoma in the United States. *Int J Cancer* 52:549-556, 1992
95. Wang Y, Zhang Y, Ma S: Racial differences in nasopharyngeal carcinoma in the United States. *Cancer Epidemiol* 37:793-802, 2013
96. Gatta G, Capocaccia R, Botta L, et al: Burden and centralised treatment in Europe of rare tumours: Results of RARECAREnet-a population-based study. *Lancet Oncol* 18:1022-1039, 2017
97. Murata T, Sato Y, Kimura H: Modes of infection and oncogenesis by the Epstein-Barr virus. *Rev Med Virol* 24:242-253, 2014
98. Fountzilas G, Psyrri A, Giannoulidou E, et al: Prevalent somatic BRCA1 mutations shape clinically relevant genomic patterns of nasopharyngeal carcinoma in Southeast Europe. *Int J Cancer* 142:66-80, 2018
99. Hung SH, Yang TH, Cheng YF, et al: Association of nasopharynx cancer with human papillomavirus infections. *Cancers (Basel)* 15:4082, 2023
100. Zhao BY, Hirayama S, Goss D, et al: Human papillomavirus-associated nasopharyngeal carcinoma: A systematic review and meta-analysis. *Oral Oncol* 159:107057, 2024
101. Dogan S, Hedberg ML, Ferris RL, et al: Human papillomavirus and Epstein-Barr virus in nasopharyngeal carcinoma in a low-incidence population. *Head Neck* 36:511-516, 2014
102. Wu SS, Chen B, Fleming CW, et al: Nasopharyngeal cancer: Incidence and prognosis of human papillomavirus and Epstein-Barr virus association at a single North American institution. *Head Neck* 44:851-861, 2022
103. Robinson M, Suh YE, Paleri V, et al: Oncogenic human papillomavirus-associated nasopharyngeal carcinoma: An observational study of correlation with ethnicity, histological subtype and outcome in a UK population. *Infect Agent Cancer* 8:30, 2013
104. Verma N, Patel S, Osborn V, et al: Prognostic significance of human papillomavirus and Epstein-Bar virus in nasopharyngeal carcinoma. *Head Neck* 42:2364-2374, 2020
105. Kano M, Kondo S, Wakisaka N, et al: The influence of human papillomavirus on nasopharyngeal carcinoma in Japan. *Auris Nasus Larynx* 44:327-332, 2017
106. Tsao SW, Tsang CM, Lo KW: Epstein-Barr virus infection and nasopharyngeal carcinoma. *Philos Trans R Soc Lond B Biol Sci* 372:20160270, 2017
107. Islam KA, Chow LK, Kam NW, et al: Prognostic biomarkers for survival in nasopharyngeal carcinoma: A systematic review of the literature. *Cancers (Basel)* 14:2122, 2022
108. Lenoci D, Resteghini C, Serafini MS, et al: Tumor molecular landscape of Epstein-Barr virus (EBV) related nasopharyngeal carcinoma in EBV-endemic and non-endemic areas: Implications for improving treatment modalities. *Transl Res* 265:1-16, 2024

Current and Future Directions of Immunotherapies in Multiple Myeloma

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OVERVIEW

Treatment of multiple myeloma (MM) has evolved significantly over the past few decades. Up-front treatment options expanded from doublet regimens to triplets and now to quadruplets. Monoclonal antibodies have significantly contributed to this paradigm shift. Their incorporation into frontline regimens demonstrated improved survival outcomes irrespective of transplantation eligibility. Autologous hematopoietic stem-cell transplant (ASCT) remains standard in frontline consolidation therapy with recent expansion of eligibility, including older adults and patients with renal failure. The growing understanding of physiologic age and frailty, as well as improvements in supportive care, has made this possible. Bispecific T-cell engager (BiTE) antibodies are heralding a new age of treatment of MM with high response rates in patients with relapsed or refractory MM. With the impressive responses seen, these treatments are being studied in earlier lines of therapy and in combination with other therapies. With this rapidly evolving field of immunotherapy in MM, the goal of this review was to discuss the latest advances in MM treatment, focusing on up-front quadruplet therapy, the role of ASCT in the modern era, and the evolving role of BiTEs in up-front therapy.

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INTRODUCTION

Significant advances in treatment paradigms for multiple myeloma (MM) have been seen recently, with over 14 treatments approved by the US Food and Drug Administration (FDA) in the past decade alone.¹ Initial treatments used one to two drug regimens with a limited survival of 6 months.² Recent long-term follow-up data from contemporary treatment approaches demonstrate sustained survival benefits, with some patients achieving durable remissions extending beyond a decade.³ Modern up-front treatment now includes 3-drug and 4-drug regimens. Cellular therapy in the form of autologous hematopoietic stem-cell transplant (ASCT) improved these outcomes and was incorporated into standard treatment of MM for eligible patients. Novel therapies harness the immune system and are being incorporated into earlier lines of treatment, including up-front treatment of MM. In this article, we discuss the latest advances in immunotherapy for MM focusing on quadruplet therapy in up-front treatment, the role of autologous ASCT in the modern era, and the evolving role of bispecific T-cell engagers (BiTEs).

Patient Case: A 75-year-old man with a history of hypertension, hyperlipidemia, and atrial fibrillation presented with back pain. Spine imaging revealed multiple lytic lesions. Biopsy showed kappa-restricted plasma cell neoplasm. Further workup revealed a 1.1 g/dL monoclonal IgG kappa in serum and 40% kappa-restricted plasma cells in the bone

marrow. Fluorescent in situ hybridization (FISH) revealed 1q gain.

QUADRUPLET VERSUS TRIPLET TREATMENT REGIMENS IN NEWLY DIAGNOSED MULTIPLE MYELOMA

Quadruplet-based regimens are increasingly used in the treatment of newly diagnosed multiple myeloma (NDMM), including both transplant-eligible and transplant-ineligible patients. The concept of combining four drugs for NDMM treatment is not new.⁴⁻⁹ However, many of these regimens are not commonly used in the United States because of the availability of more effective and/or less toxic drug classes. Recently, quadruplet regimens have evolved to include an anti-CD38 monoclonal antibody (moAb) alongside an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and a steroid.¹⁰⁻¹⁷

Transplant-Eligible Patients

Initial investigations of quadruplet-based treatments focused on patients eligible for ASCT. Some studies have incorporated minimal residual disease (MRD) to guide treatment decisions and an evolving surrogate marker for progression-free survival (PFS). The phase II GRIFFIN study demonstrated significant improvements in outcomes by adding daratumumab to the standard lenalidomide, bortezomib, and dexamethasone regimen (D-RVd v RVd).¹¹ This quadruplet approach resulted in superior PFS, with a 4-year

PRACTICAL APPLICATIONS

- Quadruplet induction regimens show improved response rates, progression-free survival (PFS), and minimal residual disease–negative rates compared with triplet regimens.
- Autologous hematopoietic stem-cell transplant has been shown to increase PFS with expanding eligibility, including in older patients.
- Bispecific antibodies have shown substantial response rates in relapsed and refractory multiple myeloma (MM).
- Bispecific antibodies are being studied in the treatment of newly diagnosed MM, in both induction and maintenance settings.

PFS rate of 87% for D-RVd compared with 70% for RVd (hazard ratio [HR] 0.45, $P = .032$).

The single-arm phase II MASTER trial assessed daratumumab, carfilzomib, lenalidomide, and dexamethasone, using MRD status to guide post-transplant therapy of consolidation and maintenance versus observation.¹⁷ At a median follow-up of 25 months, the 2-year PFS was 87%, with 80% of patients achieving MRD negativity ($<10^{-5}$). In addition, 71% of patients achieved two consecutive MRD-negative assessments and were placed on observation per study protocol. Patients with ≥ 2 high-risk mutations, defined in this study as $t(4;14)$, $t(14;16)$, $del(17p)$, gain or amplification of $1q$, and $t(14;20)$, had inferior PFS, highlighting the need for a revised approach for this population.

The CASSIOPEIA trial evaluated adding daratumumab to the standard bortezomib, thalidomide, and dexamethasone (VTd) regimen in transplant-eligible patients with NDMM and maintenance daratumumab in the post-transplant setting.¹⁰ In part 1, which focused on induction and post-transplant consolidation, patients receiving daratumumab-VTd (D-VTd) demonstrated significantly higher rates of stringent complete response (sCR; 29%) compared with VTd alone (20%; odds ratio [OR], 1.6, $P = .001$) after ASCT. The D-VTd group achieved higher rates of sCR and MRD negativity, with improvement in PFS. The median PFS was not reached in the D-VTd group but was significantly longer than the 46.7 months observed in the VTd group, representing a 53% reduction in progression or death risk (HR, 0.47, $P < .0001$). While the median overall survival (OS) was not reached in either group, the 6-year OS rate was higher in the D-VTd group (87%) compared with the VTd group (78%).¹⁸

The PERSEUS study randomly assigned 709 patients to receive either D-RVd or RVd alone followed by ASCT.¹² In the

D-RVd group, patients received daratumumab and lenalidomide maintenance therapy, while the RVd group received lenalidomide maintenance therapy alone. After a median follow-up of 48 months, the D-RVd group demonstrated a significantly lower risk of disease progression or death, with 84% PFS at 48 months compared with 68% in the RVd group (HR, 0.42, $P < .001$). The D-RVd group also had a higher rate of complete response (CR) or better (88% v 70%, $P < .001$) and MRD-negative status (75% v 48%, $P < .001$). Death occurred in 34 patients in the D-RVd group and 44 in the RVd group. Serious adverse events were reported in 57% of patients in the D-RVd group and 49% in the RVd group, with pneumonia being the most common (11% v 6%). A second primary cancer was observed in 11% of the D-RVd group and 7% of the RVd group. The results supported the benefit of D-RVd in transplant-eligible NDMM and resulted in FDA approval on July 30, 2024.

The GMMG-HD7 trial examined adding isatuximab to lenalidomide, bortezomib, and dexamethasone (Isa-RVd) in 660 patients. After induction, MRD negativity was achieved in 50% of patients in the Isa-RVd group versus 36% in the RVd group (OR, 1.82, $P = .00017$).¹⁴ Response deepened after ASCT with a 66% MRD-negative rate in the Isa-RVd group versus 48% in the RVd group. Isa-RVd significantly prolonged PFS compared with RVd, with a HR of 0.70 (95% CI, 0.52 to 0.95; $P = .0184$). The median PFS was not reached in either treatment group.¹⁹ A summary of the most recent trials comparing quadruplet and triplet regimens in transplant-eligible patients is provided in [Table 1](#).

Transplant-Ineligible Patients

The BENEFIT study evaluated adding weekly bortezomib to isatuximab, lenalidomide, and dexamethasone in patients with NDMM aged 65–79 years.¹⁶ The primary end point of MRD negativity at 10^{-5} by next-generation sequencing at 18 months showed significant benefits for Isa-RVd, with 53% of patients achieving MRD negativity compared with 26% in the isatuximab, lenalidomide, and dexamethasone group (OR, 3.16, $P < .0001$). The Isa-RVd group demonstrated higher rates of CR or better (58% v 33%, $P < .0001$) and higher MRD negativity with CR (37% v 17%, $P = .0003$). However, no significant difference was observed in survival data at the median follow-up of 23.5 months.

IMROZ is a phase III trial that assessed Isa-RVd in transplant-ineligible patients aged 18–80 years.¹⁵ At a median follow-up of 59.7 months, Isa-RVd significantly improved PFS compared with RVd alone, with an estimated 60-month PFS of 63% for the Isa-RVd group versus 45% for RVd (HR, 0.60, $P < .001$). The Isa-RVd group had higher CR rates (75% v 64%, $P = .01$) and MRD-negative CR (56% v 41%, $P = .003$). The incidence of serious adverse events was similar in both groups. Isa-RVd was approved by the FDA on September 20, 2024, as the first quadruplet regimen for transplant-ineligible patients.

TABLE 1. Key Trials Comparing Quadruplet and Triplet Regimens in Transplant-Eligible Patients With Multiple Myeloma

Trial	Regimen	Arm	No. of Patients	Age Median (range), years	Median Follow-up, months	ORR, %	CR or Better, %	PFS, months	MRD Negativity	Sustained MRD Negativity >12 Months (10 ⁻⁵), %	Safety Profile	Stem-Cell Collection
CASSIOPEIA ^{10,18,20}	Dara-VTD v VTD	VTD	542	58 (26-65)	80.1 (part 1) 70.6 (part 2)	90	26 ^a	53	10 ⁻⁵ :44% 10 ⁻⁶ :32%	30	Grade ≥3 neutropenia: 15% Grade ≥3 thrombocytopenia: 7% Serious AEs: 47%	Median CD34 ⁺ yield: 8.9× 10 ⁶ /kg Completed ASCT: 89% Plerixafor use: 8%
		Dara-VTD	543	59 (22-65)		93	39 ^a	84	10 ⁻⁵ :64% 10 ⁻⁶ :65%	65	Grade ≥3 neutropenia: 28% Grade ≥3 thrombocytopenia: 11% Serious AEs: 47%	Median CD34 ⁺ yield: 6.3× 10 ⁶ /kg Completed ASCT: 90% Plerixafor use: 22%
PERSEUS ¹²	Dara-RVD v RVD	RVD	354	59 (31-70)	47.5	94	70 ^b	47	10 ⁻⁵ :48% 10 ⁻⁶ :32%	30	Grade ≥3 neutropenia: 51% Grade ≥3 thrombocytopenia: 17% Serious AEs: 49%	Median CD34 ⁺ yield: 7.4× 10 ⁶ /kg Completed ASCT: 87% Plerixafor use: NR
		Dara-RVD	355	61 (32-70)		97	88 ^b	NR	10 ⁻⁵ :75% 10 ⁻⁶ :65%	65	Grade ≥3 neutropenia: 62% Grade ≥3 thrombocytopenia: 29% Serious AEs: 57%	Median CD34 ⁺ yield: 5.5× 10 ⁶ /kg Completed ASCT: 90% Plerixafor use: NR
GMMG-HD7 ^{14,19}	Isa-RVD v RVD	RVD	329	60 (54-65)	48	90	34	NR	10 ⁻⁵ :36% 10 ⁻⁶ :32%	30	Grade ≥3 neutropenia: 7% Grade ≥3 thrombocytopenia: 5% Serious AEs: 28%	Median CD34 ⁺ yield: 9.5× 10 ⁶ /kg Completed ASCT: 95% Plerixafor use: 22%
		Isa-RVD	331	59 (54-64)		93	44	NR	10 ⁻⁵ :50% 10 ⁻⁶ :65%	65	Grade ≥3 neutropenia: 23% Grade ≥3 thrombocytopenia: 6% Serious AEs: 28%	Median CD34 ⁺ yield: 7.7× 10 ⁶ /kg Completed ASCT: 97% Plerixafor use: 32%

Abbreviations: AE, adverse event; ASCT, autologous hematopoietic stem-cell transplant; CR, complete response; Dara, daratumumab; Dara-RVD, daratumumab + bortezomib + lenalidomide + dexamethasone; ECOG, Eastern Cooperative Oncology Group; Isa, isatuximab; Isa-RVD, isatuximab + bortezomib + lenalidomide + dexamethasone; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; PFS, progression-free survival; R, lenalidomide; Rd, lenalidomide and dexamethasone; RVD/VRd, bortezomib, lenalidomide, and dexamethasone; V, bortezomib.

^aResponses were reported 100 days after autologous stem-cell transplantation.

^bThe tumor response was obtained at any time during the trial.

The CEPHEUS study evaluated D-RVd in transplant-ineligible or transplant-deferred patients with NDMM. Of 395 randomly assigned patients receiving eight cycles of D-RVd or RVd followed by maintenance therapy, the MRD negativity rate was significantly higher in the D-RVd group (61%) compared with the RVd group (40%, OR, 2.37; $P < .0001$). The D-RVd group showed higher rates of CR or better (81% v 62%, $P < .0001$) and sustained MRD negativity for at least 12 months (49% v 26%, $P < .0001$). The risk of progression or death was 43% lower with D-RVd compared with RVd (HR, 0.57; $P = .0005$).¹³ A summary of the most recent trials comparing quadruplet and triplet regimens in transplant-ineligible NDMM is provided in [Table 2](#).

Considerations for Treatment Choice

Anti-CD38 moAb-based quadruplet induction has improved depth of response, with MRD now emerging as a surrogate end point for PFS in both transplant-eligible and transplant-ineligible patients. These regimens should be considered in all transplant-eligible patients, but the use of quadruplet therapy in transplant-ineligible patients should take a personalized approach prioritizing quality of life and minimizing toxicities. For instance, frail patients may face higher risks of treatment-related mortality and severe toxicities, such as infections or peripheral neuropathy. Therefore, treatment should be tailored to each patient's overall health status and their individual goals and preference.

Moreover, future clinical trials should aim to refine treatment strategies on the basis of frailty rather than broad categories of transplant eligibility, especially based primarily on chronologic age. As highlighted in the GEM2017FIT trial, frailty significantly affects treatment outcomes, with fit patients showing better responses to quadruplet regimens compared with frail patients.²² It is important to note that frail patients were excluded from CEPHEUS and BENEFIT studies while an unplanned post hoc analysis of the IMROZ study showed similar efficacy and safety between frail and nonfrail patients.¹⁵ In the IMROZ study, the cumulative incidence of treatment-related deaths at a median follow-up of approximately 5 years was approximately twice as high in the Isa-RVd arm compared with the RVd arm (11% v 5.5%, respectively). Infection was the most common cause of these deaths. The higher incidence of treatment-related deaths in the Isa-VRd arm was primarily driven by events occurring more than 6 months after treatment initiation. This underscores the potential harmful effects of prolonged immunosuppression from continuous anti-CD38 moAb and dexamethasone until disease progression.¹⁵

Personalized treatment should focus on attenuated dosing strategies and dynamic measures of fitness, adjusting therapies to balance efficacy and minimize adverse effects. While frailty is a well-established prognostic factor in older patients with MM, the impact of frailty-adapted treatment on outcomes remains uncertain. The FITNeS trial (ClinicalTrials.gov identifier: [NCT03720041](#)), a phase III

randomized study by the UK Myeloma Research Alliance, addresses this by comparing two up-front ixazomib, lenalidomide, and dexamethasone (IRd) dosing strategies in transplant-ineligible patients: (1) a standard reactive approach (full-dose IRd with toxicity-guided adjustments) versus (2) a frailty-adaptive approach (International Myeloma Working Group score [IMWG]-guided dosing), with early treatment cessation as the primary end point and frailty dynamics as a secondary focus. Concurrently, trials such as S2209 are evaluating frailty-tailored regimens in NDMM, randomly assigning frail or intermediate-fit patients to RVd or DRd induction followed by reduced-intensity maintenance. By moving beyond the one-size-fits-all approach of transplant eligibility, and considering individual fitness levels and preferences, clinicians can better manage the complexities of treating NDMM, improving both the survival outcomes and quality of life for these patients ([Fig 1](#)).

Patient Case Continued

The patient received D-RVd. The IgG-kappa monoclonal protein in his serum decreased to 0.5 g/dL after six cycles of D-RVd. He was evaluated for ASCT.

WHAT IS THE ROLE OF TRANSPLANT IN MULTIPLE MYELOMA?

Historical Role of ASCT in MM

For decades, MM treatment consisted of melphalan alone or in combination with prednisone with a median OS of <3 years.^{2,23} Later, the incorporation of higher doses of melphalan and other chemotherapies were noted to induce CR in relapsed or refractory MM (RRMM) at the expense of prolonged neutropenia and subsequent life-threatening infections.^{24,25} To mitigate this risk, patients' own stem cells were reinfused after exposure to high-dose chemotherapy with good efficacy.²⁶ The successes of high-dose chemotherapy with ASCT rescue in RRMM led to testing and ultimately recommendations by national and international guidelines for ASCT consolidation in the up-front setting, with key studies summarized in [Table 3](#).^{26,33-35} This recommendation persists in the era of novel agents and have been embedded in current trial designs, such as PERSEUS, GRIFFIN, and CASSIOPEIA. These trials show superior PFS compared with triplet regimens, underscoring the synergistic role of modern drug combinations with transplantation.^{11,12,20} Importantly, ASCT's long-term safety profile reinforce its position as a standard option. However, emerging data suggest potential refinement of this paradigm.

Recent studies incorporating MRD support a response-adapted approach to consolidation and maintenance. The DETERMINATION and MASTER trials revealed important insights about MRD-directed transplant strategies.^{29,36} In DETERMINATION, while patients achieving MRD negativity after RVd induction showed comparable 5-year PFS

TABLE 2. Key Trials Comparing Quadruplet and Triplet Regimens in Transplant-Ineligible Patients With Multiple Myeloma

Trial	Regimen	Arm	No. of Patients	Age Median (range), years	Median Follow-up, months	ORR, %	CR or Better, %	PFS, Months	MRD Negativity	Sustained MRD Negativity >12 Mo (10 ⁻⁵), %	Safety Profile	ECOG
IMROZ ^{15,21}	Isa-RVD v RVD	RVD	181	72 (55-80)	59.7	92	64	54.3	10 ⁻⁵ :41% 10 ⁻⁶ :23%	24	Grade ≥3 neutropenia: 37% Grade ≥3 thrombocytopenia: 28% Serious AEs: 67%	0-1:90% 2:10% ≥2:0%
		Isa-RVD	265	72 (60-80)		91	75	NR	10 ⁻⁵ :56% 10 ⁻⁶ :40%	47	Grade ≥3 neutropenia: 54% Grade ≥3 thrombocytopenia: 30% Serious AEs: 71%	0-1:89% 2:11% ≥2:0%
CEPHEUS ¹³	Dara-RVD v RVD	RVD	198	70 (31-80)	58.7	91	62	52.6	10 ⁻⁵ :39% 10 ⁻⁶ :27%	26	Grade ≥3 neutropenia: 30% Grade ≥3 thrombocytopenia: 20% Serious AEs: 67%	0:42% 1:51% 2:7% ≥2: 0%
		Dara-RVD	197	70 (42-79)		91	81	NR	10 ⁻⁵ :61% 10 ⁻⁶ :46%	49	Grade ≥3 neutropenia: 44% Grade ≥3 thrombocytopenia: 28% Serious AEs: 72%	0:36% 1:52% 2:12% ≥2:0%
BENEFIT ¹⁶	Isa-RVD v RVD	RVD	135	73 (71-76)	23.5	92	64	24-mo PFS:80%	10 ⁻⁵ :44% 10 ⁻⁶ :23%	24	Grade ≥3 neutropenia: 37% Grade ≥3 thrombocytopenia: 28% Serious AEs: 67%	0-1:93% 2:7% ≥2: 0%
		Isa-RVD	135	74 (71-76)		91	75	24-mo PFS:85%	10 ⁻⁵ :58% 10 ⁻⁶ :40%	47	Grade ≥3 neutropenia: 54% Grade ≥3 thrombocytopenia: 30% Serious AEs: 71%	0-1:89% 2:12% ≥2: 0.4%

Abbreviations: AE, adverse event; CR, complete response; Dara, daratumumab; Dara-RVD, daratumumab + bortezomib + lenalidomide + dexamethasone; ECOG, Eastern Cooperative Oncology Group; Isa, isatuximab; Isa-RVD, isatuximab + bortezomib + lenalidomide + dexamethasone; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; PFS, progression-free survival; R, lenalidomide; Rd, lenalidomide and dexamethasone; RVD/VRd, bBortezomib, lenalidomide, and dexamethasone; V, bortezomib.

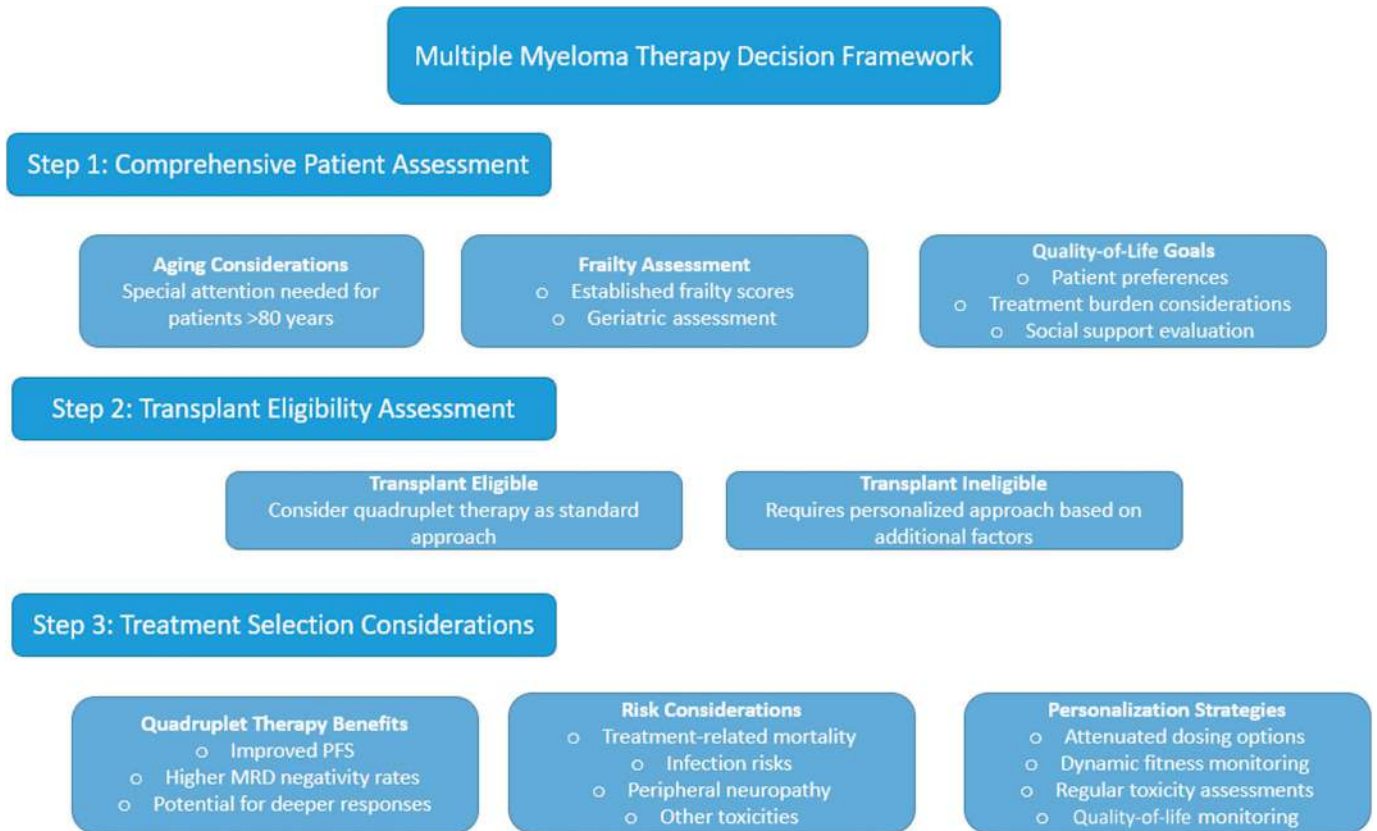


FIG 1. Multiple myeloma therapy decision framework. MRD, minimal residual disease; PFS, progression-free survival.

regardless of ASCT (59.2% v 53.5%; HR, 0.91 [0.46–1.79]), the overall MRD-negativity rate was significantly higher with ASCT (54.4% v 39.8%; OR, 0.55 [0.30–1.01]). This suggests that while ASCT increases the likelihood of achieving MRD negativity, patients who already attain deep responses with induction regimens may derive limited additional benefit from transplant consolidation. In MASTER, where MRD response directed post-transplant consolidation and maintenance after quadruplet induction, MRD negativity was achieved in 65% of patients after transplant. Three-year PFS was 85%–88% for those able to stop treatment with persistent MRD negativity and ≤ 1 high-risk mutation. However, 3-year PFS for those with ≥ 2 high-risk mutations was 60%, which again highlights the additional studies needed for this population. These findings support incorporating MRD assessment into risk-adapted algorithms to better personalize transplant decisions.

Changes in Defining Transplant Eligibility

ASCT utilization has largely been restricted to young patients with adequate organ function. Because of this, patients older than 65 or 70 years and those with end-stage renal disease (ESRD) have been excluded from pivotal clinical trials with frontline ASCT, limiting availability of strong prospective data in these populations.^{10,12,14,27,29} Safety and efficacy of ASCT in patients with renal dysfunction, including ESRD, were established using real-world data.³⁷ A Center for

International Blood and Marrow Transplant Research (CIBMTR) registry study evaluated ASCT outcomes in 1,240 patients with MM and creatinine clearance (CrCl) ≥ 60 mL/min, 185 patients with CrCl 30–59 mL/min, and 67 patients with CrCl < 30 mL/min. There was no statistically significant difference in day 100 disease response, PFS, OS and non-relapse mortality among the three groups.

Similarly, real-world and registry studies confirmed the safety and comparable efficacy of consolidation ASCT in patients aged 70 years and older.^{38–40} One prospective, phase II study included 102 patients aged 65–75 years or younger patients ineligible for ASCT. This study showed sequential multidrug induction, tandem ASCT, multidrug consolidation, and maintenance therapy can be safe and effective in these vulnerable populations.⁴¹ In this study, one quarter of patients were 70 years or older highlighting the need for the definition of ASCT eligibility to expand beyond chronologic age and better incorporate markers of biologic age.

Geriatric assessments have been shown to better identify a patient's biologic age.⁴² These assessments evaluate multiple domains to capture vulnerabilities that place older adults at increased risk of poor health care outcomes, including post-transplant outcomes.⁴³ These domains are comorbidities, physical function, cognition, mental health, nutrition, medications, and social support.⁴⁴ Many MM

TABLE 3. Nonexhaustive Summary of Clinical Trials Investigating the Role of Up-front ASCT in NDMM

Clinical Trial	Patient Population	Study Arms	ORR	PFS (M)	OS	Serious Adverse Events			Remarks
IFM 2009 ²⁷ Phase III RCT	≤65 years old	VRd × 3C + ASCT + VRd × 2C (n = 350)	CR: 59%	50 months ^a	4-year: 81%	Neutropenia: 92%	GI: 28%	Infection: 20%	No OS advantage with up-front ASCT
		VRd × 8C and ASCT at relapse (n = 350)	48% (P = .03)	36 months (HR, 0.65, P < .01) ^a	4-year: 81%	Neutropenia: 47%	GI: 7%	Infection: 9%	Increased MRD negativity with ASCT
EMN02/HO95 ²⁸ Phase III RCT	18-65 years old s/p 3-4C VCD	Single or tandem ASCT (n = 702) ± VRd consolidation ^c	VGPR: 64%	56.7 months ^a	5-year: 75.1%	Neuropathy: 14%	GI: 45%	Infection: 52%	OS advantage with ASCT in high-risk patients, especially in patients with del(17p) (HR, 0.48, P = .014) Tandem improved 5-year OS v single ASCT (HR, 0.62, P = .022) PFS improvement with VRd consolidation v none (HR, 0.77, P = .014)
		VMP (n = 495) ± VRd consolidation ^c	VGPR: 56% (P = .02)	41.9 months (HR, 0.73, P = .0001) ^a	5-year: 71.6%	Neuropathy: 58%	GI: 31%	Infection: 29%	
DETERMINATION ²⁹ Phase III RCT	18-65 years old s/p 1C RVd	2C RVd + ASCT + 2C RVd (n = 328)	CR: 46.8%	67.5 months	5-year: 81%	Any: 64.4%	GI: 18.6%	Infection: 21.1%	No statistically significant difference in PR rate, CR rate, and OS
		7C RVd (n = 357) ^b	CR: 42%	46.2 months (HR, 1.53, P < .001) ^a	5-year: 79%	Any: 49.3%	GI: 7.8%	Infection: 13.2%	
FORTE ^{30,31} Phase II RCT	18-65 years old	4C KRd + ASCT + 4C KRd (n = 158)	≥VGPR: ^a 89% sCR: 46%	4-year: 69%	4-year: 86%	Any: 11%	Pneumonia: 4%	Renal failure: 1%	5 mobilization failures (4 KRd, 1 KCd) 4 deaths (3 cardiac arrest, 1 pneumonia) Ultra-high-risk patients ^c had inferior outcome compared with other risk groups
		12C KRd (n = 157)	≥VGPR: ^a 87% sCR: 44%	4-year: 56%	4-year: 85%	Any: 19%	Pneumonia: 3%	Renal failure: 2%	
		4C KCd + ASCT + 4C KCd (n = 159)	≥VGPR: ^a 76% (P = .007) sCR: 32%	4-year: 51%	4-year: 76%	Any: 11%	Pneumonia: 3%	Renal failure: 1%	
Gay et al ³² Phase III RCT	≤65 years old; RD x4C	ASCT × 2 (n = 127)	≥VGPR: 54%	43.3 months ^a	4-year: 86%	Any: 39%	GI: 20%	Infection: 19%	No significant difference between ASCT and chemotherapy in high risk group, but small subgroups
		RCD × 6C (n = 129)	≥VGPR: 50%	28.6 months ^a (HR, 2.51, P < .0001)	4-year: 73% (P = .004)	Any: 23%	GI: 5%	Infection: 5%	

Abbreviations: ASCT, autologous hematopoietic stem-cell transplant; (s)CR: (stringent) complete response; C, cycle(s); HR, hazard ratio; KCd, carfilzomib + cyclophosphamide + dexamethasone; KR, carfilzomib + lenalidomide; KRd, carfilzomib + lenalidomide + dexamethasone; M, median; NDMM, newly diagnosed multiple myeloma; OR, odds ratio; OS, overall survival; PFS, progression-free survival; PR, partial response; R, lenalidomide; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone; SD, stable disease; s/p, status post; VCD, bortezomib + cyclophosphamide + dexamethasone; VGPR, very good partial response; VMP, bortezomib + melphalan + prednisone; VRd, bortezomib + lenalidomide + dexamethasone.

^aPrimary end point of study.

^bBoth arms received lenalidomide maintenance.

^cUltra-high-risk patients were defined by ≥2 high-risk cytogenetic abnormalities including 4(4;14), t(14;16), 17p del, del 1p, 1q gain (3 copies); 1q amplification (≥ 4 copies).

working groups advocate for use of geriatric assessments to better determine transplant eligibility.^{45,46}

Comorbidity evaluation by the Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) is independently predictive of survival after ASCT.⁴⁷ Simplified geriatric assessments attempt to combine other patient-specific and disease-specific factors with comorbidities. The Revised Myeloma Comorbidity Index is one such tool that combines organ function, age, frailty, and disease factors.⁴⁸ Frail and unfit patients identified by this tool had improved survival with transplant. However, these vulnerable groups have lower OS compared with fit patients, regardless of transplant status. Another tool is the IMWG Frailty Score, which merges independence in activities of daily living (ADLs), instrumental ADLs, comorbidities, and age.⁴⁹ In a study of older adults (65–75 years) determined to be eligible for ASCT by the treating physician, 56% of patients were unfit by the IMWG Frailty Score.⁵⁰ This study showed improved PFS with ASCT (35.6 months *v* 19.9 months, HR, 0.42, *P* = .013) in the whole cohort. In subgroup analysis, unfit patients of age 65–69 years had superior PFS with ASCT (43 months *v* 18 months, *P* = .01). However, in unfit patients aged 70 years and older, there was no difference in PFS between fit and unfit patients (18 months *v* 27 months, *P* = .33). A limitation of these tools is the exclusion of other risks of poor outcomes, which are potentially modifiable and captured on a comprehensive geriatric assessment.

Maintenance After Transplant

Two-drug to 3-drug maintenance therapy using a combination of IMiDs and PIs with or without steroids or anti-CD38 moAbs is shown to extend PFS, including in high-risk MM, as summarized in Table 4.^{61,62} Part 2 of CASSIOPIEA investigated limited-duration daratumumab maintenance for 2 years after ASCT compared with no maintenance.^{18,20} Daratumumab maintenance showed significantly prolonged PFS compared with observation. With a median follow-up of 80 months, the median PFS was not reached in the daratumumab maintenance group, while it was 45.8 months in the observation group (HR, 0.49 [95% CI, 0.40 to 0.59]; *P* < .0001). For patients treated with D-VTd induction and daratumumab maintenance, the median PFS was not reached, while those receiving VTd with observation alone had a median PFS of 72 months (HR, 0.76, *P* = .048). One limitation of this study is the control arm which contained no maintenance therapy. This study was designed before the standard use of lenalidomide maintenance after transplant. Since then, lenalidomide maintenance after transplant has been shown to improve PFS and is recommended by national and international guidelines.^{33,56,57} Daratumumab plus lenalidomide (dara-len) maintenance for 3 years has superior PFS compared with lenalidomide alone (HR, 0.53, *P* = .0361) in moAbs-naïve patients.⁶⁰ Although GRIFFIN included maintenance dara-len versus lenalidomide alone, patients did not undergo a second random assignment for maintenance, limiting the ability to interpret the impact of

daratumumab-containing doublet maintenance in patients who received quadruplet induction and consolidation.⁶³ FORTE showed increased PFS with doublet maintenance with carfilzomib–lenalidomide maintenance over single-agent lenalidomide maintenance after transplant (75% *v* 65%, HR, 0.64, *P* = .023).³⁰ However, on subgroup analysis, this finding did not hold true for patients with ≥2 high-risk mutations, defined by del(17p), t(4;14), t(14;16), gain (1q) (three copies), or amplification(1q) (>4 copies) assessed by FISH on CD138-positive cells.

Challenges in Current Era of Myeloma Therapy

Quadruplet-induction therapies using anti-CD38 moAbs, PIs, IMiDs, and steroids resulted in unprecedented depth of response in NDMM.^{10,12,14,36,63} Up-front consolidation with single ASCT after triple-drug induction led to significantly prolonged PFS but no clear OS advantage.^{27,29} However, tandem transplant, that is, 2 ASCTs within 6 months, was found to have a survival benefit in patients with less than very good partial response (VGPR) after first transplant and high-risk cytogenetics, in the setting of triplet induction and single-drug maintenance therapy.^{28,64} The role of tandem transplant in the era of quadruplet induction, multidrug consolidation, and multidrug maintenance therapy is yet to be established.⁶⁵

Unfortunately, patients with more than 1 adverse cytogenetic risk and patients with suboptimal response or progressive disease within 12 months of ASCT have poor outcomes despite these advances.^{36,66} In this population, B-cell maturation antigen (BCMA) targeting chimeric antigen receptor T-cell therapies, ciltacabtagene autoleucel (cilta-cel) and idecabtagene vicleucel (ide-cel), are proven to be efficacious.^{67–71} Cilta-cel and ide-cel were initially approved in RRMM after ≥ 4 prior lines of therapy, including IMiDs, PIs, and anti-CD38 moAbs, after demonstrating efficacy with an overall response rate (ORR, ≥ partial response, PR) of 97% (N = 97) and 73% (N = 128), respectively, in these heavily pretreated patients.^{72,73} Subsequently, both cilta-cel and ide-cel were approved for second line (in lenalidomide refractory) and third line and beyond for patients treated with IMiDs and PIs on the basis of the CARTITUDE-4 and KarMMa-3 studies showing PFS of not reached versus 12 months (HR, 0.26, *P* < .001) and 13 versus 4 months (HR, 0.49, *P* < .001) when compared with standard-of-care therapy, respectively.^{67,68} Whether these therapies will replace frontline ASCT is under investigation. The risks of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), serious hematologic adverse events including prolonged cytopenias, and delayed neurotoxicity such as Parkinson-like syndrome would need to be seriously weighed in earlier lines of therapy because of the potential impact on future treatment eligibility.

Patient Case Continued

Our 75-year-old male patient underwent a standardized geriatric assessment with the following findings: high level

TABLE 4. Nonexhaustive Summary of Post-ASCT Maintenance Therapy Studies in MM

Clinical Trial	Patient Population	Study Arms	PFS (M)	OS	Serious Adverse Events			Remarks
HOVON-65/GMMG-HD4 ^{51,52} Phase III	18-65 years old, NDMM	3C VAD + single or tandem ASCT + thalidomide maintenance ^b	28 months ^a	5-year: 55%	Second primary malignancy: 5%	Neuropathy: 18% (8% during maintenance)	Any: 46%	Improved PFS and OS with bortezomib maintenance in patients with Cr >2 mg/dL and del(17p) and in multivariable analysis ⁵³
		3C PAD induction + single or tandem ASCT + bortezomib maintenance ^b	35 months ^a	5-year: 61%	Second primary malignancy: 3%	Neuropathy: 40% (5% during maintenance)	Any: 48%	
TOURMALINE-MM3 ^{54,55} Phase III Double-blind RCT	≥PR within 1 year of induction + ASCT	Ixa ^b	26.5 months ^a	5-year: 74%	Second primary malignancy: 3%	Neuropathy: 19%	Any: 27% ^c	MRD-negative conversion with Ixa (12%) v Pbo (7%)
		Pbo ^b	21.3 months ^a (HR, 0.72, <i>P</i> = .0023)	5-year: 73%	Second primary malignancy: 3%	Neuropathy: 15%	Any: 20%	
CALGB 100104 ⁵⁶ Phase III Double-blind RCT	<71 years old patients with ≥SD 100 days after ASCT	R	46 months ^a	3-year: 88%	Second primary malignancy: 8%	Infection: 6%	Death: 15%	M EFS in R 43 months v 27 months in Pbo 8 hematologic and 10 solid tumors in R v 1 hematologic and 5 solid tumors in Pbo
		Pbo	27 months ^a (<i>P</i> < .001)	3-year: 80% (HR, 0.62; two-sided <i>P</i> = .03)	Second primary malignancy: 3% (HR, 0.53; 95% CI, 0.41 to 0.69)	Infection: 1%	Death: 23% (<i>P</i> = .03)	
IFM 2005-02 ⁵⁷ Phase III Double-blind RCT	≤65 years old with ≥SD within 6 months of ASCT; 2C R consolidation	R	41 months ^a	3-year: 80%	Second malignancy: 8%	Infection: 13%	Thromboembolic events: 6%	Benefit of R maintenance seen across all subgroups
		Pbo	23 months ^a (HR, 0.5, <i>P</i> < .001)	3-year: 84% (HR, 1.25, <i>P</i> = .29)	Second malignancy: 4%	Infection: 5%	Thromboembolic events: 2% (<i>P</i> = .01)	
GEM2014MAIN ⁵⁸ Phase III RCT	≤65 years old with ≥SD at end of VRd induction, then ASCT, ^d then 2C VRd	IRd (stop at 2 years if MRD negative or at 5 years)	6-year: 55.6% ^a	NA	Second primary malignancy: 7.6%	GI: 15%	Deep vein thrombosis: 2.9%	No PFS or OS benefit with IRd v Rd maintenance by cytogenetic risk
		Rd (stop at 2 years if MRD negative or at 5 years)	6-year: 61.3% ^a (HR, 1.14, <i>P</i> = .46)	NA	Second primary malignancy: 8.7%	GI: 2% (<i>P</i> < .0001)	Deep vein thrombosis: 1.8%	
ATLAS ⁵⁹ Phase III RCT	≥18 years old with ≥SD within 100 days of ASCT and 1 year of induction	KRd ×36 months followed by R	59.1 months ^a	NA	Second malignancy: 1%	LRTI: 8%	Any: 30% ^c	KRd patients with negative MRD after 6 cycles were switched to R starting cycle 9
		R maintenance only	41.1 months ^a (HR, 0.51; <i>P</i> = .012)	NA	Second malignancy: 2%	LRTI: 1%	Any: 22%	
FORTE ³⁰ Phase II Second randomization	18-65 years old	KR	3-year: 5% ^a	3-year: 94%	Secondary malignancy: 3.5%	TMA: 3%	Any: 14% ^c	Doublet maintenance therapy did not mitigate the risk of death and relapse in ultra-high risk patients
		R	3-year: 5% ^a (HR, 0.64, <i>P</i> = .023)	3-year: 90%	Secondary malignancy: 2.3%	TMA: 0%	Any: 8%	
CASSIOPEIA Part-2 ²⁰ Phase III Second randomization	18-65 years ≥PR after VTd ± Dara 4C + ASCT + 2C consolidation	Dara ^b	Not reached ^a	NA	Second primary malignancy: 5.5%	Pneumonia: 3%	Any: 23% ^e	During the course of the study, R was approved as SOC maintenance
		Observation	46.7 months ^a (HR, 0.53, <i>P</i> < .0001)	NA	Second primary malignancy: 2.7%	Pneumonia: 2%	Any: 19%	

(continued on following page)

TABLE 4. Nonexhaustive Summary of Post-ASCT Maintenance Therapy Studies in MM (continued)

Clinical Trial	Patient Population	Study Arms	PFS (M)	OS	Serious Adverse Events			Remarks
AURIGA ^{a,b} Phase III RCT	18-79 years old ≥ VGPR + MRD- positive after 4C induction + ASCT within 12 months; anti-CD38 monoclonal antibody naïve	Dara-R	30-month: 82.7%	NA	Secondary primary malignancy: 7.3%	Diarrhea: 3.1%	Any: 30.2%	MRD-negative conver- sion rate: ^a 50.5% (Dara-R v 18.8%) (R) (OR, 4.51, <i>P</i> < .0001) Higher CR rate (OR, 2.0, <i>P</i> = .026) and PFS (HR, 0.53, 95% CI, 0.29 to 0.97) with Dara-R
		R ^f	30-month: 66.4%	NA	Secondary primary malignancy: 4.1%	Diarrhea: 5.1%	Any: 22.4%	

Abbreviations: ASCT, autologous hematopoietic stem-cell transplant; C, cycle(s); Cr, creatinine; CR, complete response; Dara, daratumumab; EFS, event-free survival; HR, hazard ratio; IRd, ixazomib + lenalidomide + dexamethasone; Ixa, ixazomib; KR, carfilzomib + lenalidomide; KRd, carfilzomib + lenalidomide + dexamethasone; LRTI, lower respiratory tract infection; M, median; MRD, minimal residual disease; NA, not available; NDMM, newly diagnosed multiple myeloma; obs, observation; OR, odds ratio; OS, overall survival; PAD, bortezomib + doxorubicin + dexamethasone; Pbo, placebo; PFS, progression-free survival; PR, partial response; R, lenalidomide; RCT, randomized controlled trial; Rd, lenalidomide + dexamethasone; SD, stable disease; TMA, thrombotic microangiopathic purpura; V, bortezomib; VAD, vincristine + doxorubicin + dexamethasone; VRd, bortezomib + lenalidomide + dexamethasone; VTd, bortezomib + thalidomide + dexamethasone.

^aStudy primary end point.

^bMaintenance continued for 2 years.

^cIncluding 1 death.

^dMelphalan 200 mg/m² v busulfan/melphalan 140 mg/m² conditioning.

^eIncluding two deaths and natural killer cell lymphoblastic lymphoma.

^fUp to 36 months, longer at treating physician discretion.

of physical function by subjective evaluation, adequate physical function by objective measure, no mental health concerns, no nutrition concerns, mild cognitive impairment, and HCT-CI. He ultimately underwent outpatient ASCT with melphalan 140 mg/m². His course was complicated by chemotherapy-induced nausea and vomiting, Pseudomonas bacteremia, and *Clostridium difficile* colitis. He ultimately recovered. At D+100, he achieved a VGPR with M-spike of 0.1 g/dL. He subsequently was started on dara-len maintenance.

IS BISPECIFIC ANTIBODY READY FOR UP-FRONT MYELOMA THERAPY?

BiTEs bind CD3 on T cells and tumor antigens on myeloma cells, enabling T-cell-mediated killing. First described by Fudenberg, Drews, and Nisonoff in 1964,⁷⁴ BiTEs bypass MHC class I and costimulation,^{75,76} offering potent, off-the-shelf immunotherapy. This new era in MM began in 2022 with the landmark approval of teclistamab, the first BCMA-targeted bispecific. Currently, three BiTEs are FDA approved for heavily pretreated RRMM: teclistamab and elranatamab (both targeting BCMA) and talquetamab (targeting G protein-coupled receptor class C group 5 member D; GPRC5D). These breakthrough therapies are indicated for RRMM after ≥4 prior lines of therapies, including IMiDs, PIs, and anti-CD38 moAbs.⁷⁷⁻⁷⁹

In heavily pretreated patients, BiTEs have shown remarkable efficacy. Teclistamab achieved a 63% ORR and 18.4-month median duration of response (DOR), with 39% achieving CR or better.⁸⁰ Elranatamab reported a 61% ORR and 35% CR rate,⁸¹ while talquetamab showed a 70% ORR and 23% CR rate.⁸² Long-term follow-up data (≥30 months) continue to demonstrate deep, durable responses.⁸³⁻⁸⁵

BiTEs are associated with acute toxicities such as CRS and ICANS during step-up dosing, requiring vigilant monitoring and early intervention with corticosteroids and/or tocilizumab. Chronic risks include hypogammaglobulinemia (necessitating intravenous immunoglobulin and antimicrobial prophylaxis) and talquetamab-specific effects: oral (dysgeusia, xerostomia), cutaneous (nail/toenail disorders, rash), and cerebellar toxicity (ataxia, dysarthria) reported in postmarketing data.⁸⁶⁻⁸⁸

Beyond approved agents, other BiTEs targeting BCMA (eg, linvoseltamab, ABBV383), GPRC5D (eg, forimtamig), and FcRH5 (eg, cevostamab), as well as trispecific antibodies, are under investigation to enhance efficacy, reduce side effects, and concurrently target multiple tumor antigens.⁸⁹⁻⁹¹

Rationale for Using Bispecific Antibodies in NDMM

Despite recent advances, MM presents ongoing treatment challenges because of clonal heterogeneity and drug-resistant clones, with each relapse marked by clonal evolution, microenvironment changes, and progressively

shorter PFS.^{92,93} The goal in treating NDMM is to achieve a cure or functional cure—long-term disease control without continuous therapy—making it critical to use the most effective therapies up front to maximize depth and DOR.

There is compelling rationale for the use of BiTEs in NDMM. First, they leverage healthier, less exhausted T cells in NDMM, enabling more effective antimyeloma activity compared with RRMM, where T-cell dysfunction is common.⁹⁴ Second, early BiTE use prevents clonal evolution and resistance. Myeloma cells can downregulate target antigens (eg, BCMA, CD38) over time,⁹⁵ and early intervention may reduce genomic instability and high-risk mutations. Third, BiTEs synergize with standard therapies (eg, PIs, IMiDs, anti-CD38 moAbs), creating potent regimens with minimal overlapping toxicities. This aligns with the success of triplet and quadruplet therapies, which outperformed doublets in MM.^{11,96} In NDMM, BiTE-based combinations may achieve deeper responses, including MRD negativity—a key predictor of long-term outcomes⁹⁷—while fostering organ recovery and improving quality of life. Fourth, early use maximizes patient eligibility to treatment, as approximately 15% become ineligible with each line of therapy because of frailty or death. Deploying BiTEs up front ensures broader access to this effective treatment. Finally, early intervention is crucial for high-risk disease. Subgroup analyses from MajesTEC-1 and MagnetisMM-3 show ORRs of 50%–60% in high-risk cytogenetics, Revised-International Stage System stage III, or high tumor burden, suggesting BiTEs may mitigate high-risk features.^{98,99} While extramedullary disease (EMD) has inferior outcomes (ORR approximately 30%), early BiTE use could improve outcomes for this challenging population.

Bispecific Antibodies in Transplant-Eligible NDMM

Building on the success of modern induction regimens, BiTEs are rapidly being integrated into every phase of frontline therapy.¹⁰⁰⁻¹⁰² The studies highlighted in Table 5 showcase promising early data, with key features including multiarm designs in phase Ib/II trials to evaluate novel BiTE combinations in NDMM, followed by further exploration in phase III. MRD negativity is not only an efficacy end point but is also being used as a decision point for therapy modification, including treatment cessation or alteration.

MajesTEC-5 is a phase II trial evaluating teclistamab-based and talquetamab-based induction regimens in transplant-eligible NDMM.¹⁰¹ The preliminary analysis from Arms A and B with teclistamab-containing interventions (teclistamab-DRd and teclistamab-DRVd) was recently presented. The primary end point was safety; secondary end points included response rates and MRD negativity (10⁻⁵ threshold). Among 49 enrolled patients, all patients who completed Cycle 3 (n = 35) achieved MRD negativity with sustained responses in those completing Cycle 6. Stem-cell mobilization was feasible. Common grade 3 to 4 adverse events were lymphopenia (39%) and neutropenia (29%). CRS occurred in 65% of

TABLE 5. Bispecific Antibody Trials in Transplant-Eligible Patients With NDMM

Study	Patient Population	Study Intervention	Key Points	Outcome
MajesTEC-4 ¹⁰³ NCT05243797 Phase III	≥18 years old with ≥PR post-AHCT	Arm A: Tec-R Arm-B: R-alone Arm C: Tec-alone	Cohort 1 (standard dose Tec-R): Tec: 1.5 mg/kg Q weekly for 2C followed by 3 mg/kg Q2weeks for C3-6 and then 3 mg/kg Q4 weeks from C7 onwards R: 10 mg daily for C2-4 (can increase to 15 mg thereafter) Cohort 2 (lower dose Tec-R): Tec: 1.5 mg/kg on days 8 and 15 of C1, followed by 3 mg/kg Q4 weeks from C2 onwards R: 10 mg daily for C2-4 (can increase to 15 mg thereafter) Cohort 3 (lower dose Tec-alone): Tec: 1.5 mg/kg on days 8 and 15 of C1, followed by 3 mg/kg Q4 weeks from C2 onwards	Preliminary data: 94 pts were enrolled (Cohort 1, n = 32; Cohort 2, n = 32; Cohort 3, n = 30) Cohort 1 v 2 v 3: CR 100% v 90.6% v 93.3% Cohort 1: 100% MRD-negative disease 12 months Side effects: Cohort 1 v 2 v 3 Gr 3-4 neutropenia: 66% 41%; 28% All grade infection: 78% v 63% v 68% IVIg usage 72% Overall CRS rate was 43.6%, all grade 1 except 6.4% Grade 2
MajesTEC-5 ¹⁰¹ NCT05695508 Phase III	18-70 years old NDMM	Arm A: Tec-DRd followed by AHCT and then Tec-D maintenance Arm B: Tec-Dara-RVd followed by AHCT and then Tec-Dara maintenance Arm C: Induction, AHCT per standard of care followed by Tec-Dara or Tal-DR maintenance Arm D: Tec-Dara-RVd followed by Tec-Tal maintenance Arm E: Tal-DRd followed by AHCT and then Tal-Dara maintenance Arm F: Tal-Dara-RVd followed by AHCT and then Tal-Dara maintenance	Evaluation of Tec-Tal containing regimens in induction and maintenance phase of transplant-eligible NDMM patients Arm D is looking into replacing AHCT with a combination of Tec-Tal therapy Maintenance is continued for 18 months after AHCT or induction (Arm D) Optional treatment cessation is considered for sustained MRD-negativity of 12 months	Preliminary data: Of the 36 patients who completed 3C of Tec-based induction in arm A and B, all assessed patients (n = 35) achieved MRD-negative disease Median stem-cell yield: 8.7 × 10 ⁶ /kg CRS: 65% (all grade 1 and 2 only) No ICANS Gr 3 or 4 infection: 26.5%
GEM-TECTAL ¹⁰⁰ NCT05849610 Phase II	18-70 years old; high risk MM ^a ; included fit transplant-ineligible patients	Induction: 4C of Dara-RVd First intensification: 6C of Tec-Dara MRD-negative: Maintenance with Tec-Dara MRD-positive: Early rescue intervention with Tal-Dara for 6C followed by MRD-assessment to decide on Tal-Dara maintenance v investigator choice salvage regimen	The study is looking to evaluate the Tec-Dara and Tal-Dara combination as a replacement to AHCT MRD-guided treatment decision	NA

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TABLE 5. Bispecific Antibody Trials in Transplant-Eligible Patients With NDMM (continued)

Study	Patient Population	Study Intervention	Key Points	Outcome
MASTER-2 ¹⁰⁴ NCT05231629 Phase II	≥1 years old; NDMM	Induction: 6C of Dara-RVd MRD-negative Arm A: 3 more C of Dara-RVd followed by 13C of DR maintenance Arm B: AHCT followed by 13C of DR maintenance MRD-positive: Arm C: AHCT followed by 3C of Tec-Dara consolidation and then 13C of Tec-Dara maintenance Arm D: AHCT followed by 3C of DR consolidation and then 13C of DR maintenance	The study aims to evaluate whether the current quadruplet regimen can eliminate the need for AHCT and whether the addition of Tec to Dara + AHCT can improve MRD-negative outcomes MRD-guided treatment decision	NA
MagnestisMM-7 ¹⁰⁵ NCT05317416 Phase III	≥PR; within 4 months post-AHCT	Arm A: Elra Arm B: Lenalidomide	Elranatamab monotherapy v lenalidomide monotherapy post AHCT maintenance	NA
TALTEC ¹⁰² NCT06505369 Phase II	NDMM	Induction: Dara-RVd Consolidation part 1: Talq Consolidation part 2: Tec Follow-up treatment per investigator's choice (AHCT v maintenance with Rd)	The study aims to evaluate if consolidation with Tec-Tal sequence will deepen response and eliminate the need for AHCT	NA

Abbreviations: AHCT, autologous hematopoietic cell transplant; C, cycle(s); CR, complete response; CRS, cytokine release syndrome; Dara, daratumumab; DR, daratumumab + lenalidomide; Elra, elranatamab; Gr, grade; ICANS, immune effector cell–associated neurotoxicity syndrome; IVIG, intravenous immunoglobulin; M, median; mo, months; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; PR, partial response; Q, every; R, lenalidomide; Rd, lenalidomide + dexamethasone; RVd, lenalidomide + bortezomib + dexamethasone; Tal, talquetamab; Tec, teclistamab; V, bortezomib.

^aHigh-risk multiple myeloma defined as adverse cytogenetic abnormalities (del[17p], t[4;14], t[14;16], 1q amplification), Revised-International Staging System stage III, extramedullary disease.

TABLE 6. Bispecific Antibody Trials in Transplant-Ineligible Patients With NDMM

Study	Patient Population	Study Intervention	Key Points	Outcome
IFM2021-01 ¹¹⁰ NCT05572229 Phase II	>65 years old	Arm A: Tec-Dara Arm B: Tec-R		NA
MajesTEC-2 ^{111,112} NCT04722146 Phase Ib	Arms B and E: NDMM and RR MM Arm F: NDMM only	Arm B: Tec-DaraRV Arm E: Tec-DR Arm F: Tec-DaraRV		NA
MajesTEC-7 ¹¹³ NCT05552222 Phase III	NDMM, transplant-ineligible or AHCT not intended	Arm A: Tec-DR Arm B: Tal-DR Arm C: DRd		Arm A safety run-in: n = 26 (85% AHCT ineligible): ORR 92.3%, with 80.8% CR or better Estimated 12-month DOR and PFS was 100% and 96.2%
MagnetisMM-6 ¹¹⁴ NCT05623020 Phase III	NDMM	Arm A: Elra-DR Arm B: Elra-R Arm C: DRd	Part 1: Optimal study, safety, and tolerability of Elra with DR or R. Both AHCT-ineligible NDMM and RRMM Part 2: MRD and PFS. Only AHCT- ineligible NDMM	
NCT06758375 ¹¹⁵ Phase II	NDMM	Induction: 3C of RVd Consolidation: Low-dose Tec	Efficacy and safety of low-dose (1.0 mg/kg), limited-duration Tec as a consolidation After Tec consolidation: MRD-negative CR, off therapy MRD-positive CR or high-risk MM, bortezomib maintenance ≤VGPR, more Tec	NA

Abbreviations: AHCT, autologous hematopoietic cell transplant; C, cycle(s); CR, complete response; Dara, daratumumab; DOR, duration of response; DR, daratumumab + lenalidomide; DRd, daratumumab + lenalidomide + dexamethasone; Elra, elranatamab; MM, multiple myeloma; MRD, minimal residual disease; NA, not available; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PFS, progression-free survival; R, lenalidomide; Rd, lenalidomide + dexamethasone; RRMM, relapsed or refractory MM; RVd, lenalidomide + bortezomib + dexamethasone; Tal, talquetamab; Tec, teclistamab; VGPR, very good partial response.

patients, all Grade 1 to 2, with no ICANS or treatment-related deaths.

Early-phase trials such as GEM-TECTAL, TALTEC, and MajesTEC-5 are exploring whether teclistamab-based or talquetamab-based induction regimens could challenge the current paradigm of up-front mandatory ASCT in transplant-eligible patients with NDMM. These studies use MRD-driven strategies to guide therapy duration and intensity, testing whether ASCT can be safely omitted or delayed while maintaining efficacy.

Sequential antigen switch is also being explored in the treatment of MM. In GEM-TECTAL, patients with NDMM who convert to MRD positive or relapse from CR after teclistamab-based induction and intensification therapy switch to talquetamab-based therapy.¹⁰⁰ TALTEC uses sequential talquetamab consolidation followed by teclistamab consolidation in NDMM after D-RVd induction.¹⁰² Although preliminary, success in these trials could offer a less toxic alternative to ASCT, mitigating its short-term and long-term risks. However, data on late effects of BiTEs are also evolving.

Maintenance therapy aims to prolong remission and improve survival while optimizing quality of life. The MajesTEC-4/EMN30 is a phase III trial evaluating teclistamab

alone or with lenalidomide (tec-len) in patients with NDMM with less than PR after transplant.¹⁰³ The trial tests various teclistamab dosing frequencies: Cohort 1 (tec-len) studies weekly to biweekly dosing, Cohort 2 (tec-len) used biweekly to monthly dosing, and Cohort 3 (teclistamab alone) follows a similar schedule without lenalidomide. Cohort 1 (weekly/biweekly tec-len) achieved 100% MRD-negative CR at 12 months but had higher Grade 3 to 4 neutropenia or infections (66%) versus Cohort 2 (41%) and Cohort 3 (28%). CRS occurred in 44% (all ≤grade 2), with no ICANS. These results suggest teclistamab-based maintenance deepen responses, with less frequent dosing improving safety, a focus of the trial's randomized phase. Multiple additional studies are investigating post-transplant maintenance with BiTEs. MagnetisMM-7 is exploring elranatamab versus lenalidomide maintenance.¹⁰⁵ MASTER-2 compares maintenance teclistamab with daratumumab versus lenalidomide with daratumumab after transplant for patients who are MRD positive at the end of induction.¹⁰³ Further validation is needed, and its success may eventually reshape the standard of care for transplant-eligible NDMM.

Bispecific Antibodies in Transplant-Ineligible NDMM

A significant proportion of patients with NDMM are deemed transplant ineligible because of advanced age, frailty, or organ dysfunction and typically receive modified induction

therapy until progression.^{96,106} BiTEs offer a promising solution, providing safe and effective therapies for this population. Subgroup analyses from studies like MajesTEC-1, MonumentAL-1, and MagnetisMM-3, along with real-world data, show comparable efficacy and toxicity in patients older than 70 years.^{107,108} BiTEs cause limited myelosuppression and are unaffected by renal or hepatic impairment, making them suitable for patients with organ dysfunction.¹⁰⁹ Studies exploring BiTEs in transplant-ineligible NDMM are summarized in [Table 6](#) below.

Early success from the safety run-in of the phase III MajesTEC-7 trial (ClinicalTrials.gov identifier: [NCT05552222](#)) highlights the potential of combining teclistamab, daratumumab, and lenalidomide in transplant-ineligible NDMM.¹¹³ The regimen achieved a 92% ORR (VGPR or better), with 81% achieving CR or better, alongside rapid responses (median time to first response: 1.0 month). No disease progression occurred during the follow-up period with 12-month DOR and PFS of 100% and 96.2%, respectively. However, infections remained a significant concern, with grade 3 to 4 events occurring in 31% of patients despite intravenous immunoglobulin and antimicrobial prophylaxis.

Deep, sustained responses prompt re-evaluation of treatment duration. In RRMM, the LimiTec phase II trial assesses response-guided teclistamab cessation. [NCT06758375](#) evaluates a short course of low-dose teclistamab after RVD induction followed by bortezomib maintenance in MRD-positive patients. Both reflect a move toward personalized and response-driven strategies.^{115,116}

Challenges and Future Directions of Up-front Bispecific Antibodies

Although preliminary, the efficacy of BiTEs in both transplant-eligible and -ineligible NDMM suggests a potential role in up-front treatment, challenging the traditional transplant eligibility dichotomy and enabling unified frontline approaches. Larger confirmatory trials are warranted.

Incorporating BiTEs into up-front MM therapy presents significant challenges. Integrating BiTEs with current up-front regimens such as combining BiTEs with quadruplet therapy may increase toxicity without clear survival benefits, underscoring the need for optimal treatment sequencing. Patient heterogeneity further complicates this approach. While high-risk patients (eg, those with EMD or high-risk cytogenetics) may benefit from intensified therapy, frail patients face challenges because of comorbidities, physical function limitations, cognitive impairment among others. Ethically, balancing efficacy with quality of life is critical, as prolonged intensive treatment and monitoring may disproportionately burden older or frail patients. Shared decision making is essential to align therapy with individual patient goals and preferences.

Safety considerations with BiTEs are significant and warrant thoughtful planning, particularly as their use expands. CRS and ICANS can be serious, especially in older or frail patients with limited physiologic reserve. Proactive risk mitigation—including careful monitoring and early intervention—has helped reduce the incidence and severity of these toxicities.^{117,118} Infection remains a concern and underscores the need for robust prophylaxis strategies and close surveillance throughout treatment.^{88,119} Talquetamab-related dysgeusia presents a quality-of-life challenge that can affect nutritional status, often leading to noticeable weight loss. The incorporation of supportive measures—such as nutritional counseling and taste rehabilitation strategies—can help mitigate impact on daily life.^{120,121} Fixed-duration and response-guided de-escalation and discontinuation are being explored to improve quality of life and reduce costs. Emerging neurologic toxicities such as cerebellar dysfunction observed with talquetamab and longer term risks such as T-cell exhaustion or secondary malignancies will require extended follow-up.

Logistical and economic barriers also exist such as high costs, restricted availability, and the need for specialized resources to manage toxicities. Improving infrastructure is crucial for equitable access, requiring collaboration between local teams and academic centers to avoid overwhelming health care systems. Initiatives to expanding global access are equally important, given the high costs and specialized monitoring required. Balancing innovation with practical implementation will be key to maximizing benefits of BiTEs in up-front MM treatment.

CONCLUSION

MM treatment has evolved rapidly over the past decade, with triplet and quadruplet regimens incorporating anti-CD38 monoclonal antibodies and improving response rates. While ASCT remains standard for eligible patients (now defined by physiologic age rather than chronologic age), BiTEs are showing impressive results in relapsed and refractory settings and are being investigated in earlier treatment lines. This evolving treatment paradigm necessitates ongoing research to optimize patient-specific approaches. Beyond disease response and survival outcomes, incorporation of patient-reported outcomes and toxicities is needed to better understand toxicities and outcomes that are equally important to patients. As we continue to achieve improved outcomes with current treatment strategies, careful consideration of the balance between efficacy and quality of life becomes increasingly important, particularly when evaluating novel therapies that may carry risks of persistent toxicities. In addition, future investigations are needed to validate use of MRD-directed treatment and standardization of testing. Finding the optimal balance between maximizing disease control and preserving patients' functional status and well-being will be critical in determining the appropriate integration of emerging treatments into standard practice.

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REFERENCES

- US Food and Drug Administration: Novel Drug Approvals at FDA. <https://www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda>
- Alexanian R, Haut A, Khan AU, et al: Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. *JAMA* 208:1680-1685, 1969
- Al Hadidi S, Ababneh O, Schinke C, et al: Long-term follow-up of total therapy IV: A phase 3 clinical trial for standard-risk multiple myeloma. *Blood Adv* 9:950-953, 2025
- Mateos MV, Dimopoulos MA, Cavo M, et al: Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med* 378:518-528, 2018
- Palumbo A, Bringhen S, Rossi D, et al: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: A randomized controlled trial. *J Clin Oncol* 28:5101-5109, 2010
- Jackson GH, Pawlyn C, Cairns DA, et al: Carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide (KRdc) as induction therapy for transplant-eligible, newly diagnosed multiple myeloma patients (Myeloma XI+): Interim analysis of an open-label randomised controlled trial. *PLoS Med* 18:e1003454, 2021
- Morgan GJ, Davies FE, Gregory WM, et al: Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC myeloma IX randomized trial results. *Haematologica* 97:442-450, 2012
- Kumar S, Flinn I, Richardson PG, et al: Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood* 119:4375-4382, 2012
- Zervas K, Mihou D, Katodritou E, et al: VAD-Doxil versus VAD-doxil plus thalidomide as initial treatment for multiple myeloma: Results of a multicenter randomized trial of the Greek myeloma study group. *Ann Oncol* 18:1369-1375, 2007
- Moreau P, Attal M, Hulin C, et al: Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): A randomised, open-label, phase 3 study. *Lancet* 394:29-38, 2019
- Voorhees PM, Shorov DW, Laubach J, et al: Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): Final analysis of an open-label, randomised, phase 2 trial. *Lancet Haematol* 10:e825-e837, 2023
- Sonneveld P, Dimopoulos MA, Boccadoro M, et al: Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 390:301-313, 2024
- Usmani SZ, Facon T, Hungria V, et al: Author correction: Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: The randomised phase 3 CEPHEUS trial. *Nat Med* 31:1366, 2025
- Goldschmidt H, Mai EK, Bertsch U, et al: Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplant-eligible patients with multiple myeloma (GMMG-HD7): Part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. *Lancet Haematol* 9:e810-e821, 2022
- Facon T, Dimopoulos MA, Leleu XP, et al: Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 391:1597-1609, 2024
- Leleu X, Hulin C, Lambert J, et al: Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: The randomized phase 3 BENEFIT trial. *Nat Med* 30:2235-2241, 2024
- Costa LJ, Chhabra S, Medvedova E, et al: Daratumumab, carfilzomib, lenalidomide, and dexamethasone with minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma. *J Clin Oncol* 40:2901-2912, 2022
- Moreau P, Hulin C, Perrot A, et al: Bortezomib, thalidomide, and dexamethasone with or without daratumumab and followed by daratumumab maintenance or observation in transplant-eligible newly diagnosed multiple myeloma: Long-term follow-up of the CASSIOPEIA randomised controlled phase 3 trial. *Lancet Oncol* 25:1003-1014, 2024
- Mai EK, Bertsch U, Pozek E, et al: Isatuximab, lenalidomide, bortezomib, and dexamethasone induction therapy for transplant-eligible newly diagnosed multiple myeloma: Final Part 1 analysis of the GMMG-HD7 trial. *J Clin Oncol* 43:1279-1288, 2025
- Moreau P, Hulin C, Perrot A, et al: Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): An open-label, randomised, phase 3 trial. *Lancet Oncol* 22:1378-1390, 2021
- Manier S, Dimopoulos MA, Leleu AP: Isatuximab plus bortezomib, lenalidomide, and dexamethasone (VRd) for newly diagnosed multiple myeloma (NDMM) transplant-ineligible patients: Frailty subgroup analysis of IMROZ. *International Myeloma Society 21st Annual Meeting & Exposition, Riocentro Rio de Janeiro, Brazil, 2024. p P426*
- Mateos M-V, Paiva B, Cedena Romero MT, et al: GEM2017Fit phase 3 trial in fit elderly patients (aged 65-80) with newly diagnosed myeloma: Impact of daratumumab at induction and/or consolidation. *Blood* 144:678, 2024 (suppl 1)
- Group MTC: Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. *Myeloma Trialists' Collaborative Group. J Clin Oncol* 16:3832-3842, 1998
- McElwain TJ, Powles RL: High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. *Lancet* 2:822-824, 1983
- Barlogie B, Smith L, Alexanian R: Effective treatment of advanced multiple myeloma refractory to alkylating agents. *N Engl J Med* 310:1353-1356, 1984
- Barlogie B, Hall R, Zander A, et al: High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. *Blood* 67:1298-1301, 1986
- Attal M, Lauwers-Cances V, Hulin C, et al: Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med* 376:1311-1320, 2017
- Cavo M, Gay F, Beksaç M, et al: Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): A multicentre, randomised, open-label, phase 3 study. *Lancet Haematol* 7:e456-e468, 2020
- Richardson PG, Jacobus SJ, Weller EA, et al: Triplet therapy, transplantation, and maintenance until progression in myeloma. *N Engl J Med* 387:132-147, 2022
- Gay F, Musto P, Rota-Scalabrini D, et al: Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): A randomised, open-label, phase 2 trial. *Lancet Oncol* 22:1705-1720, 2021
- Mina R, Musto P, Rota-Scalabrini D, et al: Carfilzomib induction, consolidation, and maintenance with or without autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma: Pre-planned cytogenetic subgroup analysis of the randomised, phase 2 FORTE trial. *Lancet Oncol* 24:64-76, 2023
- Gay F, Oliva S, Petrucci MT, et al: Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: A randomised, multicentre, phase 3 trial. *Lancet Oncol* 16:1617-1629, 2015

33. Kumar SK, Callander NS, Adekola K, et al: Multiple myeloma, version 2.2024, NCCN clinical practice guidelines in Oncology. *J Natl Compr Canc Netw* 21:1281-1301, 2023
34. Cavo M, Rajkumar SV, Palumbo A, et al: International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood* 117:6063-6073, 2011
35. Rajkumar SV: Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. *Am J Hematol* 99:1802-1824, 2024
36. Costa LJ, Chhabra S, Medvedova E, et al: Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): Final report of the multicentre, single-arm, phase 2 trial. *Lancet Haematol* 10:e890-e901, 2023
37. Mahindra A, Hari P, Fraser R, et al: Autologous hematopoietic cell transplantation for multiple myeloma patients with renal insufficiency: A Center for International Blood and Marrow Transplant Research Analysis. *Bone Marrow Transpl* 52:1616-1622, 2017
38. Munshi PN, Hari P, Vesole DH, et al: Breaking the glass ceiling of age in transplant in multiple myeloma. *Blood* 134:782, 2019 (suppl 1)
39. Moore KLF, Genell A, Kaare A, et al: Up-front autologous stem cell transplantation in myeloma patients >65 years: A population-based study from the Nordic Myeloma Study Group. *Blood* 142:4729, 2023 (suppl 1)
40. Auner HW, Szydlo R, Hoek J, et al: Trends in autologous hematopoietic cell transplantation for multiple myeloma in Europe: Increased use and improved outcomes in elderly patients in recent years. *Bone Marrow Transpl* 50:209-215, 2015
41. Palumbo A, Gay F, Falco P, et al: Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. *J Clin Oncol* 28:800-807, 2010
42. Diebel LWM, Rockwood K: Determination of biological age: Geriatric assessment vs biological biomarkers. *Curr Oncol Rep* 23:104, 2021
43. Jayani R, Rosko A, Olin R, et al: Use of geriatric assessment in hematopoietic cell transplant. *J Geriatr Oncol* 11:225-236, 2020
44. Dotan E, Walter LC, Beechinor R, et al: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Older Adult Oncology V.1.2025. National Comprehensive Cancer Network
45. Palumbo A, Bringhen S, Ludwig H, et al: Personalized therapy in multiple myeloma according to patient age and vulnerability: A report of the European Myeloma Network (EMN). *Blood* 118:4519-4529, 2011
46. Cook G, Larocca A, Facon T, et al: Defining the vulnerable patient with myeloma—a frailty position paper of the European Myeloma Network. *Leukemia* 34:2285-2294, 2020
47. Berro M, Chhabra S, Piñana JL, et al: Predicting mortality after autologous transplant: Development of a novel risk score. *Biol Blood Marrow Transpl* 26:1828-1832, 2020
48. Engelhardt M, Domm AS, Dold SM, et al: A concise revised Myeloma Comorbidity Index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients. *Haematologica* 102:910-921, 2017
49. Palumbo A, Bringhen S, Mateos MV, et al: Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report. *Blood* 125:2068-2074, 2015
50. Belotti A, Ribolla R, Cancelli V, et al: Transplant eligibility in elderly multiple myeloma patients: Prospective external validation of the international myeloma working group frailty score and comparison with clinical judgment and other comorbidity scores in unselected patients aged 65-75 years. *Am J Hematol* 95:759-765, 2020
51. Sonneveld P, Scheid C, van der Holt B, et al: Bortezomib induction and maintenance treatment improves survival in patients with newly diagnosed multiple myeloma: extended follow-up of the HOVON-65/GMMG-HD4 trial. *Blood* 122:404, 2013
52. Sonneveld P, Schmidt-Wolf IGH, van der Holt B, et al: Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol* 30:2946-2955, 2012
53. Sonneveld P, Salwender H-J, Van Der Holt B, et al: Bortezomib induction and maintenance in patients with newly diagnosed multiple myeloma: Long-term follow-up of the HOVON-65/GMMG-HD4 trial. *Blood* 126:27, 2015
54. Dimopoulos MA, Gay F, Schjesvold F, et al: Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): A double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 393:253-264, 2019
55. Dimopoulos MA, Rajkumar SV, Lonial S, et al: Interim analyses of overall survival (OS) from the TOURMALINE MM3 & MM4 studies of ixazomib maintenance following primary therapy in multiple myeloma (MM). *Blood* 138:1656, 2021 (suppl 1)
56. McCarthy PL, Owzar K, Hofmeister CC, et al: Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 366:1770-1781, 2012
57. Attal M, Lauwers-Cances V, Marit G, et al: Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med* 366:1782-1791, 2012
58. Rosiñol L, Oriol A, Rios R, et al: Lenalidomide and dexamethasone maintenance with or without ixazomib, tailored by residual disease status in myeloma. *Blood* 142:1518-1528, 2023
59. Dytfeld D, Wróbel T, Jamrozik K, et al: Carfilzomib, lenalidomide, and dexamethasone or lenalidomide alone as maintenance therapy after autologous stem-cell transplantation in patients with multiple myeloma (ATLAS): Interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 24:139-150, 2023
60. Badros A, Foster L, Anderson LD, et al: Daratumumab with lenalidomide as maintenance after transplant in newly diagnosed multiple myeloma: The AURIGA study. *Blood* 145:300-310, 2025
61. Kaiser MF, Hall A, Walker K, et al: Daratumumab, cyclophosphamide, bortezomib, lenalidomide, and dexamethasone as induction and extended consolidation improves outcome in ultra-high-risk multiple myeloma. *J Clin Oncol* 41:3945-3955, 2023
62. Leypoldt LB, Tichy D, Besemer B, et al: Isatuximab, carfilzomib, lenalidomide, and dexamethasone for the treatment of high-risk newly diagnosed multiple myeloma. *J Clin Oncol* 42:26-37, 2024
63. Voorhees PM, Kaufman JL, Laubach J, et al: Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: The GRIFFIN trial. *Blood* 136:936-945, 2020
64. Hari P, Pasquini MC, Stadtmauer EA, et al: Long-term follow-up of BMT CTN 0702 (StAMINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM). *J Clin Oncol* 38, 2020 (suppl 15; abstr 8506)
65. Chen YH, Fogel L, Sun AY, et al: The efficacy and safety of tandem transplant versus single stem cell transplant for multiple myeloma patients: A systematic review and meta-analysis. *Diagnostics (Basel)* 14:1030, 2024
66. Suzuki K, Shimazu Y, Minakata D, et al: Efficacy of autologous stem cell transplantation for myeloma patients with suboptimal response: A multicenter retrospective analysis. *Transpl Cell Ther* 29:688.e1-688.e13, 2023
67. San-Miguel J, Dhakal B, Yong K, et al: Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med* 389:335-347, 2023
68. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al: Ide-cel or standard regimens in relapsed and refractory multiple myeloma. *N Engl J Med* 388:1002-1014, 2023
69. Hillengass J, Cohen AD, Agha ME, et al: The phase 2 CARTITUDE-2 trial: Updated efficacy and safety of ciltacabtagene autoleucel in patients with multiple myeloma and 1-3 prior lines of therapy (cohort A) and with early relapse after first line treatment (cohort B). *Blood* 142:1021, 2023 (suppl 1)
70. Usmani S, Patel K, Hari P, et al: KarMMa-2 Cohort 2a: Efficacy and Safety of Idecabtagene Vicleucel in Clinical High-Risk Multiple Myeloma Patients with Early Relapse after Frontline Autologous Stem Cell Transplantation. New Orleans, Louisiana, American Society of Hematology, 2022, pp 875-877
71. Dhodapkar M, Alsina M, Berdeja J, et al: KarMMa-2 cohort 2c: Efficacy and safety of idecabtagene vicleucel in patients with clinical high-risk multiple myeloma due to inadequate response to frontline autologous stem cell transplantation. *Blood* 140:7441-7443, 2022 (suppl 1)
72. Munshi NC, Anderson LD, Shah N, et al: Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med* 384:705-716, 2021
73. Berdeja JG, Madduri D, Usmani SZ, et al: Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): A phase 1b/2 open-label study. *Lancet* 398:314-324, 2021
74. Fudenberg HH, Drews G, Nisonoff A: Serologic demonstration of dual specificity of rabbit bivalent hybrid antibody. *J Exp Med* 119:151-166, 1964
75. Caraccio C, Krishna S, Phillips DJ, et al: Bispecific antibodies for multiple myeloma: A review of targets, drugs, clinical trials, and future directions. *Front Immunol* 11:501, 2020
76. Dahlen E, Veitonmäki N, Norlén P: Bispecific antibodies in cancer immunotherapy. *Ther Adv Vaccin Immunother* 6:3-17, 2018
77. Administration FaD: FDA approves teclistamab-cqyv for relapsed or refractory multiple myeloma. FDA. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma>
78. Administration FaD: FDA grants accelerated approval to elranatamab-bcmm for multiple myeloma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-elranatamab-bcmm-multiple-myeloma>
79. Administration FaD: FDA grants accelerated approval to talquetamab-tgvs for relapsed or refractory multiple myeloma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-talquetamab-tgvs-relapsed-or-refractory-multiple-myeloma>
80. Moreau P, Garfall AL, van de Donk N, et al: Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 387:495-505, 2022
81. Lesokhin AM, Tomasson MH, Arnulf B, et al: Elranatamab in relapsed or refractory multiple myeloma: Phase 2 MagnetisMM-3 trial results. *Nat Med* 29:2259-2267, 2023
82. Chari A, Minnema MC, Berdeja JG, et al: Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med* 387:2232-2244, 2022
83. Garfall AL, Nooka AK, van de Donk NWCJ, et al: MM-336 long-term follow-up from the phase 1/2 MajesTEC-1 trial of teclistamab in patients with relapsed/refractory multiple myeloma (RRMM). *Clin Lymphoma Myeloma Leuk* 24:S548, 2024

84. Prince HM, Bahlis NJ, Rodríguez-Otero P, et al: MagnetisMM-3: Long-Term update and efficacy and safety of less frequent dosing of elranatamab in patients with relapsed or refractory multiple myeloma. *Blood* 144:4738, 2024 (suppl 1)
85. Rasche L, Schinke C, Touzeau C, et al: MM-492 long-term efficacy and safety results from the phase 1/2 MonumentTAL-1 study of talquetamab, a GPRC5D×CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). *Clin Lymphoma Myeloma Leuk* 24:S561-S562, 2024
86. Chari A, Krishnan A, Rasche L, et al: Clinical management of patients with relapsed/refractory multiple myeloma treated with talquetamab. *Clin Lymphoma Myeloma Leuk* 24:665-693.e14, 2024
87. Chari A, Touzeau C, Schinke C, et al: Safety and activity of talquetamab in patients with relapsed or refractory multiple myeloma (MonumentTAL-1): A multicentre, open-label, phase 1–2 study. *Lancet Haematol* 12:e269-e281, 2025
88. Mazahreh F, Mazahreh L, Schinke C, et al: Risk of infections associated with the use of bispecific antibodies in multiple myeloma: A pooled analysis. *Blood Adv* 7:3069-3074, 2023
89. Bumma N, Richter J, Jagannath S, et al: Linvoseltamab for treatment of relapsed/refractory multiple myeloma. *J Clin Oncol* 42:2702-2712, 2024
90. Eckmann J, Fauti T, Biehl M, et al: Forintamig, a novel GPRC5D-targeting T-cell bispecific antibody with a 2+1 format, for the treatment of multiple myeloma. *Blood* 145:202-219, 2025
91. Richter J, Thomas SK, Krishnan AY, et al: Cevostamab in patients with heavily pretreated relapsed/refractory multiple myeloma (RRMM): Updated results from an ongoing phase I study demonstrate clinically meaningful activity and manageable safety and inform the doses and regimen for combination studies. *Blood* 144:1021, 2024 (suppl 1)
92. Dimopoulos MA, Petrucci MT, Foà R, et al: Impact of maintenance therapy on subsequent treatment in patients with newly diagnosed multiple myeloma: Use of "progression-free survival 2" as a clinical trial end-point. *Haematologica* 100:e328-e330, 2015
93. Morgan GJ, Walker BA, Davies FE: The genetic architecture of multiple myeloma. *Nat Rev Cancer* 12:335-348, 2012
94. Cortes-Selva D, Perova T, Skerget S, et al: Correlation of immune fitness with response to teclistamab in relapsed/refractory multiple myeloma in the MajesTEC-1 study. *Blood* 144:615-628, 2024
95. Lee H, Ahn S, Maity R, et al: Mechanisms of antigen escape from BCMA- or GPRC5D-targeted immunotherapies in multiple myeloma. *Nat Med* 29:2295-2306, 2023
96. Facon T, Kumar S, Plesner T, et al: Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med* 380:2104-2115, 2019
97. Landgren O, Devlin SM: Minimal residual disease as an early endpoint for accelerated drug approval in myeloma: A roadmap. *Blood Cancer Discov* 6:13-22, 2025
98. Costa LJ, Bahlis NJ, Usmani SZ, et al: MM-328 efficacy and safety of teclistamab in patients with relapsed/refractory multiple myeloma (RRMM) with high-risk (HR) features: A subgroup analysis from the phase 1/2 MajesTEC-1 study. *Clin Lymphoma Myeloma Leuk* 24:S546-S547, 2024
99. Touzeau C, Bahlis NJ, Maisel C, et al: P907: Efficacy and safety of elranatamab in high-risk patients with relapsed/refractory multiple myeloma: A subgroup analysis from MAGNETISMM-3. *Hemasphere* 7:e16622f0, 2023
100. Rodríguez-Ortero P, Mateos M-V, Palacios JLL, et al: Early Treatment with Bispecific T-Cell Redirectors (Teclistamab or Talquetamab) + Daratumumab in Newly Diagnosed High-Risk Multiple Myeloma: An Open-Label, Phase 2, Pilot Study (GEM-TECTAL). *International Myeloma Society 20th Annual Meeting and Exposition*. Athens, Greece, 2023
101. Raab MS, Weinhold N, Kortüm KM, et al: Phase 2 study of teclistamab-based induction regimens in patients with transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM): Results from the GMMG-HD10/DSMM-XX (MajesTEC-5) trial. *Blood* 144:493, 2024 (suppl 1)
102. Loigom D, Slørdahl TSS, Lysén A, et al: A phase II study measuring MRD negativity after bispecific T-cell redirectors talquetamab and teclistamab consolidation used in sequence as part of first line treatment in transplant eligible multiple myeloma patients (TALTEC), Nordic myeloma study group. *Blood* 144:7016, 2024 (suppl 1)
103. Zamagni E, Silzle T, Špička I, et al: Phase 3 study of teclistamab (tec) in combination with lenalidomide (len) and tec alone versus len alone in newly diagnosed multiple myeloma (NDMM) as maintenance therapy following autologous stem cell transplantation (ASCT): Safety run-in (SRI) results from the Majestic-4/EMN30 trial. *Blood* 144:494, 2024 (suppl 1)
104. Dhakal B, Silbermann R, Schmidt TM, et al: MRD-guided sequential therapy for deep response in newly diagnosed multiple myeloma (NDMM)- Master-2 trial. *Blood* 144:2000.1, 2024 (suppl 1)
105. Mateos Manteca MV, Grosicki S, Kim K, et al: MagnetisMM-7: An open-label, multicenter, randomized phase 3 study of elranatamab versus lenalidomide in post-transplant patients with newly diagnosed multiple myeloma. *J Clin Oncol* 41, 2023 (suppl 16; abstr TPS8066)
106. Durie BGM, Hoering A, Sexton R, et al: Longer term follow-up of the randomized phase III trial SWOG S0777: Bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J* 10:53, 2020
107. Dima D, Sannareddy A, Ahmed N, et al: Toxicity and efficacy outcomes of teclistamab in patients with relapsed-refractory multiple myeloma (RRMM) above the age of 70 years: A multicenter study. *Blood* 142:3330, 2023 (suppl 1)
108. Pasvolosky O, Dima D, Feng L, et al: Outcomes of elderly patients with relapsed refractory multiple myeloma (RRMM) treated with teclistamab: A multicenter study from the U.S. Multiple Myeloma Immunotherapy Consortium. *Blood* 144:934, 2024 (suppl 1)
109. Lachenal F, Lebreton P, Bouillie S, et al: Teclistamab in relapsed refractory multiple myeloma patients on dialysis: A French experience. *Blood* 142:4739, 2023 (suppl 1)
110. Study of Teclistamab in Combination in Elderly Patients with Multiple Myeloma (IFM2021-01). <https://clinicaltrials.gov/study/NCT05572229?term=IFM2021-01&rank=1>
111. Searle E, Quach H, Wong S, et al: P30 Single Cohort Results from Majestic-2: Teclistamab (Tec) in combination with subcutaneous daratumumab (dara) and lenalidomide (len) in patients with multiple myeloma (MM). *HemaSphere* 7:27, 2023
112. Searle E, Quach H, Wong SW, et al: Teclistamab in combination with subcutaneous daratumumab and lenalidomide in patients with multiple myeloma: Results from one cohort of MajesTEC-2, a Phase1b, multicohort study. *Blood* 140:394-396, 2022 (suppl 1)
113. Touzeau C, Beksac M, Terpos E, et al: Safety results from the phase 3 MajesTEC-7 study in patients (pts) with transplant ineligible/not intended newly diagnosed multiple myeloma (NDMM). *J Clin Oncol* 42, 2024 (suppl 16; abstr 7506)
114. Grosicki S, Yeh S-P, Huang JSY, et al: MagnetisMM-6: An open-label, multicenter, randomized phase 3 study of elranatamab + daratumumab + lenalidomide (EDR) versus daratumumab + lenalidomide + dexamethasone (DRd) in transplant ineligible (TI) patients with newly diagnosed multiple myeloma (NDMM). *J Clin Oncol* 41, 2023 (suppl 16; abstr TPS8065)
115. ClinicalTrials.gov: Low Dose Teclistamab in Newly Diagnosed Multiple Myeloma Patients. <https://clinicaltrials.gov/study/NCT06758375?term=NCT06758375&rank=1>
116. Razzo B, Grady C, Susanibar-Adaniya S, et al: A phase 2, single-arm, non-inferiority study of limited-duration teclistamab for relapsed and refractory multiple myeloma (LimiTec). *Blood* 142:3394, 2023 (suppl 1)
117. Scott SA, Marin EM, Maples KT, et al: Prophylactic tocilizumab to prevent cytokine release syndrome (CRS) with teclistamab: A single-center experience. *Blood Cancer J* 13:191, 2023
118. Korst C, Groen K, Bosman PWC, et al: Prophylactic tocilizumab reduces the incidence of cytokine release syndrome in relapsed/refractory myeloma patients treated with teclistamab: Implications for outpatient step-up dosing. *Hemasphere* 8:e132, 2024
119. Rajee N, Anderson K, Einsele H, et al: Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: Consensus recommendations from an expert panel. *Blood Cancer J* 13:116, 2023
120. Laheij A, van de Donk N: Characterization of dysgeusia and xerostomia in patients with multiple myeloma treated with the T-cell redirecting GPRC5D bispecific antibody talquetamab. *Support Care Cancer* 32:20, 2023
121. Naqvi S, Shrestha A, Alzubi M, et al: Weight loss and dysgeusia in relapsed/refractory multiple myeloma patients treated with talquetamab. *EJHaem* 5:789-792, 2024

Treatment of Older Patients With ALL

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OVERVIEW

Older patients with ALL often have high-risk disease characterized by adverse-risk cytogenetic and molecular abnormalities, as well as Philadelphia chromosome (Ph)-positive and Ph-like phenotypes. They often have comorbidities resulting in poor tolerance to chemotherapy and are at risk of developing therapy-related myeloid neoplasms (t-MNs). In Ph-negative ALL, the duration and intensity of chemotherapy was reduced, and outcomes improved with the addition of inotuzumab ozogamicin (InO) and blinatumomab into the frontline setting. However, t-MNs are still being observed, prompting the development of chemotherapy-free regimens with InO and blinatumomab as well as chimeric antigen receptor (CAR) T-cell therapies in high-risk disease. In Ph-positive ALL, chemotherapy and allogeneic hematopoietic stem-cell transplantation (HSCT) were historically considered a standard of care. However, the introduction of blinatumomab and newer-generation BCR::ABL1 tyrosine kinase inhibitors (TKIs) into the frontline setting significantly improved outcomes. The combination of blinatumomab and ponatinib induced high rates of complete molecular responses and excellent survival, without reliance on HSCT. A subset of patients with elevated WBC count at diagnosis are at particular risk of CNS and systemic relapse and may require additional strategies such as incorporating one to two cycles of high-dose methotrexate/cytarabine into consolidation, and potentially CAR T cells. In T-cell ALL, adding venetoclax into the frontline setting has improved outcomes. In early T-cell precursor ALL, HSCT is still needed. To further improve outcomes in older patients, novel agents such as subcutaneous blinatumomab, CAR T cells, newer-generation TKIs, and menin inhibitors should be investigated in the frontline setting.

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INTRODUCTION

Approximately 6,600 new cases of ALL and 1,300 deaths related to ALL were reported in the United States in 2024.¹ The incidence of ALL decreases with age; 25% of patients are age 20–60 years, and 11% are age 60 years and older.^{1–3} The excellent outcomes achieved in the pediatric population with cure rates ≥80% have not been replicated in adults and older patients where cure rates are approximately 40%–50%.^{2,4–11}

Several factors account for the significant difference in outcomes between pediatric and adult patients, particularly the tolerance to chemotherapy and the disease biology. Children have a higher tolerance to cytotoxic chemotherapy and better drug metabolism, while most older patients have comorbidities contributing to chemotherapy intolerance.^{12,13} Childhood ALL is characterized by a more favorable disease biology such as hyperdiploidy and t(12;21) or ETV6::RUNX1 fusion (each accounting for 25% of pediatric ALL v <5% of adult ALL), and a lower incidence of aggressive ALL subtypes such as the Philadelphia chromosome (Ph) and Ph-like phenotypes (each <5% of pediatric ALL v 25% of adult ALL). ALL in adults is also characterized by high-risk cytogenetic and molecular abnormalities including complex karyotype (≥five chromosomal abnormalities including at

least one structural abnormality) and TP53 mutation. These high-risk features are associated with resistance to chemotherapy, higher rates of mortality during induction and in remission, and inferior survival.^{7,14–23} Finally, even when comparing apples-to-apples (eg, Ph-positive ALL; hyperdiploidy/ETV6::RUNX1; chemotherapy; stem-cell transplant; chimeric antigen receptor [CAR] T-cell therapy; antibodies), the results are always better in pediatric ALL due to yet undefined biological factors.

Over the past decade, significant advances have been accomplished in the treatment of older ALL, driven by a better understanding of the disease biology and the incorporation of targeted therapies and immunotherapies into treatment regimens. These include agents targeting cell surface antigens (CD19, CD20, and CD22) and BCR::ABL1 tyrosine kinase inhibitors (TKIs).^{24–31} With these treatments, the long-term survival in adults is approximately 80%–90% in Ph-positive B-cell ALL (B-ALL),^{27,32–34} 80% in Ph-negative B-ALL including Burkitt's leukemia,^{7,31,35–38} and 70–80% in T-cell ALL (T-ALL).^{39,40} In patients at high risk of relapse (eg, hypodiploidy/near triploidy, complex karyotype, KMT2A rearrangement, Ph-like phenotype, early T-cell precursor [ETP]-ALL), allogeneic hematopoietic stem-cell transplantation (HSCT) in first remission is recommended.^{15,41,42}

PRACTICAL APPLICATIONS

- The addition of immunotherapies (blinatumomab and inotuzumab ozogamicin) to reduced-intensity chemotherapy has improved the survival of older patients with Philadelphia chromosome (Ph)-negative ALL. Confirmatory trials are ongoing.
- Chemotherapy-free regimens are being evaluated in patients age 70 years and older with Ph-negative ALL to reduce mortality and decrease the risk of developing therapy-related myeloid neoplasms.
- In Ph-positive ALL, the chemotherapy-free regimen of blinatumomab and tyrosine kinase inhibitors induced high molecular response rates and improved survival with less reliance on stem-cell transplantation.
- In T-cell ALL, the addition of venetoclax and adjusted doses of pegylated asparaginase to chemotherapy backbone may improve outcomes, particularly in early T-cell precursor ALL.
- The incorporation of novel therapies in the frontline setting of older ALL, such as chimeric antigen receptor T cells, subcutaneous blinatumomab, and menin inhibitors, might further improve outcomes.

Herein, we review the treatment landscape of older patients with ALL (age 60+ years), including chemoimmunotherapy combinations and chemotherapy-free regimens, and discuss strategies to reduce nonrelapse mortality (NRM) and improve overall outcomes.

HISTORICAL TREATMENT OF ALL WITH CYTOTOXIC CHEMOTHERAPY

Historically, the treatment of adults with Ph-negative B-ALL has relied on intensive chemotherapy followed by HSCT in first remission with modest outcomes. Results from the SEER database showed a long-term survival of <20% in older ALL. Survival improved with each decade (before 2000 v 2000–2010 v after 2010) and was better in patients age 60–69 years compared with patients age 70 years and older.^{20,23} An analysis from the National Cancer Institute's SEER cancer registry linked to Medicare enrollment data and insurance claims reported the outcome of 795 older patients with ALL. The 3-year overall survival (OS) rate was 15% overall and was significantly worse with increasing age (70–74 v 75–79 v ≥80 years) and in patients with comorbidities.⁴³

The hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen was originally evaluated in 288 patients with ALL, resulting in a complete remission (CR) rate of 92% and a 5-year OS rate of

38%.^{5,44} This represented a significant improvement in outcomes compared with previous regimens. Survival was further improved with the addition of the anti-CD20 antibody rituximab.³⁵ In younger patients (<60 years), the 3-year OS was higher in those who received rituximab compared with those who did not, 75% versus 47% ($P = .003$). However, in older patients (>60 years), survival did not improve with rituximab, possibly because of a higher mortality rate from infectious complications.¹¹ Reports from the German Multicenter Study Group for Adult ALL (GMALL) 2002 protocol showed similar findings. A total of 180 patients with B-ALL received chemotherapy with (63%) or without (37%) rituximab. The addition of rituximab improved survival in patients with standard-risk disease (3-year OS, 75% v 54%) and high-risk disease (3-year OS, 75% v 40%).⁴⁵

ROLE OF HSCT IN OLDER PATIENTS WITH ALL

HSCT is associated with a 3-year leukemia-free survival (LFS) rate of 35% in patients with ALL older than 60 years.⁴⁶ The Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMTR) analyzed the outcome of 418 older patients with ALL who underwent reduced-intensity conditioning (RIC)-HSCT. The median age was 60 years (range, 55–76 years) and the RIC regimen consisted mostly of fludarabine in combination with either busulfan (34%) or melphalan (26%).⁴⁷ Seventy-eight (19%) patients developed grade 2–4 acute graft-versus-host disease. After a median follow-up of 56 months, the incidence of relapse was 41% with a cumulative incidence of NRM of 25%. The LFS and OS rates were 34% and 42%, respectively.⁴⁷ Over the past decade, cyclophosphamide has been increasingly used as a backbone of immunosuppression after HSCT from haploidentical donors. Results from the EBMTR registry showed that this strategy improved outcomes, with a 2-year LFS of 65%.⁴⁸

TREATMENT OF NEWLY DIAGNOSED PH-NEGATIVE B-ALL

Chemoimmunotherapy Combinations

To improve the treatment tolerability in older patients with B-ALL, strategies have focused on reducing the chemotherapy intensity and duration, while relying more on immunotherapies (Table 1).⁸ The CD3-CD19 bispecific T-cell engager blinatumomab, and the antibody-drug conjugate inotuzumab ozogamicin (InO) are both approved for relapsed/refractory B-ALL.^{28,29} These agents have been incorporated into frontline regimens with low-intensity chemotherapy, improving survival from 20% to approximately 50% among older patients.⁷

In the SWOG 1318 study, 29 older patients (median age, 75 years; range, 66–84 years) received induction and consolidation therapy with blinatumomab for four to five cycles, followed by prednisone, vincristine, 6-mercaptopurine, methotrexate (POMP) maintenance for 18 months. The

TABLE 1. Frontline Regimens Incorporating Blinatumomab and/or InO in Older Patients With Ph-Negative B-ALL

Clinical Trial	MD Anderson ⁴⁹	INITIAL-1 ⁵⁰	EWALL-INO ⁵¹	A041703 ⁵⁶	SWOG 1318 ⁵²	GMALL-Bold ⁵³
Regimen	Mini-HCVD + InO then blinatumomab	InO then chemotherapy	InO then chemotherapy	InO then blinatumomab	Blinatumomab then POMP maintenance	Chemotherapy then blinatumomab
No./median follow-up	83/10 years	45/2.7 years	131/2.6 years	33/1.8 years	29/3.1 years	50/2 years
Age, years, median (range)	67 (60-88)	64 (56-80)	68 (55-84)	71 (60-84)	75 (66-84)	66 (56-76)
CR/CRi rate, %	99	100	90	97	66	85
MRD negativity rate, %	93	71	80	NA	92	82
Allogeneic SCT, No. (%)	5 (7)	NA	11 (9)	NA	1	3 (6)
Relapse, No. (%)	12 (14)	NA	29 (22)	9 (27)	NA	6 (12)
Overall survival rate, %	50 (5-year)	73 (3-year)	55 (2-year)	84 (1-year)	37 (3-year)	67 (3-year)

Abbreviations: B-ALL, B-cell ALL; CR, complete remission; CRi, complete remission with incomplete count recovery; GMALL, German Multicenter Study Group for Adult ALL; HCVD, hyperfractionated cyclophosphamide, vincristine, dexamethasone; InO, inotuzumab ozogamicin; MRD, measurable residual disease by multiparameter flow cytometry; NA, not available; Ph, Philadelphia chromosome; POMP, prednisone, vincristine, 6-mercaptopurine, methotrexate; SCT, stem-cell transplantation.

overall response rate (ORR) was 66% (all CR). After a median follow-up of 3.1 years, the 3-year OS was 37%.⁵²

Blinatumomab was added sequentially to a reduced-intensity chemotherapy backbone in the GMALL Bold trial. Fifty patients (median age, 66 years; range, 56–76 years) received induction with one cycle of chemotherapy and one cycle of blinatumomab, followed by three cycles of blinatumomab alternating with age-adjusted chemotherapy cycles. Three patients underwent HSCT. After a median follow-up of 2 years, the estimated 3-year OS rate was 67%.⁵³ Adding blinatumomab improved the rates of measurable residual disease (MRD) negativity (82% v 55%) and survival (3-year OS, 67% v 49%) compared with chemotherapy alone.⁵³

Another low-intensity chemoimmunotherapy regimen, the mini-hyper-CVD (reduced dosing of hyperfractionated cyclophosphamide, vincristine, and dexamethasone) plus InO regimen, added sequential blinatumomab in a phase II trial of older patients with newly diagnosed B-ALL.⁵⁴ Patients received four cycles of mini-hyper-CVD and InO, followed by four cycles of blinatumomab. Maintenance consisted of 12 cycles of POMP intercalated with three cycles of blinatumomab.⁹ This design aimed to reduce the reliance on chemotherapy, while deepening response, and reducing the risk of hepatic sinusoidal obstruction syndrome (SOS) by fractionating and reducing the exposure of InO to a maximum cumulative dose of 2.7 mg/m². Eighty-three patients have been treated: 49 without sequential blinatumomab and 34 with blinatumomab. The median age was 67 years (range, 60–88 years) and 28 (34%) patients were age 70 years and older. Among evaluable patients, 25 of 64 (39%) had *TP53* mutation, 7 of 49 (14%) had *CRLF2* overexpression, and 19 of 67 (28%) had high-risk cytogenetics defined as hypodiploidy/near triploidy, tetraploidy, complex karyotype, and *KMT2A* rearrangement. The ORR was 99%, with MRD negativity rates of 93% and 94% by multiparameter flow cytometry (MFC) and next-generation sequencing

(NGS; sensitivity 1×10^{-6}), respectively.⁴⁹ No early deaths were observed. After a median follow-up of 121 months, the 5-year progression-free survival (PFS), OS, and continuous remission duration (CRD) rates were 48%, 50%, and 79%, respectively. Outcomes were better in patients age 60–69 years compared with those age 70 years and older, with a median OS of 75 months versus 36 months, respectively.⁴⁹ The high CRD rate, contrasting with a relatively lower OS, suggests that leukemia-unrelated deaths occurred in older patients. Despite chemotherapy dose reduction, NRM was observed in 38 (46%) patients, mostly secondary to infectious complications ($n = 9$) and therapy-related myeloid neoplasms (t-MNs; $n = 8$). NRM was higher in patients age 70 years and older (64%) compared with those age 60–69 years (36%).⁴⁹

Induction therapy with InO was investigated in the INITIAL-1 trial. Forty-five older patients (median age, 64 years; range, 56–80 years) received two to three cycles of dexamethasone with InO, followed by chemotherapy.⁵⁰ All patients responded, and 71% of responders achieved MRD negativity. After a median follow-up of 2.7 years, the 3-year event-free survival (EFS) and OS rates were 55% and 73%, respectively.⁵⁰

The EWALL-INO trial evaluated low-intensity chemotherapy with InO as frontline therapy among 131 older patients (median age, 68 years; range, 55–84 years). The ORR and MRD negativity rates were 90% and 80%, respectively, and the 2-year OS rate was 73%.⁵¹

These results highlight improved outcomes with the integration of InO and blinatumomab into the frontline therapy of older patients with Ph-negative B-ALL.

Chemotherapy-Free Regimens

To further improve the outcome of older patients, reducing or eliminating chemotherapy could decrease the risk of

developing toxicities and t-MNs. Chemotherapy-free regimens with blinatumomab and InO are being investigated.

In a phase II trial, patients age 70 years and older or those age 60–70 years unfit for chemotherapy received induction with InO in combination with dexamethasone, vincristine, and blinatumomab (days 15–28), followed by up to four consolidation cycles of blinatumomab and InO. The total cumulative InO dose was 2.7 mg/m², and patients with CD20-positive disease also received two doses of rituximab during cycles 1–4. Twelve injections of intrathecal (IT) chemotherapy, alternating cytarabine and methotrexate, were given for CNS prophylaxis.⁵⁵ Fourteen patients with a median age of 76 years (range, 65–84 years) were treated; eight (57%) were age 75 years and older, 7 of 14 (50%) had *TP53* mutation, 6 of 13 (46%) had high-risk cytogenetics defined as hypodiploidy/near triploidy, *KMT2A* rearrangement, and complex karyotype, and 1 of 14 (7%) had Ph-like B-ALL. Thirteen (93%) patients responded, all with negative MRD by MFC (87% after cycle 1) and 92% by NGS (75% after cycle 1). After a median follow-up of 15 months, the 1-year PFS, CRD, and OS rates were 64%, 70%, and 73%, respectively. With this short follow-up, no t-MNs have been observed.⁵⁵

The ALLIANCE A041703 trial investigated InO induction followed by blinatumomab consolidation in 33 patients age 60 years and older with newly diagnosed B-ALL. InO was given at the dose of 1.8 mg/m² in cycle 1 followed by 1.5 mg/m² in cycle 2 if CR/CR with incomplete count recovery (CRi) was achieved. Blinatumomab was given for two or three cycles in both responders and nonresponders. Eight doses of IT methotrexate were given for CNS prophylaxis. The cumulative CR rate was 97% after cycle 2 of InO. After a median follow-up of 22 months, nine patients have relapsed, eight patients have died (two in remission and six with relapsed disease), and one patient had possible SOS at the time of death. The 1-year EFS rate was 75% and 1-year OS rate was 84%.⁵⁶

The ECOG-ACRIN E1910 phase III trial randomly assigned patients to receive consolidation chemotherapy with or without blinatumomab. Among 488 patients (median age, 51 years; range, 30–70 years) with newly diagnosed Ph-negative B-ALL who received induction therapy, 224 achieved MRD-negative remission and were randomly assigned to receive chemotherapy (n = 112) or chemotherapy and blinatumomab (n = 112).³¹ After a median follow-up of 43 months, the 3-year OS was 85% in the blinatumomab-chemotherapy group versus 68% in the chemotherapy-only group (*P* = .002).^{31,57} The magnitude of benefit from the addition of blinatumomab was more evident in patients younger than 55 years compared with patients age 55 years and older, with 3-year OS rates of 90% versus 70%, respectively.³¹ This could possibly be explained by a higher rate of blinatumomab discontinuation in older patients. These positive results led to the approval of blinatumomab by the Food and Drug Administration (FDA) as consolidation therapy for Ph-negative B-ALL.⁵⁸

Ongoing Clinical Trials

The Golden Gate randomized phase III trial is investigating induction/consolidation with low-intensity chemotherapy and blinatumomab versus chemotherapy alone. Eligible patients are age 55 years and older or age 40–55 years unfit to receive intensive therapy.⁵⁹ Fourteen patients have been treated, with a median age of 70 years (range, 57–78 years), including seven (50%) patients age 70 years and older. Six patients had grade 1–2 neurologic adverse events attributed to blinatumomab, all except one were reversible. Thirteen (93%) patients achieved CR including 11 (85%) with negative MRD. Four patients underwent HSCT and two have relapsed.⁶⁰ The Alliance A042001 is an ongoing randomized phase II trial (ClinicalTrials.gov identifier: [NCT05303792](https://clinicaltrials.gov/ct2/show/study/NCT05303792)) comparing mini-hyper-CVD with InO versus dose-adjusted hyper-CVAD in patients age 50 years and older. Results from these randomized studies are awaited and could lead to the regulatory approval of immunotherapies in the frontline setting of B-ALL.

TREATMENT OF Ph-POSITIVE ALL

Intensive Chemotherapy and TKIs

Over the past two decades, combinations of BCR::ABL1 TKIs and chemotherapy have significantly improved the survival of patients with Ph-positive ALL, with less reliance on HSCT.³⁴ Nonetheless, many patients eventually relapsed, many because of the acquisition of *T315I* mutation and a low rate of deep molecular response.⁶¹ Therefore, newer and more potent TKIs, such as ponatinib, were evaluated in the frontline setting.^{32,62} Long-term follow-up from the hyper-CVAD and ponatinib trial showed a complete molecular response (CMR; undetectable BCR::ABL1 transcripts) rate of 86% and a 6-year OS rate of 75%. Twenty of 86 (23%) patients underwent HSCT. In an 8-month landmark analysis, the 6-year OS rate was 70% among patients who underwent HSCT and 87% among those who did not (*P* = .13).⁶³ Findings from this trial questioned the role of HSCT in first remission among patients with Ph-positive ALL.

Low-Intensity Regimens

Older patients might not be good candidates for intensive chemotherapy or HSCT because of their poor chemotherapy tolerance and the increased risk of treatment-related mortality. In a randomized trial of imatinib combined with low-intensity versus high-intensity chemotherapy, a higher early mortality rate was observed in those treated with intensive chemotherapy (6.7% v 0.7%; *P* = .01).⁶⁴ Dasatinib and nilotinib have each been added to low-intensity regimens, resulting in high CR rates, but modest long-term survivals. The combination of dasatinib, vincristine, and dexamethasone in patients age 55 years and older resulted in a CR rate of 96% and a 5-year OS rate of 36%.⁶¹ Similarly, nilotinib with the same combination led to a CR rate of 94% and 4-year OS rate of 47% among 79 older patients with a median age of

66 years (range, 55–85 years).⁶⁵ These findings highlight that the outcome of older patients treated with low-intensity therapy and TKIs remains modest, despite some patients experiencing long-term survival.

In the PhALLCON randomized phase III trial, patients with newly diagnosed Ph-positive ALL received reduced-intensity chemotherapy with either ponatinib (n = 164) or imatinib (n = 81).²⁷ Patients who received ponatinib had higher rates of MRD-negative CR compared with those who received imatinib (34.4% v 16.7%; $P = .002$), particularly in patients age 60 years and older (40.0% v 10.3%). HSCT was performed in 30% and 37% of patients who received ponatinib or imatinib, respectively.²⁷ Results from the PhALLCON trial led to the FDA approval of ponatinib as frontline therapy in Ph-positive ALL.⁶⁶

Blinatumomab-Based Regimens

Treatment with single-agent blinatumomab was shown to be effective in patients with relapsed/refractory Ph-positive ALL, resulting in a CMR rate of 88% among responders and a median OS of 9 months.⁶⁷ In a retrospective analysis, the combination of blinatumomab and TKIs led to a CMR rate of 75% and a 1-year OS rate of 73%.^{68–70} Phase II clinical trials evaluated blinatumomab in combination with dasatinib and ponatinib in patients with newly diagnosed Ph-positive ALL, including those age 60 years and older (Table 2).

In the D-ALBA trial, 63 patients (median age, 54 years; range, 24–82 years) received induction with dasatinib and corticosteroids for approximately 3 months followed by the addition of two to five cycles of blinatumomab consolidation. Twelve doses of IT chemotherapy were administered for CNS prophylaxis. The CMR rate increased from 15% after induction to 42% after two cycles of blinatumomab and 72% after five cycles of blinatumomab.²⁴ Approximately half of the patients underwent HSCT in CR, and nine relapses (four CNS relapses) were observed. After a median follow-up of 53 months, the 4-year OS rate was 81%.⁷¹

A similar study investigated dasatinib and prednisone given for 3 months followed by blinatumomab and dasatinib for three cycles among 24 older patients (median age, 73 years; range, 65–87 years). Only one patient underwent HSCT. The CMR rate was 63% and the 3-year OS was 75%. Eight patients relapsed, three of them with a new *T315I* mutation.^{72,74}

Blinatumomab was also combined with ponatinib in a concomitant rather than sequential fashion.²⁶ Seventy-six patients (median age, 50 years; range, 18–83 years) were treated with up to five cycles of blinatumomab in combination with ponatinib. Ponatinib was dosed at 30 mg/d in cycle 1, and reduced to 15 mg/d once CMR was achieved and maintained for at least 5 years.³³ The rates of CMR and MRD negativity by NGS were 83% and 96%, respectively. Ten relapses were observed, including five isolated CNS relapses.

This resulted in an amendment that increased the number of prophylactic IT doses from 12 to 15. After a median follow-up of 29 months, the estimated 3-year OS rate was 88%.³³ Only two patients underwent HSCT, compared with approximately half of the patients in the D-ALBA trial. Patients with a WBC count higher than $70 \times 10^9/L$ at baseline and those with *VPREB1* deletion were at higher risk of relapse, with a 3-year cumulative incidence of relapse of 52% each. By multivariate analysis, WBC count higher than $70 \times 10^9/L$ at diagnosis was the only independent factor associated with a higher risk of relapse ($P = .0047$).⁷⁵ In addition to increasing the total doses of IT chemotherapy, introducing one to two cycles of high-dose methotrexate and cytarabine during consolidation and potentially incorporating CAR T-cell therapy into frontline regimens could help further mitigate the risk of CNS and systemic relapses in patients receiving low-intensity therapy.⁷⁶

The GIMEMA ALL2820 phase III trial compared ponatinib and sequential blinatumomab (two to five cycles) with chemotherapy and imatinib. All patients received 15 doses of triple IT chemotherapy (cytarabine, methotrexate, and steroids) for CNS prophylaxis. A total of 133 patients received blinatumomab and ponatinib; their median age was 57 years (range, 20–87 years).⁷³ The rate of molecular response (undetectable or positive nonquantifiable *BCR::ABL1* transcripts) was 46% after ponatinib induction and 74% after two cycles of blinatumomab. Four patients relapsed, of them three with the *IKZF1^{plus}* genotype; HSCT was performed in 12% of the patients. After a median follow-up of 8.5 months, the estimated 18-month OS was 95%.⁷³

TREATMENT OF OLDER PATIENTS WITH T-ALL

T-ALL accounts for about 10%–25% of ALL cases and encompasses three major immunophenotypic and biological subtypes: thymic (CD1a+), mature (surface CD3+), and early (both negative) as well as its subcategory of ETP-ALL (positive myeloid markers, negative CD8, CD5 expression <75%). ETP-ALL is associated with a poor prognosis, and may benefit from the incorporation of venetoclax into frontline therapy, followed by HSCT in responders. Near-ETP ALL has a gene expression profile similar to ETP-ALL but with higher levels of CD5 expression.^{77–80} Although the outcomes in B-ALL have significantly improved with the use of immunotherapies and targeted therapies, advances in T-ALL are lagging behind. In the absence of effective T-cell-targeted therapies, treatment of T-ALL has relied on standard chemotherapies, including high-dose methotrexate and cytarabine, nelarabine, asparaginase, and venetoclax.

In a retrospective analysis of 171 patients with newly diagnosed T-ALL or T-cell lymphoblastic lymphoma (LBL), those with ETP-ALL/LBL had significantly inferior survival compared with non-ETP-ALL/LBL, with 5-year OS rates of 32% versus 63%, respectively ($P < .001$).⁸¹ In non-ETP-ALL, the addition of nelarabine improved outcomes, with 5-year

TABLE 2. Blinatumomab and BCR::ABL1 Tyrosine Kinase Inhibitor Combinations in Frontline Ph-Positive ALL

Clinical Trial	D-ALBA ⁷¹	SWOG 1318 ⁷²	MD Anderson ³³	GIMEMA ALL2820 ⁷³
Regimen	Blinatumomab + dasatinib	Blinatumomab + dasatinib	Blinatumomab + ponatinib	Blinatumomab + ponatinib
No./median follow-up	63/4.4 years	24/4.3 years	76/2.4 years	133/0.7 years
Age, years, median (range)	54 (24-82)	73 (65-87)	50 (18-83)	57 (20-87)
CR rate, %	98	92	96	96
CMR rate, %	72	63	83 (96 by NGS)	74
Allogeneic SCT, No. (%)	30 (48)	1 (4)	2 (3)	16 (12)
Relapse, No. (%)	9 (14)	8 (33)	10 (13)	4 (3)
CNS relapse, No. (%)	4 (6)	NA	5 (7)	1 (0.7)
Overall survival rate, %	81 (4-year)	75 (3-year)	88 (3-year)	95 (1.5-year)

Abbreviations: CMR, complete molecular response (undetectable *BCR::ABL1* transcript by PCR); CR, complete remission; NA, not available; NGS, next-generation sequencing; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; SCT, stem-cell transplantation.

OS rates of 83% versus 38% with and without nelarabine, respectively ($P = .003$).⁸¹

Further improvement in outcome was driven by the addition of venetoclax and pegylated asparaginase to the hyper-CVAD and nelarabine combination, particularly in patients with ETP-ALL.^{81,82} One hundred forty-five patients were treated, including 46 (34%) who received venetoclax. The 2-year OS rate was 88% with venetoclax, versus 74% without venetoclax ($P = .16$).⁸²

A phase I/II study evaluated the lower-intensity backbone of mini-hyper-CVD plus nelarabine, pegylated asparaginase, and venetoclax in 22 patients (median age, 46 years; range, 20–70 years), including 18% who were age 60 years and older.⁸³ The CR/CRi rate was 57% among 21 evaluable patients and 75% in the subset of four patients with T-ALL. After a median follow-up of 26 months, the median OS was 7.1 months and the 1-year OS rate was 29%.⁸³ Venetoclax was also combined with mini-hyper-CVD in a phase Ib study of patients age 60 years and older with newly diagnosed ALL and patients age 18 years and older with relapsed/refractory ALL.⁸⁴ Nineteen patients were enrolled, including eight with T-ALL (newly diagnosed, $n = 3$; relapsed/refractory, $n = 5$). Among the 11 newly diagnosed patients, 10 (91%) achieved a CR, all with negative MRD, and two (40%) of the five patients with relapsed/refractory T-ALL achieved CR, including one with negative MRD.⁸⁴

TREATMENT-RELATED COMPLICATIONS IN OLDER PATIENTS WITH ALL

Treatment with chemotherapy, even at reduced dosing, has been associated with a high risk of complications in older patients with ALL, including death in remission.⁴⁹ This is primarily related to infectious complications and t-MNs driven by previous chemotherapy but also by genomic instability and age-related clonal hematopoiesis.^{21,85} Chemotherapy could lead to clonal evolution and promote the

development of myelodysplastic syndromes or AML.^{86–89} The presence of *TP53* mutations as clonal hematopoiesis of indeterminate potential in the myeloid component of patients with ALL could be associated with higher risks of developing t-MNs during and after treatment.^{89,90}

Recently, we assessed the frequency and risk factors of t-MNs after ALL therapy. A total of 875 patients with newly diagnosed ALL treated with hyper-CVAD- or mini-hyper-CVD-based regimens were analyzed.⁹¹ Their median age was 45 years (range, 18–87 years), and 53 of 283 (19%) evaluable patients had a *TP53* mutation. Seven patients had molecular testing performed both at ALL and t-MN diagnosis, of whom six shared at least one mutation between the two time points. Five of these six shared a *TP53* mutation, including one patient who acquired an additional *TP53* mutation at the time of t-MN diagnosis. With a median follow-up of 46.1 months, 35 (4%) patients developed a t-MN after a median of 38.2 months between ALL and t-MN diagnosis. Myelodysplastic syndromes, AML, and chronic myelomonocytic leukemia accounted for 24 (68%), 10 (29%), and one (3%) t-MN case, respectively. Older age and the presence of *TP53* mutation at diagnosis were the only factors predicting for the development of t-MNs. The incidence of t-MNs was 7% in patients age 60 years and older compared with 3% in those younger than 60 years ($P = .009$), and 9% in patients with *TP53* mutation compared with 1% in those with wild-type *TP53* ($P = .008$). The cumulative incidence of t-MN was highest among patients age 60 years and older with *TP53* mutation and lowest among those younger than 60 years without a *TP53* mutation (5-year rate, 25% v 1%; $P = .002$). The median OS after the diagnosis of a t-MN was 8.9 months with a 2-year OS rate of 20%.⁹¹

Omitting chemotherapy in older patients, particularly those age 70 years and older, could help reduce the risk of developing t-MNs. Multiple trials are currently evaluating blinatumomab and/or InO in older patients without chemotherapy, as discussed above. Another strategy relies on

using CAR T-cell therapy in the frontline and consolidation settings of high-risk B-ALL.

Treatment with CAR T cells demonstrated remarkable efficacy both in relapsed/refractory B-ALL,^{92,93} and in low disease burden or MRD.^{94,95} These encouraging results prompted the development of strategies incorporating CAR T cells into the frontline setting, particularly as consolidation in high-risk B-ALL. An ongoing phase II trial is assessing the safety and efficacy of brexucabtagene autoleucel (Brexu-cel) as consolidation therapy in patients with high-risk B-ALL who achieve remission after frontline treatment with chemotherapy, InO, and blinatumomab (ClinicalTrials.gov identifier: [NCT06287229](#)). This includes those with persistent or recurrent MRD, Ph-like signature, *TP53* mutation, low hypodiploidy/tetraploidy, complex karyotype, and *KMT2A* rearrangement.

Toxicities associated with CAR T-cell therapy, namely cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS), can be challenging in older patients. In the ZUMA-3 trial, 55 patients with a median age of 40 years received treatment with Brexu-cel. Grade ≥ 3 CRS and ICANS were observed in 24% and 25% of patients, respectively. In this trial, patients were relatively young, with only eight (15%) patients age 65 years and older.⁹⁶ Obe-cabtagene autoleucel (Obe-cel) is a novel CAR T-cell product with a fast-off rate binding to CD19 resulting in less toxicity and longer CAR T-cell persistence.⁹³ Obe-cel dosing is based on the leukemia burden before lymphodepletion. Patients with more than 20% bone marrow blasts receive 10×10^6 CAR T cells on day 1, while those with 20% blasts or less receive 100×10^6 CAR T cells. On day 10, a second dose is administered to a total dose of 410×10^6 CAR T cells.⁹³ In the FELIX phase Ib/II trial, 127 patients received Obe-cel. The median age was 47 years (range, 20–81 years) with approximately 20% of the patients age 65 years and older. The median OS was 15.6 months overall. Among patients with $<5\%$ of blasts, the rates of CRS and ICANS were 47% (no grade ≥ 3) and 8% (no grade ≥ 3), respectively.⁹³ These positive results led to the FDA approval of Obe-cel for adults with relapsed/refractory B-ALL.⁹⁷

In a phase I/II trial, a novel memory-enriched CD19-directed CAR T-cell product was shown to be safe and effective in patients with relapsed/refractory B-ALL, including those with Ph-like ALL, extramedullary disease, or relapsed post-HSCT.⁹⁸ This construct is being evaluated as definitive consolidation therapy in patients age 55 years and older with B-ALL after achieving first CR.⁹⁹ Fourteen patients were evaluable for response after receiving 200×10^6 CAR T cells. The median age was 68 years (range, 55–79 years), four had Ph-positive ALL, two had hypodiploidy/*TP53* mutation, and 11 had previous blinatumomab. Thirteen (93%) patients achieved MRD-negative CR at the time of lymphodepletion. No ICANS or grade ≥ 2 CRS were observed. At a median follow-up of 244 days, one patient with Ph-positive ALL had a molecular relapse for which they underwent HSCT and

remains alive in remission; no death was observed. Despite low disease burden, CAR T cells expanded and peaked between days 7 and 14. CAR T cells were also detected in the cerebrospinal fluid of all 10 tested patients on day 28.⁹⁹

FUTURE DIRECTIONS

The outcome of older patients with ALL has improved since the introduction of immunotherapies (blinatumomab and InO) and targeted therapies (BCR::ABL1 TKIs and venetoclax). Incorporating blinatumomab and InO in combination with low-intensity chemotherapy improved outcomes; however, the long-term OS remains relatively modest, mostly because of deaths in remission and NRM. Shifting toward chemotherapy-free regimens, such as blinatumomab with InO, could reduce the risk of complications associated with chemotherapy, mitigate the risk of developing t-MNs, and improve survival in older patients, particularly those age 70 years and older.

Treatment with blinatumomab in older patients can be associated with a higher risk of neurotoxicity requiring treatment holidays and the administration of corticosteroids.¹⁰⁰ In patients with recurrent neurologic adverse events, the dose of blinatumomab can be reduced from 28 $\mu\text{g}/\text{d}$ to 15 $\mu\text{g}/\text{d}$, 9 $\mu\text{g}/\text{d}$, or even 5 $\mu\text{g}/\text{d}$. Using InO at reduced and fractionated dosing has been shown to reduce the incidence of SOS. In the phase II trial of mini-hyper-CVD and InO, with or without blinatumomab, in the salvage setting, the rate of SOS decreased from 13% to 2% after reducing and fractionating the dose of InO. These modifications consisted of administering InO at 0.6 mg/m^2 on day 2 and 0.3 mg/m^2 on day 8 of cycle 1, and 0.3 mg/m^2 on days 2 and 8 during cycles 2–4, with a maximum cumulative dose of 2.7 mg/m^2 . All patients received ursodeoxycholic acid for SOS prophylaxis, had close monitoring of liver tests, and had the last dose of InO distanced from HSCT.^{101,102}

The improved outcomes observed with intravenous blinatumomab prompted the development of a newer subcutaneous blinatumomab formulation with the goal to improve safety and efficacy. Twenty-seven patients with relapsed/refractory B-ALL received subcutaneous blinatumomab, at two different dose levels. The rates of CR/CRi were 86%–92%, with MRD negativity rates of 75%–100%. Treatment was well tolerated, with no treatment-related grade 4 CRS or neurologic adverse events reported.¹⁰³ The favorable safety profile of the subcutaneous formulation, and the improved efficacy because of higher dose delivery, warrant its exploration in the frontline setting of older patients with B-ALL to improve outcomes while reducing morbidity and mortality.

Novel agents have been being investigated in the relapsed/refractory setting with the goal of being incorporated into frontline regimens. Menin inhibitors have shown promising activity in patients with *KMT2A* rearrangements, which accounts for approximately 5% of all ALL.¹⁰⁴ In the

AUGMENT-101 trial, patients with relapsed/refractory KMT2A-rearranged leukemia or AML with NPM1 mutation were treated with revumenib menin inhibitor. In the efficacy population, one of seven (14%) patients with ALL responded to revumenib therapy.¹⁰⁵ Exploring menin inhibitors in the frontline setting, in combination with immune therapies, might improve the outcome of KMT2A-rearranged ALL.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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In summary, treatment of older patients with ALL remains challenging. Future strategies may lead to improved outcomes, first by reducing the duration and intensity of chemotherapy while relying more on immunotherapies and targeted therapies, and second by incorporating novel agents into the frontline setting (eg, CAR T cells, subcutaneous blinatumomab, newer-generation BCR::ABL1 TKIs, and menin inhibitors).

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REFERENCES

- National Cancer Institute: SEER Cancer Stat Facts: Acute Lymphocytic Leukemia. Bethesda, MD, National Cancer Institute, 2024
- Pui CH, Yang JJ, Hunger SP, et al: Childhood acute lymphoblastic leukemia: Progress through collaboration. *J Clin Oncol* 33:2938-2948, 2015
- Howlader N, Noone AM, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2018. Bethesda, MD, National Cancer Institute, 2021
- Pui CH, Yang JJ, Bhakta N, et al: Global efforts toward the cure of childhood acute lymphoblastic leukaemia. *Lancet Child Adolesc Health* 2:440-454, 2018
- Kantarjian HM, O'Brien S, Smith TL, et al: Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol* 18:547-561, 2000
- Samra B, Jabbour E, Ravandi F, et al: Evolving therapy of adult acute lymphoblastic leukemia: State-of-the-art treatment and future directions. *J Hematol Oncol* 13:70, 2020
- Jabbour E, Short NJ, Jain N, et al: The evolution of acute lymphoblastic leukemia research and therapy at MD Anderson over four decades. *J Hematol Oncol* 16:22, 2023
- Short NJ, Kantarjian H, Jabbour E: Optimizing the treatment of acute lymphoblastic leukemia in younger and older adults: New drugs and evolving paradigms. *Leukemia* 35:3044-3058, 2021
- Jabbour E, Short NJ, Senapati J, et al: Mini-hyper-CVD plus inotuzumab ozogamicin, with or without blinatumomab, in the subgroup of older patients with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: Long-term results of an open-label phase 2 trial. *Lancet Haematol* 10:e433-e444, 2023
- Gökbuğut N: How I treat older patients with ALL. *Blood* 122:1366-1375, 2013
- Thomas DA, O'Brien S, Faderl S, et al: Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol* 28:3880-3889, 2010
- Brady SW, Roberts KG, Gu Z, et al: The genomic landscape of pediatric acute lymphoblastic leukemia. *Nat Genet* 54:1376-1389, 2022
- Lee SHR, Yang W, Gocho Y, et al: Pharmacotypes across the genomic landscape of pediatric acute lymphoblastic leukemia and impact on treatment response. *Nat Med* 29:170-179, 2023
- Marks DI: The challenges of managing older patients with acute lymphoblastic leukemia. *Am Soc Clin Oncol Educ Book* 35:e343-e351, 2015
- Roberts KG, Mullighan CG: Genomics in acute lymphoblastic leukaemia: Insights and treatment implications. *Nat Rev Clin Oncol* 12:344-357, 2015
- Roberts KG: Genetics and prognosis of ALL in children vs adults. *Hematology Am Soc Hematol Educ Program* 2018:137-145, 2018
- Liu YF, Wang BY, Zhang WN, et al: Genomic profiling of adult and pediatric B-cell acute lymphoblastic leukemia. *EBioMedicine* 8:173-183, 2016
- O'Brien S, Thomas DA, Ravandi F, et al: Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. *Cancer* 113:2097-2101, 2008
- Li S, Molony JT, Chia V, et al: Patient characteristics and treatment patterns in elderly patients newly diagnosed with acute lymphoblastic leukemia (ALL) using 100% Medicare ALL data. *Blood* 128:3981, 2016
- Geyer MB, Hsu M, Devlin SM, et al: Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis. *Blood* 129:1878-1881, 2017
- Mitchell E, Spencer Chapman M, Williams N, et al: Clonal dynamics of haematopoiesis across the human lifespan. *Nature* 606:343-350, 2022
- Goekbuğut N, Beck J, Brüeggemann M, et al: Moderate intensive chemotherapy including CNS-prophylaxis with liposomal cytarabine is feasible and effective in older patients with Ph-negative acute lymphoblastic leukemia (ALL): Results of a prospective trial from the German Multicenter Study Group for Adult ALL (GMALL). *Blood* 120:1493, 2012
- Sasaki K, Jabbour E, Short NJ, et al: Acute lymphoblastic leukemia: A population-based study of outcome in the United States based on the surveillance, epidemiology, and end results (SEER) database, 1980-2017. *Am J Hematol* 96:650-658, 2021
- Foà R, Bassan R, Vitale A, et al: Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. *N Engl J Med* 383:1613-1623, 2020
- Shen S, Chen X, Cai J, et al: Effect of dasatinib vs imatinib in the treatment of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: A randomized clinical trial. *JAMA Oncol* 6:358-366, 2020
- Jabbour E, Short NJ, Jain N, et al: Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: A US, single-centre, single-arm, phase 2 trial. *Lancet Haematol* 10:e24-e34, 2023
- Jabbour E, Kantarjian HM, Aldoss I, et al: Ponatinib vs imatinib in frontline Philadelphia chromosome-positive acute lymphoblastic leukemia: A randomized clinical trial. *JAMA* 331:1814-1823, 2024

28. Kantarjian H, Stein A, Gökbuget N, et al: Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 376:836-847, 2017
29. Kantarjian HM, DeAngelo DJ, Stelljes M, et al: Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 375:740-753, 2016
30. van der Sluis IM, de Lorenzo P, Kotecha RS, et al: Blinatumomab added to chemotherapy in infant lymphoblastic leukemia. *N Engl J Med* 388:1572-1581, 2023
31. Litgow MR, Sun Z, Mattison RJ, et al: Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. *N Engl J Med* 391:320-333, 2024
32. Jabbour E, Short NJ, Ravandi F, et al: Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: Long-term follow-up of a single-centre, phase 2 study. *Lancet Haematol* 5:e618-e627, 2018
33. Kantarjian H, Short NJ, Haddad FG, et al: Results of the simultaneous combination of ponatinib and blinatumomab in Philadelphia chromosome-positive ALL. *J Clin Oncol* 42:4246-4251, 2024
34. Jabbour E, Haddad FG, Short NJ, et al: Treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia—from intensive chemotherapy combinations to chemotherapy-free regimens: A review. *JAMA Oncol* 8:1340-1348, 2022
35. Thomas DA, Faderl S, O'Brien S, et al: Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer* 106:1569-1580, 2006
36. Hoelzer D, Walewski J, Döhner H, et al: Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: Report of a large prospective multicenter trial. *Blood* 124:3870-3879, 2014
37. Roschewski M, Dunleavy K, Abramson JS, et al: Multicenter study of risk-adapted therapy with dose-adjusted EPOCH-R in adults with untreated Burkitt lymphoma. *J Clin Oncol* 38:2519-2529, 2020
38. Evens AM, Danilov A, Jagadeesh D, et al: Burkitt lymphoma in the modern era: Real-world outcomes and prognostication across 30 US cancer centers. *Blood* 137:374-386, 2021
39. Dunsmore KP, Winter SS, Devidas M, et al: Children's oncology group AALL0434: A phase III randomized clinical trial testing nelarabine in newly diagnosed T-cell acute lymphoblastic leukemia. *J Clin Oncol* 38:3282-3293, 2020
40. Senapati J, Kantarjian HM, Jabbour E, et al: Nelarabine (NEL), pegylated asparaginase (PEG) and venetoclax (VEN) incorporated to HCVAD chemotherapy in the frontline treatment of adult patients with T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/T-LBL). *Blood* 142:963, 2023 (suppl 1)
41. Pui CH, Roberts KG, Yang JJ, et al: Philadelphia chromosome-like acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 17:464-470, 2017
42. Prockop S, Wachter F: The current landscape: Allogeneic hematopoietic stem cell transplant for acute lymphoblastic leukemia. *Best Pract Res Clin Haematol* 36:101485, 2023
43. Danese MD, Katz A, Cetin K, et al: Treatment patterns, survival, and hospitalization in adult patients with acute lymphoblastic leukemia: An observational cohort study using SEER Medicare data. *Leuk Lymphoma* 60:2015-2024, 2019
44. Kantarjian H, Thomas D, O'Brien S, et al: Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer* 101:2788-2801, 2004
45. Hoelzer D, Huettmann A, Kaul F, et al: Immunochemotherapy with rituximab improves molecular CR rate and outcome in CD20+ B-lineage standard and high risk patients; results of 263 CD20+ patients studied prospectively in GMALL study 07/2003. *Blood* 116:170, 2010
46. Roth-Guepin G, Canaan J, Ruggeri A, et al: Allogeneic stem cell transplantation in acute lymphoblastic leukemia patients older than 60 years: A survey from the acute leukemia working party of EBMT. *Oncotarget* 8:112972-112979, 2017
47. Giebel S, Labopin M, Houhou M, et al: Autologous versus allogeneic hematopoietic cell transplantation for older patients with acute lymphoblastic leukemia. An analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant* 58:393-400, 2023
48. Nagler A, Labopin M, Koc Y, et al: Outcome of T-cell-replete haploidentical stem cell transplantation improves with time in adults with acute lymphoblastic leukemia: A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Cancer* 127:2507-2514, 2021
49. Senapati J, Jabbour E, Jain N, et al: Low intensity mini-hypercvd (mHCVd), inotuzumab ozogamicin (Ino) with/without blinatumomab (Blina) in older patients with newly diagnosed Philadelphia negative B-cell acute lymphoblastic leukemia (B-ALL): 10 years update. *Blood* 144:1441, 2024 (suppl 1)
50. Stelljes M, Raffel S, Alakel N, et al: Inotuzumab ozogamicin as induction therapy for patients older than 55 years with Philadelphia chromosome-negative B-precursor ALL. *J Clin Oncol* 42:273-282, 2024
51. Chevallier P, Leguay T, Delord M, et al: Inotuzumab ozogamicin and low-intensity chemotherapy in older patients with newly diagnosed CD22+ Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia. *J Clin Oncol* 42:4327-4341, 2024
52. Advani AS, Moseley A, O'Dwyer KM, et al: SWOG 1318: A phase II trial of blinatumomab followed by POMP maintenance in older patients with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia. *J Clin Oncol* 40:1574-1582, 2022
53. Gökbuget N, Schwartz S, Faul C, et al: Dose reduced chemotherapy in sequence with blinatumomab for newly diagnosed older patients with Ph/BCR::ABL negative B-precursor adult lymphoblastic leukemia (ALL): Preliminary results of the GMALL Bold trial. *Blood* 142:964, 2023 (suppl 1)
54. Kantarjian H, Ravandi F, Short NJ, et al: Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: A single-arm, phase 2 study. *Lancet Oncol* 19:240-248, 2018
55. Senapati J, Jabbour E, Short NJ, et al: Chemotherapy free regimen of inotuzumab ozogamicin and blinatumomab in frontline therapy of older patients with Philadelphia negative B-cell acute lymphoblastic leukemia. *Blood* 144:1442, 2024 (suppl 1)
56. Wieduwilt M, Yin J, Kour O, et al: S117: Chemotherapy-free treatment with inotuzumab ozogamicin and blinatumomab for older adults with newly-diagnosed, Ph-negative, CD22-positive, B-cell acute lymphoblastic leukemia: Alliance A041703. *Hemasphere* 7:e08838b7, 2023
57. Luger SM, Sun Z, Mattison RJ, et al: Assessment of outcomes of consolidation therapy by number of cycles of blinatumomab received in newly diagnosed measurable residual disease negative patients with B-lineage acute lymphoblastic leukemia: In the ECOG-ACRIN E1910 randomized phase III National Clinical Trials Network Trial. *Blood* 142:2877, 2023 (suppl 1)
58. Food and Drug Administration: FDA approves blinatumomab as consolidation for CD19-positive Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia. 2024. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-blinatumomab-consolidation-cd19-positive-philadelphia-chromosome-negative-b-cell>
59. Jabbour E, Aldoss I, Fleming S, et al: Blinatumomab alternating with low-intensity chemotherapy (CT) treatment for older adults with newly diagnosed Philadelphia (Ph)-negative B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is well tolerated and efficacious: Safety run-in results for the phase 3 randomized controlled golden gate study. *Blood* 140:6134-6136, 2022 (suppl 1)
60. Elias J, Aldoss I, Fleming S, et al: Blinatumomab alternating with low-intensity chemotherapy (LIC) in older adults with newly diagnosed B-cell precursor acute lymphoblastic leukemia (ALL): Safety run-in follow-up for the phase 3 golden gate study. *EHA* 2024, Abstract P416
61. Rousselot P, Coudé MM, Gökbuget N, et al: Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. *Blood* 128:774-782, 2016
62. Jabbour E, Kantarjian H, Ravandi F, et al: Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: A single-centre, phase 2 study. *Lancet Oncol* 16:1547-1555, 2015
63. Kantarjian H, Short NJ, Jain N, et al: Frontline combination of ponatinib and hyper-CVAD in Philadelphia chromosome-positive acute lymphoblastic leukemia: 80-months follow-up results. *Am J Hematol* 98:493-501, 2023
64. Chalandon Y, Thomas X, Hayette S, et al: Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood* 125:3711-3719, 2015
65. Ottmann OG, Pfeifer H, Cayuela J-M, et al: Nilotinib (Tasigna®) and low intensity chemotherapy for first-line treatment of elderly patients with BCR-ABL1-positive acute lymphoblastic leukemia: Final results of a prospective multicenter trial (EWALL-PH02). *Blood* 132:31, 2018 (suppl 1)
66. Food and Drug Administration: FDA grants accelerated approval to ponatinib with chemotherapy for newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. 2024. <http://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-ponatinib-chemotherapy-newly-diagnosed-philadelphia-chromosome>
67. Martinelli G, Boissel N, Chevallier P, et al: Long-term follow-up of blinatumomab in patients with relapsed/refractory Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukaemia: Final analysis of ALCANTARA study. *Eur J Cancer* 146:107-114, 2021
68. Assi R, Kantarjian H, Short NJ, et al: Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive leukemia. *Clin Lymphoma Myeloma Leuk* 17:897-901, 2017
69. McCloskey JK, Gagnon J, McCabe T, et al: Blinatumomab in combination with tyrosine kinase inhibitors safely and effectively induces rapid, deep, and durable molecular responses in relapsed and refractory Philadelphia positive acute leukemias. *Blood* 134:3812, 2019 (suppl 1)
70. Couturier MA, Thomas X, Raffoux E, et al: Blinatumomab + ponatinib for relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia in adults. *Leuk Lymphoma* 62:620-629, 2021
71. Foà R, Bassan R, Elia L, et al: Long-term results of the dasatinib-blinatumomab protocol for adult Philadelphia-positive ALL. *J Clin Oncol* 42:881-885, 2024
72. Advani AS, Moseley AB, O'Dwyer KM, et al: Long-term follow up for SWOG 1318: Combination of dasatinib, prednisone, and blinatumomab for older patients with Philadelphia-chromosome (Ph) positive acute lymphoblastic leukemia (ALL). *Blood* 142:1499, 2023 (suppl 1)

73. Chiaretti S, Leoncin M, Elia L, et al: Efficacy and toxicity of frontline ponatinib plus blinatumomab for adult Ph+ ALL patients of all ages. Intermediate analysis of the Gimema ALL2820. *Blood* 144:835, 2024 (suppl 1)
74. Advani AS, Moseley A, O'Dwyer KM, et al: Dasatinib/prednisone induction followed by blinatumomab/dasatinib in Ph+ acute lymphoblastic leukemia. *Blood Adv* 7:1279-1285, 2023
75. Short NJ, Kantarjian H, Jain N, et al: Blinatumomab and ponatinib for adults with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia: Updated results and predictors of relapse. *Blood* 144:837, 2024 (suppl 1)
76. Zhang M, Hu Y, Wei G, et al: Dasatinib and CAR-T cell therapy for newly diagnosed Ph-positive acute lymphoblastic leukemia in adults. *Blood* 142:891, 2023 (suppl 1)
77. Bond J, Graux C, Lhermitte L, et al: Early response-based therapy stratification improves survival in adult early thymic precursor acute lymphoblastic leukemia: A group for research on adult acute lymphoblastic leukemia study. *J Clin Oncol* 35:2683-2691, 2017
78. Jain N, Lamb AV, O'Brien S, et al: Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: A high-risk subtype. *Blood* 127:1863-1869, 2016
79. Zhang J, Ding L, Holmfeldt L, et al: The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature* 481:157-163, 2012
80. Coustan-Smith E, Mullighan CG, Onciu M, et al: Early T-cell precursor leukaemia: A subtype of very high-risk acute lymphoblastic leukaemia. *Lancet Oncol* 10:147-156, 2009
81. Morita K, Jain N, Kantarjian H, et al: Outcome of T-cell acute lymphoblastic leukemia/lymphoma: Focus on near-ETP phenotype and differential impact of nelarabine. *Am J Hematol* 96:589-598, 2021
82. Ravandi F, Senapati J, Jain N, et al: Longitudinal follow up of a phase 2 trial of venetoclax added to hyper-CVAD, nelarabine and pegylated asparaginase in patients with T-cell acute lymphoblastic leukemia and lymphoma. *Leukemia* 38:2717-2721, 2024
83. Short NJ, Jabbour E, Jain N, et al: A phase 1/2 study of mini-hyper-CVD plus venetoclax in patients with relapsed/refractory acute lymphoblastic leukemia. *Blood Adv* 8:909-915, 2024
84. Lusk MR, Shimony S, Keating J, et al: Venetoclax plus low-intensity chemotherapy for adults with acute lymphoblastic leukemia. *Blood Adv* 9:617-626, 2025
85. Jaiswal S, Ebert BL: Clonal hematopoiesis in human aging and disease. *Science* 366:eaan4673, 2019
86. Singh A, Balasubramanian S: The crossroads of cancer therapies and clonal hematopoiesis. *Semin Hematol* 61:16-21, 2024
87. Pich O, Cortes-Bullich A, Muiños F, et al: The evolution of hematopoietic cells under cancer therapy. *Nat Commun* 12:4803, 2021
88. Bolton KL, Ptashkin RN, Gao T, et al: Cancer therapy shapes the fitness landscape of clonal hematopoiesis. *Nat Genet* 52:1219-1226, 2020
89. Saygin C, Zhang P, Stauber J, et al: Acute lymphoblastic leukemia with myeloid mutations is a high-risk disease associated with clonal hematopoiesis. *Blood Cancer Discov* 5:164-179, 2024
90. Saiki R, Ogawa S: Adult low-hypodiploid acute lymphoblastic leukemia evolves from TP53-mutated clonal hematopoiesis. *Blood Cancer Discov* 4:102-105, 2023
91. Santos Azevedo R, Kantarjian HM, Takahashi K, et al: Older age and TP53 mutations are predictors for the development of therapy-related myeloid neoplasms in adults undergoing frontline therapy for acute lymphoblastic leukemia. *Blood* 144:728, 2024 (suppl 1)
92. Shah BD, Ghobadi A, Oluwole OO, et al: KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: Phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet* 398:491-502, 2021
93. Roddie C, Sandhu KS, Tholouli E, et al: Obecabtagene autoleucel in adults with B-cell acute lymphoblastic leukemia. *N Engl J Med* 391:2219-2230, 2024
94. Schultz LM, Baggott C, Prabhu S, et al: Disease burden affects outcomes in pediatric and young adult B-cell lymphoblastic leukemia after commercial tisagenlecleucel: A pediatric real-world chimeric antigen receptor consortium report. *J Clin Oncol* 40:945-955, 2022
95. Jain N, Elias J, Short N, et al: Brexucabtagene autoleucel (Brexu-cel) as consolidation treatment in adults with B-cell acute lymphoblastic leukemia with marrow blasts <5%, including patients (PTS) with NGS MRD negative disease. *EHA 2024, Abstract P413*
96. Hogan LE, Brown PA, Ji L, et al: Children's oncology group AALL1331: Phase III trial of blinatumomab in children, adolescents, and young adults with low-risk B-cell ALL in first relapse. *J Clin Oncol* 41:4118-4129, 2023
97. Food and Drug Administration: FDA approves obecabtagene autoleucel for adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. 2024. <http://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-obecabtagene-autoleucel-adults-relapsed-or-refractory-b-cell-precursor-acute>
98. Aldoss I, Khaled SK, Wang X, et al: Favorable activity and safety profile of memory-enriched CD19-targeted chimeric antigen receptor T-cell therapy in adults with high-risk relapsed/refractory ALL. *Clin Cancer Res* 29:742-753, 2023
99. Aldoss I, Wang X, Zhang J, et al: CD19-CAR T cells as definitive consolidation for older adults with B-cell acute lymphoblastic leukemia in first complete remission: A pilot study. *Blood* 144:966, 2024 (suppl 1)
100. Kantarjian HM, Stein AS, Bargou RC, et al: Blinatumomab treatment of older adults with relapsed/refractory B-precursor acute lymphoblastic leukemia: Results from 2 phase 2 studies. *Cancer* 122:2178-2185, 2016
101. Kantarjian H, Haddad FG, Jain N, et al: Results of salvage therapy with mini-hyper-CVD and inotuzumab ozogamicin with or without blinatumomab in pre-B acute lymphoblastic leukemia. *J Hematol Oncol* 16:44, 2023
102. Senapati J, Jabbour E, Short NJ, et al: Liver elastography for risk-assessment of liver toxicity and risk factors for sinusoidal obstruction syndrome in patients with acute lymphoblastic leukemia receiving inotuzumab ozogamicin. *Blood Cancer J* 14:129, 2024
103. Jabbour E, Zugmaier G, Agrawal V, et al: Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia. *Am J Hematol* 99:586-595, 2024
104. Richard-Carpentier G, Kantarjian HM, Tang G, et al: Outcomes of acute lymphoblastic leukemia with KMT2A (MLL) rearrangement: The MD Anderson experience. *Blood Adv* 5:5415-5419, 2021
105. Issa GC, Aldoss I, Thirman MJ, et al: Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). *J Clin Oncol* 43:75-84, 2025

New Approvals in Low- and Intermediate-Risk Myelodysplastic Syndromes

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OVERVIEW

Recent advances in defining low- and intermediate-risk myelodysplastic syndromes (MDSs) have emphasized the critical role of molecular characterization using next-generation sequencing (NGS). Molecular profiling significantly enhances diagnostic precision, classification, and risk stratification, thereby informing therapeutic decisions, including the timing of hematopoietic stem-cell transplantation (HSCT). The Molecular International Prognostic Scoring System integrates clinical and molecular data, reclassifying and upstaging a substantial number of patients compared with previous prognostic systems, possibly allowing for more tailored therapeutic interventions. The novel therapeutic agents luspatercept and imetelstat have been particularly impactful. Luspatercept, which is effective in lower-risk (LR)-MDS, especially but not only in *SF3B1*-mutated cases, promotes late-stage erythroid maturation and transfusion independence (TI). Imetelstat, a telomerase inhibitor, induces TI while demonstrating disease-modifying effects as it significantly reduces mutation allele frequencies in patients who respond. These agents exemplify personalized medicine, emphasizing treatment selection and timing based on individual molecular and clinical features. Current research focuses on optimizing therapeutic strategies and exploring combination treatments to improve clinical outcomes.

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INTRODUCTION

Myelodysplastic syndromes (MDSs) comprise a heterogeneous group of myeloid neoplasms characterized by cytopenia(s) because of impaired hematopoiesis, dysplasia, and a highly variable risk of progression to AML.¹ Historically, the diagnosis and risk stratification of MDS have relied on the assessment of bone marrow morphology and cytogenetics.²⁻⁵ Over the past two decades, significant scientific advances have shed light on the molecular underpinnings of MDS. Next-generation sequencing (NGS) panels have therefore become an increasingly important aspect of diagnostic and prognostic evaluation and, more recently, treatment selection. In this article, we discuss the current role for molecular testing in low- and intermediate-risk MDSs, review how prognostic scoring systems affect treatment decisions, and describe our current approach to treatment selection in lower risk (LR)-MDS, with a focus on recently approved agents.

ROLE OF MOLECULAR TESTING IN LOW- AND INTERMEDIATE-RISK MYELODYSPLASTIC SYNDROMES

Beginning in around 2009, a number of key studies that identified recurrent mutations in genes such as *ASXL1*, *TET2*, *EZH2*, and others in samples collected from patients with MDS were published.⁶⁻¹² These early observations suggested that specific mutations may differentially affect survival.

Subsequent analyses of larger patient cohorts have comprehensively characterized the molecular ontogeny of MDS and have elucidated the prognostic impact based on specific type(s) of mutations and the number of mutations.¹³⁻¹⁸ A majority of patients with MDS have one or more somatic mutations in genes that encode for RNA splicing factors, epigenetic modifiers, transcription factors, chromatin regulators, and cohesion molecules or are involved in cell signaling and/or DNA repair (Table 1).¹³⁻¹⁸ The molecular profile of MDS has a significant overlap with myeloproliferative neoplasms and AML although the distribution and frequency of mutations vary among the different myeloid malignancies. Mutations in splicing factor genes are particularly common in MDS.¹³

In 2022, an update to the WHO Classification of Haematolymphoid Tumors was released around the same time as another group of experts published the International Consensus Classification (ICC) of myeloid neoplasms and acute leukemias.^{20,21} While the nuances of similarities and differences between the two classification systems have been discussed extensively in other recent articles, both the WHO 5th edition and the ICC recognize several genetically defined subsets of MDSs: MDS with low blasts and isolated deletion 5q (MDS-5q), MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*), and MDS with biallelic *TP53* inactivation.²⁰⁻²³ In addition, in 2022, after the development of other prognostic

PRACTICAL APPLICATIONS

- Molecular characterization of myelodysplastic syndromes (MDSs) by next-generation sequencing is important in both classification and prognostic stratification of patients with lower- and intermediate-risk MDSs. Evaluation for germline mutations should also be considered, particularly in patients who are at risk based on personal or family history.
- The Molecular International Prognostic Scoring System (IPSS-M) integrates clinical and molecular data and improves risk stratification with respect to the Revised IPSS. The IPSS-M may support treatment decisions, especially in considering the timing of hematopoietic stem-cell transplant (HSCT).
- Luspatercept and imetelstat are novel agents approved for treatment of low- and intermediate-risk MDSs. Molecular and clinical parameters should be considered to select the ideal patient for each of these agents and to decide on the optimal time to intervene with a specific agent.

scoring systems that incorporate molecular alterations, the Molecular International Prognostic Scoring System (IPSS-M) was published as an update to the Revised IPSS (IPSS-R).^{19,24} As a result, molecular testing is increasingly important in both the classification and risk stratification of MDS.

The National Comprehensive Cancer Network (NCCN) guidelines for MDS recommend somatic mutation testing as a part of the diagnostic evaluation for patients with suspected MDS.²⁵ The feasibility of this varies globally based on resources and insurance reimbursement. In situations where universal NGS testing is not possible in all patients with suspected MDS, we recommend molecular testing for MDS-associated mutations, preferably with a panel that includes the 31 genes in the IPSS-M, in any patient where the results could potentially affect the immediate treatment decision. This includes any fit patient who is a potential candidate for allogeneic stem-cell transplant (SCT) as the IPSS-M upgrades a substantial proportion of patients classified as LR by the IPSS-R to a higher-risk category and patients who are at higher (moderate-high, high, and very high) risk based on the IPSS-M benefit from an early SCT.^{19,26,27} Molecular results may also affect treatment choice in patients with LR-MDS who need treatment for cytopenias. For example, luspatercept is particularly effective for anemia in MDS-SF3B1.²⁸

DISTINGUISHING MDS FROM CLONAL HEMATOPOIESIS

Although molecular testing is important in the diagnosis, risk stratification, and management of MDS, the presence of

TABLE 1. Frequency of Mutations in Myelodysplastic Syndromes¹⁹

Category	Gene	Frequency (%)
Splicing	<i>SF3B1</i>	24
	<i>SRSF2</i>	16
	<i>U2AF1</i>	9
	<i>ZRSR2</i>	6
Chromatin regulators	<i>ASXL1</i>	25
	<i>EZH2</i>	6
	<i>BCOR</i>	5
	<i>SETBP1</i>	3
	<i>PHF6</i>	3
	<i>BCORL1</i>	2
Transcription factors	<i>RUNX1</i>	13
	<i>ETV6</i>	2
	<i>CUX1</i>	4
	<i>CEBPA</i>	2
	<i>WT1</i>	1
	<i>GATA2</i>	1
Cohesin	<i>STAG2</i>	9
DNA methylation	<i>TET2</i>	31
	<i>DNMT3A</i>	16
	<i>IDH2</i>	4
	<i>IDH1</i>	3
Signaling	<i>CBL</i>	5
	<i>NRAS</i>	4
	<i>KRAS</i>	3
	<i>JAK2</i>	3
	<i>NF1</i>	3
	<i>SH2B3</i>	2
	<i>ETNK1</i>	2
	<i>MPL</i>	2
	<i>PTPN11</i>	2
DNA repair	<i>TP53</i>	11
	<i>PPM1D</i>	2
Other	<i>DDX41</i>	3

an MDS-associated mutation is not by itself sufficient for the diagnosis of MDS if other standard diagnostic criteria have not been met.^{20,29-32} Clonal hematopoiesis (CH) of indeterminate potential (CHIP) is defined as the presence of a somatic myeloid malignancy-associated mutation in the blood or bone marrow at a variant allele frequency (VAF) of $\geq 2\%$ ($\geq 4\%$ for X-linked mutations in males) in patients who do not have unexplained cytopenia(s) and do not meet diagnostic criteria for a myeloid neoplasm.²⁰

Clonal cytopenia of undetermined significance (CCUS) refers to CHIP in the presence of cytopenia(s).²⁰ CH increases with age and has been associated with increased mortality and an increased risk of inflammation in general, along with an increased risk of cardiovascular events, chronic obstructive pulmonary disease, and stroke.²⁹⁻³⁴ In general, CCUS has a higher risk of progression to a myeloid neoplasm compared

with CHIP, and several prognostic scoring systems have been developed to predict the risk of progression to myeloid neoplasm in patients with CH.^{35,36}

GERMLINE PREDISPOSITION TO MDS

In some cases, an NGS panel may identify a variant that is a pathogenic germline variant and not somatic. A VAF of approximately 50% in a mutation that can be associated with inherited predisposition (eg, *DDX41* or *RUNX1*) could suggest the possibility of a germline etiology. Myeloid malignancies with germline predisposition can manifest at any age, and current guidelines recommend germline testing (ideally with confirmation of blood testing via skin fibroblast testing) for any patient with MDS who is diagnosed at age <50 years, has had ≥1 additional malignancy, or is clinically suspected to have a possible germline predisposition (ie, because of a family history of MDS or leukemia).²⁵ A study of 404 patients with MDS and their related donors before hematopoietic stem-cell transplant (HSCT) found that 7% of patients with MDS had pathogenic or likely pathogenic germline variants.³⁷ Germline mutations were identified across the age spectrum, even in elderly patients, and so age cannot be used to rule out the possibility of germline predisposition. Identifying germline predisposition in patients with MDS has implications for family members, who may benefit from surveillance, and for donor selection for allogeneic HSCT. Several recent observations and reviews provide a helpful summary of current data and considerations for germline testing in patients with myeloid malignancies.^{13,38,39}

DELETION 5q MDS

MDS-5q is a genetically defined subset of MDS that includes patients with low blasts and up to one additional cytogenetic abnormality.²⁰ Patients with ≥2 cytogenetic abnormalities or with a monosomy 7 or deletion 7q have inferior outcomes and are therefore excluded from this subgroup.⁴⁰ Anemia in MDS-5q has been known for years to be highly responsive to treatment with lenalidomide. In 2006, List et al published a study of 148 patients with MDS with a deletion (del) 5q and transfusion-dependent anemia which showed that lenalidomide 10 mg once daily on days 1 through 21 or days 1 through 28 of 28-day cycles led to red blood cell TI (RBC-TI) in 67% of patients (95% CI, 59% to 74%). Responses to lenalidomide are efficient (median time to response 4.6 weeks) and durable.⁴¹ Of note, dose reductions in lenalidomide to 5 mg once daily were frequently needed because of myelosuppression. A subsequent randomized, placebo-controlled, phase III study that included patients with LR-MDS (based on the IPSS) with a del5q and transfusion-dependent anemia compared lenalidomide 10 mg once daily on days 1 through 21 and 5 mg once daily on days 1 through 28 of 28-day cycles with placebo. Patients in the lenalidomide 10- and 5-mg once daily groups achieved RBC-TI for ≥26 weeks in 56.1% and 42.6% of cases, respectively, compared with only 5.9% RBC-TI in the placebo group ($P < .001$).⁴² Lenalidomide is US Food and Drug

Administration (FDA)– and EMA-approved for the treatment of low- or intermediate-1 risk MDS (based on the IPSS) with a del 5q and up to one additional cytogenetic abnormality.

Although MDS-5q has a generally favorable prognosis, the presence of co-occurring mutations in *SF3B1* or *TP53* has been reported to modify this. *SF3B1* mutations have been reported as a possible poor prognostic factor in MDS-5q, which is somewhat unexpected since patients with *SF3B1* typically do quite well, as described in the next section. Analysis of a cohort of 123 patients with MDS-5q found that 19% had an *SF3B1* mutation and that patients with *SF3B1* mutations had worse overall survival (OS) compared with *SF3B1* wild-type (WT) patients (median OS 50 months v not reached, $P = .010$).⁴³ However, a recent multicenter presentation that included 77 patients with MDS-5q and a concurrent *SF3B1* mutation showed that although there was a trend toward a shorter median OS in these patients compared with other MDS-5q patients (median OS 66 v 82 months, $P = .1$), the OS was still quite good (>5 years) and response to lenalidomide was similar in the two groups.⁴⁴ Thus, managing patients with MDS-5q with concurrent *SF3B1* mutations in the same way as other MDS-5q patients, with lenalidomide for transfusion-dependent anemia, is recommended.

TP53 mutations are found in up to 20% of cases of MDS-5q, and previous studies suggested that these cases might have worse survival and an increased risk of progression to AML although data on this were conflicting.^{45–48} Bernard et al observed a difference in survival and outcome in MDS-5q with monoallelic versus biallelic *TP53* mutation status.⁴⁹ Montoro et al recently further studied the impact of *TP53* mutations and allelic state in 682 patients with MDS-5q. Biallelic *TP53* inactivation (via multiple *TP53* mutations, VAF >50%, or as a result of a *TP53* mutation combined with loss of heterozygosity at chromosome 17p) was associated with an increased risk of progression to AML (hazard ratio [HR], 2.9 [95% CI, 1.7 to 5.0]) and a trend toward worse OS compared with *TP53*-WT (HR, 1.2 [95% CI, 0.9 to 2.3]).⁵⁰ Patients with monoallelic *TP53* mutations with a VAF of ≥20% had similarly poor outcomes, in contrast to patients with monoallelic *TP53* mutations with a VAF of <20% who had outcomes that were similar to those of *TP53*-WT patients.⁵⁰ Therefore, in patients with MDS-5q who have a *TP53* alteration, consideration should be given both to the VAF and to whether the alteration is monoallelic versus biallelic.

SF3B1 MUTATIONS

Somatic mutations in *SF3B1* (splicing factor 3B subunit 1), which encodes an RNA splicing factor, were identified in MDS by Papaemmanuil et al in 2011.¹² *SF3B1* mutations are the most common splicing mutations in MDS and are associated with favorable outcomes.¹⁹ A study of over 500 patients with MDS showed that *SF3B1* mutations are associated with an improved OS (HR, 0.15, $P = .025$) and a LR of

progression to AML (HR, 0.33, $P = .049$) compared with *SF3B1*-WT cases.⁵¹ In 2020, the International Working Group (IWG) for the Prognosis of MDS proposed that *SF3B1*-mutated MDS should be classified as a subtype of MDS.⁵² Subsequently, both the ICC and the WHO have recognized *SF3B1*-mutated MDS as a genetically defined subtype. The WHO 5th edition defines MDS-*SF3B1* as MDS with an *SF3B1* mutation with <5% bone marrow blasts and <2% peripheral blood blasts, excluding patients with a concurrent deletion 5q, monosomy 7, complex karyotype, or biallelic *TP53* mutations.²⁰

SF3B1 mutations are highly associated with the presence of ring sideroblasts (RS), a feature well known to be associated with a better prognosis. NGS testing is still important in these cases for several reasons. First, RS may be secondary to other conditions independent of MDS, and so it is helpful to confirm clonality by identifying the *SF3B1* and, in some cases, other molecular alterations as well. MDS with RS and an *SF3B1* mutation is associated with a significantly improved survival compared with MDS with RS without an *SF3B1* mutation (HR, 0.37; $P = .003$).⁵³ In addition, there are some data that the specific *SF3B1* variant may affect outcomes. The most common *SF3B1* variant is K700E, but a variety of others occur as well.⁵⁴ Recently, the *SF3B1* E592K variant was shown to be associated with worse OS.⁵⁴ Finally, the presence of specific mutations may negate the favorable outcome that is more commonly observed in patients with MDS-*SF3B1*. Bernard et al¹⁹ showed that patients with MDS-*SF3B1* that had concurrent mutations in *BCOR*, *BCORL1*, *NRAS*, *RUNX1*, *SRSF2* or *STAG2* had a worse OS (HR for death 3.1 [95% CI, 2.4 to 4.2]; $P < .0001$) compared with MDS-*SF3B1* with other mutation patterns. Together, these data demonstrate the importance of molecular testing in both classification and risk stratification even in patients with LR-MDS.

HOW DO IPSS-R AND IPSS-M AFFECT TREATMENT DECISIONS?

The initial regulatory approvals of the hypomethylating agents (HMAs) azacitidine and decitabine in the mid-2000s were based on the results of clinical trials that used the original 1997 IPSS for risk stratification and predated the 2012 adoption of the IPSS-R, which incorporated the depth of cytopenia and more differentiated cytogenetic subclassifications into risk stratification.^{2,55} Similarly, the more recent approvals of agents such as imetelstat and luspatercept hinged on results from randomized phase III trials that used IPSS or IPSS-R for patient identification and categorization, predating the publication of the IPSS-M in 2022.^{28,56,57} The incorporation of NGS in studies of patients with MDS has identified relationships between gene mutations and clinical phenotypes that were previously unknown or poorly defined. With the availability of modernized and more complex prognostication systems, there are a percentage of patients whose disease at presentation may be upstaged by the genetic features incorporated into the newer

IPSS variations and may perhaps warrant earlier treatment initiation or intensification.

The IPSS-R identified five categories of risk but has supported the choice of treatment in an imperfect manner. The intermediate-risk category, in particular, created some difficulties in terms of optimal treatment strategy. Traditionally, patients with intermediate-risk scores of 3.5 and 4.0 were considered still as LR. The IPSS-M improves prognostication compared with the IPSS-R and may also help to optimize and refine decisions regarding the optimal timing for treatment initiation. The IPSS-M shifts patients from lower-risk to higher-risk categories in a significant proportion of cases.^{27,58} Compared with IPSS-R, the use of IPSS-M restratified 1,223 of 2,678 patient cases (46%) within its six-category risk schema; of these, 911 (74%) were upstaged and 312 (26%) were downstaged compared with the IPSS-R classifications.¹⁹ Subsequent analyses, particularly within the IPSS-R intermediate-risk categorization, have suggested that restratification with the IPSS-M was not a single gene effect but rather the cumulative contribution of prognostic mutations for each patient.²⁷ A single-center analysis of 852 consecutive patients with de novo MDS suggested that the improved survival prediction accuracy of the IPSS-M model relative to that of the IPSS-R was largely driven by increased age.⁵⁹ While concordance statistics of the IPSS-R and IPSS-M in the entire cohort were similar (0.67 and 0.68, respectively), relative to patients younger than 60 years, older patients carried not only more mutations but also more harmful ones according to the IPSS-M model, including a higher incidence of mutations in *RUNX1*, *TP53*, *SRSF2*, *DNMT3A*, *STAG2*, and *EZH2*.⁵⁹

Within the IPSS-M model, the VAFs of mutations were not prognostic, and thus, the mutation data were incorporated in a binary manner. For a portion of the genes factored into the model, only the final number of mutations was included, capped at a maximum number of two. Clone size or mutational burden could, in the future, further inform risk beyond that indicated by the IPSS-M score alone as it is clear for *TP53* mutations.

Despite the incorporation of genetic mutation data with IPSS-M, its prognostication for any one individual is less certain, similar to earlier iterations of these scoring systems. It remains unclear whether the optimal timing of treatment intervention should differ among patients whose MDS is upstaged by the presence of adverse mutations relative to those whose risk is driven more by the traditional metrics of cytopenia or blast count. None of these IPSS variations account for patient age or comorbidities, and none was intended to predict benefit from a particular therapy. That said, in recent years, several different consortia have retrospectively applied the IPSS-M schema to clinical registries to determine its potential capacity to inform treatment selection.

A multicenter European study evaluated IPSS-M scores in 397 patients with LR-MDS who had received erythroid-

stimulating agent (ESA) therapy, in which 52.6% achieved hematologic improvement (HI-E) according to IWG criteria.⁶⁰ The IPSS-M score was significantly lower in ESA responders than in nonresponders, with the very low-risk IPSS-M group enriched for ESA responders (74% v 26%, $P = .036$).⁶⁰ In cases that were restratified to a higher-risk IPSS-M category after the addition of molecular data, ESA response was unlikely. In multivariable analysis, IPSS-M score and transfusion dependence (TD) were strong predictors for ESA response, irrespective of the baseline erythropoietin level.

To address the impact of additional genetic information on the clinical efficacy of imetelstat, trial investigators retroactively applied the IPSS-R and IPSS-M to participants in the phase III portion of a clinical trial for patients who enrolled with RBC transfusion-dependent low or intermediate-1 MDS according to IPSS criteria.^{56,61} In 105 IPSS LR participants, 10 (9.5%) were upstaged to IPSS-M moderate-high or high. Among IPSS-intermediate-1 patients, 11 (22%) were upstaged to IPSS-M moderate-high or high. Within the IPSS-M risk groups, RBC-TI rates at 8 weeks were 47.8% with imetelstat versus 21.2% with placebo in patients with very low- or low-risk disease. Similarly, RBC-TI rates at 8 weeks were higher with imetelstat versus placebo (20.7% v 6.3%) in patients with moderate-low or moderate-high risk.

A retrospective analysis of patients with LR-MDS with anemia treated with luspatercept at two university medical centers found that, for 154 patients for whom IPSS-M could be calculated before the receipt of luspatercept, treatment response as defined by HI-E significantly correlate with IPSS-M disease risk ($P = .031$) but not with the IPSS-R risk score ($P = .247$).⁶² Another study of 51 patients receiving luspatercept found significant differences in RBC-TI and in HI-E across IPSS-M categories.⁶³ Among the very low- and low-IPSS-M risk group, responses were observed in 87% of patients compared with 50% in those with higher IPSS-M although it should be noted that a significant proportion of patients received either a higher dose of luspatercept or simultaneous ESA therapy.

To date, retrospective studies of IPSS-M could not accurately prognosticate whether certain risk groups, including patients within the moderate-low and moderate-high classification, would preferentially respond to HMA therapy.²⁷ Generally, HMA response duration and probability of survival were inversely related to IPSS-M risk. While IPSS-M was not designed as a dynamic model to accommodate the changes to disease risk over time, its score was not accurate in the risk stratification of patients with MDS at the time of HMA failure. A retrospective single-center analysis found that, in the setting of HMA failure, the acquisition of additional cytogenetic abnormalities or the presence of TP53 mutations drove poorer outcomes within an already high-risk clinical scenario although *U2AF1* mutations were identified as a favorable feature in HMA failure.⁶⁴

The clinical impact of mutational profiles in MDS on HSCT has been well-described in retrospective studies that included patients with LR-MDS according to earlier classification schemes.⁶⁵⁻⁶⁸ General recommendations have been that HSCT for LR-MDS should be reserved for those patients with severe cytopenia or in instances where conventional treatment modalities have failed.⁶⁹

Emerging data are available for HSCT outcomes among patients with LR-MDS who experienced upstaging or downstaging of disease according to IPSS-M restratification. A retrospective modeling decision analysis over an 8-year time horizon for 7,118 patients with MDS on the basis of IPSS-M and different timing strategies for HSCT indicated that patients with low or moderate-low risk have a prolonged life expectancy from delay in HSCT, whereas those with moderate-high-, high-, and very high-risk IPSS-M benefit more from an immediate HSCT strategy.²⁶ Comparison of this decision analysis by IPSS-M versus IPSS-R showed bidirectional changes in the preferred approach to HSCT in discrete MDS subsets. Among patients recommended for immediate HSCT by IPSS-R, 15.4% was reclassified to benefit from a delayed HSCT approach; conversely, among patients who would be recommended for a delayed HSCT approach because of low-risk IPSS, 19.1% would benefit from an immediate HSCT approach because of reclassification to a higher-risk IPSS-M classification. Recent recommendations of EMBT suggest that IPSS-M is an essential tool together with testing for germline predisposition variants to determine eligibility for transplantation, especially for patients with IPSS-R LR.⁷⁰

Measures to assess the likely tolerance of treatment and life expectancy in the setting of other comorbid conditions exist but to date have not been standardized. Nevertheless, for patients classified in the low- and moderate-low-risk categories, the median OS is 6 years and 4.5 years, respectively.¹⁹ Treatment interventions with the potential to offer prolongation of survival in addition to improved quality of life will remain highly relevant to this population, and previous clinical management algorithms developed in an era predating the more widespread use of molecular sequencing should be reconsidered. With time, IPSS-M will increasingly be incorporated into prospective clinical trials and could ultimately allow for a more individualized risk-benefit approach to future therapies under consideration. Inevitably, the growing advances in our knowledge and application of molecular data in MDS will produce refinements to prognostic scoring schemes integrating also clinical and metabolic data, in ways that may optimize clinical outcomes.

WHICH NOVEL TREATMENT SHOULD I USE IN LOW- AND INTERMEDIATE-RISK MYELODYSPLASTIC SYNDROMES?

Treatment of LR-MDS focuses on improving cytopenias, with anemia being most frequent and clinically impactful, in the attempt to abrogate TD and improve quality of life. Only

recently has prolongation of OS been considered relevant to evaluate the impact of therapy in LR-MDS.

RBC transfusions still represent a mainstay of therapy for many patients. Lenalidomide for TD MDS-5q and ESAs has been used successfully for decades, and although HMAs are active in LR-MDS, their use should be considered carefully.^{44,71-74} Since 2017, ESAs such as epoetin-alfa have been approved in the EU for anemic patients with LR-MDS with Hb < 10 g/dL and serum erythropoietin (sEPO) levels <200 U/L.^{75,76} The response rate of selected patients with TI LR-MDS is around 60%.^{76,77}

In the United States, ESAs are not specifically approved by FDA for the treatment of anemia in MDS.⁷⁸

Two novel agents have recently joined the therapeutic scene: luspatercept and imetelstat, approved in 2020 and 2024, respectively.

Luspatercept was first approved for only RS + LR-MDS post-ESA failure (or ineligibility), and later, it was also approved as first-line therapy in RBC transfusion-dependent LR-MDS, regardless of the presence of RS. Luspatercept enhances terminal erythroid maturation by trapping activin receptor type IIB ligands and therefore reducing SMAD2/3 signaling and inducing TI in patients with ESA-relapsed/ESA-refractory (R/R) TD LR-MDS, particularly, but not only, in MDS with RS.^{57,79,80} Luspatercept has been shown to be superior to ESAs in patients with treatment-naïve TD LR-MDS both with and without RS.⁸¹

Imetelstat, a specific telomerase inhibitor, is FDA-approved for patients with R/R or ESA-ineligible LR-MDS needing ≥4 RBC units over 8 weeks, and it is now also included in the NCCN guidelines as a second-line (2L) and third-line (3L) option after ESAs and/or luspatercept.²⁵

Imetelstat induced durable RBC-TI in 37% of patients with treated LR-MDS. Unlike ESAs and luspatercept, imetelstat reduced the VAF of the most frequent encountered somatic mutations (eg, *SF3B1*, *TET2*, *DNMT3A*) in treated, responsive patients. This points to a disease-modifying effect, probably by the preferential elimination of MDS clonal stem cells that are dependent on increased telomerase activity (TA).

WHAT SHOULD I CONSIDER BEFORE TREATING ANEMIA IN LR-MDS?

An important point to consider is the timing of therapies, and, as experience has been gained with ESAs, we may extrapolate observations from this setting. In fact, higher and more durable responses have been shown with early ESA intervention in anemic patients with LR-MDS although this does not seem to affect OS.^{82,83} Regardless, delaying the onset of TD is clinically impactful.

Optimizing the selection of candidate patients to specific treatments should always be considered, and several

variables important for patient selection have been identified in the past for ESAs: transfusion status, endogenous sEPO levels (sEPO <200 or 500 U/L), disease biology (eg, del 5q and RS/*SF3B1* status), additional cytopenias, and previous therapies. Identifying responders to specific agents is crucial to avoid unsuccessful therapies. Personalized approaches based on molecular and biological markers could optimize treatment strategies for patients with LR-MDS, and now evidence is starting to accumulate for novel agents.^{19,60,84}

WHY AND WHEN SHOULD I USE LUSPATERCEPT?

Luspatercept is a recombinant fusion protein consisting of a modified extracellular domain of ActRIIB and a human IgG1 Fc domain. It acts by trapping ActRIIB ligands like GDF11 and GDF8, inhibiting SMAD2/3, a pathway that is upregulated in MDS, thereby blocking terminal erythroid differentiation.⁷⁹ Luspatercept was demonstrated to induce ≥8-week RBC-TI in 37.9% of ESA R/R TD MDS-RS, compared with 13% in the placebo group ($P < .001$) after 24 weeks of treatment.⁵⁷ Extending this observation, when assessed during the entire treatment period, a greater proportion of luspatercept-treated patients achieved RBC-TI ≥8 weeks compared with placebo: 47.7% versus 15.8% ($P < .0001$; OR, 5.978 [95% CI, 2.840 to 12.581]). Moreover, responders maintained TI ≥16 weeks in the majority of cases, which is indeed clinically meaningful.⁵⁷ Some (16%) patients achieved RBC-TI later than 6 months, indicating the possibility of late responses.⁸⁵ In addition, luspatercept responders have better OS versus nonresponders (median not reached v 46 months, $P < .001$).⁸⁶ The survival benefit was particularly evident in real-world patients who obtained a complete erythroid response (HI-E +1.5 g/dL Hb and RBC-TI >8 weeks).⁸⁷ Luspatercept has shown activity in treatment-naïve RBC-TD LR-MDS, irrespective of RS status. When compared with epoetin-alfa in this setting, RBC-TI ≥12 weeks +1.5 g/dL Hb was obtained in 60.4% of cases versus 34.8% ($P < .0001$). The luspatercept effect was evaluated according to transfusion burden (< or >4 RBC-U/8 weeks), baseline sEPO (< or >200 U/L), *SF3B1*, and RS status, and in each subcategory, it demonstrated superiority versus EPO.^{81,88} Response rates of RBC-TI for ≥24 weeks were greater with luspatercept versus epoetin alfa regardless of baseline TB, sEPO category, or *SF3B1* mutation status. More recent analyses showed that RS-negative LR-MDS treated with luspatercept had long-lasting responses.⁸⁸ Luspatercept is administered subcutaneously and can be used at escalating doses, starting with 1.0 mg/kg once every 3 weeks up to 1.75 mg/kg once every 3 week. Doses should be adjusted on the basis of response and should be promptly escalated in the absence of a decrease in transfusion burden or Hb increase, maintaining treatment for at least 24 weeks. Luspatercept has a favorable toxicity profile, with G1-G2 fatigue, which fades in subsequent cycles, being the most frequent adverse event (27%). Dizziness and hypertension (20%) were also observed.⁵⁷

Based on these results, second-line luspatercept is recommended in patients with LR-MDS who have failed or lost response to ESAs and became transfusion-dependent, with a

caveat for limited anticipated responses in high transfusion burden cases (≥ 6 units/8 weeks, TI in 18% MDS-RS).⁵⁷ In the first line, luspatercept should be preferred to ESAs in treatment-naïve TD LR-MDS, especially but not only with transfusion burden > 2 U RBC/8 weeks, given the scarce response to EPO, consistent with previous findings.

WHY AND WHEN SHOULD I USE IMETELSTAT?

Imetelstat is an oligonucleotide human telomerase (hTERT) competitive inhibitor that binds the enzyme RNA template, and it is administered intravenously. TA and hTERT expressions are increased in MDS hematopoietic stem cells and correlate with clonal evolution.⁸⁹⁻⁹¹ By targeting telomerase in MDS cells, imetelstat allows for the recovery of normal hematopoiesis, improving anemia.^{92,93} Imetelstat in ESA R/R TD LR-MDS showed RBC-TI responses in 37%, lasting > 24 weeks in 23% of cases.⁹⁴ Imetelstat induced 40% of ≥ 8 -week RBC-TI versus 15% of placebo ($P < .001$).⁵⁶ Among the imetelstat responders, 70% achieved a ≥ 24 -week RBC-TI ($P < .001$), and 44.6% a ≥ 1 -year RBC-TI ($P = .002$). So, 18% of the totality of imetelstat-treated patients achieved a durable and significant TI ≥ 1 year. In addition, the hemoglobin peak at response reached a median of 13.1 g/dL in ≥ 1 -year RBC-TI responders.⁵⁶ Almost half of

the patients in the study had a transfusion burden ≥ 6 RBC units/8 weeks, an extreme difficult-to-treat population (RBC-TI in 45% of cases with MDS-RS).

In contrast to ESAs and luspatercept, imetelstat seems to have disease-modifying activity. In patients with cytogenetic and molecular alterations, responses were paralleled by cytogenetic complete response, and there was a $> 50\%$ decrease in VAF of the most frequent gene mutations (ie, *SF3B1*, *TET2*, and *DNMT3A*) and in the percentage of marrow RS.⁵⁶

The most common adverse events (AEs) in patients treated with imetelstat are related to myelosuppression: thrombocytopenia (62%) and neutropenia (68%). The degree of myelosuppression does not seem to be directly correlated with response. These cytopenias are reversible, and in the study, very few cases of neutropenic fever and bleeding episodes were observed. In long-term treated patients, the myelosuppression is easily manageable. Nonhematologic AEs are generally low-grade, and drug-induced liver injury has not been observed.

In conclusion, imetelstat treatment should be selected in patients with TD ESA R/R LR-MDS, especially in patients with a high transfusion burden, and it should not be

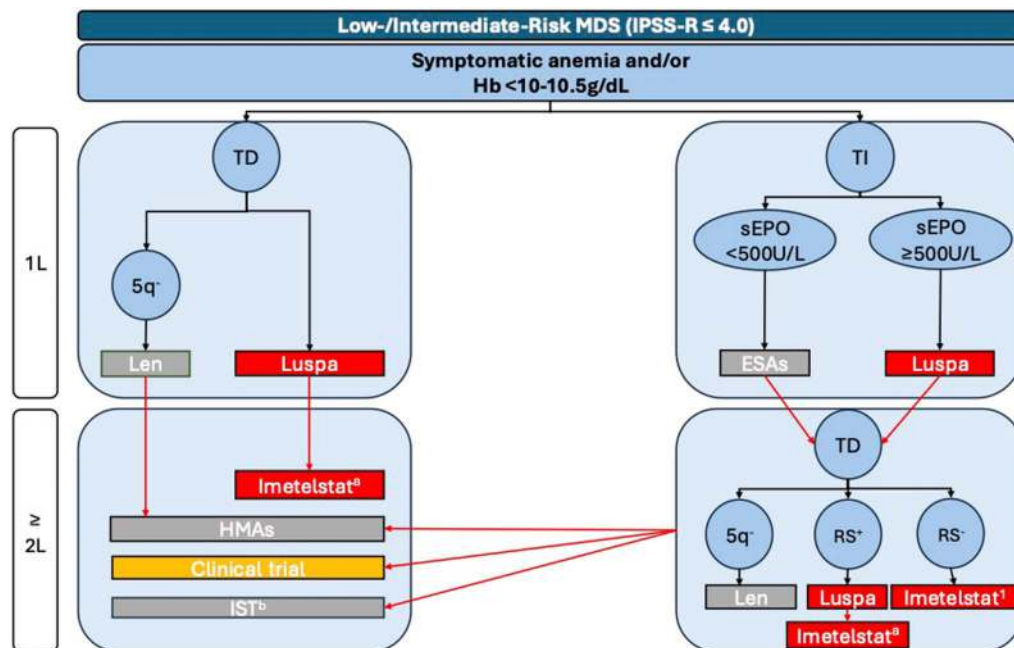


FIG 1. Current treatment algorithm for anemia in LR-MDS. As depicted in the figure, important considerations include transfusion status, disease subtypes (MDS-5q⁻ and MDS-RS), and baseline endogenous sEPO. ^aImetelstat is an option in patients with non-5q⁻ LR-MDS with ANC $\geq 1.5 \times 10^9$ and Plt $\geq 75,000 \times 10^9$ /L. Clinical benefit is maintained even in heavily transfused patients and after treatment with ESAs or Lusp. ^bIST (horse ATG and cyclosporine) is an option in young patients with LR-MDS with a hypocellular BM. 1L, first-line; 2L, second-line; ANC, absolute neutrophil count; BM, bone marrow; ESAs, erythropoiesis-stimulating agents; HMA, hypomethylating agents; IPSS-R, International Prognostic Scoring System, Revised; IST, immunosuppressive therapy (ATG-based); Len, lenalidomide; Lusp, luspatercept; LR, lower risk; MDS, myelodysplastic syndromes; RS, ring sideroblast; sEPO, serum erythropoietin; TD, transfusion-dependent; TI, transfusion-independent.

prescribed for patients with pre-existing severe cytopenias other than anemia. Recent data indicate that imetelstat is active in patients who are R/R after luspatercept, and therefore, it is also the recommended choice for third-line treatment in this setting.⁹⁵

PRACTICAL CONSIDERATIONS FOR THE TREATMENT OF ANEMIA IN LR-MDS

Treatment of anemia in LR-MDS should be started as soon as symptoms occur and/or when the Hb is <10–10.5 g/dL, that is, before myocardial remodeling takes place and of course ideally before TD.

The use of effective and early treatments of anemia can prevent iron overload and subsequent organ damage because of chronic RBC transfusions.⁹⁶

In TI patients, 1L treatment should be decided based on the well-known parameter of the endogenous sEPO level: when sEPO is <200 U/L, ESAs should be the preferred option. A novel score predicting ESA response has been proposed.¹⁹ Data comparing luspatercept versus epoetin-alfa in patients with TI LR-MDS will be produced (ClinicalTrials.gov identifier: [NCT05949684](#)). Conversely, when sEPO is >500 U/L, ESAs should not be prescribed because of a limited and short anticipated erythroid response. In this case, treatment in a clinical trial should be considered.

As alluded to above, in the TD setting, luspatercept can now be considered an optimal 1L option given its superior efficacy compared with epoetin-alfa regardless of *SF3B1* mutation status, transfusion burden, or sEPO levels. Results in RS-negative MDS cases showing a long DOR suggest electing this treatment.⁸⁸ In the 2L setting, luspatercept is indicated in TD LR-MDS-RS R/R ESAs, and given its favorable toxicity profile, route of administration is the preferred choice. On the other hand, imetelstat is recommended for RS-negative LR-MDS-RS R/R ESAs and in all patients with LR-MDS with a high transfusion burden. Current evidence shows that imetelstat is effective regardless of the number and type of previous treatments, including ESAs and luspatercept, and is therefore the best option available for 3L treatment.⁹⁵

MDS-5q patients have always been excluded in clinical trials with luspatercept (both 1L or after ESAs) and imetelstat. Only sporadic cases have been treated in real-world studies with these two agents. Therefore, we do not have data to estimate

the utility and activity of luspatercept or imetelstat in this setting. Few studies are focusing on the small subset of lenalidomide R/R MDS-5q.

Finally, based on the above evidence, the use of HMAs in TD LR-MDS should be limited to TD patients after the failure of ESAs, luspatercept, and imetelstat, but HMAs may still be considered in the setting of multiple cytopenias (especially thrombocytopenia) where they have shown activity beyond increasing hemoglobin and in the intermediate-risk patients. Because of the myelosuppression observed with HMAs, together with their schedule of administration, which compels patients to a prolonged dependence on hospital infusion centers and caregivers, providers should refrain from using them as first-line therapy in LR-MDS presenting solely with anemia.

Newly available therapies for anemia in LR-MDS, when tailored based on individual, disease, and molecular characteristics, can substantially improve LR-MDS patient outcomes, and a therapeutic algorithm for their reasoned use can be proposed ([Fig 1](#)).

FUTURE DIRECTIONS

Despite all these advancements, a portion of patients remain unresponsive or relapse, underscoring the need for further research and new approaches. Anti-inflammatory treatments targeting the IL1 β -inflammasome axis or IRAK-4 aim to address anemia in LR-MDS by mitigating inflammation and so far have good results with no safety concerns.^{97–99}

In addition, enasidenib and ivosidenib for IDH2- and IDH1-mutated LR-MDS and novel TGF β pathway inhibitors are showing encouraging results.^{100,101}

Finally, combination or *add-on* strategies exploiting drugs with different mechanisms of action, like ESAs + canakinumab or ESAs + luspatercept, are now under clinical evaluation.^{102–104} Moreover, the concept of sequential therapy for LR MDS anemia is now applicable, given the availability of three agents: ESAs, luspatercept, and imetelstat that are not exclusive and can be administered sequentially in case of failure. It will be extremely and increasingly important to identify genomic, transcriptomic, and cytokine profiles predictive of response to further personalize therapies and select the optimal agent to avoid treatment failures.

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REFERENCES

1. Sekeres MA, Taylor J: Diagnosis and treatment of myelodysplastic syndromes: A review. *JAMA* 328:872-880, 2022
2. Greenberg P, Cox C, LeBeau MM, et al: International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 89:2079-2088, 1997
3. Vardiman JW, Thiele J, Arber DA, et al: The 2008 revision of the WHO classification of myeloid neoplasms and acute leukemia: Rationale and important changes. *Blood* 114:937-952, 2008
4. Valent P, Horny H, Bennett JM, et al: Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: Consensus statements and report from a working conference. *Leuk Res* 31:727-736, 2007
5. Marshall D, Roboz GJ: Standardizing the initial evaluation for myelodysplastic syndromes. *Curr Hematol Malig Rep* 8:361-369, 2013
6. Gelsi-Boyer V, Trouplin V, Adélaïde J, et al: Mutations of polycomb-associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. *Br J Haematol* 145:788-800, 2009
7. Langemeijer SMC, Kuiper RP, Berends M, et al: Acquired mutations in TET2 are common in myelodysplastic syndromes. *Nat Genet* 41:838-842, 2009
8. Delhommeau F, Dupont S, Della Valle V, et al: Mutation in TET2 in myeloid cancers. *N Engl J Med* 360:2289-2301, 2009
9. Sanada M, Suzuki T, Shih LY, et al: Gain-of-function of mutated C-BL tumour suppressor in myeloid neoplasms. *Nature* 460:904-908, 2009
10. Ernst T, Chase AJ, Score J, et al: Inactivating mutations of the histone methyltransferase gene EZH2 in myeloid disorders. *Nat Genet* 42:722-726, 2010
11. Boulwood J, Perry J, Pellagatti A, et al: Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. *Leukemia* 24:1062-1065, 2010
12. Papaemmanuil E, Cazzola M, Boulwood J, et al: Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *N Engl J Med* 365:1384-1395, 2011
13. Yoshida K, Sanada M, Shiraishi Y, et al: Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature* 478:64-69, 2011
14. Bejar R, Stevenson K, Abdel-Wahab O, et al: Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med* 364:2496-2506, 2011
15. Damm F, Kosmider O, Gelsi-Boyer V, et al: Mutations affecting mRNA splicing define distinct clinical phenotypes and correlate with patient outcome in myelodysplastic syndromes. *Blood* 119:3211-3218, 2012
16. Papaemmanuil E, Gerstung M, Malcovati L, et al: Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood* 122:3616-3699, 2013
17. Walter MJ, Shen D, Shao J, et al: Clonal diversity of recurrently mutated genes in myelodysplastic syndromes. *Leukemia* 27:1275-1282, 2013
18. Haferlach T, Nagata Y, Grossmann V, et al: Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia* 28:241-247, 2014
19. Bernard E, Tuechler H, Greenberg PL, et al: Molecular international prognostic scoring system for myelodysplastic syndromes. *NEJM Evid* 1:1-14, 2022
20. Khoury JD, Solary E, Abal O, et al: The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. *Leukemia* 36:1703-1719, 2022
21. Arber DA, Orazi A, Hasserjian RP, et al: International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. *Blood* 140:1200-1228, 2022
22. Gurbuxani S, Hochman MJ, DeZern AE, et al: The times, they are a-changing: The impact of next-generation sequencing on diagnosis, classification, and prognostication of myeloid malignancies with focus on myelodysplastic syndrome, AML, and germline predisposition. *Am Soc Clin Oncol Educ Book* 43:e390026, 2023
23. Hasserjian RP, Germing U, Malcovati L: Diagnosis and classification of myelodysplastic syndromes. *Blood* 142:2247-2257, 2023
24. Bersanelli M, Travaglino E, Meggendorfer M, et al: Classification and personalized prognostic assessment on the basis of clinical and genomic features in myelodysplastic syndromes. *J Clin Oncol* 39:1223-1233, 2021
25. Greenberg PL, Attar E, Bennet JM, et al: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myelodysplastic Syndromes v2. 2025
26. Tentori CA, Gregorio C, Robin M, et al: Clinical and genomic-based decision support system to define the optimal timing of allogeneic hematopoietic stem-cell transplantation in patients with myelodysplastic syndromes. *J Clin Oncol* 42:2873-2886, 2024
27. Sauter E, Robin M, Bersanelli M, et al: Real-world validation of molecular international prognostic scoring system for myelodysplastic syndromes. *J Clin Oncol* 41:2827-2842, 2023
28. Platzbecker U, Della Porta MG, Santini V, et al: Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naïve, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): Interim analysis of a phase 3, open-label, randomised controlled trial. *Lancet (London, England)* 402:373-385, 2023
29. Genovese G, Kahler AK, Handsaker RE, et al: Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med* 371:2477-2487, 2014
30. Jaiswal S, Fontanillas P, Flannick J, et al: Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 371:2488-2498, 2014
31. Miller PG, Qiao D, Rojas-Quintero J, et al: Association of clonal hematopoiesis with chronic obstructive pulmonary disease. *Blood* 139:357-368, 2022
32. Arends CM, Liman TG, Strzelecka PM, et al: Associations of clonal hematopoiesis with recurrent vascular events and death in patients with incident ischemic stroke. *Blood* 141:787-799, 2023
33. Singh J, Li N, Ashraf E, et al: Clonal hematopoiesis of indeterminate potential as a prognostic factor: A systematic review and meta-analysis. *Blood Adv* 8:3771-3784, 2024
34. DeZern AE, Malcovati L, Ebert BL: CHIP, CCUS, and other acronyms: Definition, implications, and impact on practice. *Am Soc Clin Oncol Educ Book* 39:400-410, 2019
35. Weeks LD, Niroula A, Neuberg D, et al: Prediction of risk for myeloid malignancy in clonal hematopoiesis. *NEJM Evid* 2, 2023. <https://doi.org/10.1056/EVIDOa2200310>
36. Xie Z, Komrokji RS, Al Ali N, et al: Risk prediction for clonal cytopenia: Multicenter real-world evidence. *Blood* 144:2033-2044, 2024
37. Feurstein SK, Trotter AM, Estrada-Merly N, et al: Germline predisposition variants occur in myelodysplastic syndrome patients of all ages. *Blood* 140:2533-2548, 2022
38. Godley LA, DiNardo CD, Bolton K: Germline predisposition in hematologic malignancies: Testing, management, and implications. *Am Soc Clin Oncol Educ Book* 44:e432218, 2024
39. Trotter AM, Feurstein S, Godley LA: Germline predisposition to myeloid neoplasms: Characteristics and management of high versus variable penetrance disorders. *Best Pract Res Clin Haematol* 37:101537, 2024
40. Mallo M, Cervera J, Schanz J, et al: Impact of adjunct cytogenetic abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. *Leukemia* 25:110-120, 2011
41. List A, Dewald G, Bennett J, et al: Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 355:1456-1465, 2006
42. Fenaux P, Giagounidis A, Selleslag D, et al: A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. *Blood* 118:3765-3776, 2011
43. Meggendorfer M, Haferlach C, Kern W, et al: Molecular analysis of myelodysplastic syndrome with isolated deletion of the long arm of chromosome 5 reveals a specific spectrum of molecular mutations with prognostic impact: A study on 123 patients and 27 genes. *Haematologica* 102:1502-1510, 2017
44. Komrokji RS, Schwabkey ZI, Al Ali NH, et al: Myelodysplastic syndromes with concomitant SF3B1 mutation and deletion of the long arm of chromosome 5 (SF3B1del5q): Outcomes and Response to Treatment. *Blood* 144:1845-1847, 2024 (suppl 1)
45. Kulasekararaj AG, Smith AE, Mian SA, et al: TP53 mutations in myelodysplastic syndrome are strongly correlated with aberrations of chromosome 5, and correlate with adverse prognosis. *Br J Haematol* 160:660-672, 2013
46. Sebaa A, Ades L, Baran-Marzack F, et al: Incidence of 17p deletions and TP53 mutation in myelodysplastic syndrome and acute myeloid leukemia with 5q deletion. *Genes Chromosomes Cancer* 51:1086-1092, 2012

47. Jädersten M, Saft L, Smith A, et al: TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. *J Clin Oncol* 29:1971-1979, 2011
48. Chan O, Ali NA, Sallman DA, et al: Therapeutic outcomes and prognostic impact of gene mutations including TP53 and SF3B1 in patients with del(5q) myelodysplastic syndromes (MDS). *Clin Lymphoma Myeloma Leuk* 22:e467-e476, 2022
49. Bernard E, Nannya Y, Hasserjian RP, et al: Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med* 26:1549-1556, 2020
50. Montoro MJ, Palomo L, Haferlach C, et al: Influence of TP53 gene mutations and their allelic status in myelodysplastic syndromes with isolated 5q deletion. *Blood* 144:1722-1731, 2024
51. Malcovati L, Papaemmanuil E, Bowen DT, et al: Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. *Blood* 118:6239-6246, 2011
52. Malcovati L, Stevenson K, Papaemmanuil E, et al: SF3B1-mutant MDS as a distinct disease subtype: A proposal from the International Working Group for the prognosis of MDS. *Blood* 136:157-170, 2020
53. Malcovati L, Karimi M, Papaemmanuil E, et al: SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. *Blood* 126:233-241, 2015
54. Choi IY, Ling JP, Zhang J, et al: The E592K variant of SF3B1 creates unique RNA missplicing and associates with high-risk MDS without ring sideroblasts. *Blood Adv* 8:3961-3971, 2024
55. Greenberg PL, Tuechler H, Schanz J, et al: Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 120:2454-2465, 2012
56. Platzbecker U, Santini V, Fenaux P, et al: Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): A multinational, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet (London, England)* 403:249-260, 2024
57. Fenaux P, Platzbecker U, Mufti GJ, et al: Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med* 382:140-151, 2020
58. Zamanillo I, Poza M, Ayala R, et al: Impact of IPSS-M implementation in real-life clinical practice. *Front Oncol* 13:1199023, 2023
59. Wu J, Zhang Y, Qin T, et al: IPSS-M has greater survival predictive accuracy compared with IPSS-R in persons ≥ 60 years with myelodysplastic syndromes. *Exp Hematol Oncol* 11:73-12, 2022
60. Raddi MG, Consagra A, Rigodanza L, et al: Impact of mutational burden and IPSS-M on response to ESAs in lower risk myelodysplastic neoplasms. *Blood* 142:4595, 2023 (suppl 1)
61. Komrokji RS, Santini V, Fenaux P, et al: Efficacy of imetelstat in achieving red blood cell transfusion independence (RBC-TI) across different risk subgroups in patients with lower-risk myelodysplastic syndromes (LR-MDS) relapsed/refractory (R/R) to erythropoiesis-stimulating agents (ESAs) in IMerge phase 3 study. *Blood* 142:194, 2023 (suppl 1)
62. Consagra A, Lanino L, Al Ali NH, et al: Response to luspatercept can be predicted and improves overall survival in the real-life treatment of LR-MDS. *Hemasphere* 9:e70086, 2025
63. Jonasova A, Sotakova S, Belohlavkova P, et al: Experience with luspatercept therapy in patients with transfusion-dependent low-risk myelodysplastic syndromes in real-world clinical practice: Exploring the positive effect of combination with erythropoietin alfa. *Front Oncol* 14:1398331, 2024
64. Urrutia S, Chien KS, Li Z, et al: Performance of IPSS-M in patients with myelodysplastic syndrome after hypomethylating agent failure. *Am J Hematol* 98:E281-E284, 2023
65. Bejar R, Stevenson KE, Caughy B, et al: Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. *J Clin Oncol* 32:2691-2698, 2014
66. Della Porta MG, Galli A, Bacigalupo A, et al: Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol* 34:3627-3637, 2016
67. Lindsley RC, Saber W, Mar BG, et al: Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. *N Engl J Med* 376:536-547, 2017
68. Nazha A, Hu ZH, Wang T, et al: A personalized prediction model for outcomes after allogeneic hematopoietic cell transplant in patients with myelodysplastic syndromes. *Biol Blood Marrow Transplant* 26:2139-2146, 2020
69. DeFilipp Z, Ciurea SO, Cutler C, et al: Hematopoietic cell transplantation in the management of myelodysplastic syndrome: An evidence-based review from the American Society for Transplantation and Cellular Therapy Committee on practice guidelines. *Transpl Cell Ther* 29:71-81, 2023
70. Gurnari C, Robin M, Adès L, et al: Clinical-genomic profiling of MDS to inform allo-HSCT: Recommendations from an international panel on behalf of the EBMT. *Blood*, 2025
71. Musto P, Maurillo L, Spagnoli A, et al: Azacitidine for the treatment of lower risk myelodysplastic syndromes: A retrospective study of 74 patients enrolled in an Italian named patient program. *Cancer* 116:1485-1494, 2010
72. Saba HI, Rosenfeld CS, Issa JP, et al: Clinical benefit and survival endpoints from a phase III trial comparing decitabine (DAC) vs supportive care (SC) in patients with advanced myelodysplastic syndromes (MDS). *J Clin Oncol* 23, 2005 (16 suppl; abstr 6543)
73. Jabbour E, Short NJ, Montalban-Bravo G, et al: Randomized phase 2 study of low-dose decitabine vs low-dose azacitidine in lower-risk MDS and MDS/MPN. *Blood* 130:1514-1522, 2017
74. Garcia-Manero G, Griffiths EA, Steensma D, et al: Oral cedazuridine/decitabine for MDS and CMML: A phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. *Blood* 136:674-683, 2020
75. Fenaux P, Santini V, Spiriti MAA, et al: A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin- α in anemic patients with low-risk MDS. *Leukemia* 32:2648-2658, 2018
76. Platzbecker U, Symeonidis A, Oliva EN, et al: A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes. *Leukemia* 31:1944-1950, 2017
77. Santini V, Schemenau J, Levis A, et al: Can the revised IPSS predict response to erythropoietic-stimulating agents in patients with classical IPSS low or intermediate-1 MDS? *Blood* 122:2286-2288, 2013
78. U.S. Food and Drug Administration website: Drugs@FDA: FDA-Approved Drugs. Consulted In April 2025. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=103234>
79. Martinez PA, Li R, Ramanathan HN, et al: Smad2/3-pathway ligand trap luspatercept enhances erythroid differentiation in murine β -thalassaemia by increasing GATA-1 availability. *J Cell Mol Med* 24:6162-6177, 2020
80. Platzbecker U, Gotze KS, Kiewe P, et al: Long-term efficacy and safety of luspatercept for anemia treatment in patients with lower-risk myelodysplastic syndromes: The phase II PACE-MDS study. *J Clin Oncol* 40:3800-3807, 2022
81. Della Porta MG, Garcia-Manero G, Santini V, et al: The commands trial: A phase 3 study of the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anemia due to IPSS-R very low-, low-, or intermediate-risk MDS in erythropoiesis stimulating agent-naïve patients who require RBC trans. *Blood* 136:1-2, 2020
82. Park S, Kelaïdi C, Sapena R, et al: Early introduction of ESA in low risk MDS patients may delay the need for RBC transfusion: A retrospective analysis on 112 patients. *Leuk Res* 34:1430-1436, 2010
83. Park S, Slama B, Moldovan M, et al: Early versus late onset of ESA in lower risk anemic MDS patients: Results of the GFM randomized phase III EPO-Pretar trial. *Blood* 144:349-350, 2024 (suppl 1)
84. Raddi MG, Bencini S, Peruzzi B, et al: Flow cytometric analysis of erythroid precursors and mutational signatures of lower risk myelodysplastic syndromes identify responders to erythroid stimulating agents. *Blood Cancer J* 14:127, 2024
85. Germing U, Fenaux P, Platzbecker U, et al: Improved benefit of continuing luspatercept therapy: Sub-analysis of patients with lower-risk MDS in the MEDALIST study. *Ann Hematol* 102:311-321, 2023
86. Santini V, Fenaux P, Zeidan AM, et al: Overall survival and progression-free survival of patients following luspatercept treatment in the MEDALIST trial. *Blood* 140:4079-4081, 2022 (suppl 1)
87. Consagra A, Lanino L, Al Ali NH, et al: Improved overall survival among luspatercept responders and predictors of response. *Blood* 142:1871, 2023 (suppl 1)
88. Garcia-Manero G, Santini V, Zeidan AM, et al: Long-term response analysis of transfusion independence in erythropoiesis stimulating agent-naïve patients with very low-low-or intermediate-risk myelodysplastic syndromes treated with luspatercept vs epoetin alfa in the COMMANDS trial. *Blood* 144:350, 2024 (suppl 1)
89. Briatore F, Barrera G, Pizzimenti S, et al: Increase of telomerase activity and hTERT expression in myelodysplastic syndromes. *Cancer Biol Ther* 8:883-889, 2009
90. Gürkan E, Tanrıverdi K, Başlamışlı F: Telomerase activity in myelodysplastic syndromes. *Leuk Res* 29:1131-1139, 2005
91. Mittelman M, Oster HS, Hoffman M, et al: The lower risk MDS patient at risk of rapid progression. *Leuk Res* 34:1551-1555, 2010
92. Brudigam C, Lane SW: Telomerase in hematologic malignancies. *Curr Opin Hematol* 23:346-353, 2016
93. Park HS, Choi J, See CJ, et al: Dysregulation of telomere lengths and telomerase activity in myelodysplastic syndrome. *Ann Lab Med* 37:195-203, 2017
94. Steensma DP, Fenaux P, Van Eygen K, et al: Imetelstat achieves meaningful and durable transfusion independence in high transfusion-Burden patients with lower-risk myelodysplastic syndromes in a phase II study. *J Clin Oncol* 39:48-56, 2021
95. Platzbecker U, Santini V, Zeidan AM, et al: Effect of prior treatments on the clinical activity of imetelstat in transfusion-dependent patients with erythropoiesis-stimulating agent, relapsed or refractory/ineligible lower-risk myelodysplastic syndromes. *Blood* 144:352-354, 2024 (suppl 1)
96. Oliva EN, Dimitrov BD, Benedetto F, et al: Hemoglobin level threshold for cardiac remodeling and quality of life in myelodysplastic syndrome. *Leuk Res* 29:1217-1219, 2005
97. Rodriguez-Sevilla JJ, Adema V, Chien KS, et al: The IL-1 β inhibitor canakinumab in previously treated lower-risk myelodysplastic syndromes: A phase 2 clinical trial. *Nat Commun* 15:9840, 2024
98. Garcia-Manero G, Yan L, Dummer W, et al: Phase 1b clinical study of IRAK1/4 inhibition for low-risk myelodysplastic syndromes refractory/resistant to prior therapies. *J Clin Oncol* 41, 2023 (suppl 16; abstr TPS7085)
99. Garcia-Manero G, Ooi M, Lao Z, et al: Safety and preliminary efficacy of DVF890 in adult patients with myeloid diseases: A phase 1b study. *Blood* 142:3250, 2023 (suppl 1)

100. Sebert M, Chevret S, Dimicoli-Salazar S, et al: Enasidenib (ENA) monotherapy in patients with IDH2 mutated myelodysplastic syndrome (MDS), the ideal phase 2 study by the GFM and emsco groups. *Blood* 144:1839-1840, 2024 (suppl 1)
 101. Sebert M, Platzbecker U, Ferreira DV, et al: Phase 3 study of either ivosidenib (IVO) monotherapy or azacitidine (AZA) monotherapy in patients with IDH1 mutant myelodysplastic syndromes (MDS) who are hypomethylating agent (HMA) naïve (PyramIDH). *Blood* 144:1845, 2024
 102. Sallman DA, Hunter AM, Xie Z, et al: Phase 1b/2 study evaluating the safety and efficacy of canakinumab with darbepoetin alfa in patients with lower-risk myelodysplastic syndromes (MDS) who have failed erythropoietin stimulating agents (ESA). *Blood* 142:4620, 2023 (suppl 1)
 103. Komrokji RS, Aguirre LE, Al Ali NH, et al: Activity of luspatercept and ESAs combination for treatment of anemia in lower-risk myelodysplastic syndromes. *Blood Adv* 7:3677-3679, 2023
 104. Chandhok NS, Sekeres MA: Combining lenalidomide with erythropoiesis stimulating agents: A party of one. *Leukemia* 38:473-474, 2024
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Easy as ABC: Managing Toxicities of Antibody-Drug Conjugates, Bispecific Antibodies, and CAR T-Cell Therapies

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OVERVIEW

Antibody-drug conjugates (ADCs), bispecific antibodies that engage T cells (BsAbs), and chimeric antigen receptor (CAR) T cells are widely used standard-of-care therapies that have revolutionized the treatment of lymphoid and plasma cell malignancies. With recent regulatory approvals, these therapies are poised to also revolutionize the treatment of common solid tumors and become a part of the everyday lexicon, the ABCs, of the practicing oncologist. Drawing from experience in hematology, we review the early, late, and rare toxicities of ADCs, BsAbs, and CAR T cells and provide general principles for their management.

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INTRODUCTION

The past decade in oncology has been marked by the rise of immunotherapy, which leverages the immune system to attack tumors. For many solid tumors, immune checkpoint inhibitors have supplanted standard chemotherapy, giving rise to a new set of immune-related adverse events that require oncologists to obtain new management skills compared with traditional cytotoxic chemotherapy. For hematologic cancers, the past decade was marked by the rise of alternative immunotherapies such as antibody-drug conjugates (ADCs), bispecific antibodies that engage T cells (BsAbs), and chimeric antigen receptor (CAR) T-cells ([Fig 1](#)). These new immunotherapies are accompanied by toxicities that are different from both cytotoxic chemotherapy and immune checkpoint inhibitors, and once again require new knowledge for management. With new approvals of ADCs and BsAbs for common solid tumors, and with more patients receiving CAR T-cell therapies each year, there is now a need to disseminate knowledge about these therapies to the broader community.

ADCs are the most familiar to oncologists ([Table 1](#)). ADCs target an antigen on the surface of the tumor cells, which is then endocytosed. Once inside, the chemotherapy drug conjugated to the tail of the antibody is cleaved off, thereby delivering the payload inside the tumor cell. Toxicities of ADCs are related to on-target off-tumor effects on normal cells (which is specific to the ADC target), or bystander effects of the chemotherapy payload when it is metabolized outside of the tumor.

Bispecific antibodies (BsAbs) can be designed in several ways, but the general principle is that one part of the BsAb binds to the tumor, while the other part of the BsAb binds to T cells, thereby targeting T cells to attack the tumor.

Toxicities of BsAbs are related to the cytokine release that accompanies T-cell activation, or on-target off-tumor effects specific to the BsAB target.

CAR T-cell therapy involves genetic modification of T cells. Upon infusion into the patient, the receptor part of the CAR (typically derived from an antibody fragment) binds to the tumor, triggering intracellular signaling within the CAR T cell and activation against the tumor. Toxicities of CAR T cells are related to the need for lymphodepleting chemotherapy (LDC) in advance of CAR T-cell infusion, cytokine release triggered by the CAR T cells, and on-target off-tumor effects specific to the CAR T-cell target.

Each of ADCs, BsAbs, and CAR T-cell therapies carry toxicities that may be early or late, and some important toxicities are rare but severe and require recognition for their effective management. In this Education Book, we review the toxicities of these immunotherapies, with the aim of illuminating general principles for management.

EARLY TOXICITIES OF IMMUNOTHERAPIES

The unique early toxicities of CAR T-cell therapies and BsAbs relate to cytokine release triggered by T-cell activation. This does not occur with ADCs, which have toxicities associated with their chemotherapy payloads. In this section, we will begin by reviewing the early toxicities of CAR T-cell therapies, which most potently trigger cytokine release, followed by BsAbs which are less potent, followed by the mechanistically different toxicities associated with ADCs.

Early Toxicities of CAR T-Cell Therapies

For patients receiving autologous CAR T-cell therapies, the first step is the collection of T cells through leukapheresis.

PRACTICAL APPLICATIONS

- Antibody-drug conjugates, bispecific antibodies that engage T cells, and chimeric antigen receptor T-cell therapies are immunotherapies with increasing use within oncology.
- These therapies carry unique toxicities that differ from cytotoxic chemotherapy and immune checkpoint inhibitors.
- This article provides an overview of clinical toxicities associated with these therapeutic classes.

These cells are then sent to the manufacturer, which require 2–6 weeks for engineering, quality testing, and transfer of CAR T cells to the treating center. Patients then undergo LDC, typically with fludarabine and cyclophosphamide, followed by intravenous infusion of the CAR T cells. The CAR T cells grow within the patient (expand), peak, and then rapidly contract with low-level CAR T-cell persistence over time. The acute CAR T-cell–associated toxicities are due to the release of cytokines that accompany CAR T-cell activation and expansion, with decreased toxicity once CAR T-cell numbers decline over the following days to weeks. The canonical early cytokine-associated toxicities include cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), with recent ASCO Guidelines detailing their recommended management.¹

CRS occurs when activated CAR T cells release a host of inflammatory cytokines including IL-1, IL-6, TNF- α , and IFN- γ .² However, the majority of CRS is due to the amplification of cytokine release by myeloid cells, tumor, or other immune cells, accounting for the differences in severity experienced between patients. The time to onset and severity of CRS is also dependent on the CAR T-cell product and disease. For example, CD19 CAR T-cell products for lymphoid malignancies have CRS onset within the first few days after infusion. By contrast, the myeloma-directed CAR T-cell therapy ciltacabtagene autoleucel (cilta-cel) has a median onset of 7 days, facilitating outpatient administration with delayed inpatient admissions for most patients. Risk factors for severe CRS include a high tumor burden and/or signs and symptoms of a primed systemic inflammatory state such as high ferritin, C-reactive protein (CRP), or poor performance status.^{3–5} Careful efforts to mitigate these factors before CAR T-cell therapy are key for preventing severe toxicity.⁶

The clinical hallmark of CRS onset is fever. The American Society of Transplantation and Cellular Therapy (ASTCT) has published consensus criteria for severity grading that are followed for clinical trial and registry reporting (Table 2).⁷

CRS is graded as more severe when accompanied by hypotension and/or hypoxia, which are signs of greater cytokine inflammation. As a systemic syndrome, other toxicities may also occur such as fatigue, organ injury (ie, liver enzyme or creatinine elevation), cardiac events, coagulopathy, and others. Biomarkers such as ferritin, CRP, and IL-6 increase during the initial peak of CRS, but diagnosis, grading, and management rely mainly on clinical manifestations. Clinical management is aimed at reducing symptoms until the CAR T cells contract their numbers and the inflammation subsides. Interventions consist of anticytokine therapies such as tocilizumab (ie, anti-IL-6), corticosteroids, and supportive care. Historically there was concern that therapies aimed at CRS management might impair the antitumor effects of the CAR T cells, and clinicians tolerated higher-grade toxicities before intervening. However, the pendulum has now swung toward early intervention at lower-grade toxicities or even prophylaxis with corticosteroids or anticytokine therapies,^{8–10} which generally help to prevent more severe toxicities and enable greater outpatient delivery. Despite all efforts, severe CRS sometimes still occurs and the management of tocilizumab- and corticosteroid-refractory CRS is aimed at further cytokine blockade (ie, anti-IL-1 with anakinra), or attempts to ablate the CAR T cells with cyclophosphamide or ATG.⁶

ICANS typically begins a few days after the initial onset of CRS and is graded by the immune effector cell–associated encephalopathy score at lower grades, and by the occurrence of more severe findings such as seizure, depressed level of consciousness, or cerebral edema at higher grades (Table 2). Mechanistically, ICANS is proposed to be related to an opening of the blood–brain barrier (BBB) and cytokine-mediated encephalopathy. Although ICANS may occur with any CAR T-cell therapy, it is more prominent with CD19-directed therapies, possibly because of the depletion of CD19-expressing brain mural cells that normally function to maintain the BBB.¹¹ Risk factors for the development of ICANS are otherwise similar to those associated with CRS. There are no clear biomarkers used to follow patients with ICANS, and imaging findings are typically subtle or normal outside of exceptionally severe cases characterized by cerebral edema. The typical cerebrospinal fluid (CSF) finding of ICANS is elevated protein.¹² Clinical manifestations of ICANS tend to persist longer than CRS and are mainly managed with corticosteroids and time. Severe or refractory ICANS may be managed similarly to severe CRS, with some additional reports using intrathecal chemotherapy in an attempt to ablate CAR T cells circulating within CSF.^{6,13}

Early on, it was recognized that the cytokine profile of CRS resembles that of hemophagocytic lymphohistiocytosis (HLH).^{14,15} It is generally difficult to distinguish severe CRS from HLH using biomarkers or clinical characteristics. However, it has become increasingly recognized that some patients experience a cytokine-associated HLH-like syndrome that occurs after the initial CRS has resolved, most clearly in patients receiving CD22-directed CAR T-cell

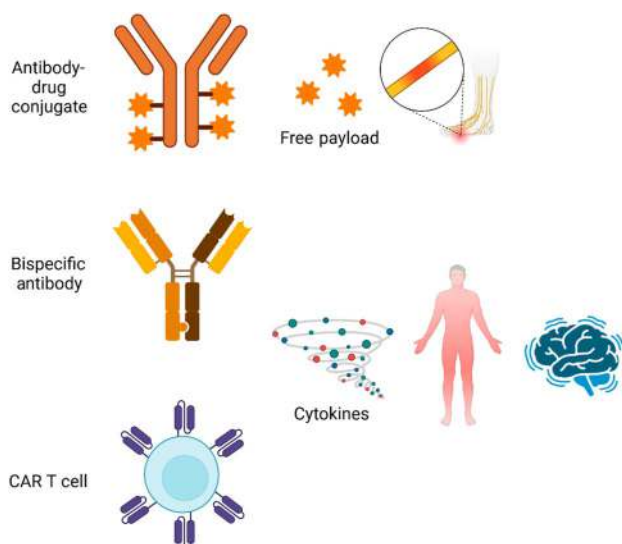


FIG 1. Off-target toxicities of ADCs, BsAbs, and CAR T cells. All three therapies are susceptible to on-target toxicities mediated by binding to normal tissues, and these on-target toxicities vary by target. Off-target toxicities are often a class effect. Toxicities of ADCs result when the conjugated drug payload (generally derived from a cytotoxic chemotherapeutic) is free outside of the tumor. The depicted example shows a toxic effect on peripheral nerves. Toxicities of BsAbs and CAR T cells are related to cytokine release from activated T cells and subsequent amplification of the cytokine storm by other immune cells. Depicted are common cytokine effects causing fever (CRS) and neurologic toxicity (ICANS). Figure created with BioRender. ADCs, antibody-drug conjugates; BsAbs, bispecific antibodies that engage T cells; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

therapies.^{16,17} This has led to expert recommendations on the identification and management of what is now termed immune effector cell–associated hemophagocytosis–like syndrome (IEC-HS).¹⁸ IEC-HS is clinically associated with cytopenias, hyperferritinemia, hypofibrinogenemia, and/or transaminase elevations occurring days to weeks after the initial CRS has resolved. IEC-HS is treated similarly to refractory CRS with anakinra and corticosteroids, with JAK inhibitors such as ruxolitinib also suggested because of its potential efficacy in HLH-like conditions.

Finally, it is important to keep a differential diagnosis in mind as sepsis, cancer progression, medication side effects, and/or other illnesses may manifest and require directed treatment. Although the duration of cytokine-associated toxicities varies between CAR T-cell products and diseases, almost all cases of new onset occur within the first 2 weeks after infusion.^{19,20}

Early Toxicities of Bispecific Antibodies

Cytokine release is also a hallmark of T-cell activation accompanying BsAbs. A recent ASCO Educational Book details the experience of BsAbs in patients with lymphoma and myeloma with guidelines on management.²¹ Compared with

CAR T-cell therapy, CRS and ICANS caused by BsAbs is qualitatively different, occurring almost always with initial dosing and tending to last only hours–days after initial onset. For this reason, initial dosing of BsAbs typically involves step-up dosing protocols whereby a low dose is given as the first infusion, with increasing doses given over subsequent days or weeks. Clinical trials and corresponding FDA labels frequently mandate short (24–48 hours) admissions after dose step-ups, although efforts are underway to facilitate fully outpatient management in clinical practice. Indeed, many centers will tolerate low-grade CRS (isolated fever) after BsAb infusion without necessitating inpatient monitoring. Risk factors for severe CRS and ICANS are less well understood for BsAbs compared with CAR T-cell therapy, but similar risks of tumor burden, systemic inflammation, and poor performance status likely apply, and intensified prophylaxis and earlier intervention may be warranted for high-risk patients. CRS and ICANS grading follow the ASTCT guidelines, and management of high-grade or prolonged toxicities are managed with anticytokine therapy (ie, tocilizumab) and corticosteroids. However, a unique consideration with BsAbs involves rechallenge after a high-grade CRS or ICANS event. In most cases, rechallenge is advised only once the previous CRS or ICANS has completely resolved, and repeat hospitalization is often recommended for additional monitoring. Once a patient has successfully received the full dose of BsAbs without high-grade toxicity, the patient may be followed with outpatient monitoring for subsequent doses. CRS and ICANS are infrequent beyond the first cycle. However, if a patient on long-term treatment needs to hold their BsAbs for a significant period of time (eg, to treat an infection), it is often recommended to reinitiate step-up dosing rather than restart at full dose. Another consideration is the use of concomitant therapies, which may decrease the risk of CRS. For example, in first-line lymphoma trials integrating BsAb with the second cycle of chemotherapy, the incidence of CRS was much lower (approximately 10%) than when the same BsAb was used as monotherapy in the relapsed/refractory setting (approximately 60%).^{22,23}

Additionally, acute toxicity may result from the tumor-targeting part of the BsAb. Examples include skin reactions caused by the melanoma-directed BsAb tebentafusp targeting gp100-expressing melanocytes, or the myeloma-directed BsAb talquetamab targeting GPRC5D in hard-keratinized structures and hair follicles.^{24,25} In most cases, therapy can continue with use of topical corticosteroids and/or dose modifications. Finally, as noted with CAR T-cell therapy, a differential diagnosis that includes infection and tumor progression must be considered.

Early Toxicities of ADCs

ADCs do not engage or activate T cells and thus do not cause CRS or ICANS. Instead, the toxicities of ADCs are related either to the antibody target or the cytotoxic drug conjugate. On-target toxicities may result from effects on normal cells

TABLE 1. Highlighted Toxicities of Approved ADCs, BsAbs, and CAR T-Cell Therapies

CAR T Cells	Target/Costim	Diseases Indicated	CAR T Toxicities	Target Toxicities
Tisagenlecleucel	CD19/4-1BB	DLBCL, FL, B-ALL	CRS, ICANS, cytopenias, infections	B-cell aplasia
Axicabtagene ciloleucel	CD19/CD28	DLBCL, FL		
Brexucabtagene autoleucel	CD19/CD28	B-ALL, MCL		
Lisocabtagene maraleucel	CD19/4-1BB	DLBCL, MCL, FL, CLL		Parkinsonism, cranial nerve palsies, hypogammaglobulinemia
Obecabtagene autoleucel	CD19/4-1BB	B-ALL		
Ciltacabtagene autoleucel	BCMA/4-1BB	Myeloma		
Idecabtagene vicleucel	BCMA/4-1BB	Myeloma		
BsAb	Target	Diseases Indicated	BsAb Toxicities	Target Toxicities
Blinatumomab	CD19/CD3	B-ALL	CRS, ICANS, cytopenias, infections	Hypogammaglobulinemia
Glofitamab	CD20/CD3	DLBCL		
Epcoritamab	CD20/CD3	DLBCL		
Mosunetuzumab	CD20/CD3	FL		Dysgeusia, nail and skin changes, hypogammaglobulinemia
Teclistamab	BCMA/CD3	Myeloma		
Elranatamab	BCMA/CD3	Myeloma		
Talquetamab	GPCR5D/CD3	Myeloma		
Tebentafusp	GP100 (HLA-A*02:01)/CD3	Uveal melanoma		Rash, hepatic
Tarlatamab	DLL3/CD3	Small cell lung CA		Dysgeusia
ADC	Target/Conjugate	Diseases Indicated	Conjugate Toxicities	Target Toxicities
Gemtuzumab ozogamicin	CD33/calicheamicin	AML	Hepatic (VOD), cytopenias, infections	Cytopenias
Inotuzumab ozogamicin	CD22/calicheamicin	B-ALL		B-cell aplasia
Brentuximab vedotin	CD30/MMAE	Hodgkin lymphoma, T-cell lymphoma, DLBCL		Low
Tisotumab vedotin	TF/MMAE	Cervical cancer	Peripheral neuropathy, cytopenias, pneumonitis	Ocular, bleeding
Enfortumab vedotin	Nectin-4/MMAE	Urothelial cancer		Alopecia, rash, hyperglycemia
Polatuzumab vedotin	CD79b/MMAE	DLBCL		Hypogammaglobulinemia
Belantamab mafodotin	BCMA/MMAF	Myeloma	Ocular, peripheral neuropathy, cytopenias	Hypogammaglobulinemia
Mirvetuximab soravtansine	FR α /DM4	Epithelial ovarian, fallopian tube, peritoneal cancer	Ocular, nausea	Low
Trastuzumab emtansine	HER2/DM1	Breast cancer	Hepatic, cytopenias	Cardiac, pneumonitis
Trastuzumab deruxtecan	HER2/exatecan	Breast cancer	Pneumonitis, cytopenias	
Loncastuximab tesirine	CD19/SG3199	DLBCL	Hepatic, cytopenias	Hypogammaglobulinemia
Sacituzumab govitecan	Trop2/SN-38	TNBC, urothelial cancer	Cytopenias, diarrhea, cholinergic syndrome, alopecia	Low

Abbreviations: ADC, antibody-drug conjugate; B-ALL, B cell acute lymphoblastic leukemia; BCMA, B cell maturation antigen; BsAb, bispecific antibodies that engage T cells; CA, cancer; CAR, chimeric antigen receptor; Costim, costimulatory domain; CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; FR α , folate receptor alpha; HER2, human epidermal growth factor receptor 2; HLA-A, human leukocyte antigen A; ICANS, immune effector cell–associated neurotoxicity syndrome; MCL, mantle cell lymphoma; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; TF, tissue factor; TNBC, triple negative breast cancer; VOD, veno-occlusive disease.

that express low amounts of the target. However, only a small percentage of the dose of ADCs end up at their tumor targets and most drug-conjugate catabolism occurs at normal tissues, independent of target expression.²⁶ Thus, ADC toxicities are often class effects, dependent on specific design features such as the linker used or the class of chemotherapeutic payload, or interpatient differences in drug metabolism or immune complex clearance.^{27,28} Indeed, it may be difficult to ascertain whether a particular toxicity is

due to the target or due to off-tumor catabolism of the drug conjugate; however, this distinction is likely more important for drug development than for patient management, which relies upon dose adjustments and supportive care regardless of mechanism.

A recent ASCO Educational Book details toxicities of commonly encountered ADCs in clinical practice.²⁹ The first acute toxicities that may occur are infusion reactions, which

TABLE 2. ASTCT Consensus Grading of CRS and ICANS

CRS	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
Hypotension	None	Not requiring vasopressors	One vasopressor with or without vasopressin	Multiple vasopressors
Hypoxia	None	Low-flow oxygen	High-flow oxygen	Positive pressure or mechanical ventilation

ICANS	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unarousable)
LOC	Awakens spontaneously	Awakens to voice	Awakens to tactile stimulus	Awakens to vigorous stimulus or unarousable
Seizure	None	None	Any clinical or EEG seizure; resolves with intervention	Prolonged (>5 min) or repetitive seizures without return to baseline in between
Motor findings	None	None	None	Deep focal motor weakness such as hemiparesis or paraparesis

NOTE. Adapted from ref. 7. ICE score (max. 10 points): Orientation (4 points): orientation to year, month, city, hospital. Naming (3 points): names three objects. Following commands (1 point): follows simple commands. Writing (1 point): writes a standard sentence. Attention (1 point): counts backward from 100 by 10.

Abbreviations: ASTCT, American Society of Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy score; LOC, level of consciousness.

typically occur with the first infusion, and are managed with premedication and slowing the rate of infusion. Other toxicities due to the cytotoxic drug conjugate resemble chemotherapy-associated side effects. Nausea and vomiting, diarrhea, mucositis, cytopenias, and hepatic toxicities may occur with initial dosing or over time. These are often managed with treatment interruptions, dose reductions, and supportive care. However, knowledge about the potential risks of individual ADCs is warranted because toxicity mechanisms may also vary by time, payload class, or tumor type (Table 1). For example, early diarrhea caused by ADCs conjugated to topoisomerase I inhibitors is atropine-responsive and hypothesized to be due to a cholinergic response to enteric nervous system injury, because it may be accompanied by cramping, sweating, and salivation.³⁰ Late diarrhea without cholinergic symptoms may be managed in these patients with loperamide as chemotherapy-associated diarrhea. Other toxicities such as peripheral neuropathy, interstitial lung disease, ocular toxicity, congestive heart failure, or alopecia likely begin at initial dosing but are worsened and become clinically apparent over time. Finally, as for other therapies, cancer progression, infection, and other intercurrent illnesses require consideration as potential causes of symptoms experienced by patients receiving ADCs.

LATE TOXICITIES OF IMMUNOTHERAPIES

Prolonged Cytopenias After CAR T-Cell Therapy

Prolonged cytopenias for patients receiving CAR T-cell therapy, now known as immune effector cell-associated hematotoxicity (ICAH^T) are typically characterized by grade

3 to 4 anemia, thrombocytopenia, or neutropenia persisting beyond 30–90 days from CAR T-cell infusion. All patients can be expected to have early cytopenias after LDC; however, some patients experience prolonged cytopenias, either with initial recovery followed by later dips observed over time, or an aplastic phenotype without early marrow recovery. Across numerous studies involving different diseases and CAR products, cytopenias after day 30 occur in approximately 25%–40% of patients, with cytopenias beyond 90 days persisting in approximately 10%–25%.^{31–40} Higher rates of prolonged cytopenias have been observed in diseases characterized by extensive marrow infiltration such as B cell acute lymphoblastic leukemia and mantle cell lymphoma, and lower rates in indolent B-cell lymphomas. Additional factors associated with severe cytopenias include advanced age, numerous previous lines of therapy, and products with CD28 as opposed to 4-1BB costimulation domains.^{39,41,42} Recovery from neutropenia occurs in the majority of patients by month 3. Thrombocytopenia also develops relatively rapidly after LDC, but may have a delayed nadir in the second month before recovery. Anemia also most commonly occurs shortly after LDC followed by recovery in the majority of patients, with only a small proportion exhibiting transfusion dependence beyond 1 month.⁴³ Baseline cytopenias before CAR T-cell therapy along with increased baseline inflammatory markers correlate with risk of developing cytopenias, and are incorporated into the CAR-HEMATOTOX score, which can help stratify patients at risk for ICAHT.⁴³

Bone marrow biopsies should be performed in patients with persisting grade 3 to 4 cytopenias beyond day 90, mainly to rule out myelodysplastic syndrome or recurrence/persistence of the primary cancer. Transfusions are the

mainstay of management, and GCSF and thrombopoietin receptor agonists may also be used. Patients with prolonged multilineage cytopenias and availability of previously collected stem cells may be considered for autologous stem-cell boosts, which have demonstrated encouraging results in retrospective series.⁴⁴⁻⁴⁶ Patients who remain aplastic without response to conventional therapies may be considered for allogeneic stem-cell transplantation, although most ICAHT will improve if given enough time.

Prolonged Cytopenias on Bispecific Antibodies

Cytopenias of grade 3 or higher beyond day 30 may be observed in approximately one third of patients receiving BsAb, but appears more common in patients with myeloma, likely reflecting the extensive marrow infiltration in this population.^{23,25,47-51} Treatment is supportive with transfusion and growth factor support for grade 4 cytopenias, as well as consideration of dose reductions and/or extending treatment intervals in patients receiving ongoing BsAb therapy. Cytopenias refractory to supportive interventions should prompt bone marrow evaluation.

Impaired Immunity and Infections After CAR T-Cell Therapy

Late infections after CAR T-cell therapy can result from prolonged B-cell aplasia, hypogammaglobulinemia, delayed T-cell reconstitution, and prolonged neutropenia. Importantly, patients are often heavily immunocompromised even before CAR T-cell therapy because of previous treatment and the consequences of the baseline malignancy itself. Additional risk factors include histology (multiple myeloma and ALL at higher risk than lymphoma), increased number of previous lines of cancer therapy, previous stem-cell transplantation, recent infections, poor performance status, and advanced age.⁵² After CAR T-cell infusion, hypogammaglobulinemia has been reported in up to 62% of patients with diffuse large B cell lymphoma (DLBCL) 1 year after anti-CD19 CAR T-cell therapy, and as high as 75% of patients with multiple myeloma 1 year after anti-B cell maturation antigen (BCMA) CAR T-cell therapy.⁵³ CD4 T cells are often low even before CAR T-cell therapy and slow to recover after CAR with the majority remaining <200 cells/ μ L at one year after treatment.^{54,55} Attention to late infections is therefore critical to the survivorship care for patients treated with CAR T cells as infections represent the most common cause of nonrelapse mortality.⁵⁶ The most common infections occurring beyond day 90 include viral respiratory pathogens including SARS-CoV-2 (COVID-19), herpes family viral reactivations (cytomegalovirus [CMV], human herpesvirus 6-6, and varicella zoster virus), and other opportunistic infections including fungi, and *Pneumocystis jirovecii* (PJP).⁵³ General mitigation strategies to reduce infection are noted in [Table 3](#).

Infectious prophylaxis to prevent certain late infections is critical including PJP prophylaxis with trimethoprim/

sulfamethoxazole and human herpesvirus (HHV) prophylaxis with acyclovir, or equivalents, in all patients. Entecavir should be included in patients with positive hepatitis B core antibodies at baseline. Prophylaxis for PJP and HHVs should continue for a minimum of 6 months, and 12 months for hepatitis B virus, but given the incidence of prolonged T-cell lymphopenia, many recommend to continue these medications until CD4 is recovered >200 cells/ μ L. Immunoglobulin replacement should be instituted for patients with IgG levels $\leq$ 400 mg/dL who develop severe or recurrent infections. Patients with multiple myeloma treated with anti-BCMA CAR T-cell therapies have higher rates of infections, so replacement therapy can be considered in patients with IgG $\leq$ 400 mg/dL even in the absence of infections.⁵³ Revaccination after CAR is also now recommended by ASTCT.⁵² Vaccines for influenza and COVID-19 should be administered as early as 3 months after CAR. Vaccines against pneumococcus (PCV20); diphtheria, tetanus, and pertussis; and hepatitis A and B should be considered as early as 6 months after CAR, and can be routinely given or guided by measuring titers against these organisms and re-vaccinating patients without detectable humoral immunity. Varicella zoster revaccination (Shingrix) may be given routinely as early as 3 months, or alternatively beginning at 12 months when a greater proportion of patients have recovered from B-cell aplasia (ie, after CD19-directed CAR T). Live virus vaccines should be avoided in patients within 12 months of CAR T-cell therapy.

Late Infections on Bispecific Antibodies

Patients treated with BsAbs have also experienced high rates of infectious complications, likely reflecting previous treatments, underlying malignancy, and prolonged dosing strategies resulting in ongoing B-cell depletion and hypogammaglobulinemia. Severe neutropenia also occurs relatively commonly after BsAb.⁵⁷ Any grade infections have been reported in approximately 20%-50% of patients with lymphoma receiving anti-CD20 BsAb, with severe infections in 15%-23%.⁵⁷ Infection rates appear even higher among patients with multiple myeloma where infections occurred in 56% and were severe in one quarter.⁵⁸ Patients are at risk for serious bacterial infections, particularly in the setting of neutropenia. Humoral and T-cell dysfunction also places these patients at risk for respiratory viral infections (ie, influenza, respiratory syncytial virus (RSV), and COVID-19), CMV reactivation, *pneumocystis jirovecii*, and invasive fungal infections. To mitigate infectious risk, all patients are recommended to receive HHV and PJP prophylaxis until a minimum of 6 months after completion of all bispecific antibody therapies, but given the long-term risk associated with CD4 T-cell lymphopenia, many recommend continuing prophylactic therapy until CD4 T-cell recovery. Routine antifungal prophylaxis is recommended in patients with prolonged neutropenia and/or ongoing requirement for systemic corticosteroids. Immunoglobulin replacement therapy is recommended for any patient with severe or recurrent infections and IgG $\leq$ 400 mg/dL, but more liberal use

TABLE 3. Long-Term Infection Mitigation Strategies in Patients Receiving CAR T-Cell Therapy

Prophylaxis	Vaccination	IVIg Replacement
PJP (minimum of 6 months and ideally until CD4 count >200 cells/ μ L) Trimethoprim/sulfamethoxazole 1 SS tab PO daily or 1 DS tab PO 3 times per week (preferred) Atovaquone 1,500 mg PO daily Dapsone 100 mg PO daily Once each month inhaled pentamidine	>3 months Influenza COVID-19 RSV >6 months (if previously unvaccinated or low titers) Pneum-20 DTap HAV HBV >12 months (if previously unvaccinated or low titers) VZV Any required live virus vaccines	Non-BCMA CARs IVIg 400-500 mg/kg every 4-6 weeks if IgG $\leq$ 400 mg/dL and recurrent or severe infections to maintain IgG level >500 mg/kg BCMA CARs IVIg 400-500 mg/kg every 4-6 weeks if IgG $\leq$ 400 mg/dL to maintain IgG level >500 mg/kg
HHV (minimum of 6 months and ideally until CD4 count >200 cells/ μ L) Acyclovir 400 mg PO twice a day Valacyclovir 500 mg PO twice a day or 1,000 mg PO QD		
HBV (minimum of 12 months and ideally until CD4 count >200 cells/ μ L) Entecavir 0.5 mg PO QD		

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; DS, double strength; DTap, diphtheria, tetanus, and pertussis; HAV, hepatitis A virus; HBV, hepatitis B virus; HHV, human herpesvirus; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; PO, orally; PJP, *Pneumocystis jirovecii*; QD, once daily; RSV, respiratory syncytial virus; SS, single strength; VZV, varicella zoster virus.

in the absence of infections can be considered in anti-BCMA-treated patients where infection rates are highest. Despite decreased responsiveness to vaccines, these patients should be vaccinated for COVID-19, influenza, RSV, and all other age-appropriate vaccinations.

Late Toxicities on Antibody-Drug Conjugates

All ADCs are associated with risks of cytopenias and infections, and ADC toxicities generally recover after treatment discontinuation. The most notable exception is peripheral neuropathy related to ADCs carrying toxins, which target microtubules. Brentuximab vedotin causes peripheral neuropathy in about 40% of patients receiving the drug as monotherapy for relapsed Hodgkin lymphoma (HL), and two thirds of patients receiving it when given in combination with chemotherapy as initial treatment. Although neuropathy most commonly improves or resolves, approximately 30% of patients report having ongoing neuropathy at 5 years of follow-up after receiving brentuximab in combination with chemotherapy in HL.^{59,60} Polatuzumab vedotin causes peripheral neuropathy in approximately half of the patients when given in combination with chemotherapy in DLBCL, but resulted in treatment discontinuation in only 4%.⁶¹ Patients receiving these monomethyl auristatin E-containing ADCs should have peripheral neuropathy assessed at baseline and then throughout therapy with dose reduction initiated for any neuropathy of grade 2, and discontinued for grades $\geq$ 3.

RARE COMPLICATIONS OF IMMUNOTHERAPIES

Quality of life, morbidity, and mortality among patients treated with ADCs, BsAbs, and CAR T cells are not only affected by immune activation symptoms and infections, but also by second malignancies, organ injuries, and neurologic and cognitive events.⁵⁶ These less common but potentially

severe life-threatening complications are outlined in this section.

Second Primary Malignancies

Although the greatest risk to the patient is the cancer for which therapy is being administered, there is a potential risk for development of a subsequent second primary malignancy. There may be multiple mechanisms by which a second primary malignancy may develop.⁶² First, albeit rarely, the CAR transgene itself may insert into an oncogene and cause a T-cell malignancy. More commonly, secondary malignancies are not due to CAR insertion. These malignancies may be initiated by underlying predisposing conditions or from genotoxic stress related to previous chemotherapy.⁶³ For example, clonal hematopoiesis may progress to myeloid malignancies in the setting of genotoxins used for LDC.⁶⁴ Additionally, the cytokines associated with these immune therapies may apply selective pressure in favor of expansion of these variant cells. Furthermore, abnormal immunoregulation and lack of immune surveillance may be present in patients at baseline,⁶⁵ and subsequent LDC or immunotherapy may further perturb the patient's immunologic repertoire. The subsequent immune dysfunction will likely impair antitumor immune surveillance mechanisms resulting in potential outgrowth of neoplastic cells including solid tumors. Finally, the efficacy of immunologic therapies may prolong the patient's lifespan, which is desirable, but time and aging further increase the risk of second malignancies.

The incidence of second primary malignancies after immunologic therapy, specifically CAR T-cell treatment, is relatively low. There have been reports of T-cell lymphomas developing after CAR T-cell therapy.⁶⁶⁻⁶⁹ A comprehensive analysis of patients treated with CAR T-cell therapy has suggested that T-cell malignancies are uncommon.⁷⁰

Furthermore, the number of cases in which the inserted transgene could be detected in the tumor cells has been very low, suggesting that insertional mutagenesis as a cause for the lymphoma is very rare. It is also unclear whether the development of subsequent myeloid malignancies is higher in patients treated with immunotherapy or ADCs compared with historical therapies. A retrospective analysis reported a cumulative incidence of myeloid neoplasms after CAR T-cell therapy of 9% at 3 years. Notably, 70% of the patients with baseline samples had preexisting clonal hematopoiesis before therapy.^{71,72} There have also been multiple reports of solid tumors developing after CAR T-cell therapy with a cumulative incidence at 5 years of 15%.⁷³ However, half of these cases were nonmelanoma skin cancers. Although many second malignancies may not directly be due to these treatments, vigilant follow-up of patients treated with immunotherapy or ADCs is appropriate.

Interstitial Lung Disease

ADCs delivering oncolytic drugs may potentially cause drug-induced lung injury, and interstitial lung disease is a potential consequence. Patients may present with non-specific findings including a dry cough, shortness of breath, fatigue, and chest pain. A meta-analysis showed that pneumonitis was the most common cause of death associated with ADCs.⁷⁴ Pneumonitis has been reported in patients treated with trastuzumab deruxtecan (13.6%), mirvetuximab soravtansine (10%), enfortumab vedotin (28%), and brentuximab vedotin (3.2%).^{75,76} The incidence of interstitial lung disease with trastuzumab emtansine and tisotumab vedotin has typically been <2% but some fatal cases have been reported.⁷⁷ It is important to differentiate interstitial lung disease from an infectious process and empiric antibiotic coverage is typically given. A workup may include bronchoalveolar lavage and a possible biopsy. Management is typically supportive, with the addition of steroids to decrease inflammation. Additional immunosuppressive agents may be added if the patient does not improve.

Hepatic Injury

Sinusoidal obstruction syndrome, formally known as veno-occlusive disease (VOD), is a known complication of ADCs such as gemtuzumab ozogamicin and inotuzumab ozogamicin.⁷⁸ This syndrome is secondary to endothelial cell damage in the liver causing microvascular thrombosis and obstruction to hepatic blood flow in the hepatic sinusoid. VOD was seen in approximately 4.6% of patients treated with gemtuzumab ozogamicin⁷⁹ and an approximately 13% of patients receiving inotuzumab ozogamicin.⁸⁰ The patients commonly present with rapid weight gain and edema, followed by the development of ascites, jaundice, and painful hepatomegaly. Supportive treatment with fluid and electrolyte management is typically given in combination with defibrotide to stabilize the endothelium and modulate vascular permeability and thrombosis.

Cardiovascular Toxicity

Although it is well known that trastuzumab may cause cardiotoxicity, ADCs that use trastuzumab as the antibody moiety (trastuzumab deruxtecan and trastuzumab emtansine) have actually shown lower rates of cardiotoxicity than that observed with trastuzumab alone. A meta-analysis of trials using trastuzumab deruxtecan reported a 1.95% incidence of decreased cardiac ejection fraction,⁸¹ and a pooled analysis of almost 2,000 patients treated with trastuzumab emtansine showed an incidence of cardiac events of 3.37%.⁸² Cases of symptomatic congestive cardiac failure in pediatric patients have been reported with gemtuzumab ozogamicin.⁸³ However, in clinical trials in adults, no statistically significant increase in cardiac adverse events have been detected with this agent. For CAR T-cell and bispecific antibody therapies, adverse cardiovascular events (aside from CRS) have largely been reported in a retrospective fashion. Among the subset of patients developing high-grade CRS after CAR T-cell therapy, up to 10% of patients may develop cardiomyopathy, but this improves in the majority of patients.⁸⁴⁻⁸⁶ In clinical trials for B-cell lymphomas, <1% of patients had long-term cardiovascular events including heart failure or cardiac arrest. A limitation of these data, however, is the potential underreporting of previous cardiotoxic therapies and the lack of consistent post-treatment surveillance.

Neurologic and Neurocognitive Complications

Late-onset neurotoxicity, distinct from ICANS, has been reported in patients who have received CAR T-cell therapies. Specifically, a neurocognitive disorder with features of parkinsonism has been reported in approximately 5% of patients treated with ciltacabtagene autoleucel.⁸⁷ This disorder was described occurring at a median of 17 days (range, 3-94 days) after recovery from acute CRS or ICANS. The syndrome did not respond to typical immunosuppressive and dopaminergic agents and had a progressive course. The disorder is incompletely understood but may be associated with targeting of BCMA-expressing neurons in the basal ganglia. Longer-term neurologic monitoring for patients receiving anti-BCMA CAR T cells is therefore indicated. In addition, cranial nerve palsies have emerged as an important delayed neurologic toxicity after anti-BCMA CAR T-cell therapy, with CNS infiltration of the CAR T cells observed, and clinical management including corticosteroids and intravenous immunoglobulin.⁸⁸⁻⁹⁰

Neurocognitive function may also be affected by CAR T-cell therapy. Longitudinal assessment of patients receiving this therapy has shown some degree of impairment even at baseline before therapy in a subset of patients. Cognitive difficulty and/or meaningful clinical depression or anxiety has been reported by patients while receiving CAR T-cell therapy⁹¹ but these effects appear to improve as 6 months. With longer-term follow-up at 6 months and 2 years, there was no additional decline.^{92,93} Although neuropsychiatric outcomes overall are good for the majority of long-term

survivors after CAR T-cell therapy, a subpopulation of patients may benefit from mental health services.

Progressive multifocal leukoencephalopathy (PML) is an often-fatal demyelinating viral infection of the central nervous system associated with John Cunningham (JC) virus. The symptoms may initially affect speech but subsequently may also result in motor dysfunction, cognitive deficits, and visual changes. These initial symptoms may then be followed by progressive neurologic decline over weeks to months. Treatment is largely supportive with a goal of maintaining and potentially restoring immune function if possible. Treatments including antiviral agents, immune globulin infusions, and immune checkpoint therapy are commonly administered in an attempt to restore immune function. PML has been associated with brentuximab vedotin and

polatuzumab vedotin, and both agents carry warnings to this effect.^{94,95} Fortunately, this is an uncommon event with <0.1% of patients developing this complication in clinical trials and in postmarket analysis.

CONCLUSION

ADCs, BsAbs, and CAR T-cell therapies are in rising use in oncology, with additional nonmalignant indications on the horizon. Each product carries its own class and product-specific toxicities related to on-target, off-target, and rare idiosyncratic effects. Knowledge of these toxicities are quickly becoming part of the ABCs of the practicing clinical oncologist, allowing these potent agents to fulfill their promise to extend life and improve health among the population of patients with cancer.

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REFERENCES

- Santomasso BD, Nastoupil LJ, Adkins S, et al: Management of immune-related adverse events in patients treated with chimeric antigen receptor T-cell therapy: ASCO guideline. *J Clin Oncol* 39: 3978-3992, 2021
- Morris EC, Neelapu SS, Giavridis T, et al: Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol* 22:85-96, 2022
- Faramand RG, Lee SB, Jain MD, et al: Baseline serum inflammatory proteins predict poor CAR T outcomes in diffuse large B-cell lymphoma. *Blood Cancer Discov* 5:106-113, 2024
- Sidana S, Patel KK, Peres LC, et al: Safety and efficacy of standard of care ciltacabtagene autoleucel for relapsed/refractory multiple myeloma. *Blood* 145:85-97, 2025
- Sesques P, Kirkwood AA, Kwon M, et al: Novel prognostic scoring systems for severe CRS and ICANS after anti-CD19 CAR T cells in large B-cell lymphoma. *J Hematol Oncol* 17:61, 2024
- Jain MD, Smith M, Shah NN: How I treat refractory CRS and ICANS after CAR T-cell therapy. *Blood* 141:2430-2442, 2023
- Lee DW, Santomasso BD, Locke FL, et al: ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transpl* 25: 625-638, 2019
- Oluwole OO, Bouabdallah K, Muñoz J, et al: Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. *Br J Haematol* 194:690-700, 2021
- Strati P, Ahmed S, Kebriaei P, et al: Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. *Blood Adv* 4:3123-3127, 2020
- Park JH, Nath K, Devlin SM, et al: CD19 CAR T-cell therapy and prophylactic anakinra in relapsed or refractory lymphoma: Phase 2 trial interim results. *Nat Med* 29:1710-1717, 2023
- Parker KR, Migliorini D, Perkey E, et al: Single-cell analyses identify brain mural cells expressing CD19 as potential off-tumor targets for CAR-T immunotherapies. *Cell* 183:126-142 e17, 2020
- Gust J, Hay KA, Hanafi LA, et al: Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov* 7:1404-1419, 2017
- Zurko JC, Johnson BD, Aschenbrenner E, et al: Use of early intrathecal therapy to manage high-grade immune effector cell-associated neurotoxicity syndrome. *JAMA Oncol* 8:773-775, 2022
- Teachey DT, Lacey SF, Shaw PA, et al: Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Cancer Discov* 6:664-679, 2016
- Grupp SA, Kalos M, Barrett D, et al: Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med* 368:1509-1518, 2013
- Shah NN, Highfill SL, Shalabi H, et al: CD4/CD8 T-cell selection affects chimeric antigen receptor (CAR) T-cell potency and toxicity: Updated results from a phase I anti-CD22 CAR T-cell trial. *J Clin Oncol* 38:1938-1950, 2020
- Frank MJ, Baird JH, Kramer AM, et al: CD22-directed CAR T-cell therapy for large B-cell lymphomas progressing after CD19-directed CAR T-cell therapy: A dose-finding phase 1 study. *Lancet* 404: 353-363, 2024
- Hines MR, Knight TE, McNeerney KO, et al: Immune effector cell-associated hemophagocytosis-like syndrome. *Transplant Cell Ther* 29:438.e1-438.e16, 2023
- Wesson W, Dima D, Suleman N, et al: Timing of toxicities and non-relapse mortality following CAR T therapy in myeloma. *Transplant Cell Ther* 30:876-884, 2024
- Ahmed N, Wesson W, Lutfi F, et al: Optimizing the post-CAR T monitoring period in recipients of axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel. *Blood Adv* 8:5346-5354, 2024

21. Braun A, Gouni S, Pulles A, et al: Bispecific antibody use in patients with lymphoma and multiple myeloma. *Am Soc Clin Oncol Educ Book* 44:e433516, 2024
22. Topp MS, Tani M, Dickinson M, et al: Glofitamab plus R-CHOP induces high response rates with a manageable safety profile in patients with previously untreated diffuse large B-cell lymphoma (DLBCL): A 12-month analysis from a phase Ib study. *Blood* 142:3085, 2023
23. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al: Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med* 387:2220-2231, 2022
24. Nathan P, Hassel JC, Rutkowski P, et al: Overall survival benefit with tebentafusp in metastatic uveal melanoma. *N Engl J Med* 385:1196-1206, 2021
25. Chari A, Minnema MC, Berdeja JG, et al: Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med* 387:2232-2244, 2022
26. Nguyen TD, Borgeau BM, Balthasar JP: Mechanisms of ADC toxicity and strategies to increase ADC tolerability. *Cancers (Basel)* 15:713, 2023
27. D'Arienzo A, Verrazzo A, Pagliuca M, et al: Toxicity profile of antibody-drug conjugates in breast cancer: Practical considerations. *EClinicalMedicine* 62:102113, 2023
28. Taylor RP, Lindorfer MA: Antibody-drug conjugate adverse effects can be understood and addressed based on immune complex clearance mechanisms. *Blood* 144:137-144, 2024
29. Shastri M, Gupta A, Chandralapathy S, et al: Rise of antibody-drug conjugates: The present and future. *Am Soc Clin Oncol Educ Book* 43:e390094, 2023
30. Schlam I, Tarantino P, Tolanev SM: Managing adverse events of sacituzumab govitecan. *Expert Opin Biol Ther* 23:1103-1111, 2023
31. Abramson JS, Palomba ML, Gordon LI, et al: Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): A multicentre seamless design study. *Lancet* 396:839-852, 2020
32. Abramson JS, Solomon SR, Arnason J, et al: Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: Primary analysis of the phase 3 TRANSFORM study. *Blood* 141:1675-1684, 2023
33. Wang M, Siddiqi T, Gordon LI, et al: Lisocabtagene maraleucel in relapsed/refractory mantle cell lymphoma: Primary analysis of the mantle cell lymphoma cohort from TRANSCEND NHL 001, a phase I multicenter seamless design study. *J Clin Oncol* 42:1146-1157, 2024
34. Morschhauser F, Dahiya S, Palomba ML, et al: Lisocabtagene maraleucel in follicular lymphoma: The phase 2 TRANSCEND FL study. *Nat Med* 30:2199-2207, 2024
35. Locke FL, Ghobadi A, Jacobson CA, et al: Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): A single-arm, multicentre, phase 1-2 trial. *Lancet Oncol* 20:31-42, 2019
36. Wang M, Munoz J, Goy A, et al: KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 382:1331-1342, 2020
37. Locke FL, Miklos DB, Jacobson CA, et al: Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med* 386:640-654, 2022
38. Neelapu SS, Chavez JC, Sehgal AR, et al: Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). *Blood* 143:496-506, 2024
39. Logue JM, Peres LC, Hashmi H, et al: Early cytopenias and infections after standard of care idecabtagene vicleucel in relapsed or refractory multiple myeloma. *Blood Adv* 6:6109-6119, 2022
40. Jain T, Olson TS, Locke FL: How I treat cytopenias after CAR T-cell therapy. *Blood* 141:2460-2469, 2023
41. Xia Y, Zhang J, Li J, et al: Cytopenias following anti-CD19 chimeric antigen receptor (CAR) T cell therapy: A systematic analysis for contributing factors. *Ann Med* 54:2951-2965, 2022
42. Bachy E, Le Gouill S, Di Blasi R, et al: A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med* 28:2145-2154, 2022
43. Rejeski K, Perez A, Sesques P, et al: CAR-HEMATOTOX: A model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. *Blood* 138:2499-2513, 2021
44. Mohan M, Szabo A, Patwari A, et al: Autologous stem cell boost improves persistent immune effector cell associated hematotoxicity following BCMA directed chimeric antigen receptor T (CAR T) cell therapy in multiple myeloma. *Bone Marrow Transpl* 59:647-652, 2024
45. Rejeski K, Burchert A, Iacoboni G, et al: Safety and feasibility of stem cell boost as a salvage therapy for severe hematotoxicity after CD19 CAR T-cell therapy. *Blood Adv* 6:4719-4725, 2022
46. Molinos-Quintana Á, Martínez-Cibrian N, Alonso-Saladríguez A, et al: Successful allogeneic CD34(+) hematopoietic stem cell boost for prolonged cytopenias following CAR T-cell therapy in B-cell acute lymphoblastic leukemia. On behalf of the Spanish Group for Hematopoietic Transplantation and Cellular Therapy (GETH-TC). *Bone Marrow Transpl* 60:250-253, 2025
47. Budde LE, Sehn LH, Matasar M, et al: Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: A single-arm, multicentre, phase 2 study. *Lancet Oncol* 23:1055-1065, 2022
48. Thieblemont C, Phillips T, Ghesquieres H, et al: Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell-engaging antibody, in relapsed or refractory large B-cell lymphoma: Dose expansion in a phase I/II trial. *J Clin Oncol* 41:2238-2247, 2023
49. Phillips TJ, Carlo-Stella C, Morschhauser F, et al: Glofitamab in relapsed/refractory mantle cell lymphoma: Results from a phase I/II study. *J Clin Oncol* 43:318-328, 2025
50. Lesokhin AM, Tomasson MH, Arnulf B, et al: Elranatamab in relapsed or refractory multiple myeloma: Phase 2 MagnetisMM-3 trial results. *Nat Med* 29:2259-2267, 2023
51. Moreau P, Garfall AL, van de Donk N, et al: Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 387:495-505, 2022
52. Shahid Z, Jain T, Divoerti V, et al: Best practice considerations by the American society of transplant and cellular therapy: Infection prevention and management after chimeric antigen receptor T cell therapy for hematological malignancies. *Transplant Cell Ther* 30:955-969, 2024
53. Kampouri E, Little JS, Rejeski K, et al: Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. *Transpl Infect Dis* 25:e14157, 2023 (suppl 1)
54. Logue JM, Zucchetti E, Bachmeier CA, et al: Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. *Haematologica* 106:978-986, 2021
55. Baird JH, Epstein DJ, Tamaresis JS, et al: Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma. *Blood Adv* 5:143-155, 2021
56. Cordas Dos Santos DM, Tix T, Shouval R, et al: A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy. *Nat Med* 30:2667-2678, 2024
57. Gongunata AS, Mohlere V, Abid MB: Risk of infections with bispecific antibodies in B-cell non-Hodgkin lymphomas and multiple myeloma—The current state. *Br J Haematol* 205:1197-1201, 2024
58. Reynolds G, Cliff ERS, Mohyuddin GR, et al: Infections following bispecific antibodies in myeloma: A systematic review and meta-analysis. *Blood Adv* 7:5898-5903, 2023
59. Younes A, Gopal AK, Smith SE, et al: Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 30:2183-2189, 2012
60. Straus DJ, Długosz-Danecka M, Connors JM, et al: Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol* 8:e410-e421, 2021
61. Tilly H, Morschhauser F, Sehn LH, et al: Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. *N Engl J Med* 386:351-363, 2022
62. Patel SA, Spiegel JV, Dahiya S: Second primary cancer after chimeric antigen receptor-T-cell therapy: A review. *JAMA Oncol* 11:174-181, 2025
63. Morton LM, Dore GM, Schonfeld SJ, et al: Association of chemotherapy for solid tumors with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. *JAMA Oncol* 5:318-325, 2019
64. Tix T, Alhomoud M, Shouval R, et al: Second primary malignancies after CAR T-cell therapy: A systematic review and meta-analysis of 5,517 lymphoma and myeloma patients. *Clin Cancer Res* 30:4690-4700, 2024
65. Li YR, Halladay T, Yang L: Immune evasion in cell-based immunotherapy: Unraveling challenges and novel strategies. *J Biomed Sci* 31:5, 2024
66. Bishop DC, Clancy LE, Simms R, et al: Development of CAR T-cell lymphoma in 2 of 10 patients effectively treated with piggyBac-modified CD19 CAR T cells. *Blood* 138:1504-1509, 2021
67. Hamilton MP, Sugio T, Noordenbos T, et al: Risk of second tumors and T-cell lymphoma after CAR T-cell therapy. *N Engl J Med* 390:2047-2060, 2024
68. Levine BL, Pasquini MC, Connolly JE, et al: Unanswered questions following reports of secondary malignancies after CAR-T cell therapy. *Nat Med* 30:338-341, 2024
69. Verdun N, Marks P: Secondary cancers after chimeric antigen receptor T-cell therapy. *N Engl J Med* 390:584-586, 2024
70. Hsieh EM, Myers RM, Yates B, et al: Low rate of subsequent malignant neoplasms after CD19 CAR T-cell therapy. *Blood Adv* 6:5222-5226, 2022
71. Gurney M, Baranwal A, Rosenthal A, et al: Features and factors associated with myeloid neoplasms after chimeric antigen receptor T-cell therapy. *JAMA Oncol* 10:532-535, 2024
72. Alkhateeb HB, Mohty R, Greipp P, et al: Therapy-related myeloid neoplasms following chimeric antigen receptor T-cell therapy for Non-Hodgkin Lymphoma. *Blood Cancer J* 12:113, 2022
73. Ghilardi G, Fraietta JA, Gerson JN, et al: T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy. *Nat Med* 30:984-989, 2024
74. Zhu Y, Liu K, Wang K, et al: Treatment-related adverse events of antibody-drug conjugates in clinical trials: A systematic review and meta-analysis. *Cancer* 129:283-295, 2023
75. Markides DM, Hita AG, Merlin J, et al: Antibody-drug conjugates: The toxicities and adverse effects that emergency physicians must know. *Ann Emerg Med* 85:214-229, 2025
76. Zhu Z, Shen G, Li J, et al: Incidence of antibody-drug conjugates-related pneumonitis in patients with solid tumors: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 184:103960, 2023
77. Yong WP, Teo FS, Teo LL, et al: Clinical best practices in optimal monitoring, early diagnosis, and effective management of antibody-drug conjugate-induced interstitial lung disease or pneumonitis: A multidisciplinary team approach in Singapore. *Expert Opin Drug Metab Toxicol* 18:805-815, 2022
78. Corbacioglu S, Carreras E, Ansari M, et al: Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: A new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant* 53:138-145, 2018
79. Castaigne S, Pautas C, Terré C, et al: Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): A randomised, open-label, phase 3 study. *Lancet* 379:1508-1516, 2012
80. Kantarjian HM, DeAngelo DJ, Advani AS, et al: Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: Results from the open-label, randomised, phase 3 INO-VATE study. *Lancet Haematol* 4:e387-e398, 2017

81. Soares LR, Vilbert M, Rosa VDL, et al: Incidence of interstitial lung disease and cardiotoxicity with trastuzumab deruxtecan in breast cancer patients: A systematic review and single-arm meta-analysis. *ESMO Open* 8:101613, 2023
82. Pondé N, Ameye L, Lambertini M, et al: Trastuzumab emtansine (T-DM1)-associated cardiotoxicity: Pooled analysis in advanced HER2-positive breast cancer. *Eur J Cancer* 126:65-73, 2020
83. McNerney KO, Oranges K, Seif AE, et al: Acute left ventricular dysfunction following gemtuzumab ozogamicin in two pediatric AML patients. *J Pediatr Hematol Oncol* 44:e507-e511, 2022
84. Alvi RM, Frigault MJ, Fradley MG, et al: Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *J Am Coll Cardiol* 74:3099-3108, 2019
85. Ganatra S, Redd R, Hayek SS, et al: Chimeric antigen receptor T-cell therapy-associated cardiomyopathy in patients with refractory or relapsed non-Hodgkin lymphoma. *Circulation* 142:1687-1690, 2020
86. Koeckerling D, Reddy RK, Barker J, et al: Cardiovascular events after chimeric antigen receptor T-cell therapy for advanced hematologic malignant neoplasms: A meta-analysis. *JAMA Netw Open* 7:e2437222, 2024
87. Cohen AD, Parekh S, Santomaso BD, et al: Incidence and management of CAR-T neurotoxicity in patients with multiple myeloma treated with ciltacabtagene autoleucel in CARTITUDE studies. *Blood Cancer J* 12:32, 2022
88. Van De Donk NWCJ, Sidana S, Schecter JM, et al: Clinical experience with cranial nerve impairment in the CARTITUDE-1, CARTITUDE-2 cohorts A, B, and C, and cartitude-4 studies of ciltacabtagene autoleucel (Cilta-cel). *Blood* 142:3501, 2023 (suppl 1)
89. Kumar AD, Atallah-Yunes SA, Rajeeve S, et al: Delayed neurotoxicity after CAR-T in multiple myeloma: Results from a global IMWG registry. *Blood* 144:4758, 2024 (suppl 1)
90. Kathari YK, Ahmad H, Kallen ME, et al: Immune-mediated facial nerve paralysis in a myeloma patient post B-cell maturation antigen-targeted chimeric antigen receptor T cells. *Haematologica* 109:682-688, 2024
91. Ruark J, Mullane E, Cleary N, et al: Patient-reported neuropsychiatric outcomes of long-term survivors after chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant* 26:34-43, 2020
92. Maillet D, Belin C, Moroni C, et al: Evaluation of mid-term (6-12 months) neurotoxicity in B-cell lymphoma patients treated with CAR T cells: A prospective cohort study. *Neuro Oncol* 23:1569-1575, 2021
93. Ursu R, Maillet D, Belin C, et al: Long-term neurologic safety in patients with B-cell lymphoma treated with anti-CD19 chimeric antigen receptor T-cell therapy. *Neurology* 99:511-515, 2022
94. Carson KR, Newsome SD, Kim EJ, et al: Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: A report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. *Cancer* 120:2464-2471, 2014
95. Sehn LH, Herrera AF, Flowers CR, et al: Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol* 38:155-165, 2020

Which Is the Best Tyrosine Kinase Inhibitor for Newly Diagnosed Chronic Myelogenous Leukemia?

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OVERVIEW

The choice of frontline therapy for a patient with chronic phase chronic myeloid leukemia (CP-CML) can have a profound effect on the long-term clinical outcome. Currently, five tyrosine kinase inhibitors (TKIs—imatinib, dasatinib, nilotinib, bosutinib, and asciminib) are available for frontline therapy, but no single TKI is optimal for all patients. EUTOS long-term survival (ELTS) risk score, comorbidities, and treatment-free remission (TFR) priority are the key determinants of frontline TKI selection. Higher ELTS score, low age and comorbidity score, and a high priority for achievement of TFR would all favor the frontline use of a more potent TKI than imatinib. However, no TKI has improved survival compared with imatinib. In children with CP-CML, imatinib, dasatinib, and nilotinib have similar long-term efficacy, with ease of administration and impact of toxicities on quality of life being key considerations. Recent adult trials of reduced-dose dasatinib frontline showed that efficacy may be equivalent to standard-dose dasatinib with a better tolerability and safety profile, but experience is limited in patients with high-risk ELTS scores. The ASC4FIRST trial has confirmed that tolerability and molecular response with asciminib are superior to those with both imatinib and the second-generation (2G)-TKIs. While the overall treatment failure rate was lower with asciminib, the rate of BCR::ABL1 mutations that emerged with asciminib appeared to be higher. The risk of emergent mutations appears to be highly associated with the presence of ASXL1 mutations in the CML cells at diagnosis, but more work is needed to understand the implications of this finding.

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INTRODUCTION

One of the most important and complex decisions confronting the clinician when a patient with newly diagnosed chronic phase chronic myeloid leukemia (CP-CML) first attends clinic is the selection of the optimal frontline tyrosine kinase inhibitor (TKI). This is ideally a joint decision made by the clinician and the patient after all the relevant issues have been discussed. It is still the case in 2025 that there is no single TKI which is going to be the optimal choice for every patient with CP-CML and the decision should be patient-specific. Patient factors (age, comorbidities, cardiovascular risk profile, motivation for treatment-free remission [TFR], lifestyle, and work considerations) and disease factors (EUTOS long-term survival [ELTS] score, additional chromosomal abnormalities (ACAs), and potentially additional genomic abnormalities) will all need to be considered and, where appropriate, discussed with the patient, based on their specific priorities. Transformation to blast crisis is the most life-threatening concern at this early stage (Table 1), but TKI toxicity leading to mortality and morbidity is also a significant danger to consider. Quality of life is a critically important consideration as TKIs will be needed over the long term and may be required lifelong for many patients. The ultimate goal of therapy for most patients will be TFR, and since this will, in many cases,

be a key determinant of drug selection, it is preferable that this is discussed with the patient in broad terms before TKI selection.

FRONTLINE TKI CHOICES IN 2025

Imatinib fundamentally changed the landscape and prognosis for patients with CP-CML when first introduced in the early 2000s. Patients who were previously looking at limited survival in the absence of an allograft were now able to consider CP-CML as a chronic controllable disease, similar to hypertension and diabetes mellitus. The pivotal IRIS study demonstrated a marked improvement in the 10-year rate of overall survival (OS) at 84% while also demonstrating the long-term efficacy and safety of imatinib therapy.³ Adverse events associated with imatinib therapy are usually not life-threatening or life-shortening and include fluid retention, muscle cramps, and GI toxicity—mainly diarrhea.⁴ However, quality of life is significantly impaired on imatinib, particularly in younger patients.⁵ In addition, imatinib is significantly less potent than the second-generation TKIs (2G-TKIs), resulting in higher rates of treatment failure, resistance, transformation to blast crisis (Table 2), and inferior deep molecular responses (DMRs), a pivotal criteria for TFR eligibility.^{1,2}

PRACTICAL APPLICATIONS

- Five tyrosine kinase inhibitors (TKIs) are currently broadly available for frontline therapy in patients with chronic phase chronic myeloid leukemia, and all are potentially suitable in different clinical settings.
- EUTOS long-term survival risk score, comorbidities, and treatment-free remission priority are the key determinants of frontline TKI selection.
- Recent trials of reduced dose second-generation (2G) TKIs frontline have suggested that efficacy may be equivalent to standard-dose 2G TKI with a better tolerability and safety profile.
- The ASC4FIRST trial has confirmed that tolerability and molecular response with asciminib are superior to those with both imatinib and the 2G-TKIs.
- Genomic profiling at diagnosis will likely contribute to TKI selection, but further validation is needed.

The 2G-TKI nilotinib has increased potency compared with imatinib but generally requires twice-daily administration with specific fasting requirements, which can be difficult for some patients. The 10-year rate of DMR, defined as MR4.5 (BCR::ABL1(IS) <0.0032%), was 61% for patients treated with 300 mg twice daily of nilotinib compared with 39% for those managed on imatinib in ENESTnd.¹ This also translated into superior rates of TFR eligibility by 10 years with nilotinib compared with imatinib (49% v 30%, respectively).¹ However, the biggest drawback of nilotinib is the associated cardiovascular risk which is a major complication of therapy, and given that TKI therapy may be required for decades, this is a significant consideration when selecting nilotinib. The 10-year rate of cardiovascular events with 300 mg twice daily of nilotinib was 11%, whereas it was only 4% with imatinib (Table 3).¹ Alarming, the rate for patients older than 60 years was 35% over the 10-year follow-up compared with 8.5% on imatinib.

Dasatinib, another 2G-TKI, is usually prescribed as a once daily dose of 100 mg with no specific administration instruction and certainly has increased potency compared with imatinib.² The 5-year rate of MR4.5 was 42% with 100 mg once daily of dasatinib compared with 33% with imatinib.² As with nilotinib, dasatinib is not only associated with improved progression-free survival (PFS) compared with imatinib but also associated with serious toxicities which are predominantly pulmonary (Table 3).² The risk of pleural effusion was approximately 8% within the first year of dasatinib therapy and cumulatively increased to 26% by 5 years, whereas <1% of imatinib-treated patients developed pleural effusions.² The risk of pleural effusion is substantially higher in older patients. The more serious concern though is that of

pulmonary arterial hypertension which has a 5% incidence by 5 years of dasatinib compared with <1% with imatinib.² However, the effusion risk appears to be dose-related as dose modification post-therapeutic drug monitoring led to a lower frequency of pleural effusions.¹² These data were further corroborated by MD Anderson investigators who demonstrated that the risk of effusion was 5% with 50 mg once daily dasatinib compared with 21% in 100 mg once daily dasatinib while also achieving equivalent molecular responses.¹³ With regard to cardiovascular toxicity, however, the risk associated with dasatinib is less well defined. The numerical 5-year risk appeared to be lower in DASISION compared with the 5-year risk associated with nilotinib in ENESTnd, but the incidence rates per 100 years calculated by the MD Anderson actually appear to be similar.¹⁴

Finally, bosutinib, which is also available as frontline therapy in some regions of the world, is another 2G-TKI with superior efficacy to imatinib. While cardiovascular events were infrequently observed with bosutinib,¹⁵ the incidence of GI toxicity was substantially higher than that observed on imatinib therapy (Table 3). Diarrhea was observed in 68% of bosutinib-treated patients, whereas it was only 21% in patients treated with imatinib.¹⁶ Similar to the other 2G-TKIs, bosutinib had superior rates of major molecular response (MMR) and DMR compared with imatinib.

Despite the superiority of 2G-TKIs in terms of DMR and lower rates of blastic transformation, this did not translate into improved OS (Table 1) compared with imatinib in the early studies (ENESTnd,¹ DASISION,² BELA¹⁶). This might have partially been driven by the rates of serious adverse events associated with the more potent TKIs. However, while we know how the 2G-TKIs compare against a first-generation TKI (ie, imatinib), there have been limited data on how they truly compare with each other in a clinical trial situation. The first study to compare two 2G-TKIs head-to-head was the Japanese trial comparing dasatinib with nilotinib.¹⁷ The primary end point of MR4.5 at 18 months was 32.6% with nilotinib and 30.8% with dasatinib.¹⁷ In fact, virtually, all the molecular targets were achieved at nearly identical rates with these two drugs. This raises the interesting possibility that 2G-TKIs are achieving maximal inhibition of BCR::ABL1 kinase activity and that we have reached a ceiling of response which can only be improved upon by targeting additional pathways. From a practical perspective though, this means that selection of a 2G-TKI can largely be based on the question of tolerability and toxicity. Interestingly, in the Japanese study, the rates of discontinuation for adverse events were also very similar (nilotinib discontinuation: 33% v dasatinib discontinuation: 35%).¹⁷ It is only when looking at specific toxicities that differences emerge. As predicted, pleural effusions were seen in patients on dasatinib (grade 3 to 4 4.9%) and not observed on nilotinib.¹⁷ Conversely, liver toxicity and elevated lipase were more common with nilotinib.¹⁷ Cardiovascular toxicity was only infrequently observed in this study, which does not really assist in differentiating between the two 2G-TKIs.

TABLE 1. CML-Related Versus Non-CML-Related Deaths in ENESTnd¹ and DASISION²

Deaths	ENESTnd-IM Cohort, %	ENESTnd-NIL Cohort, %	DASISION-IM Cohort, %	DASISION-DAS Cohort, %
Total	10.2	11.3	10.0	10.0
CML-related	4.9	2.4	6.6	3.4
Non-CML-related	5.3	8.9	3.4	6.6

NOTE. Data from ENESTnd are from the 10-year outcome analysis, whereas data from DASISION are from the 5-year analysis. Abbreviations: CML, chronic myeloid leukemia; DAS, dasatinib; IM, imatinib; NIL, nilotinib.

There have recently been several studies investigating the use of 2G-TKIs at reduced dose in the frontline setting, predominantly using dasatinib. Most notably, the Phase II MD Anderson study of dasatinib 50 mg/day, described earlier, showed surprisingly good molecular responses and better tolerability than full-dose dasatinib.¹³ More importantly, the rates of pleural effusion were lower and patients were able to achieve DMR successfully despite the lower TKI dose. Similarly, the French/Canadian OPTIM-dasatinib study was also able to demonstrate comparable molecular outcomes despite dose modification of dasatinib based on therapeutic drug monitoring.¹² All patients commenced 100 mg once daily of dasatinib and underwent therapeutic drug monitoring. Of the 80 patients with elevated dasatinib drug levels, patients were randomly assigned to continue on 100 mg once daily of dasatinib versus dose modification.¹² The 12-month cumulative incidence of pleural effusions in the dose-modified cohort was 4% compared with 15% in the 100 mg once daily dasatinib ($P = .009$). There was also no statistical difference in the molecular response rates observed between the groups at 12 and 36 months, confirming that dose-modified dasatinib is not only safe but also efficacious. Similarly, the Australian CML12 (DIRECT) study,¹⁸ reported in abstract form, confirmed the OPTIM results, with

interim analysis of DIRECT demonstrating no difference in molecular outcomes with dose reduction of dasatinib. Other studies have supported these findings including the Japanese DAVLEC study which commenced older patients (age >70 years) on 20 mg once daily of dasatinib with the potential to increase the dose in the event of inadequate response assuming no significant toxicity.¹⁹ While a larger validation study is required, DAVLEC did enable 60% of patients to achieve an MMR ($BCR::ABL1 < 0.1\%$ IS) by 12 months, which is actually superior to the 12-month results from DASISION where the 12-month MMR rate with dasatinib 100 mg once daily was 46%.¹⁹ These surprising results may be related to improved tolerability, enabling more consistent administration of TKI. However, there are limited data regarding the use of low-dose dasatinib in the high-risk ELTS setting, and so this dose may be inadequate in truly high-risk patients. Moreover, while the rates of pleural effusion are lower with low-dose dasatinib compared with full doses,¹³ drug-induced pleural effusions remain a significant issue in the elderly, with real-world reports from Italy suggesting that it is almost 20% within the first 3–6 months of therapy, although many of these patients were started on 100 mg once daily of dasatinib.²⁰ An alternative strategy is being tested in the DASHit trial where newly diagnosed patients were randomly assigned

TABLE 2. Transformation Rates in CP-CML in Patients Being Treated With Frontline TKIs

Clinical Trial (follow-up time)	Frontline TKI (dose)				
	Imatinib	Nilotinib	Dasatinib	Bosutinib	Asciminib
IRIS ³ (10 years)	7% (400 mg once daily)				
TOPS ⁶ (42 months)	4.5% (400 mg once daily) 2.5% (800 mg total daily dose)				
CML-IV ⁷ (10 years)	6% (400 mg once daily) 5% (800 mg total daily dose)				
TIDEL-II ⁸ (40 months)	3.5% (600 mg)				
ENESTnd ¹ (10 years)	8.5% (400 mg once daily)	4% (300 mg twice daily) 2% (400 mg twice daily)			
ENESTfirst (24 months)		0.6% (300 mg twice daily)			
DASISION ² (5 years)	7% (400 mg once daily)		5% (100 mg once daily)		
BFORE ⁹ (5 years)	3% (400 mg once daily)			2% (400 mg once daily)	
ASCEND ¹⁰ (21 months)					1% (80 mg total daily dose)
ASC4First ¹¹ (16 months)	3% (400 mg once daily)		1% (2G-TKI cohort)		1% (80 mg total daily dose)

Abbreviations: 2G, second-generation; CML, chronic myeloid leukemia; CP, chronic phase; TKI, tyrosine kinase inhibitor.

TABLE 3. Notable Toxicities Associated With the Various Frontline TKI Options in Chronic Phase Chronic Myeloid Leukemia

TKI	Conventional Dosing	Common Toxicity	Optimal Patient
Imatinib	400 mg once daily	Peripheral and periorbital edema GI toxicities such as nausea, vomiting, and diarrhea	Older or multimorbid patient Low-risk ELTS
Dasatinib	100 mg once daily	Cytopenias Pleural effusions Pulmonary hypertension	Younger patient, highly motivated for TFR Higher-risk ELTS
Nilotinib	300 mg twice daily	Hypertension Hypercholesterolaemia Pancreatitis Type 2 diabetes Arterio-occlusive events including cardiovascular disease, peripheral vascular events, and cerebrovascular events	Younger patient without cardiovascular risk factors or history, highly motivated for TFR Higher-risk ELTS
Bosutinib	400 mg once daily	Pancreatitis GI toxicities such as nausea, vomiting, and diarrhea	
Asciminib	80 mg once daily	Pancreatitis	Older multimorbid patients, highly motivated for TFR Higher-risk ELTS

Abbreviations: ELTS, EUTOS long-term survival; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

to dasatinib 100 mg per day versus dasatinib 100 mg/day for 5 days per week with the weekend off. Early results suggest equivalent molecular response and improved tolerability.²¹

Ponatinib, a third-generation TKI, is generally not available in the frontline, but there are some data worth reviewing including the EPIC study,²² where ponatinib 45 mg once daily was compared with imatinib 400 mg once daily in patients with newly diagnosed CP-CML. Unfortunately, the trial was prematurely terminated because of increased arterio-occlusive events observed in the other ponatinib studies (Table 3). At trial termination, the median follow-up for patients was 5 months and very few patients reached 12 months on the study. For the few assessable patients, 80% of the ponatinib-treated patients (n = 8 of 10) achieved MMR by 12 months, whereas only 38% of the imatinib group (n = 5 of 13) reached the same milestone. However, it is difficult to interpret the molecular data with any great confidence given the short follow-up and the low patient numbers. Importantly though, 7% of the ponatinib patients developed an arterio-occlusive event compared with only 2% in the imatinib cohort by the end of follow-up.²² The MD Anderson also conducted a frontline ponatinib study in 51 patients with CP-CML, which investigated 30–45 mg once daily of ponatinib.²³ The median duration of ponatinib therapy was 13 months with the rates of 12-month MMR, MR₄, and MR_{4.5} being 81%, 68%, and 55% respectively. Serious cardiovascular events were observed in 16% of patients.²³

While ponatinib is clearly superior to imatinib in achieving faster and deeper molecular responses, the arterio-occlusive risk argues against the wider use of ponatinib.²² The French TIPI trial, reported in abstract form, is, however, a novel strategy being investigated for frontline ponatinib therapy.²⁴

After an initial 6 months of treatment with ponatinib 30 mg daily, patients were switched to 400 mg once daily of imatinib.²⁴ At 6 months, the cumulative incidence of MMR was 44%, which increased to 66% by 12 months.²⁴ Regarding the rates of DMR in anticipation of potential TFR, the 12-month MR₄ rate was 33%.²⁴ There were no serious cardiovascular events reported by the 18-month follow-up, but there was a single sudden death at month 2.5 of the study.²⁴ Given the unavoidable toxicity of ponatinib and the excellent other options available, ponatinib is not currently considered a suitable TKI to be considered as frontline therapy in standard clinical practice.

THREE BROAD TREATMENT STRATEGIES

The overall strategies for TKI selection for each patient with CP-CML can be considered as follows:

1. Use the best drug from the start to minimize the need to switch for treatment failure or intolerance, reduce the risk of progression to blast crisis, and maximize the prospect of TFR;
2. Use imatinib first and save the more potent drugs for those who need them—for either intolerance or resistance; or
3. Use the best drug first and switch to the safest/cheapest drug once a safe haven is achieved.

Strategies 2 and 3 may be justified based on the lower overall cost and may also reduce the total burden of organ toxicities associated with 2G-TKI, particularly when used in the long term. Perhaps the best test of the relative merits of strategies 1 and 2 is the Italian SUSTENIM trial (interim analysis reported in abstract form).²⁵ In this Italian trial, nilotinib is compared head to head with imatinib with early switch to nilotinib where there is a nonoptimal molecular response.²⁵

The primary end point of MR4.5 at 24 months was achieved by 18% who started on imatinib versus 29.4% in those on nilotinib from the outset, suggesting that the salvage approach was not as effective if achievement of DMR was a goal of therapy.²⁵ The nilotinib arm also showed a higher rate of transformation-free survival and OS—the first time any 2G-TKI has shown an improvement in survival, albeit a modest improvement.

The third strategy has some advocates since it only uses the more expensive and possibly more toxic TKI for a relatively short period in most cases. The argument here is that the more potent drug minimizes the risk of transformation and is only continued long term where molecular response remains in the nonoptimal range. However, the relative effectiveness of this approach is still unproven, awaiting final reports from studies including TIPI²⁴ and the New Zealand KISS trials.²⁶

While option 1 may be the costliest in the early years of patient treatment, maximizing the initial molecular responses to ideally reach TFR eligibility more rapidly has longer-term benefits including improved financial burden associated with long-term TKI supply and the toxicity burden associated with lengthy TKI treatment (Fig 1). The lower rate of achievement of eligibility for TFR with imatinib likely translates into less patients achieving TFR, at least over the first 10–15 years. This results in more patients requiring ongoing TKI therapy relative to those commenced on 2G-TKI from the outset. In the most comprehensive long-term trial, ENESTnd, the rate of TFR eligibility after 10 years of therapy was around 30% for imatinib compared with 50% for nilotinib.¹ The financial burden of more potent TKIs is particularly relevant in countries where the patient faces the full or partial cost given the availability of generic imatinib although some of the 2G-TKIs are also entering generic production.²⁹ In the United States, third-party payer coverage is a key determinant of frontline choice.

STAMP INHIBITORS—A NEW ERA IN CML THERAPY?

In recent years, the development of investigative agents targeting the myristoyl site of ABL1, replicating the N-terminus controller, has introduced a new wave of potential TKIs to the therapeutic landscape. Asciminib is the first-in-class Specifically Targeting the ABL Myristoyl Pocket (STAMP) inhibitor and has been investigated in the frontline setting as monotherapy in two key trials, ASC4-First¹¹ and the Australasian CML13/ASCEND¹⁰ study. In ASC4First, asciminib had superior rates of MMR at 48 weeks compared with imatinib (69% v 40%, respectively, $P < .001$). The MMR rates for asciminib and 2G TKIs were similar at 48 weeks,¹¹ but a recent update suggested that, with further follow-up, asciminib MMR rates were superior to both imatinib and 2G-TKIs.³⁰ Asciminib is better tolerated, with markedly lower rates of discontinuation for adverse events and less GI and hepatic toxicity (Table 3). Arterio-occlusive events occurred in 1% of asciminib-treated patients by the

Low Priority for TFR

Optimal TKI	Low ELTS	Intermediate ELTS	High ELTS
High CVS risk	1. Imatinib 2. Asciminib 3. Modified-dose 2G-TKI	1. Imatinib 2. Asciminib 3. Modified-dose 2G-TKI	1. Asciminib 2. Modified-dose 2G-TKI 3. Imatinib
Intermediate CVS risk	1. Imatinib 2. Asciminib 3. Modified-dose 2G-TKI	1. Asciminib 2. Modified-dose 2G-TKI 3. Imatinib	1. Asciminib 2. 2G-TKI 3. Imatinib
Low CVS risk	1. Asciminib 2. Imatinib 3. Modified-dose 2G-TKI	1. Asciminib 2. Modified-dose 2G-TKI 3. Imatinib	1. Asciminib 2. 2G-TKI 3. Imatinib

High Priority for TFR

Optimal TKI	Low ELTS	Intermediate ELTS	High ELTS
High CVS risk	1. Asciminib 2. Modified-dose 2G-TKI	1. Asciminib 2. Modified-dose 2G-TKI	1. Asciminib 2. 2G-TKI
Intermediate CVS risk	1. Asciminib 2. Modified-dose 2G-TKI	1. Asciminib 2. Modified-dose 2G-TKI	1. Asciminib 2. 2G-TKI
Low CVS risk	1. Asciminib 2. 2G-TKI	1. Asciminib 2. 2G-TKI	1. Asciminib 2. 2G-TKI

FIG 1. Choosing the optimal TKI for each patient depends on many factors. Three factors are fundamental: CVS risk profile, ELTS risk score, and priority for TFR.^{27,28} This figure illustrates how the authors would rank their preferred TKI in each of these subgroups. Where the number 1 choice is not available or contraindicated because of a specific comorbidity, the next option would be preferred. Where 2G-TKI is indicated, this means that any of the TKIs dasatinib, nilotinib, or bosutinib can be selected depending on other variables (Table 3). Where modified-dose 2G-TKI is indicated, it would be theoretically possible to select any 2G-TKI at reduced dose, but the data currently available only support dasatinib as a reduced dose daily or standard dose given 5 days per week. We have not recommended modified-dose 2G-TKI in cases of high ELTS as there are very limited data to support this. We do not recommend full-dose 2G-TKI (bosutinib may be an exception here) in patients with high CVS risk except in cases with a high ELTS score where the higher risk of a vascular event needs to be weighed against the higher risk of blast phase transformation. 2G, second generation; CVS, cardiovascular; ELTS, EUTOS long-term survival; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

end of the follow-up period compared with 2% of 2G-TKI patients and none of the imatinib-treated cohort. The Australasian ASCEND study had similar results to ASC4First, with 79% of patients achieving MMR by 12 months while also demonstrating asciminib's ability to achieve DMR, with the 24-month MR4.5 rate being 53%.¹⁰ These studies demonstrate the efficacy and tolerability of asciminib compared with other TKIs in the frontline setting, but more long-term data are required. The overall rate of treatment failure was low for asciminib in both studies, but the rate of emergent BCR::ABL1 mutations appeared to be higher for asciminib compared with the other arms. In the ASCEND-CML study,

nearly all the patients who developed BCR::ABL1 mutations were found to have *ASXL1* mutations at diagnosis, raising the possibility that *ASXL1* patients may warrant a different frontline approach, but this needs further investigation.³¹ In most cases, the emergent mutations will be responsive to another TKI, particularly in the case of myristoyl site mutations which are fully sensitive to all the TKIs except other STAMP inhibitors.

ELTS RISK SCORE

The ELTS score, developed in the TKI era, has replaced the original prognostic scoring system, the Sokal score, because of increased accuracy in discriminating higher-risk patients.³² The development and validation study in almost 3,000 imatinib-treated patients demonstrated that the ELTS score identified 14% of the cohort as high-risk, whereas 24% of the same cohort was deemed high-risk by the Sokal score.³² The 6-year risk of CML-related death in the high-risk ELTS group was 15% compared with 9% in the high-risk Sokal cohort.³² It has become generally accepted that the lower rates of blast crisis observed with 2G-TKIs compared with imatinib make 2G-TKIs a better frontline choice in most patients in this high-risk group.

This might suggest that patients with low ELTS scores have little to gain from taking more potent TKIs frontline. However, data from the SUSTRENIM study suggest that the greatest benefit in terms of achievement of MR4 was seen in the low ELTS risk cohort. MR4 achievement for nilotinib and imatinib arms was 82% and 47%, respectively, in this low-risk group ($P < .001$).²⁵

OTHER HIGH-RISK INDICATORS

The effect of ACAs in the TKI era has been somewhat controversial. More recent data from the German CML IV trial demonstrate inferior survival probabilities in imatinib-treated patients with high-risk genetic events at diagnosis compared with those with low-risk abnormalities.^{33,34} High-risk ACAs based on cytogenetics include +8, +Ph, i(17q), +19, +17, +21, complex aberrant karyotypes, -7/7q-, 3q26.2, and 11q23 abnormalities. Dutch data also confirmed inferior PFS and OS in patients with high-risk ACAs.³⁵ Corroborating data from the MD Anderson demonstrated that specific high-risk cytogenetic abnormalities including i(17q), -7/7q- and 3q26 rearrangements present at diagnosis result in dismal cytogenetic responses and MMR rates in TKI-treated patients.³⁶ While it is unclear whether more potent TKIs truly alter the clinical outcome in patients with high-risk ACA, these results suggest that it would be prudent to avoid imatinib in these patients if comorbidities permit.

The swift adoption of next-generation sequencing (NGS) has enabled rapid expansion of genomic information in malignancies including CML. Patients with NGS-detectable additional genetic abnormalities, including variants affecting known cancer genes and aberrant arrangements associated

with the Philadelphia translocation, have inferior failure-free survival and molecular outcomes if treated with imatinib.³⁷ Interim data suggest that more potent TKIs (including 2G-TKIs and asciminib) negate the impact of the Philadelphia-associated rearrangements observed with imatinib although the cancer-associated gene variants remain an inferior prognostic marker.³¹ More importantly, *ASXL1* variants at diagnosis seem to be the primary driver of poor outcomes even in patients treated with more potent TKIs.³¹ Strategies to overcome the inferior outcomes associated with *ASXL1* and other cancer gene variants are currently being investigated in the Australasian CML14/ASCENDance study which combines asciminib with low-dose dasatinib in patients with cancer gene variants or high-risk ACAs.

TFR—HOW DOES IT AFFECT THE TKI CHOICE?

Most patients are highly motivated to achieve TFR as quickly as possible, as long as it is safe. Rates of long-term TFR achievement on imatinib are still below 30% in most reports.^{38,39} Longer-term data from patients attempting TFR with 2G-TKIs are lacking, but the higher rates of sustained DMR coupled with high early rates of TFR achievement^{40–42} provide hope that more patients will achieve long-term TFR on 2G-TKI therapy. Moreover, patients are reaching TFR eligibility with shorter durations of TKI exposure when treated with 2G-TKIs, which is an added benefit. The current asciminib frontline studies all have TFR extensions that will hopefully provide further clarity regarding how many more patients can achieve TFR with this new approach.

PEDIATRIC APPROACH TO FRONTLINE THERAPY

CML is rare in children, accounting for 2%–4% of all pediatric leukemias. The annual incidence is 1–2 per 1,000,000 in people younger than 20 years,⁴³ mostly occurring in older children and adolescents.⁴⁴ Given its rarity, management recommendations are derived from smaller, single-arm clinical trials and adult guidelines, despite evidence that disease biology and clinical presentation may differ in children.^{45–47} The I-CML-Ped Registry, which has recruited 718 children from 17 countries (F. Millot, personal communication, March 2025), has helped elucidate these unique features.

Imatinib and the 2G-TKIs are all reasonable treatment options for children with newly diagnosed CML. After the Children's Oncology Group phase I study demonstrating that imatinib doses of 260 and 340 mg/m² once daily were equivalent to adult once daily doses of 400 and 600 mg, respectively,⁴⁸ the French Phase IV imatinib study (using 260 mg/m²),⁴⁹ European CML-Paed II study (using 300 mg/m² once daily),⁵⁰ and Italian CML-Petit-01 study (using 340 mg/m² once daily)⁵¹ confirmed imatinib's efficacy in children. Outcomes were similar to those reported in adults (Table 4). In addition to the common toxicities described in adults, 20%–47% of children exhibited a slowing of vertical growth.^{49,50} Several studies suggested

TABLE 4. Summary of Pediatric Studies in Chronic Myeloid Leukemia

Characteristics	Imatinib			Nilotinib	Dasatinib
	Millot et al ⁴⁹	Suttorp et al ⁵⁰	Giona et al ⁵¹	Hijiya ^{52,53}	Gore ⁵⁴
Dose, mg/m ² total daily dose	260	300	340	230	60 (tablets) 72 (PFOS)
Sample size	44	148 (140 chronic phase)	47	25	84
Median age, years (range)	11.5 (0.8-17)	13.2 (1.3-18)	11.8 (2.8-17.9)	13 (10-16)	12.3 (1.8-17.8)
CCyR at 12 months, %	61	63	96	84	92
MMR, %					
12 months	31	42	66	64	52
18 months	55	59	Approximately 82	68	65
24 months	60	69	Approximately 82	68	70
Progression-free survival	98% at 31 months	97% at 18 months	60% at 10 years	91.6% at 66 months	93% at 48 months
Overall survival, %	97.7	94.1	100	81.6	100
Toxicity, %					
Any adverse events	100	66		100	82
Grade 3/4 adverse events	45	36		72	38
Common toxicities	Neutropenia 88% (27% grade 3/4) Thrombocytopenia 32% Anemia 23% Cramps 34% Myalgia 32% (5% grade 3/4) Arthralgia 23% Nausea 29% Diarrhea 20% Fatigue 16%	Anemia 66% Neutropenia 49% (15% grade 3/4) Thrombocytopenia 27% Nausea 37% Diarrhea 9% Cramps/bone or joint pain 28% Infection 26%	Neutropenia 24% Thrombocytopenia 22% Arthralgia/myalgia 20% ↓ Bone density 19% Anemia 4% Nausea/vomiting 4% Abdominal pain 4%	↑ Bilirubin 53% Headache 47% Pyrexia 38% ↑ ALT 36%	Nausea/vomiting 20% Rash 19% Diarrhea 18% Fatigue 11%
Temporary interruption	25	18	9	80	10
Permanent cessation, %					
Total	30	47	47	40	27
Lack of efficacy	20	21	16	12	7
Intolerant	4.5	6	13	24	1
Other	4.5	20	18	4	19
Growth impairment	20%	47.2%	22%	25% crossed ≥2 percentile lines	2%

Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; PFOS, powder for oral suspension.

that growth deceleration was more pronounced in prepubertal patients although a meta-analysis did not confirm this.⁵⁵ Furthermore, the impact of imatinib on height only

reached significance in studies with follow-up <3 years, prompting the authors to cautiously suggest that it may be a short-term effect.

2-3 BOXED CLINICAL SCENARIOS

CASE 1: 78-year-old man with recent onset peripheral vascular disease and poorly controlled diabetes with low ELTS score.

In this setting, the main goals would be to avoid transformation and to avoid toxicity, particularly worsening of his vascular disease and increasing the risk of arterial vascular events (AOEs; [Table 5](#)). The priority for TFR is relatively low because of the limited life expectancy. Full-dose nilotinib would be a poor choice given the high risk of AOEs in this setting. Similarly, full-dose dasatinib would lead to a high risk of pleural effusions and a significant risk of AOEs and should ideally be avoided. Bosutinib would be a reasonable choice given its lower risk of cardiovascular toxicity, but GI toxicity is a significant issue for elderly patients. Reduced-dose dasatinib would be a reasonable choice since particularly in patients with low/intermediate ELTS risk scores, it appears to be as efficacious as full-dose dasatinib and the risk of pleural effusion is substantially lower at this dose. Imatinib would be an excellent choice given the overall safety profile and this patient's low ELTS risk score. Patients with low ELTS risk scores have a very low risk of blast phase transformation. In regions where asciminib is approved and available, it may also be a good option since it has a much higher probability of achieving MMR than imatinib and a better tolerability profile. However, there is some evidence of a higher rate of AOEs with asciminib compared with imatinib based on the ASC4FIRST study, which is consistent with the findings in ASCEMBL.

Our recommendation: First preference is imatinib, but consider reduced-dose dasatinib.

CASE 2: 21-year-old female elite swimmer with high ELTS risk score and no comorbidities who may want to start a family in 5-10 years.

Imatinib would be a less favored choice given the high priority for TFR to be achieved as soon as possible and the high ELTS risk score. The risk of death secondary to disease progression after frontline imatinib in patients categorized as high ELTS risk was 15% at 6 years.³² Based on the 10-year ENESTnd data, transformation-free survival for high-risk patients was 90.3% with nilotinib 300 mg twice a day versus 80.9% with imatinib. In addition, there would only be an approximately 30% probability of TFR eligibility after 10 years of imatinib compared with 49% for nilotinib 300 mg twice a day.¹ One of the second-generation TKIs (2G-TKIs) or asciminib would be preferred. They have all demonstrated superior efficacy to imatinib in this setting. The tolerability profile of asciminib would make it a good choice for this patient—particularly, the much lower incidence of GI toxicity. Rates and severity of fatigue may be similar across all the TKIs, however, which may still limit her capacity to swim competitively at the elite level. Reduced-dose dasatinib has not been adequately assessed in the high-risk ELTS setting.

Our recommendation: First preference would be asciminib after confirming that the BCR::ABL1 transcript includes ABL exon 2. If not available locally, or the cost is an unreasonable burden, any full-dose 2G-TKI would be preferred with the possibility of reducing the dose once optimal molecular response is achieved.

CASE 3: 11-year-old male school student with high ELTS risk score. He is otherwise well and is a keen football player.

Needing to avoid food 2 hours before and 1 hour after nilotinib, and its twice-daily dosing creates practical difficulties for young patients attempting to schedule meals before and after school. This requirement may be particularly challenging with the increased appetite and more frequent snacking associated with the adolescent growth spurt, as well as the social role of eating together with friends (often at inconsistent times) during adolescence and young adulthood. These inconveniences may increase the risk of suboptimal adherence. This boy's high ELTS score (which is the only scoring system predicting progression-free survival in children)⁶⁴ may prompt use of a 2G-TKI to achieve a deeper remission at an earlier time point. Achievement of MR4.5 should be the goal as this may allow an attempt at discontinuation, coinciding with the age that this patient may be considering fathering children. The toxicity rates of imatinib and dasatinib are similar, but the cramps and musculoskeletal side effects of imatinib may limit this patient's football participation and hence increase his risk of poor adherence. Frequent, nonjudgmental discussions about barriers and enablers of adherence are worthwhile. Growth and pubertal development should be monitored carefully, along with thyroid function.

Our recommendation: First preference would be dasatinib. If access or cost was a barrier, imatinib would be a very good option.

TABLE 5. Selecting the Best Second-Generation Tyrosine Kinase Inhibitor

Characteristic	Nilotinib	Dasatinib	Bosutinib
Work schedule makes fasting and/or twice daily dosing difficult	–	+++	++
History of liver disease	–	++	++
History of CVS disease	–	+	++
GI disease	++	+	+
Pancreatitis	–	++	?
Pulmonary disease	++	–	++
QT prolongation	–	++	++

NOTE. Number of + indicates recommendation level, – indicates less optimal option.

Abbreviation: CVS, cardiovascular disease.

No randomized studies comparing 2G-TKIs with imatinib have been conducted in children. Phase II studies of dasatinib and nilotinib in newly diagnosed children have demonstrated deeper responses at 12 months than historical imatinib results, but MMR rates appear to be similar by 18–24 months^{52–54,56} (Table 4). The overall frequency of toxicities and the proportion ceasing 2G-TKIs were also comparable with imatinib. While children share some common 2G-TKI toxicities with adults, there are notable differences. For example, dasatinib-associated pleural/pericardial effusions and pulmonary artery hypertension are very uncommon in children,^{52,57} with no cases in the phase II study. Long-term follow-up of the phase II pediatric nilotinib study identified no cardiovascular events or grade 3/4 hyperglycemia. However, given that many children will continue to take these drugs for decades, it remains to be seen whether these toxicities may emerge during adulthood. Growth deceleration has been observed with both nilotinib and dasatinib.^{53,54,58}

Pediatric studies of bosutinib, ponatinib, and asciminib have been limited to children who are resistant or intolerant to other TKIs.^{59–61} In that setting, bosutinib demonstrated comparable efficacy with other 2G-TKIs, with diarrhea being a common toxicity.⁵⁹ Ponatinib has not been associated with vascular complications in children,⁶⁰ but there have been no phase II studies in pediatric CML. The interim report of the pediatric phase I study of asciminib has not identified any new safety signals in the nine enrolled children, with all remaining on drug at data cutoff.⁶¹ Currently, none of these agents are recommended for frontline management of pediatric CML.

Similar to adult practice, attainment of TFR is an increasingly important goal in pediatric CML. Several groups have demonstrated the feasibility of this approach in children, with the largest studies from Japan (N = 22) and India (N = 45) reporting successful TFR in 50% and 71%.^{62,63} All discontinuation failures occurred within the first 4–6 months, and

all reattained MMR after resuming TKI. As yet, it is unclear whether frontline 2G-TKIs will enable earlier discontinuation attempts in children.

While long-term outcomes appear to be comparable between imatinib, dasatinib, and nilotinib, some experts advocate using 2G-TKIs for children with high ELTS scores because of their earlier deeper responses.⁶⁴ In practice, the choice of TKI is usually determined by cost, access, ease of administration, and side effect profile.⁶⁵ Generic imatinib remains the most cost-effective option, and many lower-income countries have difficulty in accessing 2G-TKIs.⁶⁶ The requirement to avoid food before and after nilotinib and its twice-daily schedule create practical challenges for many young patients. This is an important consideration as complex dosing schedules have been associated with poorer adherence (drug compliance) in adolescents in other settings. While all three TKIs have similar toxicity rates in clinical trials, fatigue, GI, and musculoskeletal side effects (more pronounced with imatinib) can significantly affect quality of life, which may also affect adherence and hence the chance of TFR.

CML DIAGNOSIS MADE IN PREGNANCY

This uncommon scenario presents an even more complex challenge. Treatment with a TKI should ideally start as soon as possible after the diagnosis of CP-CML is made since the risk of blastic transformation is highest while the CML is untreated. However, TKIs are not recommended during pregnancy, especially in the first trimester, because of the higher risk of fetal malformations that have been observed in this setting.⁶⁷ This is particularly the case for dasatinib, which is contraindicated in any stage of pregnancy.⁶⁸ Hydroxyurea is sometimes used for disease control in pregnancy although alternative treatments like interferon alpha may be considered safer to induce and maintain hematologic remission. With the advent of pegylated interferon formulations, these medications require less frequent administration with improved tolerability.

Recent studies have suggested that TKI usage in the third trimester may represent an acceptable risk to the fetus.⁶⁹ Ultimately, the mother will be the one to decide where the best pathway lies here in terms of balancing the interests of the mother and the baby in different directions according to the decisions made.

When counseling the patient, it is helpful to indicate that the risk of blast transformation if CML is left untreated for 9–12 months is real but likely relatively low. The ELTS score would have some relevance here. In a patient with high-risk ELTS or other high-risk features who is diagnosed early in pregnancy, a termination may be the preferred option. At the other extreme, a patient with low-risk CML who is diagnosed with CP-CML in the third trimester would have a very low risk of transformation if therapy was delayed by 3–4 months.

CONCLUSIONS

Selection of best frontline therapy became more complex when several 2G TKIs were approved in this setting. The recent approval in the United States and elsewhere of asciminib for frontline therapy has been a great step forward for patients, but has made selection of optimal therapy even harder in many cases. Where the cost of drugs is not a major issue, asciminib would arguably be the best choice for most adult patients. If a patient was being considered for imatinib, the markedly higher rate of molecular response and consequent greater prospect of TFR would make asciminib a more attractive option. Added to that would be the much better tolerability of asciminib compared with imatinib. If the clinician was considering a 2G-TKI, the potential advantage of asciminib would be the better tolerability profile and arguably greater safety. In addition, the most recent analysis of the ASC4First trial suggests that molecular response (MMR and MR₄) may be superior for asciminib compared with 2G TKIs.³⁰ Examples where asciminib would not be the best frontline choice include frail elderly patients with high cardiovascular risk where imatinib might be safer,

patients with the rare BCR::ABL1 transcript which does not include ABL exon 2 (e13a3 or e14a3) where asciminib would be unable to bind, and patients with thrombocytopenia at baseline where imatinib may be preferred.

To further complicate the situation, low-dose 2G-TKI (in particular dasatinib) may offer a similar profile of efficacy and safety as asciminib at a considerably lower cost, particularly if the 2G-TKI is generic. We need randomized trials comparing lower-dose 2G-TKIs with asciminib (and later, other STAMP inhibitors) before we can make a more evidence-based choice here. In high-risk cases, it is likely that we will need new therapeutic strategies to improve outcomes, including combining ATP-competitive TKIs with STAMP inhibitors and combinations targeting pathways in addition to BCR::ABL1.

In the rare case of childhood CML, imatinib, dasatinib, and nilotinib are all reasonable frontline treatment options. Efforts to optimize adherence and consideration of how the specific side effects of each drug may affect the young person's lifestyle and quality of life are critical given that many are likely to require treatment for decades.

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REFERENCES

- Kantarjian HM, Hughes TP, Larson RA, et al: Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia* 35:440-453, 2021
- Cortes JE, Saglio G, Kantarjian HM, et al: Final 5-year study results of DASISION: The dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. *J Clin Oncol* 34:2333-2340, 2016
- Hochhaus A, Larson RA, Guilhot F, et al: Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med* 376:917-927, 2017
- O'Brien SG, Guilhot F, Larson RA, et al: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 348:994-1004, 2003
- Efficace F, Baccarani M, Breccia M, et al: Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. *Blood* 118:4554-4560, 2011
- Baccarani M, Druker BJ, Branford S, et al: Long-term response to imatinib is not affected by the initial dose in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: Final update from the Tyrosine kinase inhibitor Optimization and Selectivity (TOPS) study. *Int J Hematol* 99:616-624, 2014
- Kalmanti L, Saussele S, Laussek M, et al: Safety and efficacy of imatinib in CML over a period of 10 years: Data from the randomized CML-study IV. *Leukemia* 29:1123-1132, 2015
- Yeung DT, Osborn MP, White DL, et al: TIDEL-II: First-line use of imatinib in CML with early switch to nilotinib for failure to achieve time-dependent molecular targets. *Blood* 125:915-923, 2015
- Brümmendorf TH, Cortes JE, Milojkovic D, et al: Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: Final results from the BFORE trial. *Leukemia* 36:1825-1833, 2022
- Yeung D, Shanmuganathan N, Reynolds J, et al: Asciminib monotherapy as frontline treatment of chronic-phase chronic myeloid leukemia: Results from the ASCEND study. *Blood* 144:1993-2001, 2024
- Hochhaus A, Wang J, Kim DW, et al: Asciminib in newly diagnosed chronic myeloid leukemia. *N Engl J Med* 391:885-898, 2024

12. Rousselot P, Mollica L, Guilhot J, et al: Dasatinib dose optimisation based on therapeutic drug monitoring reduces pleural effusion rates in chronic myeloid leukaemia patients. *Br J Haematol* 194: 393-402, 2021
13. Jabbour E, Sasaki K, Haddad FG, et al: Low-dose dasatinib 50 mg/day versus standard-dose dasatinib 100 mg/day as frontline therapy in chronic myeloid leukemia in chronic phase: A propensity score analysis. *Am J Hematol* 97:1413-1418, 2022
14. Jain P, Kantarjian H, Boddu PC, et al: Analysis of cardiovascular and arteriothrombotic adverse events in chronic-phase CML patients after frontline TKIs. *Blood Adv* 3:851-861, 2019
15. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al: Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: Results from the randomized BFORE trial. *J Clin Oncol* 36: 231-237, 2018
16. Cortes JE, Kim DW, Kantarjian HM, et al: Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: Results from the BELA trial. *J Clin Oncol* 30:3486-3492, 2012
17. Matsumura I, Ohtake S, Atsuta Y, et al: Nilotinib vs dasatinib in achieving MR4.5 for de novo chronic myeloid leukemia: the randomized JALSG CML212 study. *Blood Adv* 8:5237-5247, 2024
18. Yeung DT, Grigg A, Shanmuganathan N, et al: Pro-active dasatinib dose reduction based on trough levels may minimise toxicity and preserve efficacy—Interim analysis of the ALLG CML 12 direct study. *Blood* 134:4150, 2019 (suppl 1)
19. Murai K, Ureshino H, Kumagai T, et al: Low-dose dasatinib in older patients with chronic myeloid leukaemia in chronic phase (DAVLEC): A single-arm, multicentre, phase 2 trial. *Lancet Haematol* 8: e902-e911, 2021
20. Latagliata R, Stagno F, Annunziata M, et al: Frontline dasatinib treatment in a "real-life" cohort of patients older than 65 years with chronic myeloid leukemia. *Neoplasia* 18:536-540, 2016
21. La Rosee P, Pfirrmann M, Fabisch C, et al: Improved tolerability with dasatinib 5 days compared to 7 days per week in patients with chronic myeloid leukemia in chronic phase. Final results of the DasaHIT trial. *Oncol Res Treat* 47:124-125, 2024
22. Lipton JH, Chuah C, Guerci-Bresler A, et al: Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: An international, randomised, open-label, phase 3 trial. *Lancet Oncol* 17: 612-621, 2016
23. Haddad FG, Sasaki K, Nasr L, et al: Results of ponatinib as frontline therapy for chronic myeloid leukemia in chronic phase. *Cancer* 130:3344-3352, 2024
24. Nicolini FE, Charbonnier A, Escoffre-Barbe M, et al: 18-months follow-up of the trial of imatinib after ponatinib induction (TIPI) in the front-line treatment of chronic phase (CP) chronic myeloid leukemia (CML) setting. *Blood* 144:478, 2024 (suppl 1)
25. Pane F, Castagnetti F, Piciocchi A, et al: International, prospective study comparing nilotinib versus imatinib with early switch to nilotinib to obtain sustained treatment-free remission in patients with chronic myeloid leukemia (SUSTRENIM trial): Analysis of the eligibility to treatment discontinuation. *Blood* 142:3169, 2023 (suppl 1)
26. Pemberton L, Sharples K, Kim Y, et al: P675: Imatinib therapy in previously untreated chronic myeloid leukaemia patients who achieve MMR after 12 months therapy with dasatinib: A strategy to avoid long term off target toxicity. *Hemasphere* 7:e4174924, 2023
27. Hughes TP, Ross DM: Moving treatment-free remission into mainstream clinical practice in CML. *Blood* 128:17-23, 2016
28. Atallah E, Sweet K: Treatment-free remission: The new goal in CML therapy. *Curr Hematol Malig Rep* 16:433-439, 2021
29. Lyman GH, Henk HJ: Association of generic imatinib availability and pricing with trends in tyrosine kinase inhibitor use in patients with chronic myelogenous leukemia. *JAMA Oncol* 6:1969-1971, 2020
30. Cortes JE, Hochhaus A, Hughes TP, et al: Asciminib (ASC) demonstrates favorable safety and tolerability compared with each investigator-selected tyrosine kinase inhibitor (IS TKI) in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) in the pivotal phase 3 ASC4FIRST study. *Blood* 144:475, 2024 (suppl 1)
31. Shanmuganathan N, Wadham C, Yeung DT, et al: Strong association between cancer gene variants at diagnosis, especially ASXL1, and emergence of kinase domain mutation-driven resistance in CML patients despite frontline treatment with more potent BCR:ABL1 inhibitors. *Blood* 144:991, 2024 (suppl 1)
32. Pfirrmann M, Clark RE, Prejzner W, et al: The EUTOS long-term survival (ELTS) score is superior to the Sokal score for predicting survival in chronic myeloid leukemia. *Leukemia* 34:2138-2149, 2020
33. Hehlmann R, Voskanyan A, Lauseker M, et al: High-risk additional chromosomal abnormalities at low blast counts herald death by CML. *Leukemia* 34:2074-2086, 2020
34. Hehlmann R, Lauseker M, Voskanyan A, et al: Impact of emerging ACA on survival in chronic myeloid leukemia (CML). *Leukemia* 36:2544-2547, 2022
35. Kockerols CCB, Geelen IGP, Levin M-D, et al: High-risk additional cytogenetic aberrations in a Dutch chronic phase chronic myeloid leukemia patient population. *Haematologica* 108:3156-3159, 2023
36. Wang W, Cortes JE, Tang G, et al: Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. *Blood* 127:2742-2750, 2016
37. Shanmuganathan N, Wadham C, Shahrin N, et al: Impact of additional genetic abnormalities at diagnosis of chronic myeloid leukemia for first-line imatinib-treated patients receiving proactive treatment intervention. *Haematologica* 108:2380-2395, 2023
38. Ross DM, Pagani IS, Shanmuganathan N, et al: Long-term treatment-free remission of chronic myeloid leukemia with falling levels of residual leukemic cells. *Leukemia* 32:2572-2579, 2018
39. Etienne G, Guilhot J, Rea D, et al: Long-term follow-up of the French Stop imatinib (STIM1) study in patients with chronic myeloid leukemia. *J Clin Oncol* 35:298-305, 2017
40. Takahashi N, Nishiaki K, Nakaseko C, et al: Treatment-free remission after two-year consolidation therapy with nilotinib in patients with chronic myeloid leukemia: STAT2 trial in Japan. *Haematologica* 103:1835-1842, 2018
41. Hughes TP, Clementino NCD, Fominykh M, et al: Long-term treatment-free remission in patients with chronic myeloid leukemia after second-line nilotinib: ENESTop 5-year update. *Leukemia* 35: 1631-1642, 2021
42. Kimura S, Imagawa J, Murai K, et al: Treatment-free remission after first-line dasatinib discontinuation in patients with chronic myeloid leukaemia (first-line DADI trial): A single-arm, multicentre, phase 2 trial. *Lancet Haematol* 7:e218-e225, 2020
43. Institute NC: SEER*Explorer: An interactive website for SEER cancer statistics. Surveillance Research Program, Data source(s): SEER Incidence Data, November 2023 Submission (1975-2021). SEER 22 registries. 2024. <https://seer.cancer.gov/statistics-network/explorer/>
44. Ries LAG, Smith MA, Gurney JG, et al: Cancer incidence and survival among children and adolescents: United States SEER program 1975-1995, in National Cancer Institute, SEER Program. Bethesda, MD, NIH Pub. No. 99-4649, 1999
45. Krumbholz M, Dolnik A, Sträng E, et al: A high proportion of germline variants in pediatric chronic myeloid leukemia. *Mol Cancer* 23:206, 2024
46. Krumbholz M, Karl M, Tauer JT, et al: Genomic BCR-ABL1 breakpoints in pediatric chronic myeloid leukemia. *Genes Chromosomes Cancer* 51:1045-1053, 2012
47. Hijiya N, Schultz KR, Metzler M, et al: Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. *Blood* 127:392-399, 2016
48. Champagne MA, Capdeville R, Krailo M, et al: Imatinib mesylate (ST1571) for treatment of children with Philadelphia chromosome-positive leukemia: Results from a Children's Oncology Group phase 1 study. *Blood* 104:2655-2660, 2004
49. Millot F, Baruchel A, Guilhot J, et al: Imatinib is effective in children with previously untreated chronic myelogenous leukemia in early chronic phase: Results of the French national phase IV trial. *J Clin Oncol* 29:2827-2832, 2011
50. Suttrop M, Schulze P, Glauche I, et al: Front-line imatinib treatment in children and adolescents with chronic myeloid leukemia: Results from a phase III trial. *Leukemia* 32:1657-1669, 2018
51. Giona F, Putti MC, Micalizzi C, et al: Long-term results of high-dose imatinib in children and adolescents with chronic myeloid leukaemia in chronic phase: The Italian experience. *Br J Haematol* 170: 398-407, 2015
52. Hijiya N, Maschan A, Rizzari C, et al: The long-term efficacy and safety of nilotinib in pediatric patients with CML: A 5-year update of the DIALOG study. *Blood Adv* 7:7279-7289, 2023
53. Hijiya N, Maschan A, Rizzari C, et al: A phase 2 study of nilotinib in pediatric patients with CML: Long-term update on growth retardation and safety. *Blood Adv* 5:2925-2934, 2021
54. Gore L, Kearns PR, de Martino ML, et al: Dasatinib in pediatric patients with chronic myeloid leukemia in chronic phase: Results from a phase II trial. *J Clin Oncol* 36:1330-1338, 2018
55. Gupta P, Banothu KK, Halder P, et al: Effect of imatinib mesylate on growth in pediatric chronic myeloid leukemia: A systematic review and meta-analysis. *J Pediatr Hematol Oncol* 45:227-234, 2023
56. Hijiya N, Maschan A, Rizzari C, et al: Phase 2 study of nilotinib in pediatric patients with Philadelphia chromosome–positive chronic myeloid leukemia. *Blood* 134:2036-2045, 2019
57. Zwaan CM, Rizzari C, Mechinaud F, et al: Dasatinib in children and adolescents with relapsed or refractory leukemia: Results of the CA180-018 phase I dose-escalation study of the innovative therapies for Children with Cancer Consortium. *J Clin Oncol* 31:2460-2468, 2013
58. Yoo JW, Jo S, Ahn MB, et al: Front-line tyrosine kinase inhibitors in pediatric chronic myeloid leukemia: A study on efficacy and safety. *Cancers (Basel)* 15:3862, 2023
59. Brivio E, Pennesi E, Willems ME, et al: Bosutinib in resistant and intolerant pediatric patients with chronic phase chronic myeloid leukemia: Results from the phase I part of study ITCC054/COG AAML1921. *J Clin Oncol* 42:821-831, 2024
60. Rossoff J, Huynh V, Rau RE, et al: Experience with ponatinib in paediatric patients with leukaemia. *Br J Haematol* 189:363-368, 2020
61. Hijiya N, Shimada H, Kapoor S, et al: Pharmacokinetics and safety of asciminib (ASC) in pediatric patients (pts) with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP): Interim results from the ASC4KIDS study. *J Clin Oncol* 42, 2024 (suppl 16; abstr 6562)
62. Roy Moulik N, Keerthivasagam S, Chatterjee G, et al: Treatment-free remissions in children with chronic myeloid leukemia (CML): A prospective study from the Tata Memorial Hospital (TMH) pediatric CML (pCML) cohort. *Am J Hematol* 100:210-217, 2025
63. Shima H, Kada A, Tanizawa A, et al: Discontinuation of tyrosine kinase inhibitors in pediatric chronic myeloid leukemia. *Pediatr Blood Cancer* 69:e29699, 2022

64. Millot F, Guilhot J, Suttorp M, et al: Prognostic discrimination based on the EUTOS long-term survival score within the International Registry for Chronic Myeloid Leukemia in children and adolescents. *Haematologica* 102:1704-1708, 2017
 65. Hijjiya N, Suttorp M: How I treat chronic myeloid leukemia in children and adolescents. *Blood* 133:2374-2384, 2019
 66. Roy Moulik N, Harriss-Buchan A, Saglio G, et al: Challenges in management of pediatric chronic myeloid leukemia (pCML) in the low-middle income countries (LMICs): Insights from an International CML Foundation (iCMLf) Multi-National Survey. *Pediatr Hematol Oncol* 41:290-295, 2024
 67. Pye SM, Cortes J, Ault P, et al: The effects of imatinib on pregnancy outcome. *Blood* 111:5505-5508, 2008
 68. Cortes JE, Abruzzese E, Chelysheva E, et al: The impact of dasatinib on pregnancy outcomes. *Am J Hematol* 90:1111-1115, 2015
 69. Robertson HF, Apperley JF: Treatment of CML in pregnancy. *Hematol Am Soc Hematol Educ Program* 2022:123-128, 2022
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When and How Long to Treat Chronic Lymphocytic Leukemia?

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OVERVIEW

Chronic lymphocytic leukemia (CLL) remains an incurable disease, except in rare cases treated with allogeneic stem-cell transplantation or favorable-risk CLL treated with chemo-immunotherapy. Treatment initiation follows the Rai and Binet staging systems, but the International Workshop on Chronic Lymphocytic Leukemia criteria emphasize active disease rather than stage alone. Early treatment in asymptomatic, high-risk patients has not shown an overall survival benefit, even with targeted therapies such as Bruton's tyrosine kinase and BCL2 inhibitors. The watch-and-wait strategy remains standard, although future trials may refine early treatment indications for specific high-risk groups.

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INTRODUCTION

According to the WHO classification, chronic lymphocytic leukemia (CLL) as well as small lymphocytic lymphoma (SLL) belong to the mature B-cell neoplasm.¹ Most of these diseases are characterized by slow proliferation; however, because of the presence or absence of driver mutations as well as the genetic evolution, the prognosis may vary a lot. Despite the general good prognosis because of the mostly slow progression after diagnosis as well as because of the excellent treatment options, some patients with CLL or SLL experience a rapid progression and short progression-free survival (PFS) time because of the presence of dismal driver mutations and genetic evolution.² With a median age of 72 years at diagnosis, in particular, younger patients still have a shorter overall survival (OS) in comparison with the age-matched general population, requiring significant improvement in their treatment management.^{3,4}

The article here is highlighting several questions with respect to the frontline treatment of CLL such as time point of initiation of first treatment, choice of treatment with respect to continuous versus time-limited, and finally the potential or future role of measurable residual disease (MRD).

WHEN TO START TREATMENT IN NEWLY DIAGNOSED CHRONIC LYMPHOCYTIC LEUKEMIA?

With the exception of allogeneic stem-cell transplantation, which has proven durable, relapse-free survival in a minority of patients being suitable for allogeneic stem-cell transplantation⁵ or carrying very favorable risk profile and showing deep response to chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab,⁶ CLL is still an incurable disease. Chimeric antigen receptor (CAR) T-cells,

which show promising result with curative potential in other lymphoma, achieve only in a minority of patients with CLL longer-lasting remissions,⁷ and only very few cases with long-term follow up were reported as potentially cured.⁸ In summary, as in other indolent lymphoma, the paradigm as in other mature B-cell lymphoma is to start treatment only in advanced-stage disease in clinically symptomatic disease.⁹

Treatment initiation relies on the stage of the disease. Because of the early bone marrow (BM) infiltration of this type of lymphoma, two separate staging systems were implemented decades ago on the basis of clinical lymphadenopathy and laboratory staging: the Rai et al¹⁰ and the similar Binet et al¹¹ staging systems, which are still valid to date. These systems assess the extent of disease burden and are determined through thorough clinical examination, including palpation of lymph nodes, spleen, and liver, alongside complete blood counts. The Rai system uses a combination of lymphocytosis, lymphadenopathy, splenomegaly, and anemia/thrombocytopenia to define stages:

- Stage 0: Lymphocytosis only (absolute lymphocyte count $>5 \times 10^9/L$).
- Stage I: Lymphocytosis and enlarged lymph nodes.
- Stage II: Lymphocytosis, enlarged lymph nodes, and enlarged spleen or liver.
- Stage III: Lymphocytosis and anemia (hemoglobin <11 g/dL).
- Stage IV: Lymphocytosis and thrombocytopenia (platelet count $<100 \times 10^9/L$).

The Binet system categorizes patients on the basis of the number of involved lymphoid areas (lymph nodes, spleen, and liver) and the presence of anemia or thrombocytopenia:

- Stage A: Fewer than three involved lymphoid areas, normal hemoglobin, and platelet counts.

PRACTICAL APPLICATIONS

- Treatment initiated should be based on the presence of active disease as defined by the International Workshop on Chronic Lymphocytic Leukemia (CLL) criteria.
- Because of the lack of overall survival (OS) benefit, early treatment is not indicated even in the presence of CLL with very high-risk profile.
- Symptomatic advanced-stage disease should be treated with targeted agents, either as continuous treatment or as time-limited combinations.
- For the choice of therapy, weighting efficacy in terms of OS and progression-free survival versus duration and severity (grade) of adverse events and benefit of time of treatment should be considered.
- Measurable residual disease (MRD)-guided treatment strategy offers the unique potential to personalize therapy duration, but since more mature data from ongoing and future trials are needed, MRD-driven treatment duration should not be used in routine practice.

- Stage B: Three or more involved lymphoid areas, normal hemoglobin, and platelet counts.
- Stage C: Any number of involved lymphoid areas, presence of anemia (hemoglobin <10 g/dL), and/or thrombocytopenia (platelet count <100 × 10⁹/L).

However, besides advanced stage according to the Rai and Binet classifications the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria,⁹ CLL should be considered classifying the disease as active or inactive. The criteria classify activity of the disease as progressive BM failure, indicated by worsening anemia (hemoglobin <10 g/dL) or thrombocytopenia (platelet count <100 × 10⁹/L), which correlated with advanced stage of the disease, as Rai III/IV or Binet C. It is crucial to note that stable, long-standing thrombocytopenia just below the threshold of 100 × 10⁹/L may not automatically warrant treatment. For intermediate-stage (Rai II/III or Binet B), massive, rapidly progressive or symptomatic splenomegaly also indicates for an active disease requiring treatment. Additionally, massive or progressive lymphadenopathy causing symptoms and a progressive lymphocytosis, defined by a rapid increase in lymphocyte count (≥50% increase over 2 months) or a lymphocyte doubling time (LDT) of <6 months, are considered signs of an active disease and imply treatment initiation.⁹ LDT is calculated by analyzing lymphocyte counts over time. It is important to exclude other causes of lymphocytosis, such as infections. CLL can also cause active

symptoms that are related to autoimmune complications, especially autoimmune hemolytic anemia or immune thrombocytopenia. Autoimmune cytopenia poorly responsive to corticosteroids is another indication for treatment. In rarer cases, CLL is presenting symptomatically in extranodal compartments, such as in the skin, kidneys, lungs, or central nervous system, and results in functional impairment, which would also be considered a treatment indication. Generally, as soon as constitutional symptoms, that is, unintentional weight loss ≥10% within the previous 6 months, significant fatigue (Eastern Cooperative Oncology Group performance status 2 or worse), fevers ≥38.0°C (100.5°F) for 2 or more weeks without evidence of infection, and night sweats for ≥1 month without evidence of infection, that are attributable to CLL arise, the disease should be considered active and treatment should be initiated.

Hypogammaglobinemia per se, but also in association with infections as well as paraproteinemia do not constitute an indication for treatment. However, changes in these protein abnormalities may be monitored during treatment. Regarding the often markedly elevated leukocyte count in CLL, leukostasis is rare because of the characteristics and surface of CLL cells, which are very small in contrast to other lymphoma cells. In rare cases, it was reported in patients with leukocyte counts >1,000 × 10⁹/L. Therefore, the absolute lymphocyte count should not be the sole determinant for treatment initiation.

The iwCLL criteria provide the gold standard for treatment initiation, focusing on active disease rather than simply the presence of CLL. The relationship between stage and treatment initiation is summarized in [Table 1](#).

However, the question whether patients with CLL, which is associated with a higher risk for rapid disease progression, should receive early treatment in asymptomatic stage has been addressed in several clinical trials. The first trials were performed decades ago and compared chlorambucil versus observation in patients with CLL Rai stage I and II and reported no OS benefit.¹² In the following years, other trials comparing chlorambucil-based treatments to observation¹³ came to the identical conclusion that earlier treatment offers no OS benefit. Other therapeutic approaches, such as interferon-α 2b versus observation, were evaluated in

TABLE 1. When to Treat Chronic Lymphocytic Leukemia According to iwCLL Criteria

Rai Stage	Binet Stage	When to Treat
Rai 0	Binet A	Only when active disease is present
Rai I or II	Binet B	Only when active disease is present
Rai III or IV	Binet C	Treatment generally indicated

Abbreviation: iwCLL, International Workshop on Chronic Lymphocytic Leukemia.

early-stage disease as well, which confirmed no benefit in OS or PFS for patients with CLL and high risk for disease progression.¹⁴ Within two phase III trials of the German CLL study group, other chemotherapy regimens such as fludarabine alone or the chemoimmunotherapy regimen combining fludarabine, cyclophosphamide, and the anti-CD20 antibody rituximab (FCR) showed no benefit versus observation in patients with early asymptomatic-stage CLL with adverse risk factors.^{15,16} Although PFS was increased with the CLL1 trials for the fludarabine group¹⁶ and 5-year event-free survival (EFS) was significantly increased in the CLL7 trial in the chemoimmunotherapy arm,¹⁵ not surprisingly, both trials have confirmed a higher rate of adverse events (AEs) during early treatment in comparison with observation.

However, with the revolutionized landscape of CLL treatment by the development of targeted therapies, current clinical trials address the same question by using targeted therapies. Covalent Bruton's tyrosine kinase (BTK) inhibitors (eg, ibrutinib, acalabrutinib, and zanubrutinib) and BCL2 inhibitors (eg, venetoclax) in combination with CD20 antibodies or as monotherapy have demonstrated remarkable efficacy in parallel with good tolerability and have become standard first-line and relapse options, and were considered to be more appropriate treatment options for early intervention instead of chemotherapy-containing regimen.

The CLL12 trial of the German CLL study group investigated early treatment intervention with the BTK inhibitor ibrutinib versus placebo in patients with CLL and an intermediate- to very high-risk assessed profile by the CLL-International Prognostic Index (IPI) score.¹⁷ The results show no benefit with respect to OS for early intervention with ibrutinib, although EFS is significantly prolonged.¹⁸ Ongoing clinical trials such as the EVOLVE trial led by B. Hill (ClinicalTrials.gov identifier: [NCT04269902](#)), investigating early treatment with the BCL2 inhibitor venetoclax combined with the anti-CD20 antibody obinutuzumab versus the delayed combination of venetoclax and obinutuzumab in patients with CLL and a high or very high CLL-IPI or high-risk cytogenetics, continue to explore targeted agents and combination therapies to assess the optimal time point of treatment for CLL in the era of targeted therapy (Table 2). A different approach, aiming at improving immune dysfunction in newly diagnosed patients with CLL at high risk of severe infections by short-duration treatment with acalabrutinib and venetoclax, is being tested in the ongoing phase 2-3 PreVent-ACaLL trial (ClinicalTrials.gov identifier: [NCT03868722](#)).

Although several efforts have been made to improve OS in the group of patients with asymptomatic early-stage but higher-risk CLL, the watch-and-wait strategy remains appropriate for asymptomatic patients with early-stage disease. Considering the excellent outcome of frontline and relapse treatments with targeted agents, the positive effect of an early treatment on OS is certainly difficult to prove. However, future trials in that setting may require to

select patients more specifically, for example, only very high CLL with *TP53* aberration. The results show that we should continue to initiate treatment on the basis of the presence of active disease as defined by the iwCLL criteria. In summary, these results for early-stage CLL are good news for patients, although it certainly needs careful communication and explanation why early treatment is not indicated even in the presence of CLL with very high-risk profile despite the excellent treatment armamentarium, offering improved outcomes for individuals with CLL.

TIME-LIMITED THERAPY VERSUS INDEFINITE THERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIA

The development of treatment options for CLL has taken incredible progress over the past 15 years. Although chemoimmunotherapy was widely used in frontline²⁰ and relapsed line in the past, indefinite therapy with BTK inhibitors including ibrutinib as first-in-class²¹ and targeted time-limited combination regimens have become the preferred first-line treatment for CLL today.²² To assess the pros and cons between time-limited therapy versus indefinite therapy for CLL, we need to take a step back and ask the patients living with cancer, what truly is important for their day-to-day life (Fig 1). Asking the patient panel at the Danish Cancer Society, representing patients living with active cancer, or having been through cancer treatment, and their relatives, the answer was clear: (1) avoiding longer and repeated visits at the hospital in outpatient or inpatient setting (eg, because of treatment-related complications, but also due to treatment administration and frequency of controls, eg, for prophylaxis of tumor lysis syndrome), and (2) also accepting more severe toxicities as long as for a known limited period of time.²⁰

Thus, the fortunate situation with several treatment options improving OS and PFS in CLL forces us as hematologists to consider the CLL treatment balance, weighting efficacy in terms of OS and PFS versus duration and severity (grade) of AEs.²³ For different treatment options, this means taking the time on treatment and the need for the patient to spend time in the hospital (as outpatient or inpatient) into account. Furthermore, the improved outcome for treatment of relapsed/refractory CLL with time-limited therapy as well as with indefinite therapy²⁴⁻²⁸ emphasizes the need to consider the impact of first-line therapy on the outcome of subsequent lines of therapy.^{22,29} Finally, the risk of developing resistance mutations upon therapy needs to be considered when choosing between treatment options.^{30,31} While we are waiting for the CLL17 trial comparing indefinite ibrutinib versus time-limited ibrutinib plus venetoclax versus time-limited obinutuzumab plus venetoclax to read out, we have to rely on indirect comparisons of targeted time-limited combination therapy versus indefinite therapy with BTK inhibitors for CLL.

Addressing first the patient group with the most aggressive CLL phenotype in terms of *TP53* aberrated disease (del(17p) and/or *TP53* mutations), ibrutinib monotherapy as first-line

TABLE 2. Randomized Phase III Trials in Early-Stage CLL

Trial	Trial Arms	CLL Stage and RF	Outcome for Early Intervention	Reference
Interferon-alpha 2b (iFN alpha) for early-phase CLL with high risk for disease progression: results of a randomized multi-centre study	iFN alpha (n = 21) v observation (n = 23)	Binet A	No benefit in PFS and OS	Langenmayer et al ¹⁴
Chlorambucil in indolent CLL	Chlorambucil (n = 301) v observation (n = 308)	Binet A	No benefit in OS, improved disease control	Dighiero et al ¹³
Chlorambucil in indolent CLL	Chlorambucil + prednisone (n = 460) v observation (n = 466)	Binet A	No benefit in OS, improved disease control	Dighiero et al ¹³
Treatment of early CLL: intermittent chlorambucil versus observation	Chlorambucil (n = 48) v observation	Rai stage I and II	No benefit in OS	Shustik et al ¹²
Early, risk-adapted treatment with fludarabine in Binet stage A CLL patients: Results of the CLL1 trial of the German CLL Study Group	Fludarabine (n = 93) v observation (n = 96)	Binet A and adverse RF: type of BM infiltration, lymphocyte doubling time <12 months, serum beta-2-microglobulin >3.5 mg/L, serum thymidine kinase >7 U/L	No OS benefit, improvement in PFS, more AEs	Hochstetter et al ¹⁶
Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk CLL: a randomized phase 3 trial (CLL7)	FCR (n = 100) v observation (n = 101)	Binet A and ≥2 RF: rapid lymphocyte doubling time (<12 months) serum thymidine kinase >10 U/L, uIGHV, high-risk FISH	No benefit in OS, benefit in 5-year EFS, higher toxicity	Herling et al ¹⁵
The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage CLL	Ibrutinib (n = 182) v placebo (n = 181)	Binet A and intermediate- to very high-risk comprehensive risk score ¹⁹	No benefit in OS, benefit in EFS	Langerbeins et al ¹⁸

Abbreviations: AE, adverse event; BM, bone marrow; CLL, chronic lymphocytic leukemia; EFS, event-free survival; FCR, fludarabine-cyclophosphamide-rituximab; FISH, fluorescent in situ hybridization; iFN, interferon; OS, overall survival; PFS, progression-free survival; RF, risk factors; uIGHV, IGHV unmutated.

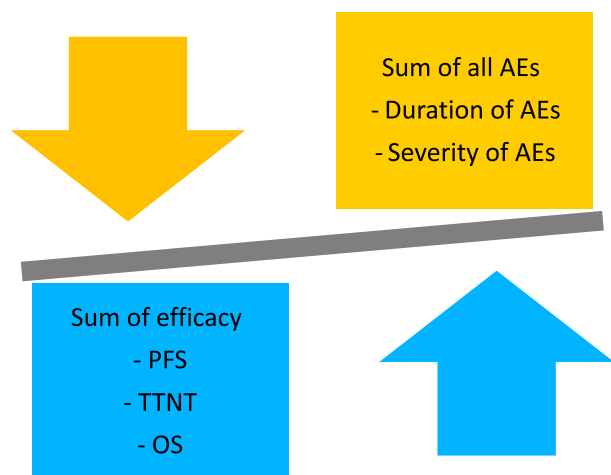


FIG 1. Treatment considerations for balancing efficacy and AEs. AE, adverse event; OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment.

treatment resulted in estimated 61% PFS and 79% OS at 6 years.^{32,33} Comparing this with triple combination treatment with ibrutinib plus venetoclax plus obinutuzumab for 12 cycles followed by 3–24 additional cycles of ibrutinib monotherapy guided by MRD for first-line treatment of CLL patients with TP53 aberrations resulted in 79.9% PFS and 92.6% OS is reported at 3 years.³⁴ For doublet treatment of comorbid patients with TP53 aberrated CLL, 12 cycles of obinutuzumab plus venetoclax resulted in a 40.6% estimated PFS and 60.0% OS at 5 years.^{35,36} Fixed-duration ibrutinib plus venetoclax for 15 cycles resulted in an estimated 81% PFS and 96% OS at 3 years for a more fit patient population with TP53 aberrations.³⁷ Continuous treatment with acalabrutinib plus obinutuzumab yielded an estimated PFS of 74.8% and acalabrutinib monotherapy yielded an estimated PFS of 76.2%; there was no difference in OS for both treatments in a cross-trial analysis.^{38–40} Zanubrutinib monotherapy in the frontline setting for patients with TP53 aberrated CLL reported an estimated 88.9% PFS and 93.6% OS at 2 years.⁴¹

Thus, with all the caveats of cross-trial comparisons and considering the different fitness of patients in the different trials, PFS and OS rates upon indefinite monotherapy with covalent BTK inhibitors compared with time-limited doublet and triplet regimens for patients with treatment-naïve TP53 aberrated CLL are in similar ranges, although PFS rates appear to be more favorable. However, high discontinuation rates for indefinite BTK inhibitors outside clinical trials may limit the translation of clinical trial efficacy to daily clinical practice, with 33% discontinuation rate reported for patients with del(17p) CLL in the frontline setting after 1 year on ibrutinib therapy.^{42,43} Hence, BTK inhibitor monotherapy may be far from indefinite for patients with treatment-naïve TP53 aberrated CLL in daily clinical practice. Furthermore, it seems that the risk of developing resistance mutations upon indefinite therapy with BTK inhibitors is higher than what is

seen for patients treated with time-limited combination therapies.³¹

Some of the pivotal trials testing time-limited therapy for first-line treatment of CLL did exclude patients with TP53 aberrations because of comparator arms with chemo-immunotherapy considered below standard of care for patients with TP53 aberrations. Thus, the clinical trials on which to base comparison of indefinite versus time-limited therapy for TP53 wildtype CLL differs a bit from the abovementioned.

Obinutuzumab plus venetoclax as time-limited treatment was approved in the United States and the European Union on the basis of the CLL14 trial for frail patients with coexisting conditions and the GAIA-CLL13 trial for fit patients (Table 3).^{48,49} For patients with immunoglobulin heavy chain variable region genes (IGHV) unmutated CLL (being associated with higher risk for early relapse), estimated PFS was 55.8% and OS 80.5% at 5 years for frail patients in the CLL14 trial while PFS was 73.9% at 4 years for fit patients in the GAIA-CLL13 trial (and 80.9% for patients treated with the triplet of ibrutinib, venetoclax, and obinutuzumab). For patients with IGHV mutated (mIGHV) CLL (being associated with higher risk for early relapse), estimated PFS was 76.5% and OS 86.6% at 5 years for frail patients in the CLL14 trial, while PFS was 91.8% at 4 years for fit patients in the GAIA-CLL13 trial (and 94.4% for patients treated with the triplet).^{30,36}

Ibrutinib plus venetoclax has become an additional time-limited first-line treatment option for CLL, which has been approved in the European Union but not in the United States. For patients with TP53 wildtype CLL, frail patients in the GLOW trial receiving 15 cycles of ibrutinib plus venetoclax resulted in an estimated 69.8% PFS at 42 months for IGHV unmutated CLL (Table 3). For fit patients in the FLAIR trial, providing longer MRD-guided ibrutinib plus venetoclax, patients with IGHV unmutated status achieved an estimated PFS of 98.3% at 3 years. In both trials, patients with IGHV mutated CLL had a better PFS with 90.0% and 94.3% after 42 months and 3 years, respectively.^{52,53}

For comparison, patients with IGHV unmutated (uIGHV) CLL achieved 85.7% PFS and 77.1% PFS at 4 years upon indefinite acalabrutinib with or without obinutuzumab, respectively.⁵⁴ For indefinite zanubrutinib therapy, PFS rates at 5 years were estimated at 75.8% (reporting jointly on IGHV mutated and unmutated CLL).⁵⁵ For IGHV unmutated CLL, time-limited doublet treatment with acalabrutinib plus venetoclax, with or without obinutuzumab, was reported with 82.8% and 68.9% PFS at 3 years, respectively.⁵⁶

Further emphasizing the importance of time of treatment from a patient perspective, quality of life (QoL) data from the GAIA-CLL13 trial demonstrated improved QoL during treatment with venetoclax plus obinutuzumab, while the triplet treatment with ibrutinib plus venetoclax plus

TABLE 3. Selection of Relevant Phase III Studies Using Targeted Agents in Treatment-Naïve Patients With Advanced CLL

Trial	Trial Arms	Main Patient/Disease Characteristics	Outcome	Reference
Trials comparing continuous treatment with BTKi v CIT				
RESONATE-2: Ibrutinib as initial therapy for patients with CLL	I (n = 136) v Clb (n = 133)	Age ≥65 years, no <i>TP53</i> mut/del(17p) included	Superior PFS and OS, higher response rate for I	Burger et al ⁴⁴
ECOG 1912: Ibrutinib-rituximab or chemoimmunotherapy for CLL	I + R (n = 354) v FCR (n = 175)	No <i>TP53</i> mut/del(17p) included	Superior PFS and OS for I + R	Shanafelt et al ⁴⁵
FLAIR: Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial	I + R (n = 386) v FCR (n = 385)	Fit for FCR, no <i>TP53</i> mut/del(17p) included	Superior PFS for I + R, no difference in OS	Hillmen et al ⁴⁶
ELEVATE-TN: Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naïve CLL	Acalabrutinib (n = 179) ± O (n = 179) v O + Clb (n = 177)	<i>TP53</i> mut/del(17p) included	Benefit in OS for A + O v O + Clb, longer PFS in A + O v O + Clb and A mono v O + Clb, more grade 3 + 4 infections in A + O arm	Sharman et al ⁴⁷
SEQUOIA: Zanubrutinib versus bendamustine and rituximab in untreated CLL and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial	Zanubrutinib (n = 241) v bendamustine/rituximab (n = 238)	Treatment-naïve, age >65 years or age ≤65 years + comorbidities, no <i>TP53</i> mut/del(17p) included	Superior PFS in zanubrutinib v BR	Tam et al ⁴¹
Trials comparing time-limited targeted combination treatment v CIT				
CLL14: Venetoclax-obinutuzumab for previously untreated CLL	Ven-O (six cycles) followed by Ven six cycles (n = 216) v Clb + O (Clb-O; six cycles) followed by 6 cycles of Clb (n = 216)	Less fit (CIRS score >6), <i>TP53</i> mut/del(17p) included	Superior PFS and uMRD in Ven-O v CIT	Fischer et al ⁴⁸
CLL13: First-line venetoclax combinations in chronic lymphocytic leukemia	CIT (n = 229) v RV (n = 237) v O + Ven (GV; n = 229) v O + I + Ven (GIV; n = 237)	Fit (CIRS score ≤6), no <i>TP53</i> mut/del(17p) included	Superior PFS in GV and GIV v CIT, higher uMRD in GV and GIV arm, RV not superior in PFS or uMRD compared with CIT, more grade 3 and 4 infections in GIV and CIT arms	Eichhorst et al ⁴⁹
GLOW: Fixed-duration ibrutinib plus venetoclax (I + V) versus chlorambucil plus obinutuzumab (Clb + O) for first-line treatment of CLL: Primary analysis of the Phase 3 GLOW study	Fixed-duration I plus Ven (15 cycles; I + V; n = 106) v Clb plus O (6 cycles; Clb + O; n = 105)	Age ≥65 years or <65 years and CIRS >6, no <i>TP53</i> mut/del(17p)	Benefit in PFS for I + V, reduced risk for progression or mortality with I + V, longer time to next treatment with I + V, higher rates of uMRD in BM for I + V	Kater ⁵⁰

(continued on following page)

TABLE 3. Selection of Relevant Phase III Studies Using Targeted Agents in Treatment-Naïve Patients With Advanced CLL (continued)

Trial	Trial Arms	Main Patient/Disease Characteristics	Outcome	Reference
FLAIR: Chronic lymphocytic leukemia therapy guided by measurable residual disease	MRD-driven duration I + V (n = 260) v FCR (n = 263)	Fit for FCR, no severe cardiac comorbidities, <i>TP53</i> mut/del(17p) included	Superior PFS in MRD-guided I + V, higher rates of uMRD in BM and pB (at any time) for I + V	Munir et al ⁵¹
AMPLIFY: Fixed-duration aca-labrutinib combinations in untreated chronic lymphocytic leukemia	Fixed-duration AV (n = 291) with (AVO; n = 286) and without O v investigator's choice of CIT (n = 290)	Fit for FCR or BR, no <i>TP53</i> mut/del(17p) included	Superior PFS in AV and AVO v FCR/BR, higher uMRD rates in AVO >FCR/BR >AV	Brown et al ⁵⁷

Abbreviations: A, acalabrutinib; BM, bone marrow; BR, bendamustine-rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CIT, chemoimmunotherapy; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; CIRS, cumulative illness rating scale; del, deleted; FCR, fludarabine-cyclophosphamide-rituximab; I, ibrutinib; MRD, measurable residual disease; mut, mutated; O/G, obinutuzumab; OS, overall survival; PFS, progression-free survival; pB, peripheral blood; R, rituximab; uMRD, undetectable MRD; Ven, venetoclax.

obinutuzumab did not demonstrate improved QoL until after end of treatment.³⁰ As a further notion on potential immune dysfunction from triplet treatment, higher mortality, maybe due to COVID-19, acting as the canary bird for immunosuppression, was reported for the triplet of acalabrutinib plus venetoclax plus obinutuzumab compared with the doublet of acalabrutinib plus venetoclax in the AMPLIFY trial.⁵⁷ Also, in the GAIA-CLL13 trial, higher frequency of infections was reported for the triplet of ibrutinib plus venetoclax plus obinutuzumab compared with the doublet of venetoclax plus obinutuzumab.⁴⁹

While awaiting results from the CLL17 trial (ClinicalTrials.gov identifier: [NCT04608318](#)) comparing head-to-head indefinite ibrutinib monotherapy to time-limited obinutuzumab plus venetoclax and time-limited ibrutinib plus venetoclax, the clinical decision on best treatment option for your patient relies on cross-trial comparisons. Taking the patient perspective to (1) avoid longer and repeated visits at the hospital and (2) also accept more severe toxicities for a known limited period, the CLL treatment balance favors time-limited therapy for IGHV mutated and IGHV unmutated patients. Even for patients with TP53 aberrations, repeated time-limited therapy may yield equivalent results to indefinite BTK inhibitor treatment with respect to OS. This is also reflected in the recently updated European Society for Medical Oncology (ESMO) guidelines and National Comprehensive Cancer Network guidelines (version 2, 2025) having time-limited treatment options included for TP53 aberrated CLL while preferring time-limited treatment for TP53 wildtype CLL in the frontline setting.^{22,58} However, for all other patient groups, ESMO guidelines prefer time-limited combination therapy over continuous BTK inhibitor therapy.^{22,58}

IS THERE A ROLE FOR MRD TESTING IN CHRONIC LYMPHOCYTIC LEUKEMIA?

The concept of inducing deep remissions in hematologic diseases has been studied in detail, and MRD-guided treatment modifications are now standard practice in acute lymphoblastic leukemia, acute myeloid leukemia, and chronic myeloid leukemia. The utilization of MRD in CLL has been applied to prognosticate disease response at the end of treatment and has been validated through both prospective trials and retrospective data across various chemoimmunotherapy regimens, regardless of the specific regimen used.^{59,60} Subgroup analysis of the CLL8 data comparing FCR with fludarabine and cyclophosphamide demonstrated that FCR achieves a significantly higher undetectable MRD (uMRD) rate (63% v 35%, $P < .0001$). However, within each MRD status group, PFS and OS remain similar between the two regimens.⁶¹ Consolidation using alemtuzumab in MRD-positive patients after chemoimmunotherapy has been shown to improve outcome in patients who become MRD-negative after consolidation both in terms of PFS and OS as demonstrated in phase II NCRN CLL207 and phase III German CLL4B trials.^{62,63} Similarly, the GALACTIC trial found that obinutuzumab consolidation after chemoimmunotherapy

significantly improved PFS in consolidated patients compared with those who did not receive consolidation, with outcomes comparable with those who attained uMRD after chemoimmunotherapy.⁶⁴ However, with the advent of targeted therapies with limited toxicities, the treatment landscape of CLL has completely shifted away from chemoimmunotherapy. The significance of MRD varies across these newer treatment approaches. It is now clear that while BTK inhibitors (BTKi) are highly effective as continuous therapy, they have a very low probability of achieving uMRD even with the addition of anti-CD20 antibodies, but limited-duration treatment with BCL2 inhibitors in various combinations with anti-CD20 antibodies or ibrutinib has a high probability of attaining uMRD. The MRD is now being used in clinical trials to cease additional therapy or introduce further treatment to achieve deeper responses, leading to the concept of personalized therapy, hence limiting toxicity but also reducing the risk of development of resistant clones.

The utility of MRD-defined therapy has been explored in various clinical trials using combination of BTKi ibrutinib and BCL2 inhibitor venetoclax. In the MRD-guided arm of CAPTIVATE trial, the patients were randomly assigned on the basis of MRD status at the end of three cycles of ibrutinib lead-in followed by 12 cycles of ibrutinib plus venetoclax. Patients attaining confirmed uMRD status were randomly assigned to ibrutinib or placebo, and 4-year PFS was 95% in patients treated with ibrutinib and 88% in patients treated with placebo. Patients with detectable MRD (dMRD) status were randomly assigned to ibrutinib or ibrutinib plus venetoclax (I + V) for another year. In the dMRD arm, another year of ibrutinib plus venetoclax improved the peripheral blood (PB)-uMRD rates from 50% to 69% and BM-uMRD rates from 31% to 66%, and 30-month PFS was 95% for patients treated with ibrutinib and 97% for patients treated with ibrutinib plus venetoclax. All cohorts in the MRD-guided therapy had an estimated PFS of >95% at 30-month follow-up, suggesting that this is a feasible approach.^{65,66} It is noticeable that in the fixed-duration cohort of this trial, the 4-year PFS rates were 90% for patients with uMRD 3 months after treatment compared with 66% for those with dMRD, although there were no differences in OS.⁶⁷

FLAIR is an adaptive, phase III, open-label randomized trial that used the approach of incorporating experimental arms in the form of MRD-guided duration of ibrutinib plus venetoclax to compare with ibrutinib, ibrutinib with rituximab, and FCR in young, fit patients. The concept was based on phase II CLARITY study in relapsed CLL patients where total duration of MRD-adjusted ibrutinib plus venetoclax was double the time required to achieve uMRD. In this trial, 53 patients received 12–36 months of I + V on the basis of achievement of uMRD in PB and BM.⁶⁸ In FLAIR, patients achieving uMRD after 12, 18, or 24 months of ibrutinib plus venetoclax would receive 2, 3, and 4 years of ibrutinib plus venetoclax, respectively, whereas dMRD would continue a maximum treatment of 6 years of ibrutinib plus venetoclax. At a median of 44 months of follow-up, MRD-guided

ibrutinib plus venetoclax resulted in 3-year PFS of 97.2% compared with 76.8% with FCR.⁵¹ Importantly, MRD-guided approach resulted in a statistically significant difference in OS with 3-year OS of 98% with ibrutinib plus venetoclax versus 93% with FCR. On the basis of MRD stopping rules, 48.3% stopped ibrutinib plus venetoclax at 2 years, 60.1% at 3 years, and 68.1% at 4 years. Higher rates of uMRD were observed in ibrutinib plus venetoclax group compared with FCR in patients with uIGHV resulting in higher proportion achieving MRD stopping rules and statistically significant outcomes in terms of PFS (hazard ratio [HR], 0.07 [95% CI, 0.02 to 0.19]) and OS (HR, 0.23 [95% CI, 0.06 to 0.81]); there was a trend in improvement of PFS (HR, 0.54 [95% CI, 0.21 to 1.38]) and OS (HR, 0.61 [95% CI, 0.20 to 1.82]) in patients with mIGHV CLL as well, but this was not statistically significant.⁵¹ On the basis of this evidence, although the current regulatory approval in Europe for ibrutinib plus venetoclax is for 15 cycles of fixed-duration therapy, MRD-guided individualized approach in FLAIR is conceptually compelling and challenging the concept of fixed duration. The update with longer follow-up of FLAIR comparing all the cohorts is awaited to inform whether this data set will allow implementation of the regimen in routine clinical practice.

MRD-guided therapy has been explored in the context of triplet using targeted therapies. In GAIA-CLL13, ibrutinib plus venetoclax plus obinutuzumab triplet arm (with MRD-driven ibrutinib continuation) was compared with fixed-duration chemoimmunotherapy (CIT), venetoclax-rituximab and venetoclax-obinutuzumab. In the ibrutinib plus venetoclax plus obinutuzumab arm with dMRD after 12 months of triplet, 15 of 231 patients continued ibrutinib for a maximum of 36 months. At a median of 51 months, ibrutinib plus venetoclax plus obinutuzumab and fixed-duration venetoclax plus obinutuzumab was superior in terms of PFS to CIT (85.5%, 81.8%, and 62.0%, respectively).⁴⁹ Interestingly, the study showed the benefit of ibrutinib plus venetoclax plus obinutuzumab over venetoclax plus obinutuzumab in unmutated IGHV patients (HR, 0.58, $P = .025$) suggesting that this MRD-risk adapted approach may be beneficial in high-risk patients.³⁰

MRD-guided risk-adapted approach has also been explored in other phase II trials. In the BOVEN study, zanubrutinib is combined with obinutuzumab and venetoclax in a stepwise manner. The combination is continued till 8 months and then dMRD patients continue zanubrutinib and venetoclax till the achievement of uMRD in PB and BM. The study met its end point on the basis of complex mathematical model to achieve uMRD rates. At a median follow-up of 26 months, 89% of patients have achieved uMRD in PB and BM with 92% of patients stopping therapy at 40 months at the latest follow-up.^{69,70} Similar results have been reported with the combination of acalabrutinib, venetoclax, and obinutuzumab with uMRD rates of 86% reported in BM resulting in discontinuation of treatment.^{71,72} In the phase II Next STEP trial, MRD-guided stopping after ibrutinib and venetoclax or intensification with additional six cycles of ibrutinib and obinutuzumab resulted in 94% PFS and 98% OS at 2 years.⁷³

Several questions remain regarding using MRD-guided approaches in CLL. Whether MRD should be used proactively to define duration of therapy is only explored in the FLAIR trial, whereas numerous trials have used MRD as a reactive measure to instigate cessation or continue therapy. These are two different approaches, and long-term outcomes may be different. The durability of response to proactive approach used in FLAIR may be the defining factor to ascertain whether this approach should become a standard approach to treat uIGHV patients. It is also clear that the MRD response to ibrutinib plus venetoclax in mIGHV and uIGHV patients is different.^{51,74} Using MRD-guided approach may result in overtreatment with ibrutinib plus venetoclax for mIGHV patients but the longer follow-up may provide further information.

One of the challenges for using the concept of MRD testing and reporting is the standardization of approaches in real-world practice. While clinical trials develop central MRD analysis, this is difficult to establish in day-to-day practice. Flow cytometry, real-time quantitative polymerase chain reaction, and next generation sequencing have all been used in clinical trials but cannot be consistently applied in routine practice. There are also challenges in the timing for testing and monitoring MRD, the choice of compartment for MRD assessment (PB or BM), and the definition for depth of uMRD; MRD4 (10^{-4} , or 1 in 10,000 leukocytes), MRD5 (10^{-5} or 1 in 100,000 leukocytes), and MRD6 (10^{-6} or 1 in 1,000,000 leukocytes) have been used in various trials, although MRD4 is currently the standard approved by the iwCLL guideline. It is important to follow the laid standards by consortium such as ERIC (18–22).^{75–79}

With all caveats, it is possible to implement MRD testing in routine clinical practice if the MRD assessments are used to define duration of therapy. In FLAIR, routine MRD assessment was performed in more than 1,500 patients at various time points. In the GAIA, CAPTIVATE, BOVEN, and SEQUIOA trials, MRD assessments at predefined time points were routinely assessed to randomize or define duration of therapy. Flow cytometry was the commonest technique used in clinical trials, and it can be applied in routine clinical practice, albeit requiring resource and effort.

FLAIR and CAPTIVATE trials have opened the debate of comparing MRD-guided therapy to established fixed-duration approaches and continuous targeted therapies. Although these trials may provide clarity with longer follow-up, it is important to test this hypothesis in future clinical trials. The phase III MAJIC trial (ClinicalTrials.gov identifier: [NCT05057494](https://clinicaltrials.gov/ct2/show/study/NCT05057494)) is comparing acalabrutinib with venetoclax to venetoclax plus obinutuzumab given in MRD-guided manner.⁸⁰ CLL18 is a phase III randomized trial comparing fixed-duration versus MRD-guided pirtobrutinib plus venetoclax versus a control arm of standard-of-care fixed-duration venetoclax plus obinutuzumab. This phase III trial will directly evaluate the comparison between fixed-duration and MRD-guided approaches.

MRD remains a powerful tool for assessing treatment response in CLL beyond conventional complete remission criteria, with strong evidence supporting its role as a surrogate marker for PFS. Given the heterogeneity of CLL in both patient characteristics and disease biology, a standardized, fixed-duration treatment approach may not be ideal. An MRD-guided treatment strategy offers the unique potential to personalize therapy duration, minimizing side effects while maximizing treatment response, potentially leading to better long-term remission. Although current evidence supports further research in this direction, more mature data from ongoing and future trials are needed before integrating this approach into routine practice. It is also very important to assess the patient's QoL and cost-benefit analysis of these various treatment approaches.

FUTURE DIRECTIONS

Although the overall prognosis of CLL has improved significantly with the targeted treatment options, there is still a

significant proportion of patients with early relapses of their disease, which requires improvement of therapy. Currently ongoing clinical phase III trials in the United States and Europe evaluate the optimization of frontline therapy of CLL with an MRD-driven approach.

Furthermore, new combinations including next-generation BCL2 inhibitors as well as noncovalent binding BTK inhibitors are being evaluated as oral combinations. CAR T-cells are so far only approved for relapse treatment in the United States,⁷ and it is unclear if they will be evaluated in frontline therapy of CLL one day. Other cellular approaches such as bispecific antibodies are in general more easily accessible since they are off the shelf and currently evaluated in clinical trials in relapsed CLL. They may be used one day as consolidation therapy in dMRD CLL after combination therapy in frontline. As long as CLL is an incurable disease for the majority of patients with decreased life expectancy, in particular in younger patients, there is still need for improvement.

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REFERENCES

1. Alaggio R, Amador C, Anagnostopoulos I, et al: The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. *Leukemia* 36:1720-1748, 2022
2. Landau DA, Tausch E, Taylor-Weiner AN, et al: Mutations driving CLL and their evolution in progression and relapse. *Nature* 526:525-530, 2015
3. Cherng HJ, Jammal N, Paul S, et al: Clinical and molecular characteristics and treatment patterns of adolescent and young adult patients with chronic lymphocytic leukaemia. *Br J Haematol* 194:61-68, 2021
4. Hemminki K, Zitricky F, Försti A, et al: Complex relationships between diagnostics and survival in chronic lymphocytic leukemia in Denmark, Finland, Norway, and Sweden. *Cancers (Basel)* 16:3229, 2024
5. Kramer I, Stilgenbauer S, Dietrich S, et al: Allogeneic hematopoietic cell transplantation for high-risk CLL: 10-year follow-up of the GCLLSG CLL3X trial. *Blood* 130:1477-1480, 2017
6. Thompson PA, Tam CS, O'Brien SM, et al: Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood* 127:303-309, 2016
7. Siddiqi T, Maloney DG, Kenderian SS, et al: Lisocabtagene maraleucel in chronic lymphocytic leukaemia and small lymphocytic lymphoma (TRANSCEND CLL 004): A multicentre, open-label, single-arm, phase 1-2 study. *Lancet* 402:641-654, 2023
8. Melenhorst JJ, Chen GM, Wang M, et al: Decade-long leukaemia remissions with persistence of CD4(+) CAR T cells. *Nature* 602:503-509, 2022
9. Hallek M, Cheson BD, Catovsky D, et al: iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood* 131:2745-2760, 2018
10. Rai KR, Sawitsky A, Cronkite EP, et al: Clinical staging of chronic lymphocytic leukemia. *Blood* 46:219-234, 1975
11. Binet JL, Auquier A, Dighiero G, et al: A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer* 48:198-206, 1981

12. Shustik C, Mick R, Silver R, et al: Treatment of early chronic lymphocytic leukemia: Intermittent chlorambucil versus observation. *Hematol Oncol* 6:7-12, 1998
13. Dighiero G, Maloum K, Desablens B, et al: Chlorambucil in indolent chronic lymphocytic leukemia. French Cooperative Group on Chronic Lymphocytic Leukemia. *N Engl J Med* 338:1506-1514, 1998
14. Langenmayer I, Nerl C, Knauf W, et al: Interferon-alpha 2b (IFN alpha) for early-phase chronic lymphocytic leukaemia with high risk for disease progression: Results of a randomized multicentre study. *Br J Haematol* 94:362-369, 1996
15. Herling CD, Cymbalista F, Groß-Ophoff-Müller C, et al: Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): A randomized phase 3 trial. *Leukemia* 34:2038-2050, 2020
16. Hoehstetter MA, Busch R, Eichhorst B, et al: Early, risk-adapted treatment with fludarabine in Binet stage A chronic lymphocytic leukemia patients: Results of the CLL1 trial of the German CLL study group. *Leukemia* 31:2833-2837, 2017
17. Langerbeins P, Giza A, Robrecht S, et al: Reassessing the chronic lymphocytic leukemia International Prognostic Index in the era of targeted therapies. *Blood* 143:2588-2598, 2024
18. Langerbeins P, Robrecht S, Nieper P, et al: Ibrutinib in early-stage chronic lymphocytic leukemia: The randomized, placebo-controlled, double-blind, phase III CLL12 trial. *J Clin Oncol* 43:392-402, 2025
19. Pflug N, Bahl J, Shanafelt TD, et al: Development of a comprehensive prognostic index for patients with chronic lymphocytic leukemia. *Blood* 124:49-62, 2014
20. Hallek M, Fischer K, Fingerle-Rowson G, et al: Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomised, open-label, phase 3 trial. *Lancet* 376:1164-1174, 2010
21. Farooqui MZ, Valdez J, Martyr S, et al: Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: A phase 2, single-arm trial. *Lancet Oncol* 16:169-176, 2015
22. Eichhorst B, Ghia P, Niemann CU, et al: ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. *Ann Oncol* 35:762-768, 2024
23. Niemann CU: BTK inhibitors: Safety + efficacy = outcome. *Blood* 142:679-680, 2023
24. Kater AP, Wu JQ, Kipps T, et al: Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. *J Clin Oncol* 38:4042-4054, 2020
25. Kater AP, Levin MD, Dubois J, et al: First-line venetoclax combinations versus chemoimmunotherapy in fit patients with relapsed or refractory chronic lymphocytic leukaemia (HOVON141/VISION): Primary analysis of an open-label, randomised, phase 2 trial. *Lancet Oncol* 23:818-828, 2022
26. Munir T, Brown JR, O'Brien S, et al: Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol* 94:1353-1363, 2019
27. Byrd JC, Hillmen P, Ghia P, et al: Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. *J Clin Oncol* 39:3441-3452, 2021
28. Brown JR, Eichhorst B, Hillmen P, et al: Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med* 388:319-332, 2023
29. Niemann CU: Cost-effectiveness targeting CLL. *Blood* 136:1896-1898, 2020
30. Furstentau M, Kater AP, Robrecht S, et al: First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 25:744-759, 2024
31. Jain N, Croner LJ, Allan JN, et al: Absence of BTK, BCL2, and PLCG2 mutations in chronic lymphocytic leukemia relapsing after first-line treatment with fixed-duration ibrutinib plus venetoclax. *Clin Cancer Res* 30:498-505, 2024
32. Ahn IE, Tian X, Wiestner A: Ibrutinib for chronic lymphocytic leukemia with TP53 alterations. *N Engl J Med* 383:498-500, 2020
33. Ahn IE, Farooqui MZ, Tian X, et al: Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. *Blood* 131:2357-2366, 2018
34. Huber H, Tausch E, Schneider C, et al: Final analysis of the CLL2-GIVE trial: obinutuzumab, ibrutinib, and venetoclax for untreated CLL with del(17p)/TP53mut. *Blood* 142:961-972, 2023
35. Al-Sawaf O, Robrecht S, Zhang C, et al: Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study. *Blood* 144:1924-1935, 2024
36. Al-Sawaf O, Zhang C, Jin HY, et al: Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. *Nat Commun* 14:2147, 2023
37. Allan JN, Flinn IW, Siddiqi T, et al: Outcomes in patients with high-risk features after fixed-duration ibrutinib plus venetoclax: Phase II CAPTIVATE study in first-line chronic lymphocytic leukemia. *Clin Cancer Res* 29:2593-2601, 2023
38. Sharman JP, Miranda P, Roos J, et al: Quality-adjusted survival time without symptoms or toxicity of acalabrutinib with or without obinutuzumab in patients with treatment-naïve chronic lymphocytic leukemia. *Leuk Lymphoma* 64:1243-1252, 2023
39. Sharman J: Acalabrutinib ± Obinutuzumab vs. Obinutuzumab + Chlorambucil in Treatment-Naïve Chronic Lymphocytic Leukemia: 5-Year Follow-Up of ELEVATE-TN. 2022: EHA Library, 357528. EHA annual meeting 2022 (Abstract), p 666
40. Davids MS, Sharman JP, Ghia P, et al: Acalabrutinib-based regimens in frontline or relapsed/refractory higher-risk CLL: Pooled analysis of 5 clinical trials. *Blood Adv* 8:3345-3359, 2024
41. Tam CS, Brown JR, Kahl BS, et al: Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): A randomised, controlled, phase 3 trial. *Lancet Oncol* 23:1031-1043, 2022
42. Aarup K, Rotbain EC, Enggaard L, et al: Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib. *Eur J Haematol* 105:646-654, 2020
43. Mato AR, Roeker LE, Allan JN, et al: Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial. *Am J Hematol* 93:1394-1401, 2018
44. Burger JA, Tedeschi A, Barr PM, et al: Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med* 373:2425-2437, 2015
45. Shanafelt TD, Wang XV, Kay NE, et al: Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med* 381:432-443, 2019
46. Hillmen P, Pitchford A, Bloor A, et al: Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): Interim analysis of a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 24:535-552, 2023
47. Sharman JP, Egyed M, Jurczak W, et al: Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve chronic lymphocytic leukaemia (ELEVATE TN): A randomised, controlled, phase 3 trial. *Lancet* 395:1278-1291, 2020
48. Fischer K, Al-Sawaf O, Bahl J, et al: Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med* 380:2225-2236, 2019
49. Eichhorst B, Niemann CU, Kater AP, et al: First-line venetoclax combinations in chronic lymphocytic leukemia. *N Engl J Med* 388:1739-1754, 2023
50. Kater AP: Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *N Engl J Med Evid* 1:EVID02200006, 2022
51. Munir T, Cairns DA, Bloor A, et al: Chronic lymphocytic leukemia therapy guided by measurable residual disease. *N Engl J Med* 390:326-337, 2024
52. Wierda WG, Shah NN, Cheah CY, et al: Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in patients with B-cell malignancies: Analysis of the Richter transformation subgroup from the multicentre, open-label, phase 1/2 BRUIN study. *Lancet Haematol* 11:e682-e692, 2024
53. Niemann CU, Munir T, Moreno C, et al: Fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 24:1423-1433, 2023
54. Sharman JP, Egyed M, Jurczak W, et al: Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. *Leukemia* 36:1171-1175, 2022
55. Shadman M, Munir T, Robak T, et al: Zanubrutinib versus bendamustine and rituximab in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma: median 5-year follow-up of SEQUOIA. *J Clin Oncol* 43:780-787, 2025
56. Brown J, Mashima K, Fernandes S, et al: Mutations detected in real world clinical sequencing during BTK inhibitor treatment in CLL. *Res Sq* [10.21203/rs.3.rs-3837426/v1](https://doi.org/10.21203/rs.3.rs-3837426/v1)
57. Brown JR, Seymour JF, Jurczak W, et al: Fixed-duration acalabrutinib combinations in untreated chronic lymphocytic leukemia. *N Engl J Med* 392:748-762, 2025
58. Wierda WG, Brown J, Abramson JS, et al: Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 2.2024. *J Natl Compr Cancer Netw* 22:175-204, 2024
59. Fisher A, Goradia H, Martinez-Calle N, et al: The evolving use of measurable residual disease in chronic lymphocytic leukemia clinical trials. *Front Oncol* 13:1130617, 2023
60. Rios-Olals FA, Hilal T: Measurable residual disease in chronic lymphocytic leukemia: Current understanding and evolving role in clinical practice. *Curr Treat Options Oncol* 24:907-928, 2023
61. Bottcher S, Ritgen M, Fischer K, et al: Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: A multivariate analysis from the randomized GCLLSG CLL8 trial. *J Clin Oncol* 30:980-988, 2012
62. Varghese AM, Howard DR, Pocock C, et al: Eradication of minimal residual disease improves overall and progression-free survival in patients with chronic lymphocytic leukaemia, evidence from NCRN CLL207: A phase II trial assessing alemtuzumab consolidation. *Br J Haematol* 176:573-582, 2017
63. Schweighofer CD, Ritgen M, Eichhorst BF, et al: Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukaemia (CLL) in first remission: Long-term follow-up of a randomized phase III trial of the German CLL Study Group (GCLLSG). *Br J Haematol* 144:95-98, 2009
64. Munir T, Emmerson J, Hockaday A, et al: Obinutuzumab as consolidation after chemo-immunotherapy: Results of the UK National Cancer Research Institute phase II/III GALACTIC trial. *Br J Haematol* 199:707-719, 2022

65. Wierda WG, Allan JN, Siddiqi T, et al: Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: Primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE study. *J Clin Oncol* 39:3853-3865, 2021
66. Tam CS, Allan JN, Siddiqi T, et al: Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: Primary analysis of the CAPTIVATE FD cohort. *Blood* 139:3278-3289, 2022
67. Allan J, Siddiqi T, Kipps T, et al: Treatment outcomes after undetectable MRD with first-line ibrutinib (ibr) plus venetoclax (ven): Fixed duration treatment (placebo) versus continued ibr with up to 5 years median follow-up in the CAPTIVATE study. *Blood* 140:224-227, 2022 (suppl 1)
68. Hillmen P, Rawstron AC, Brock K, et al: Ibrutinib plus venetoclax in relapsed/refractory chronic lymphocytic leukemia: The CLARITY study. *J Clin Oncol* 37:2722-2729, 2019
69. Soumerai JD, Mato AR, Dogan A, et al: Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: A multicentre, single-arm, phase 2 trial. *Lancet Haematol* 8:e879-e890, 2021
70. Soumerai JDDA, Seshan V, Flaherty K, et al: Long-term follow-up of multicenter phase II trial of zanubrutinib, obinutuzumab, and venetoclax (BOVEN) in previously untreated patients with CLL/SLL. *Hematol Oncol* 41:233-235, 2023
71. Davids MS, Lampson BL, Tyekucheva S, et al: Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: A single-arm, open-label, phase 2 study. *Lancet Oncol* 22:1391-1402, 2021
72. Davids MS, Ryan CE, Lampson BL, et al: Phase II study of acalabrutinib, venetoclax, and obinutuzumab in a treatment-naïve chronic lymphocytic leukemia population enriched for high-risk disease. *J Clin Oncol* 43:788-799, 2025
73. Levin M-D, Kersting S, Dubois J, et al: Improved efficacy with response- and MRD-guided ibrutinib-obinutuzumab (IO) intensification after ibrutinib-venetoclax (IV) in first line chronic lymphocytic leukemia (CLL) patients: Primary analysis of the HOVON 158/Next STEP Phase 2 Trial. *Blood* 144:1013, 2024 (suppl 1)
74. Allan JN, Siddiqi T, Kipps TJ, et al: Treatment outcomes after undetectable MRD with first-line ibrutinib (ibr) plus venetoclax (ven): Fixed duration treatment (placebo) versus continued ibr with up to 5 years median follow-up in the CAPTIVATE study. *Blood* 140:224-227, 2022 (suppl 1)
75. Rawstron AC, Fazi C, Agathangelidis A, et al: A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: An European Research Initiative on CLL study. *Leukemia* 30:929-936, 2016
76. Rawstron AC, Bottcher S, Letestu R, et al: Improving efficiency and sensitivity: European Research Initiative in CLL (ERIC) update on the international harmonised approach for flow cytometric residual disease monitoring in CLL. *Leukemia* 27:142-149, 2013
77. Rawstron AC, Villamor N, Ritgen M, et al: International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. *Leukemia* 21:956-964, 2007
78. Raponi S, Della Starza I, De Propriis MS, et al: Minimal residual disease monitoring in chronic lymphocytic leukaemia patients. A comparative analysis of flow cytometry and ASO IgH RQ-PCR. *Br J Haematol* 166:360-368, 2014
79. Logan AC, Gao H, Wang C, et al: High-throughput VDJ sequencing for quantification of minimal residual disease in chronic lymphocytic leukemia and immune reconstitution assessment. *Proc Natl Acad Sci USA* 108:21194-21199, 2011
80. Ryan CE, Davids MS, Hermann R, et al: MAJIC: A phase III trial of acalabrutinib + venetoclax versus venetoclax + obinutuzumab in previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Future Oncol* 18:3689-3699, 2022

Pegylated Interferons: Still a Major Player for the Treatment of Myeloproliferative Neoplasms

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OVERVIEW

Over the past 35 years, interferons have been explored in various formulations for the management of Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs), such as essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis, and remain a key tool in caring for patients with these diseases. These agents are excellent cytoreductive agents with high rates of hematologic response, are helpful in symptom management, and have a long track record of safety and manageable toxicities. More recently, they have shown promise in sustaining responses over many years, with associated reductions in driver mutations (*JAK2*, *MPL*, *CALR*) of these diseases, particularly in PV and ET. Since reductions in molecular mutant allele burden have been correlated with several response outcomes such as reductions in both thrombotic risk and disease progression, there is emerging proof that interferons may offer disease-modifying activity. These long-term benefits and their use as the preferred agent in young pregnant women who need cytoreduction make interferons often the first choice in young adult population who harbor a lifetime risk of progression. Looking forward, the prospect of sustained treatment-free responses, like chronic myeloid leukemia after deep molecular response, and normal life expectancy may also be on the frontier. Despite relative rookies such as JAK inhibitors in the MPN landscape, the veteran in the game, interferon, remains a key player.

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INTRODUCTION

The myeloproliferative neoplasms (MPNs) polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF) are hematopoietic neoplasms with characteristic driver mutations in most cases with several common clinical features including increased risk for thrombosis; significant symptoms such as fatigue, pruritus, and symptomatic splenomegaly; and predisposition to progression to either MF or AML.^{1–5} Overall, MPNs of all subtypes are associated with inferior survival compared with the general population.⁶ Activating driver mutations include those found in *JAK2* (*JAK2* V617F in >90% of patients with PV and approximately 60% of patients with ET or MF), the thrombopoietin receptor gene *MPL*, and calreticulin (*CALR*).⁷ Therapeutic goals include reducing risks of thrombotic events, managing associated symptom burden, and mitigation of transformation risk. The use of interferon- α (IFN α), now for more than 35 years, remains a powerful and safe tool in the management of these chronic diseases.

In 1957, Isaacs and Lindenmann⁸ noted that when viral particles were heated and incubated, they released a group of novel cytokines. Because of the recognition that these factors affected viral replication, they called them interferons. Interferons are a group of glycoproteins that include three

main types depending on the cell of origin: (1) IFN α from plasmacytoid dendritic cells, (2) interferon- β from hematopoietic cell types, and (3) interferon- γ from T lymphocytes and Natural Killer cells.⁹ IFN α and interferon β are considered type I interferons, whereas interferon γ is a type II interferon. In addition to affecting viral replication as part of innate immunity,¹⁰ we now understand that interferons can also affect immune cell expression.¹¹ The transmembrane receptor, IFN α receptor, can be directly bound by both IFN α and IFN β , leading to activation of Signal Transducer and Activator of Transcription proteins that subsequently lead to regulation of intracellular gene transcription.¹² In laboratory studies, this activation has been shown to lead to apoptosis of hematopoietic progenitors and colony unit megakaryocytes.^{13,14} Studies in mice have found that interferon induces differentiation in *JAK2* V617F–mutated quiescent stem cells, leading to depletion of the mutant clone over time by directly targeting progenitor cells.^{15,16} In the early 1980s, human interferons were identified and purified for clinical use.^{17,18}

Initially, commercially available nonpegylated forms of IFN α were used in clinical studies, and the development of pegylated versions allowed for longer dosing intervals and reduced toxicity. Available pegylated forms today include pegylated interferon- α 2a (PEG2A) and ropeginterferon α 2b

PRACTICAL APPLICATIONS

- Interferons have a long history of clinical efficacy and safety in myeloproliferative neoplasms (MPNs).
- Patients with low-risk polycythemia vera sustain hematologic responses longer than those receiving hydroxyurea over the long term.
- Interferon therapy has been shown to drive sustained reductions in MPN-mutant allele burdens (JAK2 and CALR), and these reductions have been correlated with reduction in several clinical outcomes such as thrombotic and progression risks.
- Interferons are the only agents suitable for managing MPNs during pregnancy.

(ROPEG) as summarized in Table 1. The biological activity of the two subtypes (2a and 2b) is felt to be identical. ROPEG is the only interferon with US Food and Drug Administration (FDA) approval for use in MPNs although PEG2A, widely available for the treatment of hepatitis B, is commonly used off-label in MPNs.

INTERFERON THERAPY IN MPNs: CLINICAL EVIDENCE

Patients With PV

With the first described use of recombinant IFN α in MPNs in 1988,¹⁹ an extensive experience with various formulations has evolved over the several decades. With many notable studies using IFN α (Table 2), the role of interferons in managing MPNs is most mature in PV. After several single-center studies,^{20,23,29} a multicenter study by the Myeloproliferative Disorders Research Consortium (MPD-RC) of PEG2A explored the role of this agent in patients with both PV and ET who were resistant or intolerant to hydroxyurea (HU).²¹ The MPD-RC 111 study evaluated the ability of PEG2A to induce complete hematologic response (CHR) and partial hematologic response (PR) and included 50 patients with high-risk PV. The overall response rate (ORR) of 60% in patients with PV included 22% CHR and 38% PR, after 12 months of therapy. Therapy was well-tolerated with most

adverse events (AEs) manageable, and only 13.9% of patients discontinued treatment because of AEs.

A contemporaneous partner study by the same organization (MPD-RC 112) extended this therapy in a randomized, phase III study comparing PEG2A with HU in the frontline setting of high-risk PV/ET.²⁴ The ORR (CHR and PR) was 42% and 48% in patients receiving HU and PEG2A, respectively, at 12 months. With respect to hematocrit control without phlebotomy, 43% and 65% of HU and PEG2A, respectively, achieved this goal. Thrombotic events were rare and similar in the two arms. While CHR rates were similar at 12 months, PEG2A therapy resulted in greater reductions in *JAK2V617F* driver mutation burden at 24 months compared with HU. Both accrual and follow-up to this trial were limited by study drug availability, leading to premature closure.

In the phase III PROUD-PV trial and its extension study, CONTINUATION-PV, early PV (no previous cytoreductive treatment or <3 years of previous HU), 254 patients were randomly assigned to receive either ROPEG or the standard therapy, HU.²⁵ Designed to demonstrate noninferiority at 12 months, similar rates of the composite primary end point of CHR with normal spleen size were seen at 1 year (21% ROPEG v 28% standard therapy) in PROUD-PV. However, in the CONTINUATION-PV extension, improved rates of CHR (71% with ROPEG v 51% with HU) and molecular responses (66% ROPEG v 27% HU) were observed. Subsequent 5-year follow-up confirmed ongoing superior CHR responses with interferon of 55.8% versus 44% in the standard arm and superior molecular responses by European LeukemiaNet criteria with ROPEG (69.1%) versus HU (21.6%).²⁶

Recently, the use of pegylated interferons in a low-risk (age <60 years and no history of thrombosis) population was explored in a randomized, phase II, open-label study comparing ROPEG with phlebotomy only.²² Both groups received low-dose aspirin, and patients in the experimental arm received a fixed dose of 100 mcg ROPEG once every 2 weeks. Nonresponders were able to cross over at 1 year in an extension study, whereas responders continued initially assigned treatment until month 24. The primary end point was maintenance of hematocrit less than or equal to 45% at 12 months in the absence of progressive disease. This composite end point was met in 52 of 64 patients (81%) receiving ROPEG and 32 of 63 patients (51%) in the standard phlebotomy group. There were no progressions in the ROPEG

TABLE 1. Pegylated Interferons in MPNs

Agent	Typical Starting Dose	FDA/EMA Approval
Ropeginterferon alfa-2b	100 mcg sc once every 2 weeks	Treatment of adults with polycythemia vera
Peginterferon alfa-2a	45-90 mcg sc once every 7 days	None

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; mcg, microgram; MPNs, myeloproliferative neoplasms; sc, subcutaneously.

TABLE 2. Notable Prospective Pegylated Interferon Trials in MPNs

Disease(s)	Agent(s)	Trial	No. of PT	Comments	Reference
ET/PV	PEG2A	Phase II	40 PV 39 ET	High hematologic response rates, complete molecular responses observed	Quintas-Cardama et al ²⁰
ET/PV	PEG2A	MPD-RC 111 Phase II	50 PV 65 ET	High response rates in previously treated patients	Yacoub et al ²¹
PV	Ropeginterferon v phlebotomy	Phase II	127	Improved hematocrit, symptom, and spleen size control with ropeginterferon	Barbui et al ²²
PV	PEG2A	PVN1 Phase II	40	High rates of hematologic and molecular responses	Kiladjian et al ²³
ET/PV	PEG2A v HU	MPD-RC 112 Phase III	168	More effective at normalizing counts and reducing JAK2 V617F VAF	Mascarenhas et al ²⁴
PV	Ropeginterferon v HU	PROUD-PV/CONTINUATION PV Phase III	257	ROPEG responses improved over time compared with HU	Gisslinger et al ²⁵ Kiladjian et al ²⁶
ET	Ropeginterferon v anagrelide	SURPASS-ET Phase III		Ongoing trial	Verstovsek et al ²⁷
ET	Ropeginterferon	ROP-ET Phase III		Ongoing trial	Kiladjian et al ²⁸

Abbreviations: ET, essential thrombocythemia; HU, hydroxyurea; MPD-RC, Myeloproliferative Disorder Research Consortium; PEG2A, pegylated interferon- α 2a; PV, polycythemia vera; ROP, ropeginterferon; ROPEG, ropeginterferon α 2b; VAF, variant allele frequency.

group and eight of 63 (13%) with standard treatment. While there was no significant change in absolute JAK2V617F variant allele frequency (VAF) in the standard group, reductions in JAK2V617F VAF of 11.9% at 1 year and 23.1% at 2 years were seen with ROPEG therapy. Based on these compelling data, ROPEG can now be considered a preferred agent in managing low-risk PV.

Patients With ET

Compared with data available about the use of IFNs in PV, their role in ET is less well established in large, randomized studies. In a retrospective, multicenter study from the German Study Group-Myeloproliferative Neoplasms, the experience of treating 127 patients (59% frontline) with ET using pegylated interferons was described.³⁰ The ORR was 89% with 54% complete responses at any time during the study with a median treatment duration of 2.3 years. There was only one transformation to MF and no transformations to AML, and thrombotic events were rare (three arterial and five venous events).

Only a single phase III randomized trial (MPD-RC 112 referenced above) has included treatment-naïve participants with ET who met study-defined criteria for high-risk disease.²⁴ High risk was defined as having at least one of these factors: 60 years or older, history of thrombosis or bleeding, platelet count $>1,500 \times 10^9/L$, vasomotor symptoms, or symptomatic splenomegaly requiring cytoreductive therapy for symptom control, or a history of diabetes or hypertension requiring therapy. Patients were randomly assigned to receive either PEG2A or HU. No significant differences were seen between the two study arms with CHR rates of 44% and

45% in PEG2A and HU therapies, respectively. As seen in patients with PV, the molecular responses were similar at 12 months, but further reductions were observed in PEG2A over time, yet increased in patients treated with HU.²⁴

With multiple smaller studies published, a meta-analysis, including both nonpegylated and pegylated forms of IFN α , examined 30 studies of over 700 patients with ET.³¹ The ORR was 80% with a CHR rate of 59% for all studies combined. Rates of thrombosis and discontinuation of therapy because of AEs were low at 1.2% and 8.8% annually.

Two ongoing studies aim to advance our knowledge in the ET population. ROG-ET is a multicenter, single-arm, phase III study in the European Union for patients with ET who are intolerant, resistant, or otherwise not eligible for other cytoreductive treatment.²⁸ SURPASS-ET (ClinicalTrials.gov identifier: [NCT04285086](https://clinicaltrials.gov/ct2/show/study/NCT04285086)), another multicenter trial, randomly assigns patients with ET in the second-line setting to either ROPEG or anagrelide, the only currently FDA-approved agent for the treatment of ET.²⁷

Patients With MF

Considerably less information is available to evaluate the response of MF to IFN α therapy although there is some consensus that its utility in advanced disease is limited. In a small study of 17 patients, patients with early primary MF, defined as low- or intermediate-1-risk disease, were enrolled and treated with nonpegylated IFN alpha-2b at 500,000 to 1 million units subcutaneously three times per week or PEG2A.³² With about 80% achieving some clinical benefit, notably four of the 15 patients (26.7%) showed

improvement in bone marrow morphology including reduction in fibrosis at 3 years, suggesting that in early MF, there may be potential for disease-modifying activity.³² In a meta-analysis of 10 studies including 141 patients with MF, the ORR was reported to be 49%, with no difference observed between pegylated or nonpegylated formulations, although treatment discontinuations were more common in nonpegylated therapy (35.8% annually) compared with pegylated (0.5% annually).³³

MOLECULAR RESPONSES: A FUTURE PARADIGM

While chronic in nature, a challenge of MPN diseases is that they generally lack a cure outside of a stem-cell transplant. Most therapy for these diseases is targeted at symptom management, reductions in thrombotic and progression risk, and improving quality of life. However, data from a large single-center retrospective study found that early treatment of PV yields improved MF-free and overall survival.³⁴ In 470 patients treated with interferon, HU, or phlebotomy only, both low- and high-risk patients had improved MF-free survival at 20 years. In a multivariable analysis, longer time on interferon was associated with a lower risk of MF and mortality, hazard ratio (HR), 0.91, $P < .001$ and HR, 0.94, $P = .012$, respectively. While limited by their retrospective nature, these data suggest that treatment with interferon can be disease-modifying. This is corroborated by additional molecular studies in PV that show that higher JAK2 VAF correlated with transformation and venous thrombotic events.^{35–37} High VAF of JAK2 has further been shown to correlate with worse hematologic blood counts, increased splenomegaly, and increased symptom burden.^{35,38–40} Interferon has been shown to induce a molecular response in patients with MPNs. In a phase II study of pegylated IFN α in PV, quantitative evaluation of the JAK2 allele by real-time polymerase chain reaction showed that the percentage of JAK2 VAF decreased in 89% of patients treated.⁴¹ In these 27 patients, the mean decrease was 44% over 12 months without a plateau. These data show that disease severity correlates with higher JAK2 VAF and that interferon therapy can modify disease outcomes with its reduction in JAK2 allele burden.

Similar results have also been observed in CALR-mutated ET. The CALR gene expression in mutant clones of hematopoietic cells leads to unregulated cell growth.⁴² Compared with JAK2-mutant disease, patients with CALR mutations are younger with a slight male predominance and tend to have less thrombosis risk.¹⁶ Similar to its impact on JAK2 VAF, the use of interferon in CALR-mutant MPNs has been shown to reduce the allele frequency. In a study of 31 patients with ET and mutated CALR, treatment with interferon resulted in a reduction of the VAF from 41% to 26% including two patients who achieved a molecular response.⁴³ CALR allele frequency correlates with disease severity.⁴³ For patients with an MPN driven by a CALR mutation, especially those who are younger and of childbearing potential, interferon therapy could be considered to reduce CALR VAF.

Given the evidence of molecular responses seen with interferon, is there a possibility of sustained responses after therapy discontinuation, analogous to that which we see in CML? Daltro de Oliveira et al⁴⁴ alluded to this possibility in a retrospective look at 381 patients treated with interferons. Of the 250 who discontinued IFN α therapy for ET, PV, or MF, 66.9% remained in CHR after a median follow-up of 72.4 months. Patients were more likely to remain in CHR without further treatment if the VAF was lower than 10% at the time of IFN α discontinuation. Interestingly, Abu-Zheinah et al⁴⁵ were also able to demonstrate that IFN α -treated patients with PV at an academic institution had similar overall survival compared with the general population. These data, while promising, warrant further investigation into the long-term impact of IFN α on life expectancy and potential for sustained treatment-free responses.

MANAGING TOXICITY

Early on, treatment with IFN α was associated with a rapid onset flu-like toxicity profile that led to a high rate of early discontinuation.^{4,46,47} Usually appearing within 1–3 hours of administration, symptoms included fever, malaise, headaches, myalgia, and joint pain.^{4,46} Symptoms are dose-dependent, however, and tend to decrease in severity within the first month of initiation of therapy.^{46,48} The formulation of interferon correlates with toxicity, with pegylated versions of interferon showing less toxicity. In addition to their decreased burden of administration, pegylated formulations of interferon are associated with an improvement in flu-like symptoms.⁴⁶ Phase II and III trials of pegylated interferon showed a discontinuation rate of 13%–15%,^{21,24} but in a systematic review of 53 studies with PV and ET and nearly 1,500 patients, the discontinuation rate was only 6.5%–8.8%.^{31,33} One strategy that has been shown to be effective in reducing the initial onset of symptoms is to initiate treatment at a lower dose and ramp up to treatment dose level.⁴⁸ This strategy is particularly effective when transitioning from another therapy such as HU; the previous therapy can be tapered down simultaneously with interferon ramp-up over 6–8 weeks. During initiation of interferon therapy and for the first three months, patients should be monitored closely with frequent laboratory studies and clinical examinations for toxicity. The most common toxicities with interferon use include cytopenias, fatigue, musculoskeletal pain, mood disorders, and autoimmune abnormalities. Pre-existing psychiatric disorders and uncontrolled autoimmune disease are generally considered contraindications to treatment with interferon. The most common hematologic toxicities are anemia, thrombocytopenia, and lymphopenia with neutropenia seen more rarely.⁴⁹ The most common psychiatric changes seen with interferon use are anxiety, irritability, and depression. Given its chronic use, interferons should be used cautiously in those with significant psychiatric symptoms. Other adverse effects seen less commonly include skin rashes, hair loss, nausea, diarrhea, weight loss, and liver, cardiac, and neurologic toxicities. The majority of these adverse effects can

be managed with interruption of interferon dosing followed by resumption at a lower dose once the toxicity recovers. Interferon use should be permanently discontinued if significant cardiovascular toxicity occurs, there is significant pulmonary function impairment, or a hypersensitivity reaction occurs.

SPECIAL CONSIDERATIONS: ADOLESCENTS AND YOUNG ADULTS AND PREGNANCY

MPNs are generally considered a disease of older adults; however, up to 20% of MPNs are diagnosed in younger patients age 40 years.⁵⁰ The long-term burden of these diseases has not been sufficiently investigated. In a retrospective cohort of adolescents and young adults with MPNs, thrombotic complications were seen in nearly a quarter of patients including 9% within the splanchnic circulation.⁵¹ While current guidelines recommend either HU or interferon as first-line treatment options for these patients, the potential to delay progression and reduce the risk of transformation via interferon presents a compelling option. Furthermore, in females of childbearing potential, reducing the allele burden before pregnancy is optimal because of the direct correlation between JAK VAF and thrombosis.³⁵⁻³⁷ In addition to the increased risk of thrombosis for patients with MPNs who become pregnant, they are also at very high risk of spontaneous abortion.^{52,53} In a systematic review of pregnancy in patients with MPNs, the use of interferon in addition to aspirin was associated with a higher odds of live birth.⁵² The use of HU is contraindicated in pregnancy because of its impacts on folate metabolism. Ruxolitinib has not been approved for pregnant patients and is also

contraindicated. Although no formal studies have been performed with interferon in pregnancy, both pharmacologic and clinical retrospective data have demonstrated safety.^{54,55} In a meta-analysis of maternal and fetal outcomes in interferon exposure during pregnancy, the risks of birth defects, live birth, spontaneous abortion, preterm delivery, stillbirth, and maternal complications were not increased in patients exposed to interferons.⁵⁶ The levels of interferon in breastmilk are miniscule, and retrospective data in multiple sclerosis do not appear to show any impact on babies being breastfed by mothers on interferon therapy.⁵⁷ Despite the lack of data and given the known adverse maternal outcomes such as thrombosis and hemorrhage, the benefits of pegylated interferon use may outweigh the risk of poorly controlled MPNs in those who need cytoreduction during pregnancy.

CONCLUSION

For decades, interferon has been used to manage patients with MPNs with excellent hematologic responses, particularly in PV, ET, and potentially early MF. While the non-pegylated formulations were plagued with toxicity and feasibility issues, the pegylated versions have largely overcome these challenges with less frequent administrations and improved tolerance. Molecular responses, not seen with other traditional agents such as HU, show evidence of targeting of the malignant clone with improved long-term event-free survival. The potential for molecular responses and disease-modifying activity with chronic exposure makes IFN α a great candidate for early intervention in MPNs, particularly in a younger population.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Barbui T, Barosi G, Birgegard G, et al: Philadelphia-negative classical myeloproliferative neoplasms: Critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 29:761-770, 2011
- Tefferi A, Barbui T: Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. *Am J Hematol* 98:1465-1487, 2023
- Tefferi A, Vannucchi AM, Barbui T: Essential thrombocythemia: 2024 update on diagnosis, risk stratification, and management. *Am J Hematol* 99:697-718, 2024
- Kiladjian J-J, Mesa RA, Hoffman R: The renaissance of interferon therapy for the treatment of myeloid malignancies. *Blood* 117:4706-4715, 2011
- Nangalia J, Green AR: Myeloproliferative neoplasms: From origins to outcomes. *Blood* 130:2475-2483, 2017
- Srour SA, Devesa SS, Morton LM, et al: Incidence and patient survival of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms in the United States, 2001-12. *Br J Haematol* 174:382-396, 2016
- Thiele J, Kvasnicka HM, Orazi A, et al: The international consensus classification of myeloid neoplasms and acute leukemias: Myeloproliferative neoplasms. *Am J Hematol* 98:544-545, 2023
- Isaacs A, Lindenmann J: Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci* 147:258-267, 1957
- Demerdash Y, Kain B, Essers MAG, et al: Yin and Yang: The dual effects of interferons on hematopoiesis. *Exp Hematol* 96:1-12, 2021
- Borden EC, Sen GC, Uze G, et al: Interferons at age 50: Past, current and future impact on biomedicine. *Nat Rev Drug Discov* 6:975-990, 2007
- Taylor M, Godlewska B, Near J, et al: Effect of interferon- α on cortical glutamate in patients with hepatitis C: A proton magnetic resonance spectroscopy study. *Psychol Med* 44:789-795, 2014

12. Ivashkiv LB, Donlin LT: Regulation of type I interferon responses. *Nat Rev Immunol* 14:36-49, 2014
13. Raefsky EL, Platanius LC, Zombos NC, et al: Studies of interferon as a regulator of hematopoietic cell proliferation. *J Immunol* 135:2507-2512, 1985
14. Wang YS, Youngster S, Bausch J, et al: Identification of the major positional isomer of pegylated interferon alpha-2b. *Biochemistry* 39:10634-10640, 2000
15. Essers MAG, Offner S, Blanco-Bose WE, et al: IFN α activates dormant haematopoietic stem cells in vivo. *Nature* 458:904-908, 2009
16. How J, Hobbs GS, Mullally A: Mutant calreticulin in myeloproliferative neoplasms. *Blood* 134:2242-2248, 2019
17. Derynck R, Content J, DeClercq E, et al: Isolation and structure of a human fibroblast interferon gene. *Nature* 285:542-547, 1980
18. Cantell K, Hirvonen S, Kauppinen HL, et al: Production of interferon in human leukocytes from normal donors with the use of Sendai virus. *Methods Enzymol* 78:29-38, 1981
19. Silver RT: Recombinant interferon-alpha for treatment of polycythemia vera. *Lancet* 2:403, 1988
20. Quintás-Cardama A, Kantarjian H, Manshouri T, et al: Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol* 27:5418-5424, 2009
21. Yacoub A, Mascarenhas J, Kosiorek H, et al: Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. *Blood* 134:1498-1509, 2019
22. Barbui T, Vannucchi AM, De Stefano V, et al: Ropeginterferon versus standard therapy for low-risk patients with polycythemia vera. *NEJM Evid 2:EVIDoa2200335*, 2023
23. Kiladjian J-J, Cassinat B, Chevet S, et al: Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood* 112:3065-3072, 2008
24. Mascarenhas J, Kosiorek HE, Prchal JT, et al: A randomized phase 3 trial of interferon- α vs hydroxyurea in polycythemia vera and essential thrombocythemia. *Blood* 139:2931-2941, 2022
25. Gisslinger H, Klade C, Georgiev P, et al: Ropeginterferon alfa-2b versus standard therapy for polycythemia vera (PROUD-PV and CONTINUATION-PV): A randomised, non-inferiority, phase 3 trial and its extension study. *Lancet Haematol* 7:e196-e208, 2020
26. Kiladjian J-J, Klade C, Georgiev P, et al: Long-term outcomes of polycythemia vera patients treated with ropeginterferon Alfa-2b. *Leukemia* 36:1408-1411, 2022
27. Verstovsek S, Komatsu N, Gill H, et al: SURPASS-ET: Phase III study of ropeginterferon alfa-2b versus anagrelide as second-line therapy in essential thrombocythemia. *Future Oncol* 18:2999-3009, 2022
28. Kiladjian JJ, Marin FF, Al-Ali HK, et al: ROP-ET: A prospective phase III trial investigating the efficacy and safety of ropeginterferon alfa-2b in essential thrombocythemia patients with limited treatment options. *Ann Hematol* 103:2299-2310, 2024
29. Crisà E, Cerrano M, Beggiato E, et al: Can pegylated interferon improve the outcome of polycythemia vera patients? *J Hematol Oncol* 10:15, 2017
30. Stegelmann F, Teichmann LL, Heide FH, et al: Clinicohematologic and molecular response of essential thrombocythemia patients treated with pegylated interferon- α : A multi-center study of the German Study Group-Myeloproliferative Neoplasms (GSG-MPN). *Leukemia* 37:924-928, 2023
31. Bewersdorf JP, Giri S, Wang R, et al: Interferon alpha therapy in essential thrombocythemia and polycythemia vera—A systematic review and meta-analysis. *Leukemia* 35:1643-1660, 2021
32. Silver RT, Vandrís K, Goldman JJ: Recombinant interferon-alpha may retard progression of early primary myelofibrosis: A preliminary report. *Blood* 117:6669-6672, 2011
33. Bewersdorf JP, Giri S, Wang R, et al: Interferon therapy in myelofibrosis: Systematic review and meta-analysis. *Clin Lymphoma Myeloma Leuk* 20:e712-e723, 2020
34. Abu-Zeinah G, Krichevsky S, Cruz T, et al: Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival. *Leukemia* 35:2592-2601, 2021
35. Guglielmelli P, Mora B, Gesullo F, et al: JAK2V617F molecular response to ruxolitinib in patients with PV and ET is associated with lower risk of progression to secondary myelofibrosis. *Blood* 140:1788-1789, 2022 (suppl 1)
36. Alvarez-Larrán A, Bellosillo B, Pereira A, et al: JAK2V617F monitoring in polycythemia vera and essential thrombocythemia: Clinical usefulness for predicting myelofibrotic transformation and thrombotic events. *Am J Hematol* 89:517-523, 2014
37. Soudet S, Le Roy G, Cadet E, et al: JAK2 allele burden is correlated with a risk of venous but not arterial thrombosis. *Thromb Res* 211:1-5, 2022
38. Vannucchi AM, Antonioli E, Guglielmelli P, et al: Clinical profile of homozygous JAK2 617V>F mutation in patients with polycythemia vera or essential thrombocythemia. *Blood* 110:840-846, 2007
39. Passamonti F, Rumi E, Pietra D, et al: A prospective study of 338 patients with polycythemia vera: The impact of JAK2 (V617F) allele burden and leukocytosis on fibrotic or leukemic disease transformation and vascular complications. *Leukemia* 24:1574-1579, 2010
40. Nielsen C, Birgens HS, Nordestgaard BG, et al: Diagnostic value of JAK2 V617F somatic mutation for myeloproliferative cancer in 49 488 individuals from the general population. *Br J Haematol* 160:70-79, 2013
41. Kiladjian J-J, Cassinat B, Turlure P, et al: High molecular response rate of polycythemia vera patients treated with pegylated interferon α -2a. *Blood* 108:2037-2040, 2006
42. Klampfl T, Gisslinger H, Harutyunyan AS, et al: Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med* 369:2379-2390, 2013
43. Verger E, Cassinat B, Chauveau A, et al: Clinical and molecular response to interferon-alpha therapy in essential thrombocythemia patients with CALR mutations. *Blood* 126:2585-2591, 2015
44. Daltro De Oliveira R, Soret-Dulphy J, Zhao LP, et al: Interferon-alpha (IFN) therapy discontinuation is feasible in myeloproliferative neoplasm (MPN) patients with complete hematological remission. *Blood* 136:35-36, 2020 (suppl 1)
45. Abu-Zeinah G, Silver RT, Abu-Zeinah K, et al: Normal life expectancy for polycythemia vera (PV) patients is possible. *Leukemia* 36:569-572, 2022
46. Kiladjian J-J, Chomienne C, Fenaux P: Interferon- α therapy in bcr-abl-negative myeloproliferative neoplasms. *Leukemia* 22:1990-1998, 2008
47. How J, Hobbs G: Use of interferon alfa in the treatment of myeloproliferative neoplasms: Perspectives and review of the literature. *Cancers* 12:1954, 2020
48. Silver RT: Long-term effects of the treatment of polycythemia vera with recombinant interferon-alpha. *Cancer* 107:451-458, 2006
49. Tefferi A, Elliot MA, Yoon SY, et al: Clinical and bone marrow effects of interferon alfa therapy in myelofibrosis with myeloid metaplasia. *Blood* 97:1896, 2001
50. Goulart H, Masarova L, Mesa R, et al: Myeloproliferative neoplasms in the adolescent and young adult population: A comprehensive review of the literature. *Br J Haematol* 205:48-60, 2024
51. England JT, Szuber N, Sirhan S, et al: Clinical features and long-term outcomes of a pan-Canadian cohort of adolescents and young adults with myeloproliferative neoplasms: A Canadian MPN Group Study. *Leukemia* 38:570-578, 2024
52. Maze D, Kazi S, Gupta V, et al: Association of treatments for myeloproliferative neoplasms during pregnancy with birth rates and maternal outcomes: A systematic review and meta-analysis. *JAMA Netw Open* 2:e1912666, 2019
53. Griesshammer M, Sadjadian P, Wille K: Contemporary management of patients with BCR-ABL1-negative myeloproliferative neoplasms during pregnancy. *Expert Rev Hematol* 11:697-706, 2018
54. Klehmet J, Begus-Nahrman Y, Taipale K, et al: Impact of interferon beta exposure on birth outcome and child development—Results from the post-authorisation safety study PRIMA. *Mult Scler Relat Disord* 77:104844, 2023
55. Pons J-C, Lebon P, Frydman R, et al: Pharmacokinetics of interferon-alpha in pregnant women and fetoplacental passage. *Fetal Diagn Ther* 10:7-10, 1995
56. Zhang M, Fu S, Ren D, et al: Maternal and fetal outcomes after interferon exposure during pregnancy: A systematic review with meta-analysis. *Front Reprod Health* 3:702929, 2021
57. Ciplea AI, Langer-Gould A, Stahl A, et al: Safety of potential breast milk exposure to IFN- β or glatiramer acetate: One-year infant outcomes. *Neurol Neuroimmunol Neuroinflamm* 7:e757, 2020

Taking a Bite Out of Small Cell Lung Cancer By Leveraging Precision-Directed Delta-Like Ligand-3 Therapies

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OVERVIEW

The therapeutic landscape of small cell lung cancer (SCLC) is undergoing a paradigm shift with the emergence of delta-like ligand-3 (DLL3)-directed therapies, particularly tarlatamab, a first-in-class bispecific T-cell engager designed to bind to cluster of differentiation-3 on T cells and DLL3 on tumors cells, demonstrating promising efficacy, including potential intracranial activity, and a manageable safety profile. By leveraging biologic insights into SCLC subtypes and DLL3 expression, these therapies mark a step forward in precision immunotherapy for this recalcitrant disease. As new DLL3-targeting agents continue to evolve through bispecific, trispecific constructs, antibody-drug conjugates, and chimeric antigen receptor-based approaches, they bring hope for improved outcomes in SCLC and other high-grade neuroendocrine carcinomas. Importantly, the thoughtful incorporation of toxicity mitigation strategies, equitable access, and multidisciplinary care models will be critical to ensure that clinical advances translate into meaningful, real-world benefits. The challenge ahead lies in balancing efficacy with patient quality of life, financial burden, and time toxicity, an effort that requires continuous innovation, collaboration, and a patient-centered approach.

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INTRODUCTION

Small cell lung cancer (SCLC) remains one of the most challenging types of lung cancer with a highly metastatic potential and is traditionally resistant to standard chemotherapies in the relapsed setting, with overall dismal outcomes. For decades, treatment options have remained limited, and survival gains for extensive-stage (ES) or metastatic SCLC have been modest despite incremental improvements in median overall survival (OS) of approximately 2–3 months with first-line chemotherapy combined with immune checkpoint inhibitors (ICIs) versus chemotherapy alone.¹ In this landscape of urgency and unmet need, a new class of precision immunotherapy with the potential to create a landmark shift in the management of SCLC has emerged: delta-like ligand-3 (DLL3)-directed bispecific T-cell engagers. These agents harness the body's immune system with precision, redirecting T cells to attack DLL3-expressing tumor cells while minimizing off-target effects.²

Tarlatamab, a first-in-class DLL3/cluster of differentiation-3 (CD3) bispecific T-cell engager (BiTE), represents a hopeful breakthrough for patients with relapsed or refractory SCLC, a population with historically poor outcomes.^{3–5} Beyond its promising efficacy, including emerging data in patients with brain metastases, tarlatamab's accelerated approval in May 2024 by the US Food and Drug Administration (FDA) marks a pivotal moment in translating molecular understanding of SCLC into real-world therapeutic

impact.^{6,7} Yet, with the innovation of this new class of therapies for an aggressive and treatment refractory solid tumor such as SCLC, medical oncologists have come to gradually better understand new bispecific T-cell engager therapy-associated challenges comprising managing unique toxicities such as cytokine release syndrome (CRS), neurotoxicity, financial burden, and the evolving logistics of initial step-up dosing requiring inpatient administration.

This review explores the rationale behind targeting DLL3, clinical data supporting tarlatamab's use, and emerging strategies to safely implement bispecific T-cell engagers in academic and community settings. As we move from scientific discovery to bedside care, it is imperative that we approach every new therapeutic innovation using a holistic approach to ensure that every patient with SCLC not only lives longer but lives better.

SCLC EPIDEMIOLOGY AND TREATMENT LANDSCAPE

SCLC is one of the most aggressive subtypes of lung cancer, accounting for 15% of all lung cancers. Per the US Veterans Administration classification system, limited-stage (LS)-SCLC constitutes SCLC confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field, whereas ES-SCLC constitutes disease that cannot be encompassed within a single radiation field and typically includes distant metastases, malignant pleural or pericardial effusions, or contralateral lung or supraclavicular lymph

PRACTICAL APPLICATIONS

- Tarlatamab is a bispecific T-cell engager (BiTE) that binds to delta-like ligand-3 (DLL3) on small cell lung cancer (SCLC) cells and cluster of differentiation-3 on T cells, thereby delivering targeted treatment to tumor cells while minimizing damage to normal tissues.
- Tarlatamab has shown promising efficacy in relapsed/refractory SCLC after progression on first-line platinum-based chemotherapy. In the extended follow-up of DeLLphi-301, the selected 10 mg group demonstrated an objective response rate of 40% and a disease control rate of 70%. Additionally, the planned interim analysis from the phase III DeLLphi-304 study showed a statistically significant overall survival benefit over standard-of-care chemotherapy for patients with SCLC who progressed on or after a single line of platinum-based chemotherapy.
- Two unique toxicities of tarlatamab include cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. Ongoing studies aim to refine the management of these toxicities, including better outpatient administration approaches along with preemptive toxicity mitigation to improve patient outcomes.
- The identification of DLL3 expression in neuroendocrine carcinomas has led to the development of innovative DLL3-targeting therapies, such as bispecific and trispecific constructs, chimeric antigen receptor-based approaches, and antibody-drug conjugates. These therapies could provide a promising therapeutic strategy for patients with these aggressive tumors that have limited treatment options.

node involvement.⁸ The incidence rate of SCLC has dropped from 9.0 per 100,000 persons in 2000 to 4.6 per 100,000 in 2020.⁹ Given the well-established link between smoking and SCLC,^{10–12} the observed decline in incidence may be attributed, at least in part, to the steady decrease in smoking trends over the past decade.¹³ However, with the recent implementation of ICIs as part of first-line regimens, the 3-year OS and 5-year OS are approaching approximately 15% and 12%, respectively, in patients with ES-SCLC, while in patients with LS-SCLC after consolidation ICI, the 3-year OS is nearing 56%.^{14–16}

The standard-of-care (SOC) first-line therapy for LS-SCLC has traditionally included concurrent chemoradiotherapy with a platinum-based agent (cisplatin or carboplatin plus etoposide) and once daily or twice daily thoracic radiotherapy, with or without prophylactic cranial irradiation.⁸ In

late 2024, maintenance durvalumab after concurrent chemotherapy with radiation was approved in LS-SCLC (ADRIATIC trial) because of significant improvement in median progression-free survival (PFS) and OS.¹⁶ The use of chemoimmunotherapy has also shown promise in the management of ES-SCLC with current SOC, including PD-L1 inhibitors atezolizumab or durvalumab in combination with platinum-etoposide chemotherapy that gained FDA approvals on the basis of the findings of the Impower 133 and CASPIAN trials, respectively. Even with these chemoimmunotherapy regimens in the first line, the degree of median OS benefit is less than three months in ES-SCLC.^{17,18} Historically, topotecan was the only approved agent for second-line use in relapsed SCLC until lurbinectedin (a transcription factor inhibitor) got accelerated FDA approval in this setting in 2020.¹⁹ Both topotecan and lurbinectedin are associated with considerable cytopenias and limited response rates. The lack of approved SOC therapies for patients who relapse after ≥two previous therapies, along with high drug resistance, highlights the need for novel precision medicine-based therapies for the management of SCLC as a highly recalcitrant cancer.²⁰

SCLC SUBTYPES AND THERAPEUTIC VULNERABILITIES

Over the past decade, a better understanding of SCLC biology has enabled its classification into four subtypes on the basis of the distinct expression of specific transcription factors: *ASCL1* (SCLC-A), *NEUROD1* (SCLC-N), *POU2F3* (SCLC-P), and *YAP1* (SCLC-Y).^{21,22} Subsequently, on the basis of comprehensive immunohistochemistry (IHC) analysis, it was noted that *YAP1* was expressed at low levels and was not exclusive of other subtypes.²³ Hence, a modified classification was proposed, including SCLC-A, SCLC-N, SCLC-P, and a biologically distinct fourth subtype: SCLC-inflamed (SCLC-I), with low expression of the three previously described transcription factors but high expression of unique genes, including immune checkpoints and human leukocyte antigens.²⁴ The neuroendocrine (NE; SCLC-A and N) and non-NE (SCLC-P and I) subtypes exhibit unique therapeutic vulnerabilities; in a subgroup analysis within the Impower 133 trial and the CASPIAN trial, the SCLC-I subtype demonstrated a numerically modest trend toward improved OS with ICI + chemotherapy combination compared with the other three subtypes.^{24,25} Additionally, patients with low NE tumors have been noted to derive greater benefit from ICIs compared with high NE tumors, owing to intact Notch signaling leading to an inflamed immune environment and thus greater immune infiltration.^{26,27}

INTERACTIONS OF *ASCL1*, *NOTCH*, AND *DLL3* IN SCLC

The Notch signaling pathway is an evolutionarily conserved developmental pathway²⁸ that regulates cell fate decisions through four main receptors (NOTCH1–4) and five canonical ligands of the Delta/Serrate/Lag-2 (DSL) family (ie, Delta-like 1,3,4 and Jagged 1,2), along with the noncanonical ligand DLK1.²⁹ In the canonical pathway, Notch receptors undergo

proteolytic processing in the Golgi (S1 cleavage) before being transported to the cell membrane, where they interact with DSL ligands (Fig 1A). Ligand-induced ubiquitylation triggers S2 (ADAM10) and S3 (γ -secretase) cleavages, releasing the Notch intracellular domain (NICD). NICD then translocates to the nucleus, modulating transcription factors such as hairy and enhancer of split 1 (*HES1*) and HES-related to YRPW motif 1 (*HEY1*).^{29,30} This suppresses *ASCL1*, a key transcriptional driver of NE differentiation in SCLC and an activator of DLL3 expression.^{31,32} Conversely, high DLL3 levels inhibit Notch signaling and are associated with a Notch-low, *HES1*-low, *ASCL1*-high, and NE phenotype of SCLC.³³ A CRISPR-based genetically engineered mouse model of SCLC proved that the loss of *Notch1* and *Notch2* is associated with accelerated tumorigenesis.³⁴

On the basis of these biological correlations, inhibiting DLL3 may reduce its suppressive effect on Notch signaling, potentially reactivating Notch-dependent tumor suppressive mechanisms, leading to decreased proliferation and increased differentiation of tumor cells. *ASCL1*, a key transcription factor driving NE differentiation, is upregulated in DLL3-high SCLC (Fig 1B).^{31,32} Since DLL3 inhibition could restore Notch activation, this may downregulate *ASCL1*, reducing the NE phenotype associated with more aggressive tumor behavior. Thus, targeting DLL3 represents an attractive therapeutic strategy in SCLC.

DLL3 EXPRESSION IN SCLC AND OTHER HIGH-GRADE NE CARCINOMAS

The Notch inhibitory ligand, DLL3, is normally expressed in the developing CNS.³⁵ DLL3 expression varies across different high-grade neuroendocrine carcinomas (NECs), with a general trend of high expression in specific tumor types such as SCLC and large cell neuroendocrine carcinoma (LCNEC) of the lung.³⁶ On the basis of reported literature, 75%–96% of SCLC tumors have high DLL3 expression (>50% positive tumor cells), predominantly expressed on the cell surface in contrast to the low and primarily cytoplasmic expression in normal cells.^{4,35–38} A recent proteomic study evaluating differential protein expression showed significantly increased DLL3 on SCLC tumor tissue compared with normal adjacent lung tissue with DLL3 expression in SCLC displaying a mutually exclusive pattern with B7H3.³⁹ Within the SCLC subsets, DLL3 expression is highest in subtype A and lowest in subtypes P and I.²⁴ This differential expression within the SCLC cohort defines the different therapeutic vulnerabilities of distinct subtypes, making it an effective therapeutic target with multiple pre-clinical and clinical developmental studies as described below focusing on maximizing its potential.

In pulmonary LCNEC, IHC analysis has revealed DLL3 positivity in 37%–54% of tumors.^{36,40} A study by Hermans et al⁴¹ for stage IV LCNEC of the lung reported DLL3 expression in 74% of tumors, with the majority (80%) having membranous or cytoplasmic staining and only 20% with perinuclear dotlike staining.

Beyond pulmonary NECs, several extrapulmonary NECs also exhibit a high prevalence of DLL3 expression: Merkel cell carcinoma (89%–91%),^{42,43} bladder NECs (68%–77%),^{44,45} castration-resistant neuroendocrine prostate cancer (NEPC; 71%–77%),⁴⁶ gastroenteropancreatic NECs (55%–77%),^{47–49} and cervical squamous cell carcinomas (81%). Recent studies further confirm these trends of high DLL3 expression in NECs of the bladder, cervix, prostate, skin, and head and neck, while corroborating its strong association with NE differentiation.^{50,51}

TARGETING DLL3 IN SCLC

Rova-T (rovalpituzumab tesirine) was an antibody-drug conjugate (ADC) designed to deliver a cytotoxic payload, tesirine (a pyrrolobenzodiazepine dimer) with DNA-damaging properties to DLL3-expressing tumor cells. This novel agent showed promising benefits in preclinical studies using patient-derived xenograft (PDX) models of SCLC, as well as increased preliminary response rates in some initial clinical studies.^{52,53} However, in 2021, it was concluded that Rova-T failed to demonstrate a survival benefit compared with the existing SOC for relapsed SCLC, topotecan, in the phase III TAHOE study.^{54,55} The toxicity associated with Rova-T was attributed to its payload rather than the use of DLL3 as a target.²⁰

Tarlatamab, a BiTE targeting DLL3 and CD3, gained accelerated approval by the FDA in May 2024 for use in ES-SCLC with disease progression on or after platinum-based chemotherapy, making it the first BiTE approved for a major solid tumor.³ Unlike monospecific human antibodies that target a single antigen, bispecific antibodies bind and target two unique antigens simultaneously.^{2,3} By binding to targets on the immune cells and tumor cells, these bispecific antibodies can redirect the immune cells to tumor cells and block the biological signaling necessary for the tumor.⁵⁶ Tarlatamab is the first BiTE targeting the DLL3.⁴ It binds to both DLL3 on tumor cells and CD3 on T cells, triggering the T cells to kill the DLL3-expressing tumor cells. This leads to the formation of cytolytic synapses and results in antigen-dependent target cell lysis by the release of perforins and granzymes, T-cell activation, and cytokine production, explaining its anticancer effect as well as its toxicities to some extent (Fig 2A).^{4,57}

EVIDENCE IN FAVOR OF TARLATAMAB IN SCLC

DeLLphi-300 Trial

The phase I study evaluating the use of tarlatamab (AMG 757) in relapsed/refractory SCLC with a median of two previous lines of therapy demonstrated an objective response rate (ORR) of 23.4% with a median duration of response (DOR) of 12.3 months along with a manageable safety profile across a wide dose range.⁵⁸ The median PFS was 3.7 months, and the median OS was 13.2 months.⁵⁸ The extended follow-up of DeLLphi-300 in August 2024 showed sustained clinical benefit with an ORR of 25%, a median DOR of 11.2 months, and a median OS of 17.5 months.⁵⁹

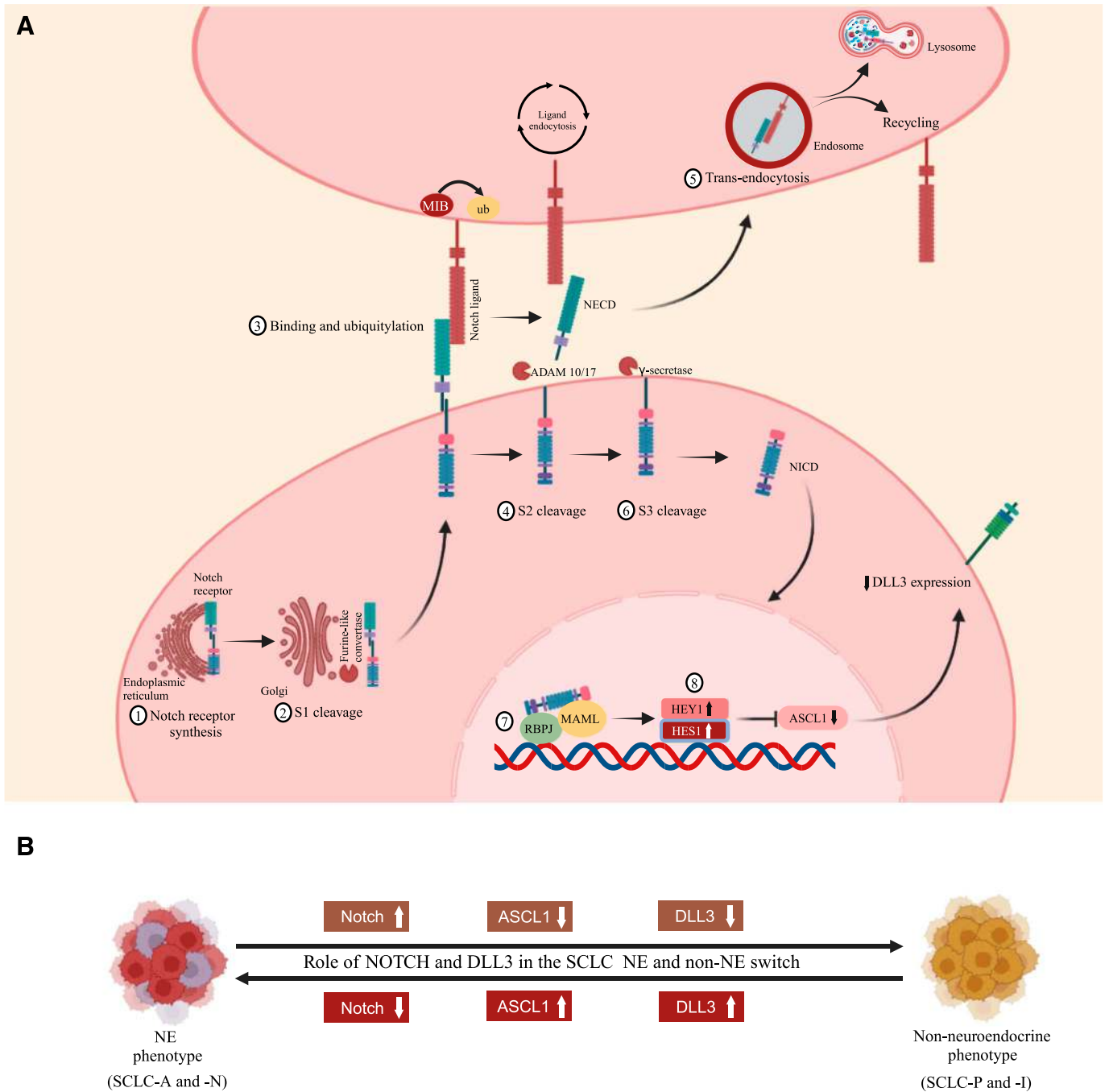


FIG 1. (A) An overview of Notch signaling pathway. (1) Synthesis of Notch receptor in endoplasmic reticulum. (2) Notch receptor undergoing S1 cleavage by furin-like convertase in the Golgi apparatus. (3) The transfer of Notch receptor to the cell membrane and its binding to the notch ligand, resulting in ligand ubiquitylation by ubiquitin ligase MIB. (4) S2 cleavage of the NECD by ADAM10/17. (5) Trans-endocytosis of the cleaved NECD followed by lysosomal degradation and recycling of the ligand. (6) S3 cleavage of the remaining Notch receptor by γ -secretase protease complex, resulting in the release of NICD. (7) Translocation of NICD into the nucleus followed by its binding to the RBPJ/MAML complex. (8) Upregulating *HES1/HEY1* and subsequently suppressing *ASCL1*, which results in decreased expression of DLL3 on the surface of the cell. (B) Role of Notch and DLL3 in SCLC NE and non-NE switch. ADAM, a disintegrin and metalloproteinase domain-containing protein; ASCL1, achaete-scute homolog; DLL3, delta-like ligand-3; HES1, hairy and enhancer of split 1; HEY1, hairy and enhancer of split related to YRPW motif1; MAML, mastermind-like transcriptional coactivator; MIB, mindbomb; NE, neuroendocrine; NECD, notch extracellular domain; NICD, notch intracellular domain; RBPJ, recombination signal binding protein for immunoglobulin kappa J region; SCLC, small cell lung cancer; SCLC-A, SCLC – ASCL1 subtype; SCLC-I, SCLC – Inflamed subtype; SCLC-N, SCLC – *NEUROD1* subtype; SCLC-P, SCLC – *POU2F3* subtype; Ub, ubiquitin. Created in [BioRender.com](https://www.biorender.com/). Naqash (2025).

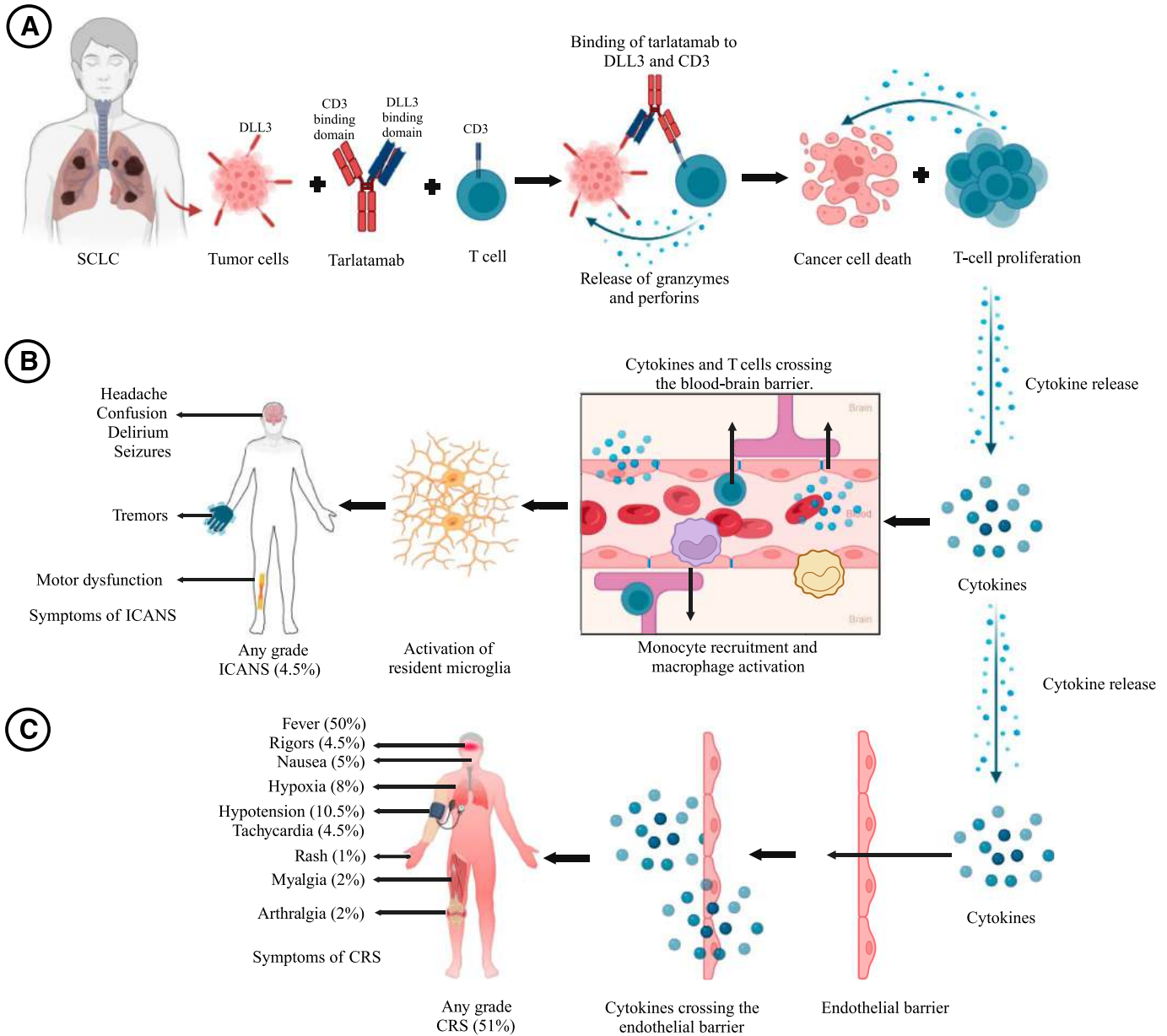


FIG 2. (A) Mechanism of action of tarlatamab in SCLC. (B) Mechanism and manifestations of ICANS. (C) Mechanism and manifestation of CRS. CD3, cluster of differentiation-3; CRS, cytokine release syndrome; DLL3, delta-like ligand-3; ICANS, immune effector cell-associated neurotoxicity syndrome; SCLC, small cell lung cancer. Created in [BioRender.com](https://www.biorender.com). Naqash (2025).

DeLLphi-301 Trial

The FDA accelerated approval of tarlatamab was granted on the basis of the results of the DeLLphi-301 trial, which was conducted in three parts, enrolling a total of 220 patients of advanced SCLC who were previously treated with two or more lines of therapy. Part 1 of the trial was a dose-comparison assessment of 176 patients randomly assigned, in a 1:1 ratio, to receive a single dose of 10 mg or 100 mg of tarlatamab intravenously during a 60-minute infusion. The 10 mg dose was selected for part 2 of the trial as the interim analysis suggested an overall more favorable benefit-to-risk profile than the 100 mg dose, with an ORR of

40% (97.5% CI, 19 to 52) in the 10-mg group and 32% (97.5% CI, 21 to 44) in the 100-mg group. The median progression-free survival in the 10-mg and 100-mg group was 4.9 months (95% CI, 2.9 to 6.7) and 3.9 months (95% CI, 2.6 to 4.4), respectively. The OS at 9 months in the 10-mg group was 68% and in the 100-mg group was 66%. Additionally, grade 3 or higher adverse events were observed in 59% of patients receiving 10 mg and 64% of those receiving 100 mg, leading to dose interruption, dose reduction, or both in 13% of patients in the 10-mg group and 29% of patients in the 100-mg group. Part-2 (dose expansion part) of the trial used 10 mg and enrolled 12 patients. The same 10 mg dose was also used for part 3 of the trial, enrolling 34 patients to

evaluate the safety of tarlatamab with inpatient monitoring reduced to 24 hours.⁶⁰ The median OS of 14.3 months in the selected 10-mg group offered a valuable benefit compared with previously approved regimens for treating recurrent SCLC after two or more lines of therapy.^{61,62} Among patients with baseline brain metastasis, the overall systemic ORR was 45.3% compared with 32.6% in those without brain metastasis.⁷ Extended follow-up of the DeLLphi-301 presented in 2024 demonstrated an ORR and disease control rate (DCR) of 40% and 70%, respectively. Approximately 26% of patients were noted to have disease control lasting at least 52 weeks. The median PFS was observed to be 4.3 months, with a median OS of 15.2 months and an estimated 46% of participants alive at 18 months.⁶ On the basis of these results, the phase III DeLLphi-304 study (ClinicalTrials.gov identifier: [NCT05740566](#)) is currently underway to compare the efficacy and safety of tarlatamab with SOC chemotherapy. According to a recent press release, interim analysis from the study demonstrated a statistically significant OS benefit for tarlatamab compared with SOC chemotherapy in the second-line setting.⁶³

Intracranial Activity of Tarlatamab in SCLC

The intracranial activity of tarlatamab cannot be fully assessed because of the fact that patients enrolled in tarlatamab trials required radiation of brain metastasis before enrollment. In the DeLLphi 300 trial, intracranial tumor shrinkage of $\geq 30\%$ in 62.5% (10 of 16) was observed in patients with baseline CNS lesions of ≥ 10 mm, while a subset of these patients had sustained tumor shrinkage long after their last radiotherapy treatment, suggesting potential intracranial activity.⁵⁹ Similarly, in the extended follow-up of DeLLphi-301 presented at ASCO 2024, tarlatamab led to $\geq 30\%$ intracranial tumor shrinkage in 59% (10 of 17) patients with baseline CNS lesions of ≥ 10 mm, with 94% (16 of 17) having intracranial disease control, further supporting its potential intracranial antitumor activity.⁷

Although DeLLphi-300 and DeLLphi-301 included patients with treated and stable brain metastasis, a recent retrospective study (n = 10 patients) reported on the safety and efficacy of tarlatamab in patients with untreated brain metastases, including one with suspected leptomeningeal disease, showing both radiographic and clinical improvements early in the course of treatment.⁶⁴

Maintenance Tarlatamab in Combination With Immune Checkpoint Therapy for ES-SCLC: DeLLphi-303 Trial

The results from DeLLphi-303, a phase Ib study investigating tarlatamab in combination with a PD-L1 inhibitor (atezolizumab or durvalumab) as first-line maintenance in ES-SCLC after induction chemoimmunotherapy, demonstrated survival benefit and a manageable safety profile, with no dose-limiting toxicities or fatal treatment-related adverse events (TRAEs). The median PFS and 9-month OS for tarlatamab with either of the PD-L1 inhibitors were 5.6 months and 89%,

respectively, compared with 2.6 months and approximately 60% with atezolizumab alone as first-line maintenance. The combination of tarlatamab with a PD-L1 inhibitor showed sustained disease control, with a DCR of 62.5% (95% CI, 51.5 to 72.6) and a median duration of disease control of 9.3 months (95% CI, 5.6 to not estimable).⁶⁵ These findings suggest that tarlatamab, in combination with PD-L1 inhibitors, has a manageable safety profile and demonstrates promising efficacy as a first-line maintenance therapy in ES-SCLC. Ongoing phase III trials, such as DeLLphi-305, are further evaluating this combination

TOXICITY PROFILE OF TARLATAMAB

Tarlatamab demonstrates a manageable safety profile with CRS, neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS), and neutropenia being the most noteworthy and unique TRAEs. In the DeLLphi-301 trial, the most commonly occurring adverse events ($>20\%$) included CRS (51%), pyrexia (35%), decreased appetite (29%), dysgeusia (29%), constipation (27%), anemia (26%), asthenia (23%), and fatigue (23%). Any-grade ICANS was seen in 4.5%, while neutropenia was seen in 14% of cases.⁶⁰ The extended follow-up of the trial presented at the 2024 World Conference on Lung Cancer reported an incidence of 53% for any-grade CRS and 15% for any-grade ICANS.⁶⁶

ICANS

Like CRS, the pathophysiology of ICANS can be attributed to the increased production of cytokines that activate the endothelial cells, increasing the blood-brain barrier's permeability.⁶⁷ The resulting elevated cytokine levels in the cerebrospinal fluid are believed to cross the blood-brain barrier and are responsible for off-target effects. The infiltration of cytokines and activated T cells into the CNS potentially triggers microglial activation and subsequent neuronal injury.⁶⁷ In the DeLLphi-301 trial, ICANS and associated neurologic events were observed in 8% of patients in the 10-mg group and 28% in the 100-mg group. Severe (grade 3 or higher) events were absent in the 10-mg group but occurred in 5% of patients in the 100-mg group. These events primarily occurred during the first treatment cycle, with a median onset of 5 days. Common symptoms of ICANS included confusion, impaired attention, tremors, and motor dysfunction, such as weakness (Fig 2B). These events led to dose modifications (interruption or reduction) in 1% of patients in the 10-mg group and 6% in the 100-mg group with a median time to resolution of 6.5 days. Most of the ICANS and CRS events did not require treatment discontinuation, and a higher safety profile was demonstrated in the 10-mg group.⁶⁰

A recent update from the DeLLphi-301 reported the incidence of any-grade ICANS and associated neurotoxicity syndrome in 24.1% of patients with brain metastasis, compared with 13.6% of those without. Grade ≥ 3 events were exclusively observed in

the 100-mg group, occurring in 9.4% of patients with brain metastasis versus 1.8% of those without.⁷

CRS

Much like other T-cell–mediated therapies, while the T-cell activation exerts a potent antitumor effect, the overproduction of proinflammatory cytokines in this pathway leads to the development of CRS.⁶⁸ In the DeLLphi-301 trial, any-grade CRS was reported in 51% (Fig 2C) of patients in the 10-mg group and 61% in the 100-mg group, with most events occurring after administering the first or second dose. The median onset of CRS was 13.1 hours after dose with a median duration of 4 days. CRS was predominantly grade 1–2 with fever (97%), hypotension (20%), and hypoxia (17%) being the most common clinical manifestations. CRS led to dose modifications (interruption or reduction) in 3% of patients in the 10-mg group and 9% in the 100-mg group. Effective management led to the resolution of CRS in 98% of cases⁶⁰ (management of CRS and ICANS—Table 1).

Optimizing CRS and ICANS Management: Lessons Learned From Bispecific T-Cell Engagers in Hematologic Malignancies

Given that CRS and ICANS are recognized toxicities of tarlatamab, a proactive and aggressive approach to their management is essential. Lessons from hematologic malignancies, where similar immune-mediated toxicities have been observed, suggest that established strategies could be adapted to mitigate these off-target effects in tarlatamab-treated patients.

Tocilizumab is a monoclonal antibody with anti-inflammatory effects that selectively binds to the interleukin-6 (IL-6) receptor, blocking IL-6 from binding to its receptor and triggering an immune response.⁶⁹ Tocilizumab gained FDA approval for the treatment of chimeric antigen receptor-T (CAR T)–cell induced CRS back in 2017 and has been deemed a reliable agent for the management of CRS, with current guidelines recommending administration in case of grade 1 refractory and grade ≥ 2 CRS, as well as grade ≥ 1 ICANS with concurrent CRS.^{70,71} Although widely used for CRS management, the lack of evidence supporting its ability to penetrate the CNS renders it unsuitable for treating isolated ICANS.⁷² The use of prophylactic tocilizumab to prevent CRS with teclistamab, a bispecific T-cell engager approved for use in relapsed/refractory multiple myeloma, showed a decrease in the incidence and severity of CRS with zero rates of hospital readmission within 14 days of discharge. Importantly, it did not increase the incidence of grade 3 or 4 neutropenia.⁷³ Some centers have already started implementing prophylactic tocilizumab before tarlatamab administration. In a retrospective study of high-risk patients who received prophylactic tocilizumab ($n = 5$), only one of the five patients was noted to have a G2 ICANS, suggesting the potential benefit of this strategy (S. Puri et al, personal communication, May 2025, poster presented at IASLC 2025 Hot Topic Small Cell Lung

Cancer Meeting). One important consideration of using this strategy is the financial implications, as each dose of the drug ranges from approximately \$2,800.00 to \$5,100 in US dollars (USD).⁷⁴ Variability in costs across inpatient and outpatient settings is influenced by factors such as billing practices, reimbursement policies, and administration-related expenses.

Anakinra is a recombinant IL-1 receptor antagonist that blocks IL-1 from binding to its receptor (IL-1R1), thereby inhibiting downstream signaling and the production of inflammatory mediators such as prostaglandins, cytokines, and chemokines.^{75,76} Early initiation of high-dose IV anakinra has shown benefits in managing CAR-T–induced refractory CRS/ICANS, leading to faster resolution without compromising therapeutic outcomes.⁷⁷ As we generate more real-world experience with tarlatamab administration, early incorporation of these strategies might help mitigate toxicity and potentially aid in safely administering tarlatamab in the outpatient setting.

TARLATAMAB ADMINISTRATION AND LOGISTICS: TRANSITIONING FROM OLD TO NEW

In a strategy to mitigate the increased risk of CRS, tarlatamab is administered using a step-up dosing schedule, starting with a dose of 1 mg for C1D1, followed by 10 mg for C1D8 and C1D15, and then on days 1 and 15 for all subsequent cycles. At the time of its accelerated approval, tarlatamab's package insert recommended monitoring patients for 22–24 hours in an appropriate health care setting, and advised patients to stay within 1 hour of the appropriate health care setting for a total of 48 hours for the first two doses (on C1D1 and C1D8) accompanied by a caregiver (Fig 3A).⁷⁸ Over the first year of drug commercialization, the conservative interpretation of this guidance has meant that most patients were initially sent to academic centers with experience giving tarlatamab on trial or with expertise in managing bispecific T-cell engagers or CAR-T–induced CRS/ICANS in hematologic malignancies. Larger community practices have similarly designated a single clinic with direct access to hospital services as an alternative. However, in these scenarios, patients are required to meet new oncologists and often travel longer distances to participate. For many with refractory SCLC, this is not a tenable strategy for receiving cancer care.

As part of the DeLLphi 300 trial, which led to the drug's approval, an outpatient cohort was introduced late in the trial in which patients could undergo 6–8 hours of outpatient follow-up ($n = 30$) after tarlatamab administration, compared with patients undergoing the typical 48-hour inpatient observation during the three doses of cycle 1 ($n = 58$; Fig 3B).⁷⁹ Since CRS symptoms have been reported most commonly around 13.1 hours after the first two doses (1 mg on C1D1 and 10 mg on C1D8), it was conceivable that shorter outpatient follow-up would be sufficient. Patients were instructed to remain within 1 hour of the study site or hospital for 72 hours after dose. Follow-up phone calls were placed between 10 and 18 hours after infusion. If patients developed fever or other CRS-related symptoms, they were

TABLE 1. Management of Unique Tarlatamab Toxicities

Category	Prophylaxis	Mild (grade 1-2)	Severe (grade 3-4)
CRS Manifestations: fever (with or without rigors), hypoxia, tachypnea, hypotension, tachycardia, nausea, fatigue, headache, rash, myalgias, and arthralgias	Step-up dosing approach Consider prophylactic glucocorticoids to lower risk (dexamethasone or equivalent 8 mg IV on C1D1, C1D8) IV hydration to prevent hypotension Close monitoring during early treatment cycles	Supportive care: acetaminophen for fever, IV fluids for hydration Consider dexamethasone (or equivalent) 8 mg IV Monitoring: temperature, blood pressure, and oxygen saturation	Withhold until event resolves, resume at next scheduled dose. Permanent discontinuation for recurrent grade 3 and all grade 4 events ICU care Consider vasopressor support for persistent hypotension Supplemental oxygen if SpO ₂ <90% Consider dexamethasone 8 mg IV once every 8 hours up to three doses Tocilizumab (IL-6 inhibitor) recommended
When resuming treatment at the next scheduled dose, closely monitor patients for 22-24 hours from the initiation of tarlatamab infusion in a controlled health care setting			
ICANS Manifestations: confusion, impaired attention, aphasia, tremors, motor weakness, cerebral edema, and seizures	Consider prophylactic corticosteroids to lower risk Consider close neurologic monitoring for early detection	Withhold until event resolves, resume at next scheduled dose Supportive care: seizure prophylaxis, IV fluids for hydration Consider dexamethasone 10 mg IV once every 6 hours or methylprednisolone 1 mg/kg IV once every 12 hours if symptoms worsen Consider neurologic monitoring for progression of symptoms	Withhold until event resolves, resume at next scheduled dose. Permanent discontinuation for recurrent grade 3 and all grade 4 events ICU care Consider high-dose corticosteroids: Dexamethasone 10 mg IV once every 6 hours or methylprednisolone 1 mg/kg IV once every 12 hours Consider repeat neuroimaging every 2-3 days if persistent grade ≥3 neurotoxicity Management of status epilepticus
When resuming treatment at the next scheduled dose, closely monitor patients for 22-24 hours from the initiation of tarlatamab infusion in a controlled health care setting			

Abbreviations: CRS, cytokine release syndrome; CxDy, cycle x day y; ICANS, immune effector cell–associated neurotoxicity syndrome; ICU, intensive care unit; IL-6, interleukin-6; IV, intravenous.

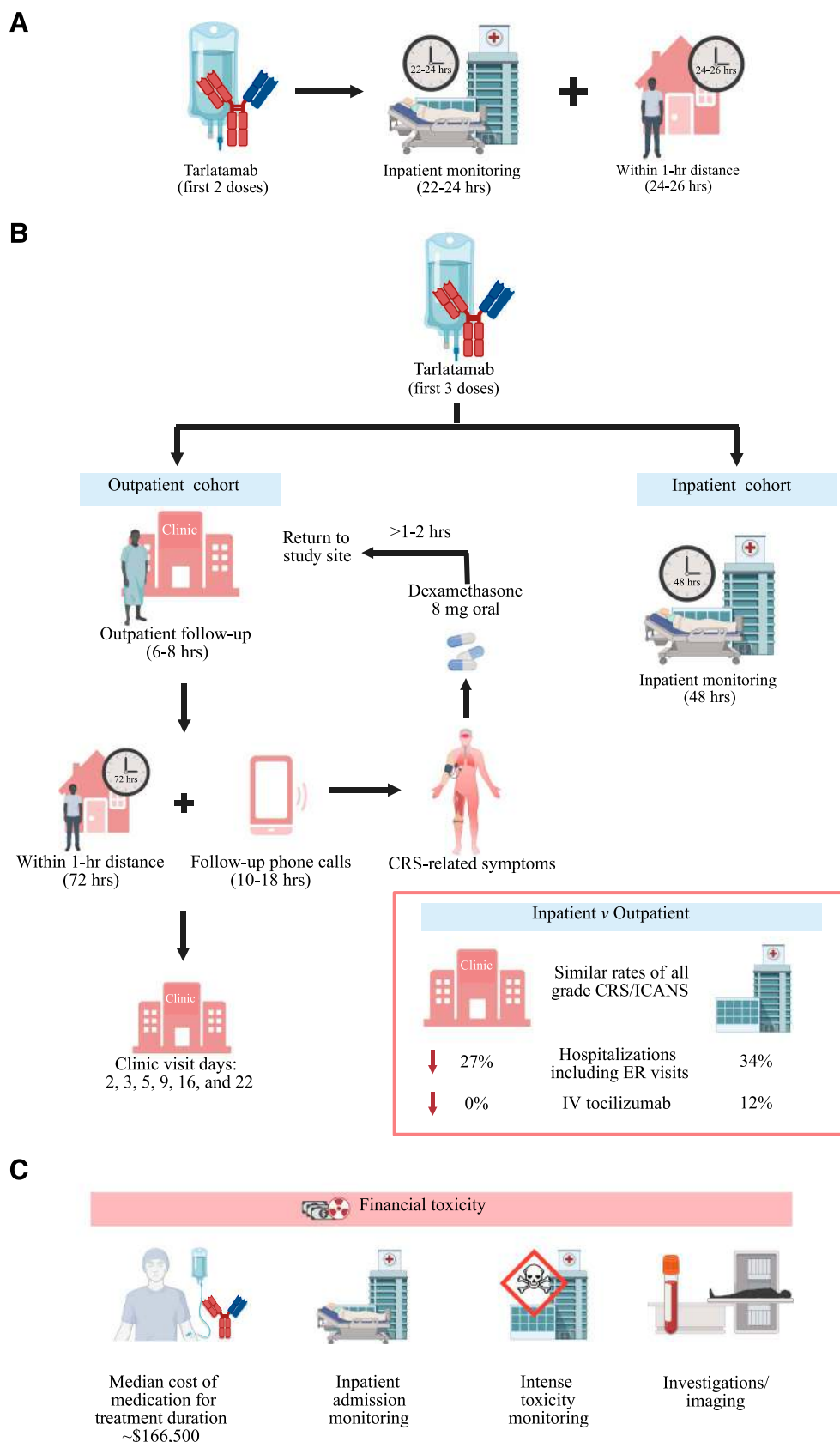


FIG 3. (A) Tarlatamab monitoring as per package insert. (B) Tarlatamab monitoring as per the DeLLphi 300 trial: inpatient versus outpatient cohort. (C) Financial toxicity limitations of tarlatamab. CRS, cytokine release syndrome; ER, emergency room; ICANS, immune effector cell–associated neurotoxicity syndrome; IV, intravenous. \$, US dollars Created in BioRender.com. Naqash (2025).

given an 8-mg dexamethasone tablet to self-administer orally, and if symptoms persisted for more than 1–2 hours, patients were instructed to return to the study site or hospital. Patients in the outpatient monitoring cohort returned to the clinic for days 2, 3, 5, 9, 16, and 22 after administration on days 1, 8, and 15 during cycle 1.

The outpatient monitoring cohort reported similar rates of TRAEs (93% in outpatient cohort v 100% in inpatient cohort) and all grade CRS (60% with outpatient observation v 62% with inpatient monitoring) with no increase in higher grade 3–4 events (0% v 3%), although IV tocilizumab was given to 0% of patients in the outpatient monitoring group and 12% of patients in the inpatient group. ICANS rates were similar between the two arms. Interestingly, hospitalizations including ER visits were slightly lower for the outpatient group (27% v 34%), perhaps because this group had more required clinic visits after infusions, where they were evaluated by skilled oncology providers who could prevent subsequent emergency room visits with careful symptom management.⁸⁰ Some institutions have started using outpatient oncology-specific urgent care centers to monitor patients for 24 hours, only admitting those who develop symptoms requiring inpatient management (J.W. Carlisle et al, personal communication May 2025, Poster Presentation ASCO 2025).

Although this initial published experience is limited, ongoing phase III trials—DeLLphi-304 in second-line SCLC, DeLLphi-305 in first-line maintenance for ES-SCLC, and DeLLphi-306 in consolidation phase of LS-SCLC—will further evaluate a shortened outpatient monitoring period after dosing, along with enhanced home-based and clinic-based monitoring strategies. As academic and community oncology investigators gain confidence in these outpatient approaches, informed by emerging data on best practices for outpatient management, the routine administration of tarlatamab will likely evolve. This progression mirrors the experience of our bone marrow transplant colleagues, who have gradually refined strategies for delivering outpatient CAR-T cell therapies while implementing safeguards to mitigate toxicity. Given the overlap in toxicity profiles, particularly the risk of CRS and ICANS, there is a strong opportunity to adapt established outpatient CAR-T frameworks to the administration of tarlatamab and other bispecific T-cell engagers. Integrating remote patient monitoring using wearable devices for continuous surveillance of patient vitals enabling early identification of warning signs such as fever, hypoxia, and hypotension, and facilitating prompt triage, can play a central role in ensuring safety. By defining eligibility criteria, caregiver requirements, clinical pathways, standardized infusion processes, order sets, patient and care team education, and institutional workflows, care coordination can be aligned with the unique characteristics of tarlatamab to potentially develop a reliable and scalable outpatient model that supports broader access to this therapy in both academic and community practices.⁸¹

QUALITY OF LIFE AND FINANCIAL TOXICITY ASSOCIATED WITH TARLATAMAB

In contrast to other SOC agents for relapsed or refractory SCLC, tarlatamab introduces several unique practical considerations at the patient level. Chief among these are its distinct toxicity profile, characteristic of T-cell-engaging therapies, including risks for CRS and ICANS. Additionally, the cost of tarlatamab is markedly higher than that of conventional therapies in this setting, raising important considerations regarding access and value-based care.

In the DeLLphi-301 trial, 51% of the patients treated with 10-mg tarlatamab experienced CRS, while only 8% developed ICANS.⁶⁰ The impact on patients was collected through patient-reported outcomes (PROs) using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and Quality of Life Questionnaire Core 13. On the basis of patients treated with the 10-mg tarlatamab dose, key symptoms, including chest pain and cough, revealed a trend toward improvement over time. Furthermore, global health status, a measure of subjective well-being and quality of life, also showcased an uptrending course as cycle length progressed.⁶⁰ However, it appears that a slight decline in global health status occurred during cycle one, which also coincides with the greatest risk for CRS/ICANS and the most intense monitoring phase. Improvement in global health status was gradual and did not cross baseline until cycle four was reached.⁶⁰ Given the lack of a SOC comparison since this study only compares two different doses of tarlatamab, it is difficult to interpret these findings fully. Further clarity of these PROs is anticipated pending results of the DeLLphi-304 trial investigating tarlatamab versus the current SOC for second-line relapsed/progressed ES-SCLC. Similar findings have been recognized among other bispecific T-cell engager and CAR-T cell therapies that portend comparable toxicities. PROs (EORTC-QLQ-C30 and EORTC QLQ-MY20: a multiple myeloma-specific module) from the MajesTEC-1 study investigating the use teclistimab for relapsed/refractory multiple myeloma did not reveal clear improvement in global health status until cycle four was reached.⁸² Additionally, patients treated with CAR-T cell therapy for various hematologic malignancies showed initial worsening in quality of life within the first week after infusion. Eventually, improvement was noted by three to six months after treatment.⁸³ Similar observations were made for depressive symptoms.⁸³

Although these questionnaires are cancer-specific, they may lack the sensitivity to detect meaningful changes or issues unique to individual cancer types, for example, even disease-specific modules such as the QLQ-LC13 for lung cancer have limitations. Many current tools were developed during the chemotherapy era, primarily focusing on acute, early-onset symptoms. However, we have come to recognize that ICIs can lead to unique immune-related adverse events (irAEs),

some of which are delayed in onset and may become chronic, particularly in patients who experience durable responses.⁸⁴ These long-term irAEs can significantly affect quality of life, yet current PRO tools often fail to capture these chronic, evolving experiences.⁸⁵ Although ICIs have slightly different mechanisms of action compared with agents such as tarlatamab, as bispecific T-cell engagers are increasingly used in earlier disease settings for solid tumors with improved survival, it becomes essential to integrate therapy-induced irAE-related quality-of-life impacts into well-designed PRO assessments.

There is significant potential for financial toxicity with tarlatamab (Fig 3C) associated not only with the price of the drug itself but also the possibility for inpatient admission monitoring. Currently, the commercial price for tarlatamab is \$31,500 (USD) for the first cycle, with a slight decrease to \$30,000 (USD) for each additional cycle thereafter.⁸⁶ On the basis of previous trials, the median time on treatment was over five months, amounting to a median of \$166,500 (USD) for the cost of medication alone.⁸⁶ This number is staggering compared with other treatment regimens currently available, ranging from less than \$1,000 (USD) to nearly \$13,000 (USD) per cycle.⁸⁷ Not only is the drug itself costly, but the addition of more intense toxicity monitoring should also be considered. Patients starting tarlatamab are typically hospitalized after the first two doses, and even for uneventful tracking, the cost of the room for one night in observation ranges in the thousands of dollars. If any bloodwork or imaging studies are needed to evaluate for a reaction, the cost of hospitalization continues to grow. The extra cost of time for either inpatient monitoring or extended outpatient postinfusion observation may also negatively affect patients and care partners from a time toxicity perspective.

Another essential aspect is the cost of therapy and hospitalization for treatments such as bispecific T-cell engagers. These are generally inordinately expensive, and the payment from Diagnosis-Related Group (DRG) reimbursement from the Inpatient Prospective Payment System does not fully cover them.⁸⁸ The bundled payment covers all costs associated with a patient's hospital stay—including the cost of drugs, nursing, investigations, intensive care, and so on. Bispecific T-cell engagers do not have dedicated DRG codes and are reimbursed under standard oncology Medicare severity-DRGs, which pay much less and cannot offset the actual cost of therapy administration in the inpatient setting. This issue was seen with the initial approval of CAR-T cell therapies for lymphoma, which forced many institutions to avoid their usage as the DRG under which they were reimbursed were not commensurate with the cost of therapy.⁸⁹ This is a source of financial loss for the hospitals. As a result, institutions are gradually trying to shift the administration of bispecific T-cell engagers or CARTs to observation stays (<48 hours in the hospital) or entirely in the outpatient setting, where these drugs can be billed separately under Medicare part B.⁹⁰

In a cohort of Danish patients with newly diagnosed, ES-SCLC, almost a quarter of their days after diagnosis were spent in contact with the health care system.⁹¹ These patients were treated with SOC chemoimmunotherapy. It is unknown what the time toxicity of tarlatamab might be, and how it might factor into patient preferences regarding treatment of their refractory SCLC. Further research examining tarlatamab's cost-effectiveness in the treatment of SCLC and its real-world impact on financial toxicity and time toxicity will be necessary to better understand the global impact of this medication on patients with SCLC.

As novel and promising treatments such as tarlatamab are introduced earlier in the treatment course or combined with existing therapies for solid tumors, many of which have complex and diverse toxicity profiles, medical oncologists will face the growing challenge of personalizing therapy even further. To meet this challenge effectively, a well-integrated multidisciplinary approach will be essential, with each specialty contributing complementary expertise to optimize patient care.⁹² For instance, palliative care providers and therapists are integral to ensure physical and psychological well-being is maintained throughout treatment, while social workers and financial advisors are necessary to counsel patients regarding the economic burden that may ensue as well as assist in overcoming these roadblocks.⁹³ As we aim to advance survival for those diagnosed with SCLC, we must also ensure that our pursuit for quantity is met with equal focus on overall quality of life.

OTHER POTENTIAL SOLID TUMOR INDICATIONS OF TARGETING DLL3

Owing to a relatively high DLL3 expression in LCNEC of the lung as described previously,⁴⁰ obritamig, a DLL3/CD3 T-cell engager (TCE), was evaluated in a phase-I clinical trial and demonstrated an ORR of 54% and a DCR of 77%, suggesting a role of DLL3-targeting therapies in pulmonary LCNEC.⁹⁴ Tarlatamab is also currently being investigated for NEPC in a phase Ib study (DeLLpro-300) where it showed that 56.3% of the patient tumors had ≥1% DLL3 tumor positivity (DLL3+). As of January 2024, an ORR of 22.2% in DLL3+ patients and a median PFS of 3.7 months in the DLL3+ NEPC were observed in the patient population.⁹⁵

OTHER EMERGING DLL3-DIRECTED THERAPIES

The demonstrated efficacy and manageable safety profile of tarlatamab not only solidify its role as a valuable therapeutic agent in previously treated SCLC populations, but also validate DLL3 as a promising therapeutic target. Building on this success, several other DLL3-targeting strategies, including TCEs, CAR-based cell therapies, and ADCs, are now being evaluated in both preclinical and clinical studies (Table 2). The tarlatamab molecule consists of two single-chain variable fragments (scFv) connected by a short, flexible linker, and includes a stable, inert, and noneffector fragment crystallizable (Fc) domain, which increases its

TABLE 2. Ongoing Trials With DLL3-Targeting Therapies

Trial	Phase	Agent	Mechanism of Action	Eligibility	Intervention	Primary Endpoint	Current Status
DeLLphi-306 (NCT06117774)	III	Tarlatamab	DLL3/CD3 BiTE	LS-SCLC that has not progressed after CCRT	Tarlatamab v placebo	PFS	Recruiting
DeLLphi-305 (NCT06211036)	III	Tarlatamab	DLL3/CD3 BiTE	ES-SCLC after platinum, etoposide, and durvalumab	Tarlatamab + durvalumab v durvalumab alone	OS	Recruiting
DeLLphi-304 (NCT05740566)	III	Tarlatamab (AMG 757)	DLL3/CD3 BiTE	SCLC that progressed or recurred after one platinum-based regimen	Tarlatamab v SOC	OS	Active, not recruiting
DeLLphi-303 (NCT05361395)	Ib	Tarlatamab	DLL3/CD3 BiTE	ES-SCLC with no previous systemic treatment for ES-SCLC, LS-SCLC with previous treatment	Tarlatamab with carboplatin, etoposide, and PD-L1 inhibitor (atezolizumab or durvalumab)	Safety	Active, not recruiting
DeLLphi-307 (NCT06502977)	II	Tarlatamab	DLL3/CD3 BiTE	ES-SCLC that progressed or recurred after one platinum-based regimen as first-line therapy (including a PD-1/PD-L1) and at least one other previous line of therapy	Tarlatamab IV infusion	ORR	Active, not recruiting
DeLLphi-308 (NCT06598306)	I	Tarlatamab	DLL3/CD3 BiTE	ES-SCLC that progressed or recurred after at least one line of platinum-based therapy	Tarlatamab administered by SC injection	Safety	Recruiting
DeLLphi-309 (NCT06745323)	II	Tarlatamab	DLL3/CD3 BiTE	Relapsed/refractory SCLC	Tarlatamab administered by IV infusion at various dose levels	ORR	Not yet recruiting
TAURUS (NCT06816394)	II	Tarlatamab	DLL3/CD3 BiTE	Advanced EP-SCLC or NEC	Tarlatamab administered as an IV infusion	ORR	Not yet recruiting
NCT06830694	II	Tarlatamab	DLL3/CD3 BiTE	Transformed SCLC from adenocarcinoma after EGFR TKI treatment failure	Tarlatamab with carboplatin, etoposide, and atezolizumab	PFS	Not yet recruiting
DeLLpro-300 (NCT04702737)	Ib	Tarlatamab (AMG 757)	DLL3/CD3 BiTE	Metastatic de novo or treatment-emergent NEPC	Tarlatamab administered as an IV infusion	Safety	Completed
NCT06788938	II	Tarlatamab	DLL3/CD3 BiTE	Advanced DLL3-expressing tumors including NEN: low-/intermediate-grade NEC, GEP-NEC, LCNEC, SCLC transformed from previously treated-NSCLC, EP-SCLC (with the exception of NEPC)	Tarlatamab administered as an IV infusion	ORR	Not yet recruiting
DAREON-5 (NCT05882058)	II	Tarlatamab	DLL3/CD3 BiTE	Relapsed/refractory ES-SCLC and other relapsed/refractory NECs	BI 764532 IV infusions at two different doses	ORR, safety	Active, not recruiting
DAREON-7 (NCT06132113)	I	BI 764532	DLL3/CD3 BiTE	Locally advanced or metastatic NEC including pulmonary LCNEC, EP-NEC, NEC of unknown primary site	BI 764532 IV infusions in combination with SOC (platinum and etoposide)	Safety	Recruiting

(continued on following page)

TABLE 2. Ongoing Trials With DLL3-Targeting Therapies (continued)

Trial	Phase	Agent	Mechanism of Action	Eligibility	Intervention	Primary Endpoint	Current Status
DAREON™-8 (NCT06077500)	I	BI 764532	DLL3/CD3 BiTE	ES-SCLC	BI 764532 in combination with SOC (platinum, etoposide, and anti-PD-L1)	Safety	Recruiting
DAREON™-9 (NCT05990738)	Ib	BI 764532	DLL3/CD3 BiTE	Relapsed/refractory SCLC after platinum-based chemotherapy	IV BI 764532 in combination with a single-agent chemotherapy	Safety	Recruiting
NCT05879978	I/II	Obixtamig (BI 764532)	DLL3/CD3 BiTE	Advanced, metastatic, or relapsed SCLC and other NECs expressing DLL3	Obixtamig (BI 764532) in combination with ezabenlimab	Safety	Recruiting
NCT04429087	I	BI 764532	DLL3/CD3 BiTE	Locally advanced or metastatic SCLC, pulmonary LCNEC, and other NECs expressing DLL3	BI 764532 administered by parenteral route	MTD, safety	Recruiting
NCT05916313	I	BI 764532	DLL3/CD3 BiTE	Primary progressive diffuse glioma expressing DLL3	BI 764532 monotherapy administered by repeated IV infusions	Safety	Recruiting
NCT04471727	I/II	MK-6070 (HPN 328)	TriTAC binding DLL3, CD3, and albumin	Relapsed/refractory SCLC, NEPC, high-grade NECs, and other advanced DLL3-expressing malignancies	MK-6070 monotherapy and MK-6070 with atezolizumab or ifinatamab deruxtecan	MTD, RDE, PK, PD, safety	Recruiting
NCT06780137	I/II	Gocatamig (MK-6070)	TriTAC binding DLL3, CD3 and albumin	ES-SCLC after at least one previous line of systemic therapy that included platinum-based chemotherapy	MK-6070 monotherapy and MK-6070 with ifinatamab deruxtecan	Safety, ORR	Recruiting
NCT05461287	I	QLS31904	Bispecific antibody targeting DLL3 and CD3	Advanced solid DLL3-expressing tumors including SCLC and other NECs	QLS31904 IV monotherapy	Safety, MTD, RP2D	Recruiting
NCT05619744	I	R07616789	Multispecific antibody targeting DLL3 and CD3/CD137	Relapsed ES-SCLC or high-grade NEC of any other origin	R07616789 IV infusion + tocilizumab rescue therapy for CRS	Safety, ORR, DOR, PFS, OS	Completed
SKYBRIDGE (NCT05652686)	I/II	Peluntamig (PT217)	Bispecific antibody targeting DLL3 and CD47	Unresectable advanced or metastatic SCLC, pulmonary LCNEC, EP-NEC	PT217 monotherapy and in combination with chemotherapy (carboplatin + etoposide) and/or ICI combination (atezolizumab)	MTD, RDE, safety	Recruiting
NCT05978284	I/II	ZG006	Trispecific TCE targeting two distinct DLL3 epitopes and CD3	SCLC and NEC with no standard treatment available/intolerant to standard treatments	ZG006 administered as an IV infusion	MTD, RP2D, safety	Recruiting
CAR T-cell therapies							
NCT03392064	I	AMG 119	DLL3-directed autologous CAR T cells	Relapsed/refractory SCLC	One-time IV infusion at different cell dose levels	Safety	Suspended
NCT05680922	I	LB2102	DLL3-directed autologous CAR T cells	Unresectable SCLC, pulmonary LCNEC, combined SCLC, or combined LCNEC	Multiple doses to be tested to establish a recommended dose	RDE, safety, RP2D	Recruiting
CAR NK therapy							

(continued on following page)

TABLE 2. Ongoing Trials With DLL3-Targeting Therapies (continued)

Trial	Phase	Agent	Mechanism of Action	Eligibility	Intervention	Primary Endpoint	Current Status
NCT05507593	I	NK-92	DLL3-directed CAR NK cells	Relapsed/refractory ES-SCLC	IV infusion at different cell dose levels	Safety, MTD	Unknown status
ADCs							
NCT06179069	I	ZL-1310	DLL3-targeted ADC	Metastatic/ES-SCLC	ZL-1310 as monotherapy, in combination with atezolizumab, and in combination with atezolizumab + carboplatin	Safety	Recruiting
NCT06613009	I	IBI3009	DLL3-targeted ADC	Unresectable/metastatic/ES-SCLC	IBI3009 as monotherapy	Safety	Recruiting
NCT06443489	I	SH-4849	DLL3-targeted ADC	Advanced solid tumors	SH-4849 as monotherapy	Safety, MTD, RP2D	Recruiting
NCT06424665	I	FZ-AD005	DLL3-targeted ADC	Advanced solid tumors (especially SCLC or LCNEC)	FZ-AD005 as monotherapy	Safety, ORR	Recruiting

Abbreviations: ADC, antibody-drug conjugate; BiTE, bispecific T-cell engager; CAR T, chimeric antigen receptor-T; CCRT, concurrent chemoradiation therapy; CD3, cluster of differentiation-3; CRS, cytokine release syndrome; DLL3, delta-like ligand-3; DOR, duration of response; EGFR, epidermal growth factor receptor; EP-NEC, extrapulmonary neuroendocrine carcinoma; EP-SCLC, extrapulmonary small cell lung cancer; ES-SCLC, extensive-stage small cell lung cancer; GEP-NEC, gastroenteropancreatic neuroendocrine carcinoma; ICI, immune checkpoint inhibitor; IV, intravenous; LCNEC, large cell neuroendocrine carcinoma; LS-SCLC, limited-stage small cell lung cancer; MTD, maximum tolerated dose; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NEPC, neuroendocrine prostate cancer; NK, natural killer; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; RDE, recommended dose for expansion; RP2D, recommended phase II dose; SC, subcutaneous; SCLC, small cell lung cancer; SOC, standard of care; TCE, T-cell engager; TKI, tyrosine kinase inhibitor; TriTAC, trispecific T cell-activating construct.

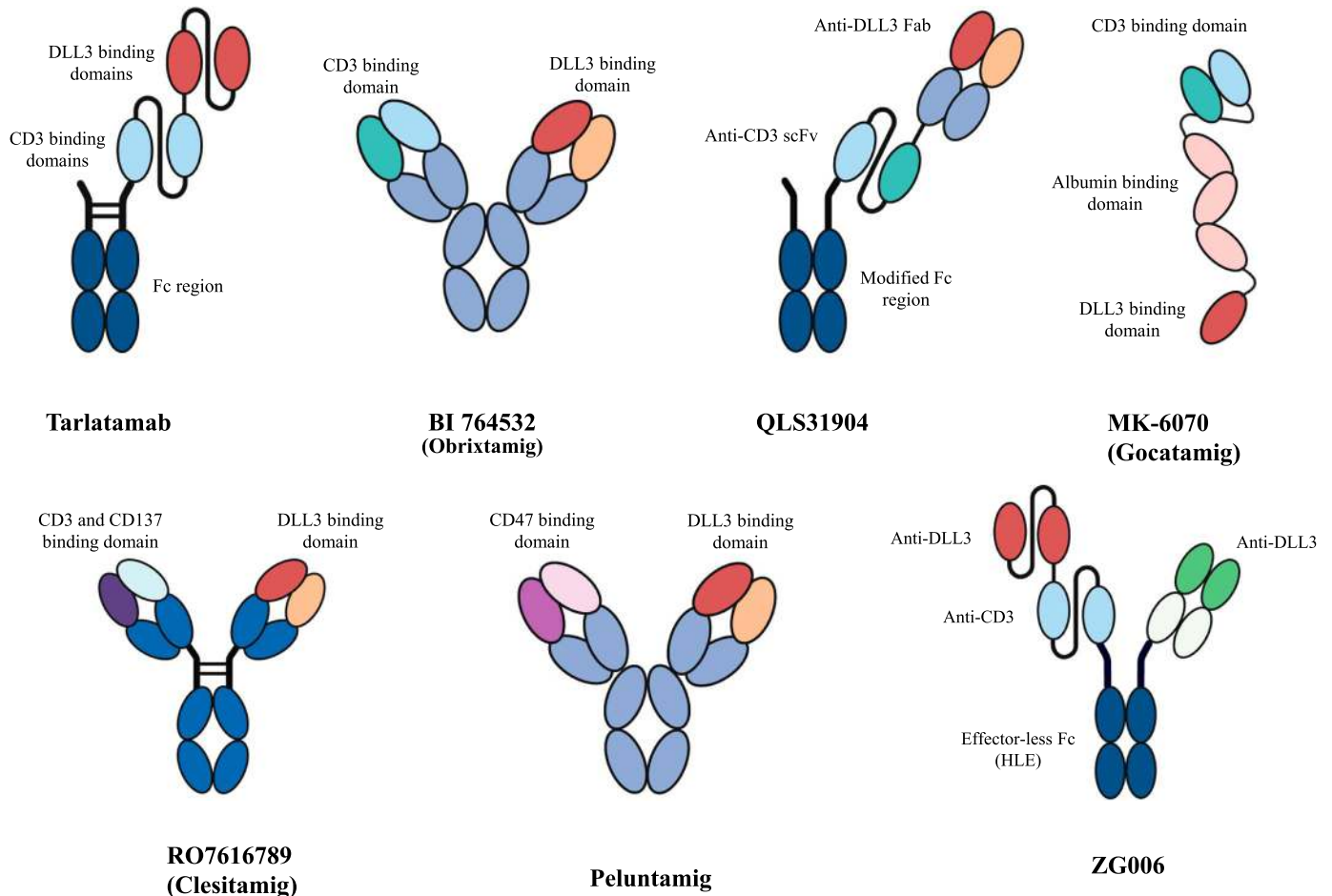


FIG 4. Structure of tarlatamab and other DLL3-targeting immune-cell engagers (adapted with modifications from Dima Biotech¹⁰⁹ and with permission from Rudin et al²⁰; Peluntamig structure courtesy of Phanes Therapeutics; ZG006 structure adapted from Wang et al¹¹⁰). CD3, cluster of differentiation-3; DLL3, delta-like ligand-3. Created in [BioRender.com](https://www.biorender.com). Naqash (2025).

serum half-life (Fig 4).²⁰ BI764532 is a bispecific DLL3/CD3 TCE that differs from tarlatamab in having an IgG-like structure with two fragment antigen-binding (Fab) domains, while QLS31904 is a bispecific T-cell engager composed of three components: a Fab domain specific to DLL3, an scFv directed against CD3, and a modified Fc region that facilitates heterodimerization of heavy chains correctly while minimizing unwanted Fc receptor interactions.⁹⁶⁻⁹⁸ MK-6070, a trispecific T-cell-activating construct features three distinct binding domains: an N-terminal domain targeting DLL3, a middle domain binding to human serum albumin to extend its half-life, and a C-terminal domain engaging CD3 on T cells.⁹⁹ RO7616789 is another trispecific antibody that targets not only DLL3 and CD3 but also has a CD137-binding domain to enhance T-cell activation through costimulatory signaling.¹⁰⁰ Additionally, evaluation of ZG006, another trispecific TCE, targeting two distinct DLL3 epitopes on tumor cells and CD3 on T cells is currently underway. This strategy involves binding two different sites on the DLL3 molecule, with dual-epitope targeting potentially enhancing the binding affinity and specificity leading to improved efficacy through more robust engagement of

DLL3-expressing tumor cells.¹⁰¹ Peluntamig (PT217) is an anti-DLL3/anti-CD47 bispecific antibody whose DLL3 binding improves the binding of its anti-CD47 moiety to the tumor cells, blocking the interaction of CD47 with signal regulatory protein alpha (SIRPalpha) in turn preventing CD47/SIRPalpha-mediated signaling and inhibition of phagocytosis. This CD47 blockade leads to macrophage activation and phagocytosis of DLL3-expressing tumor cells along with the T-cell-mediated immune response.¹⁰²

These DLL3-targeting TCEs share the same fundamental mechanism as tarlatamab but differ from it in their structural design incorporating additional functional domains aimed at enhancing efficacy, half-life, and T-cell activation. These variations may affect clinical performance and safety profiles, highlighting the importance of ongoing clinical trials to determine their optimal use in treating DLL3-expressing cancers.

Additionally, several CAR-based cell therapies directed against DLL3 are in various stages of development and testing for use in SCLC. AMG119 is a CAR T-cell therapy

wherein patient's autologous T cells are genetically modified *ex vivo* to express a transmembrane CAR targeting DLL3.¹⁰³ LB2102 is another such agent currently undergoing clinical evaluation for use in ES-SCLC and LCNEC, while ALLO-213 is an allogeneic CAR agent demonstrating benefit in a pre-clinical setting and yet to be tested in a phase I clinical trial.^{104,105} The efficacy of DLL3 CAR natural killer-92 cells has been demonstrated in preclinical mouse models and is currently being evaluated in a phase I clinical trial.¹⁰⁶

Despite the lack of clinical success observed with Rova-T, interest in ADCs targeting DLL-3 remains strong, with ongoing efforts to develop more effective and safer agents. Recently, interim results from the phase Ia/Ib trial of the DLL3 targeting ADC, ZL-1310 demonstrated an ORR of 74% across all dose levels in 19 patients with recurrent ES-SCLC, along with a favorable pharmacokinetic and safety profile.¹⁰⁷ Several other novel DLL3-directed ADCs including IBI3009, FZ-AD005, and SHR-4849 are currently being evaluated in phase I clinical trials.¹⁰⁸

DLL3 has also emerged as a compelling target for radioligand therapies (RLTs) in treating neuroendocrine neoplasms, especially SCLC.¹¹¹ RLTs generally comprise three components: a molecule that targets cancer cells, a chelating agent that binds a radioisotope, and a linker that connects the molecule and the radioisotope. RLTs involve conjugating radioactive isotopes to tumor-specific targeting molecules such as DLL-3, delivering cytotoxic radiation directly to DLL3-positive tumor cells. Preclinical studies have shown promising results, with ongoing research aimed at optimizing delivery mechanisms and minimizing off-target effects,^{112,113} spurring interest in advancing RLTs to clinical trials. Interestingly, ABD-147 is a targeted radiopharmaceutical therapy delivering the potent alpha-emitting radioisotope Actinium-225 to DLL3-expressing tumors. ABD-147 is engineered to bind specifically to DLL3 on tumor cells, delivering Actinium-225 to induce

double-stranded DNA breaks, leading to tumor cell death. There is an ongoing phase 1a/b study of ABD-147 in high-grade neuroendocrine carcinomas of the lung (NCT06736418).^{114,115}

CONCLUSION

The emergence of DLL3-targeting therapies, particularly tarlatamab, represents a pivotal moment in the evolution of precision immunotherapy for SCLC—a historically treatment-resistant and aggressive malignancy. Beyond the promising clinical activity, tarlatamab has catalyzed a broader conversation around redefining how we evaluate efficacy, manage toxicity, and deliver care for patients with SCLC. With the risk of CRS and ICANS, logistical hurdles for inpatient or prolonged outpatient monitoring, and a much higher price tag, agents such as tarlatamab should force solid tumors oncologists, institutions, and policymakers to rethink how we deliver cancer care. Looking ahead, the pipeline of DLL3-directed agents is rapidly expanding. As new generations of bispecifics, trispecifics, ADCs, and CAR-based DLL3-targeted strategies enter clinical development, the focus must now shift toward optimizing outpatient administration models, addressing disparities in access, refining quality-of-life assessments, and exploring biologically enriched patient subsets most likely to benefit. Improving how we measure what matters will be critical—PROs that capture time toxicity, financial burden, and long-term quality of life with meaningful benefit with this novel class of immunotherapies. The real-world success of this therapeutic class will hinge not only on continued innovation but also on the thoughtful integration of multidisciplinary care, supportive infrastructure, and policy reform to reduce financial toxicity. The road ahead offers both opportunity and responsibility—to ensure that these scientific advances translate into tangible, lasting outcomes in SCLC with the patient experience at the center of every decision (Fig 4).

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REFERENCES

- Wang X, Chiang AC: Big decisions on small cell lung cancer: A focus on clinical care updates and patient perspectives. *Am Soc Clin Oncol Educ Book* 44:e432520, 2024
- Huehls AM, Coupet TA, Sentman CL: Bispecific T-cell engagers for cancer immunotherapy. *Immunol Cell Biol* 93:290-296, 2015
- (FDA) USFDA: FDA grants accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tarlatamab-dlle-extensive-stage-small-cell-lung-cancer?utm_medium=email&utm_source=govdelivery
- Goyal PK, Sangwan K: Tarlatamab-dlle: A new hope for patients with extensive-stage small-cell lung cancer. *Curr Treat Options Oncol* 25:1337-1344, 2024
- Cohen S, Brennan B, Banerjee M, et al: Temporal trends in small cell lung cancer: Analysis of the U.S. Surveillance, Epidemiology and End Results (SEER) database. *J Clin Oncol* 41, 2023 (suppl 16; abstr e20641)
- Sands J, Cho BC, Ahn MJ, et al: OA10.03 tarlatamab sustained clinical benefit and safety in previously treated SCLC: DeLLphi-301 phase 2 extended follow-up. *J Thorac Oncol* 19:S30-S31, 2024
- Dingemans A-MC, Ahn M-J, Blackhall FH, et al: DeLLphi-301: Tarlatamab phase 2 trial in small cell lung cancer (SCLC)—Efficacy and safety analyzed by presence of brain metastasis. *J Clin Oncol* 42, 2024 (suppl 16; abstr 8015)
- Ganti AKP, Loo BW, Bassetti M, et al: Small cell lung cancer, version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw* 19:1441-1464, 2021
- Upreti D, Seaton R, Niroula A, et al: Trends in the incidence and survival outcomes in patients with small cell lung cancer in the United States: An analysis of the SEER database. *Cancer Med* 14: e70608, 2025
- Thomas A, Mian I, Tlemsani C, et al: Clinical and genomic characteristics of small cell lung cancer in never smokers: Results from a retrospective multicenter cohort study. *Chest* 158:1723-1733, 2020
- Varghese AM, Zakowski MF, Yu HA, et al: Small-cell lung cancers in patients who never smoked cigarettes. *J Thorac Oncol* 9:892-896, 2014
- Torres-Durán M, Curiel-García M, Ruano-Ravina A, et al: Small-cell lung cancer in never-smokers. *ESMO Open* 6:100059, 2021
- Arrazola RA, Griffin T, Lunsford NB, et al: US cigarette smoking disparities by race and ethnicity—Keep going and going. *Prev Chronic Dis* 20:E45, 2023
- Paz-Ares L, Chen Y, Reinmuth N, et al: Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. *ESMO Open* 7:100408, 2022
- Liu SV, Dziadziuszko R, Sugawara S, et al: OA01.04 five-year survival in patients with ES-SCLC treated with atezolizumab in IMpower133: Imbrella a extension study results. *J Thorac Oncol* 18: S44-S45, 2023
- Cheng Y, Spigel DR, Cho BC, et al: Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. *N Engl J Med* 391:1313-1327, 2024
- Horn L, Mansfield AS, Szczesna A, et al: First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 379:2220-2229, 2018
- Paz-Ares L, Dvorkin M, Chen Y, et al: Durvalumab plus platinum—etoposide versus platinum—etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): A randomised, controlled, open-label, phase 3 trial. *Lancet* 394:1929-1939, 2019
- Trigo Y, Subbiah V, Besse B, et al: Lurbinectedin as second-line treatment for patients with small-cell lung cancer: A single-arm, open-label, phase 2 basket trial. *Lancet Oncol* 21:645-654, 2020
- Rudin CM, Reck M, Johnson ML, et al: Emerging therapies targeting the delta-like ligand 3 (DLL3) in small cell lung cancer. *J Hematol Oncol* 16:66, 2023
- Rudin CM, Poirier JT, Byers LA, et al: Molecular subtypes of small cell lung cancer: A synthesis of human and mouse model data. *Nat Rev Cancer* 19:289-297, 2019
- Puri S, Naqash AR, Elliott A, et al: Real-world multiomic characterization of small cell lung cancer subtypes to reveal differential expression of clinically relevant biomarkers. *J Clin Oncol* 39, 2021 (suppl 15; abstr 8508)
- Baine MK, Hsieh M-S, Lai WV, et al: SCLC subtypes defined by ASCL1, NEUROD1, POU2F3, and YAP1: A comprehensive immunohistochemical and histopathologic characterization. *J Thorac Oncol* 15:1823-1835, 2020
- Gay CM, Stewart CA, Park EM, et al: Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell* 39:346-360.e7, 2021
- Xie M, Yuko M, Rodriguez-Canales J, et al: Molecular classification and biomarkers of outcome with immunotherapy in extensive-stage small-cell lung cancer: Analyses of the CASPIAN phase 3 study. *Mol Cancer* 23:115, 2024
- Nabet BY, Hamidi H, Lee MC, et al: Immune heterogeneity in small-cell lung cancer and vulnerability to immune checkpoint blockade. *Cancer Cell* 42:429-443.e4, 2024
- Roper N, Velez MJ, Chiappori A, et al: Notch signaling and efficacy of PD-1/PD-L1 blockade in relapsed small cell lung cancer. *Nat Commun* 12:3880, 2021
- Fleming RJ: Structural conservation of Notch receptors and ligands. *Semin Cell Develop Biol* 9:599-607, 1998
- Sprinzak D, Blacklow SC: Biophysics of Notch signaling. *Annu Rev Biophys* 50:157-189, 2021

30. Zhang H, Yang Y, Li X, et al: Targeting the Notch signaling pathway and the Notch ligand, DLL3, in small cell lung cancer. *Biomed Pharmacother* 159:114248, 2023
31. Borromeo MD, Savage TK, Kollipara RK, et al: ASCL1 and NEUROD1 reveal heterogeneity in pulmonary neuroendocrine tumors and regulate distinct genetic programs. *Cell Rep* 16:1259-1272, 2016
32. Augustyn A, Borromeo M, Wang T, et al: ASCL1 is a lineage oncogene providing therapeutic targets for high-grade neuroendocrine lung cancers. *Proc Natl Acad Sci USA* 111:14788-14793, 2014
33. Kim JW, Ko JH, Sage J: DLL3 regulates Notch signaling in small cell lung cancer. *iScience* 25:105603, 2022
34. Hong D, Knelson EH, Li Y, et al: Plasticity in the absence of NOTCH uncovers a RUNX2-dependent pathway in small cell lung cancer. *Cancer Res* 82:248-263, 2022
35. Sabari JK, Lok BH, Laird JH, et al: Unravelling the biology of SCLC: Implications for therapy. *Nat Rev Clin Oncol* 14:549-561, 2017
36. Ali G, Di Stefano I, Poma AM, et al: Prevalence of delta-like protein 3 in a consecutive series of surgically resected lung neuroendocrine neoplasms. *Front Oncol* 11:729765, 2021
37. Rojo F, Corassa M, Mavroudis D, et al: International real-world study of DLL3 expression in patients with small cell lung cancer. *Lung Cancer* 147:237-243, 2020
38. Khosla AA, Jatwani K, Singh R, et al: Bispecific antibodies in lung cancer: A state-of-the-art review. *Pharmaceuticals* 16:1461, 2023
39. Lin E, Khosla A, Smrecek NK, et al: P3.13D.01 proteomic characterization of antibody drug conjugate target expression profiles in small cell lung cancer (SCLC). *J Thorac Oncol* 19:S359, 2024
40. Ogawa H, Sakai Y, Nishio W, et al: DLL3 expression is a predictive marker of sensitivity to adjuvant chemotherapy for pulmonary LCNEC. *Thorac Cancer* 11:2561-2569, 2020
41. Hermans BCM, Derks JL, Thunnissen E, et al: DLL3 expression in large cell neuroendocrine carcinoma (LCNEC) and association with molecular subtypes and neuroendocrine profile. *Lung Cancer* 138:102-108, 2019
42. Xie H, Kaye FJ, Isse K, et al: Delta-like protein 3 expression and targeting in Merkel cell carcinoma. *Oncologist* 25:810-817, 2020
43. Rand J, Balzer BL, Frishberg DP, et al: Prevalence of delta-like protein 3 expression in Merkel cell carcinoma. *J Am Acad Dermatol* 85:749-750, 2021
44. Koshkin VS, Garcia JA, Reynolds J, et al: Transcriptomic and protein analysis of small-cell bladder cancer (SCBC) identifies prognostic biomarkers and DLL3 as a relevant therapeutic target. *Clin Cancer Res* 25:210-221, 2019
45. Hwang J, McGrath J, Lozada JR, et al: Molecular correlates of Delta-like-ligand 3 (DLL3) expression in neuroendocrine neoplasms (NENs). *J Clin Oncol* 40, 2022 (suppl 16; abstr 4127)
46. Puca L, Gavyert K, Sailer V, et al: Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. *Sci Transl Med* 11:eaav0891, 2019
47. Yin L, Wang R, Ma X, et al: Exploring the expression of DLL3 in gastroenteropancreatic neuroendocrine neoplasms and its potential diagnostic value. *Sci Rep* 15:3287, 2025
48. Liverani C, Bongiovanni A, Mercatali L, et al: Diagnostic and predictive role of DLL3 expression in gastroenteropancreatic neuroendocrine neoplasms. *Endocr Pathol* 32:309-317, 2021
49. Cimic A, Vranic S, Arguello D, et al: Molecular profiling reveals limited targetable biomarkers in neuroendocrine carcinoma of the cervix. *Appl Immunohistochem Mol Morphol* 29:299-304, 2021
50. Serrano AG, Rocha P, Freitas Lima C, et al: Delta-like ligand 3 (DLL3) landscape in pulmonary and extra-pulmonary neuroendocrine neoplasms. *npj Precis Oncol* 8:268, 2024
51. Lozada JR, Elliott A, Evans MG, et al: Expression patterns of DLL3 across neuroendocrine and non-neuroendocrine neoplasms reveal broad opportunities for therapeutic targeting. *Cancer Res Commun* 5:318-326, 2025
52. Saunders LR, Bankovich AJ, Anderson WC, et al: A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. *Sci Transl Med* 7:302ra136, 2015
53. Rudin CM, Pietanza MC, Bauer TM, et al: Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: A first-in-human, first-in-class, open-label, phase 1 study. *Lancet Oncol* 18:42-51, 2017
54. Blackhall F, Jao K, Greillier L, et al: Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-high SCLC: Results from the phase 3 TAHOE study. *J Thorac Oncol* 16:1547-1558, 2021
55. Uprety D, Remon J, Adjei AA: All that glitters is not gold: The story of rovalpituzumab tesirine in SCLC. *J Thorac Oncol* 16:1429-1433, 2021
56. Suurs FV, Lub-de Hooge MN, de Vries EGE, et al: A review of bispecific antibodies and antibody constructs in oncology and clinical challenges. *Pharmacol Ther* 201:103-119, 2019
57. Owen DH, Giffin MJ, Bailis JM, et al: DLL3: An emerging target in small cell lung cancer. *J Hematol Oncol* 12:61, 2019
58. Paz-Ares L, Champiat S, Lai WV, et al: Tarlatamab, a first-in-class DLL3-targeted bispecific T-cell engager, in recurrent small-cell lung cancer: An open-label, phase I study. *J Clin Oncol* 41:2893-2903, 2023
59. Dowlati A, Hummel H-D, Champiat S, et al: Sustained clinical benefit and intracranial activity of tarlatamab in previously treated small cell lung cancer: DeLLphi-300 trial update. *J Clin Oncol* 42:3392-3399, 2024
60. Ahn M-J, Cho BC, Felipe E, et al: Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med* 389:2063-2075, 2023
61. Chung HC, Piha-Paul SA, Lopez-Martin J, et al: Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: Results from the KEYNOTE-028 and KEYNOTE-158 studies. *J Clin Oncol* 15:618-627, 2020
62. Ready N, Farago AF, de Braud F, et al: Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. *J Thorac Oncol* 14:237-244, 2019
63. Amgen: First global phase 3 trial showing substantial survival advantage over chemotherapy, for patients with progression on or after platinum-based chemotherapy, 2025. <https://investors.amgen.com/news-releases/news-release-details/indelltra-demonstrated-superior-overall-survival-small-cell>
64. Zhang B, Shah KB, Parma M, et al: Rapid intracranial response with tarlatamab in patients with untreated brain metastases from SCLC—A real-world case series: Case report. *J Thorac Oncol* 10.1016/j.jtho.2025.02.023 [epub ahead of print on March 24, 2025]
65. Lau S, Ahn MJ, Moskovitz M, et al: OA10.04 tarlatamab with a PD-L1 inhibitor as first-line maintenance after chemo-immunotherapy for ES-SCLC: DeLLphi-303 phase 1b study. *J Thorac Oncol* 19:S31-S32, 2024
66. Sands J, Cho BC, Ahn MJ, et al: OA10.03 tarlatamab sustained clinical benefit and safety in previously treated SCLC: DeLLphi-301 phase 2 extended follow-up. Presented at the World Conference on Lung Cancer, San Diego, CA, 2024
67. Markouli M, Ullah F, Unlu S, et al: Toxicity profile of chimeric antigen receptor T-cell and bispecific antibody therapies in multiple myeloma: Pathogenesis, prevention and management. *Curr Oncol* 30:6330-6352, 2023
68. Van De Vyver AJ, Marrer-Berger E, Wang K, et al: Cytokine release syndrome by T-cell-redirecting therapies: Can we predict and modulate patient risk? *Clin Cancer Res* 27:6083-6094, 2021
69. Sebba A: Tocilizumab: The first interleukin-6-receptor inhibitor. *Am J Health Syst Pharm* 65:1413-1418, 2008
70. Le RQ, Li L, Yuan W, et al: FDA approval summary: Tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist* 23:943-947, 2018
71. Santomaso BD, Nastoupil LJ, Adkins S, et al: Management of immune-related adverse events in patients treated with chimeric antigen receptor T-cell therapy: ASCO guideline. *J Clin Oncol* 39:3978-3992, 2021
72. Morris EC, Neelapu SS, Giavridis T, et al: Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol* 22:85-96, 2022
73. Scott SA, Marin EM, Maples KT, et al: Prophylactic tocilizumab to prevent cytokine release syndrome (CRS) with teclistamab: A single-center experience. *Blood Cancer J* 13:191, 2023
74. Drugs.com: Actemra prices, coupons, copay cards & patient assistance. [https://www.drugs.com/price-guide/actemra#:~:text=Actemra%20\(tocilizumab\)%20is%20a%20member,on%20the%20pharmacy%20you%20visit](https://www.drugs.com/price-guide/actemra#:~:text=Actemra%20(tocilizumab)%20is%20a%20member,on%20the%20pharmacy%20you%20visit)
75. Cavalli G, Dinarello CA: Anakinra therapy for non-cancer inflammatory diseases. *Front Pharmacol* 9:1157, 2018
76. Pariano M, Pieroni S, De Luca A, et al: Anakinra activates superoxide dismutase 2 to mitigate inflammasome activity. *Int J Mol Sci* 22:6531, 2021
77. Gazeau N, Liang EC, Wu QV, et al: Anakinra for refractory cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome after chimeric antigen receptor T cell therapy. *Transplant Cell Ther* 29:430-437, 2023
78. IMDELLTRA® (tarlatamab-dlle) prescribing information. <https://www.imdelltrahcp.com/starting-imdelltra/dosing-and-administration>
79. Chiang AC, Garcia MEQ, Carlisle J, et al: Tarlatamab for patients with small cell lung cancer: 6-8 hour outpatient vs 48 hour inpatient monitoring in cycle 1. *Ann Oncol* 24:1-26, 2024
80. Chiang AC, Olmedo Garcia ME, Carlisle JW, et al: Safety of tarlatamab with 6-8-h outpatient versus 48-h inpatient monitoring during cycle 1: DeLLphi-300 phase 1 substudy. *ESMO Open* 10:104538, 2025
81. Majhail NS, Cox T, Larson S, et al: Outpatient administration of chimeric antigen receptor T-cell therapy using remote patient monitoring. *JCO Oncol Pract* 10.1200/OP-25-00062 [epub ahead of print on April 18, 2025]
82. Martin TG, Moreau P, Usmani SZ, et al: Teclistamab improves patient-reported symptoms and health-related quality of life in relapsed or refractory multiple myeloma: Results from the phase II MajesTEC-1 study. *Clin Lymphoma Myeloma Leuk* 24:194-202, 2024
83. Johnson PC, Dhawale T, Newcomb RA, et al: Longitudinal patient-reported outcomes in patients receiving chimeric antigen receptor T-cell therapy. *Blood Adv* 7:3541-3550, 2023
84. Johnson DB, Nebhan CA, Moslehi JJ, et al: Immune-checkpoint inhibitors: Long-term implications of toxicity. *Nat Rev Clin Oncol* 19:254-267, 2022
85. Gadgeel SM: Patient-reported outcomes in the era of immunotherapy trials. *J Clin Oncol* 16:516-518, 2021
86. Reuters: US FDA approves Amgen drug for small cell lung cancer, 2024. <https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-approves-amgen-drug-small-cell-lung-cancer-bloomberg-reports-2024-05-16/#:~:text=The%20U.S.%20Food%20and%20Drug,that%20has%20worsened%20despite%20chemotherapy>

87. CADTH Reimbursement Reviews and Recommendations, Lurbinectedin (Zepzelca): CADTH reimbursement recommendation: Indication: For the treatment of adult patients with stage III or metastatic small cell lung cancer who have progressed on or after platinum-containing therapy. Canadian Agency for Drugs and Technologies in Health, Ottawa, ON, 2023
88. Services CfMM: MS-DRG classifications and software. <https://www.cms.gov/medicare/payment/prospective-payment-systems/acute-inpatient-pps/ms-drg-classifications-and-software>
89. Manz CR, Porter DL, Bekelman JE: Innovation and access at the mercy of payment policy: The future of chimeric antigen receptor therapies. *J Clin Oncol* 38:384-387, 2020
90. Medicare: Medicare part B. <https://www.medicare.gov/providers-services/original-medicare/part-b>
91. Ording AG, Skjøth F, Poulsen LØ, et al: Time toxicity of systemic anticancer therapy for metastatic lung cancer in routine clinical practice: A nationwide cohort study. *JCO Oncol Pract* 10.1200/OP-24-00526 [epub ahead of print on December 20, 2024]
92. Crawford SM: Multidisciplinary team working contributes to lung cancer survival. *BMJ* 361:k1904, 2018
93. Avancini A, Belluomini L, Borsati A, et al: Integrating supportive care into the multidisciplinary management of lung cancer: We can't wait any longer. *Expert Rev Anticancer Ther* 22: 725-735, 2022
94. Wermke M, Gambardella V, Kuboki Y, et al: 670P Phase I trial of the delta-like ligand-3 (DLL3)/CD3 IgG-like T cell engager BI 764532 in patients (pts) with DLL3-positive tumors: Updated data. *Ann Oncol* 35:S525-S526, 2024
95. Aggarwal RR, Rottey S, Bernard-Tessier A, et al: Phase 1b study of tarlatamab in de novo or treatment-emergent neuroendocrine prostate cancer (NEPC). *J Clin Oncol* 42, 2024 (suppl 16; abstr 5012)
96. Wermke M, Felip E, Kuboki Y, et al: First-in-human dose-escalation trial of BI 764532, a delta-like ligand 3 (DLL3)/CD3 IgG-like T-cell engager in patients (pts) with DLL3-positive (DLL3+) small-cell lung cancer (SCLC) and neuroendocrine carcinoma (NEC). *J Clin Oncol* 41, 2023 (suppl 16; abstr 8502)
97. Hipp S, Voynov V, Drobits-Handl B, et al: A bispecific DLL3/CD3 IgG-like T-cell engaging antibody induces antitumor responses in small cell lung cancer. *Clin Cancer Res* 26:5258-5268, 2020
98. Hipp S, Voynov V, Drobits-Handl B, et al: A bispecific DLL3/CD3 IgG-like T-cell antibody induces anti-tumor responses in small cell lung cancer. *Clin Cancer Res* 26:5258-5268, 2020
99. Austin RJ, Lemon BD, Aaron WH, et al: TriTACs, a novel class of T-cell-engaging protein constructs designed for the treatment of solid tumors. *Mol Cancer Ther* 20:109-120, 2021
100. Su P-L, Chakravarthy K, Furuya N, et al: DLL3-guided therapies in small-cell lung cancer: From antibody-drug conjugate to precision immunotherapy and radioimmunotherapy. *Mol Cancer* 23:97, 2024
101. Wang Q, Chai X, Lin R, et al: 686TiP Preliminary phase I results from a first-in-human study of ZG006, a trispecific anti-T cell engager targeting CD3/DLL3/DLL3, as monotherapy in patients with advanced small cell lung cancer or neuroendocrine carcinoma. *Ann Oncol* 35:S532-S533, 2024
102. NCI: Anti-DLL3/anti-CD47 bispecific antibody PT217. <https://www.cancer.gov/publications/dictionaries/cancer-drug/def/peluntamig>
103. Byers LA, Chiappori A, Smit M-AD: Phase 1 study of AMG 119, a chimeric antigen receptor (CAR) T cell therapy targeting DLL3, in patients with relapsed/refractory small cell lung cancer (SCLC). *J Clin Oncol* 37, 2019 (suppl 15; abstr TPS8576)
104. Sands J, Schoenfeld A, Schwarzenberger P, et al: 702 Phase 1 study of DLL3-directed chimeric antigen receptor T-cells in subjects with extensive stage small cell lung cancer. *J Immunotherap Cancer* 11:A797, 2023
105. Zhang Y, Tacheva-Grigorova SK, Sutton J, et al: Allogeneic CAR T cells targeting DLL3 are efficacious and safe in preclinical models of small cell lung cancer. *Clin Cancer Res* 29:971-985, 2023
106. Liu M, Huang W, Guo Y, et al: CAR NK-92 cells targeting DLL3 kill effectively small cell lung cancer cells in vitro and in vivo. *J Leukoc Biol* 112:901-911, 2022
107. Zailab: ZL-1310, an investigational DLL3-targeted antibody-drug conjugate (ADC), demonstrates promising objective response rates and safety profile in extensive-stage small cell lung cancer, 2024. <https://ir.zailaboratory.com/news-releases/news-release-details/zl-1310-investigational-dll3-targeted-antibody-drug-conjugate>
108. Nature-Reviews-Drug-Discovery: DLL3 draws two antibody-drug conjugate deals, 2025. <https://www.nature.com/articles/d41573-025-00011-3>
109. DIMA Biotechnology: DLL3—A Target for Small Cell Lung Cancer Treatment. 2024. <https://www.dimabio.com/blog/dll3-a-target-for-small-cell-lung-cancer-treatment>
110. Wang Q, Chai X, Lin R, et al: Trial in progress: A Phase I first-in-human study of ZG006, a trispecific anti-t cell engager targeting CD3/DLL3/DLL3, as monotherapy in patients with advanced small cell lung cancer or neuroendocrine carcinoma. Presented at ESMO Congress 2024, Barcelona, Spain, September 13-17, 2024
111. Su PL, Chakravarthy K, Furuya N, et al: DLL3-guided therapies in small-cell lung cancer: From antibody-drug conjugate to precision immunotherapy and radioimmunotherapy. *Mol Cancer* 23:97, 2024
112. Tully KM, Tendler S, Carter LM, et al: Radioimmunotherapy targeting delta-like ligand 3 in small cell lung cancer exhibits antitumor efficacy with low toxicity. *Clin Cancer Res* 28:1391-1401, 2022
113. Korsen JA, Gutierrez JA, Tully KM, et al: Delta-like ligand 3-targeted radioimmunotherapy for neuroendocrine prostate cancer. *Proc Natl Acad Sci USA* 119:e2203820119, 2022
114. Saboury B, Bodei L, Ulaner GA, et al: A phase 1a/b, open-label, dose-escalation study of 225Ac-ABD147 for locally advanced or metastatic small cell lung cancer and large cell neuroendocrine carcinoma of the lung following platinum-based chemotherapy. Proceedings of the 116th Annual Meeting of the American Association for Cancer Research, Chicago, IL, April 25-30, 2025; AACR, Philadelphia, PA, 2025. Abstract nr CT107/2. <https://www.abstractsonline.com/pp8/#!/20273/presentation/10568>
115. OncLive: FDA grants fast track designation to ABD-147 for ES-SCLC. 2024. <https://www.onclive.com/view/fda-grants-fast-track-designation-to-abd-147-for-es-sclc>

Bispecific Antibodies in Non–Small Cell Lung Cancer: From Targeted Innovation to Real-World Integration

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OVERVIEW

Bispecific antibodies have ushered in a transformative era in treating non–small cell lung cancer (NSCLC), enabling dual–pathway targeting with promising clinical outcomes in previously refractory disease subsets. Recent US Food and Drug Administration approvals—including amivantamab, an epidermal growth factor receptor (EGFR)/mesenchymal-epithelial transition factor–targeting monoclonal antibody for EGFR exon 20 insertions and frontline EGFR–mutant (Exon 19 and 21) NSCLC, and zenocutuzumab for tumors harboring neuregulin 1 fusions—highlight their expanding therapeutic footprint. However, a new spectrum of on–target toxicities and implementation challenges are essential considerations as part of this innovation. This review dissects the evolving clinical data for bispecific antibodies in NSCLC, focusing on amivantamab, and provides a practical framework for managing dermatologic, infusion-related, and class-specific adverse events. We explore quality-of-life outcomes, financial toxicity, and the role of subcutaneous formulations in improving patient adherence and treatment experience. Furthermore, we highlight an emerging PD-1/vascular endothelial growth factor-A bispecific antibody (ivonescimab) and its potential to reshape frontline therapy paradigms in NSCLC. By integrating clinical trial evidence with real-world considerations, this review aims to equip oncologists with the tools to optimize the use of bispecific antibodies in NSCLC and guide future therapeutic integration.

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INTRODUCTION

Bispecific antibody therapy has recently revolutionized the care of key subgroups of non–small cell lung cancer (NSCLC), with two US Food and Drug Administration (FDA) approvals or new indications in 2024. Amivantamab, a bispecific antibody targeting the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET), received accelerated FDA approval in May 2021 for NSCLC harboring EGFR exon 20 insertions, followed by an expanded frontline indication for exon 20 mutations in combination with chemotherapy in March 2024, followed by an approval for combination with chemotherapy after progression after osimertinib for “classical” EGFR mutations in September 2024, and recent approval in combination with lazertinib in the frontline-sensitizing EGFR mutation setting in August 2024. Zenocutuzumab, a human epidermal growth factor receptor (HER)2 and HER3 bispecific antibody, was FDA approved in December 2024 for NSCLC and pancreatic adenocarcinoma harboring neuregulin 1 (NRG1) fusions. These two therapeutics address unmet needs in disease subtypes historically resistant to therapy.

Drug availability is just the first step in expanding the treatment armamentarium for patients with lung cancer.

Streamlined implementation and side-effect management are essential. Both agents, and those on the horizon, have unique toxicities based on their antibody construct, mechanism of action, or related on–target side effects. In this study, we review the therapeutic landscape affected by these bispecific antibodies, focusing on adverse event (AE) monitoring, mitigation, and prevention, patient-reported outcomes (PROs), and financial toxicity. We hope that shared knowledge will facilitate the safe and timely incorporation of bispecific antibodies in various practice settings.

OPTIMIZING THE USE OF AMIVANTAMAB AND ADVERSE EFFECT MANAGEMENT

Amivantamab is a fully human, low-fucose, IgG1 bispecific antibody engineered to target both EGFR and MET. Its dual binding allows for ligand-independent inhibition of EGFR and MET signaling pathways, receptor degradation by trogocytosis, and Fc-mediated effector functions including antibody-dependent cellular cytotoxicity.¹ Pharmacokinetically, amivantamab has a terminal half-life of approximately 11.3 days, supporting biweekly dosing after an initial loading phase.² It exhibits dose-proportional increases in exposure across the therapeutic range and maintains steady-state concentrations by cycle 2. Pharmacodynamic

PRACTICAL APPLICATIONS

- Amivantamab is a bispecific antibody targeting epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor, demonstrating efficacy in patients with non-small cell lung cancer (NSCLC) harboring EGFR exon 20 insertions as well as in combination for activating EGFR mutations (Exon 19 and 21) in both the frontline and relapsed settings.
- Infusion-related reactions (IRRs), cutaneous toxicities, and venous thromboembolism can be limiting factors affecting quality of life with amivantamab, but there are effective emerging supportive strategies. Enhanced steroid premedication reduces the risk of IRRs, prophylactic dermatologic regimens such as oral antibiotics and topical formulations as validated in the COCOON trial, and concomitant anticoagulation can mitigate the severity of these toxicities. Multidisciplinary care with early dermatology referral is recommended to manage skin toxicities appropriately.
- Zenocutuzumab targets human epidermal growth factor receptor (HER)2 and HER3 and received accelerated approval in advanced NSCLC and pancreatic adenocarcinoma harboring neuregulin 1 gene fusions.
- Ivonescimab, a PD-1/vascular endothelial growth factor bispecific antibody, aims to enhance immune response while inhibiting angiogenesis, showing promise in lung cancer treatment with ongoing phase III trials.

analyses reveal target engagement and receptor down-regulation in both EGFR-mutant and MET-altered NSCLC.

There are now multiple indications for amivantamab combinations in patients with EGFR-mutated NSCLC, both the classical sensitizing exon-19 deletion and L858R and the heterogeneous EGFR exon 20 population (Table 1). The mechanism of action and common clinical toxicities are shown in Figure 1.

Dermatologic Toxicity With Amivantamab and Other EGFR-Targeted Therapy

The cutaneous toxicities of the tyrosine kinase inhibitors, specifically early EGFR inhibitors, have been well described.⁷ Bispecific antibodies present potential novel anticancer activity but also present new and challenging adverse reactions.⁸ In the phase III PAPILLON trial, which randomly assigned patients with NSCLC to amivantamab-chemotherapy and chemotherapy alone, found that all-grade cutaneous AEs

in the amivantamab-chemotherapy group included paronychia (56%), rash (54%), acneiform dermatitis (31%), and stomatitis (25%).³ While direct comparisons between trials should be done with caution, the phase III EURTAC trial that randomly assigned patients with NSCLC to erlotinib and chemotherapy alone found that all-grade cutaneous AEs included rash (67%) and alopecia (14%).⁹ The reporting of cutaneous adverse reactions in clinical trials often lacks specifics, and real-world experiences are necessary to clarify cutaneous toxicities further.

The initial results of the supportive care COCOON trial (ClinicalTrials.gov identifier: [NCT06120140](https://clinicaltrials.gov/ct2/show/study/NCT06120140)) were recently reported at the 2025 European Lung Cancer Congress.¹⁰ COCOON is a phase II, randomized, open-label, multicenter study evaluating the effectiveness of a prophylactic dermatologic regimen. This report included 138 of a planned 200 patients undergoing therapy with amivantamab plus lazertinib in the frontline setting. Patients in arm A received an enhanced regimen consisting of an oral tetracycline (doxycycline or minocycline) for 12 weeks, then a topical antibiotic (clindamycin 1%) for weeks 13+, an antibacterial wash (chlorhexidine 4%) for the nails, and at least daily use of a ceramide-based noncomedogenic moisturizer. Participants in arm B received standard of care. At a mean 12 weeks of follow-up, the enhanced regimen decreased the incidence of grade ≥ 2 dermatologic AEs by 50%, grade 3 dermatologic AEs by 50%, and approximately 50% reduction in treatment discontinuation secondary to AEs, when compared with the standard of care for patients with EGFR-mutated NSCLC on dual EGFR-targeted therapy. Longer term follow-up data as well as considerations on ease of use and out-of-pocket costs are awaited with this supportive regimen.

While additional studies and data are pending, the literature that stems from EGFR inhibitor use can guide the management of these reactions. Tables 2 and 3 offer treatment guidance for acneiform dermatitis and paronychia on the basis of the best available evidence for EGFR inhibitor reactions and case reports/series of amivantamab. While pruritus is frequently associated with acneiform dermatitis and management of this should result in symptom improvement, topical corticosteroids, antihistamines, and/or oral gabapentin can be considered for supportive measures.³⁵ Thorough management guidelines for xerosis cutis,⁷ oral mucositis,³⁶ and hand-foot syndrome³⁷ exist and are cited here for further reference.

Amivantamab has been associated with severe variants of acneiform dermatitis affecting the scalp that closely resemble erosive pustular dermatosis^{16,38-40} (Fig 2). Onset can be insidious, as compared with the acneiform eruption, sometimes taking up to 9 months to manifest, and is refractory to typical preventative and grade 1 management strategies.⁴¹ Severe, grade 3 AEs almost always require treatment breaks and consideration of dose reductions. Early suspicion and referral to dermatology is essential. Anecdotal evidence and case reports suggest propranolol and low-dose

TABLE 1. Phase III Clinical Trial Results for Amivantamab in Non–Small Cell Lung Cancer

Trial (ClinicalTrials.gov)	Patient Population	Combination Regimen	n	ORR	Median PFS	Overall Survival	Primary Outcome
PAPILLON ³ (NCT04538664)	EGFR exon 20 frontline	Amivantamab plus platinum-doublet chemotherapy v	153	73%	11.4 months (95% CI, 9.8 to 13.7)	HR for death on interim analysis 0.67 (95% CI, 0.42 to 1.09; <i>P</i> = .11)	PFS
		Chemotherapy alone	155	47%	6.7 months (95% CI, 5.6 to 7.3)		
MARIPOSA ⁴ (NCT04487080)	Sensitizing EGFR mutations frontline	Amivantamab + lazertinib v	429	86%	23.7 months (95% CI, 19.1 to 27.7)	HR for death 0.80 (95% CI, 0.61 to 1.05) for amivantamab-lazertinib as compared with osimertinib	PFS
		Osimertinib v	429	85%	16.6 months (95% CI, 14.8 to 18.5)		
		Lazertinib	216	NR	18.5 months (95% CI, 14.8 to 20.1)		
MARIPOSA-2 ⁵ (NCT04988295)	Sensitizing EGFR mutations with progression on osimertinib	Amivantamab + lazertinib + chemotherapy v	263	63%	8.3 months (95% CI, 6.8 to 9.1)	HR for death 0.77 (95% CI 0.49-1.21) for amivantamab + chemotherapy versus chemotherapy	PFS, TEAEs, TESAEs
		Amivantamab + chemotherapy v	131	64%	6.3 months (95% CI, 5.6 to 8.4)		
		Chemotherapy alone	263	36%	4.2 months (95% CI, 4.0 to 4.4)	HR for death on interim analysis 0.96 (95% CI 0.67-1.35) for amivantamab-lazertinib–chemotherapy versus chemotherapy	
PALOMA-3 ⁶ (NCT05388669)	Sensitizing EGFR mutations with progression on osimertinib and chemotherapy	Subcutaneous amivantamab + lazertinib v	206	30%	6.1 months (95% CI, 4.3 to 8.1)	HR for death, 0.62 (95% CI, 0.42 to 0.92; <i>P</i> = .2)	PK (C _{trough} on C2D1 or C4D1 and C2 AUC _{D1-D15})
		Intravenous amivantamab + lazertinib	212	33%	4.3 months (95% CI, 4.1 to 5.7)		

Abbreviations: C, cycle; C_{trough}, observed serum concentration; D, day of cycle; EGFR, epidermal growth factor receptor; HR, hazard ratio; NR, not reached; ORR, objective response rate; PFS, progression free survival; PK, pharmacokinetics; TEAEs, treatment-emergent adverse events; TESAEs, treatment-emergent serious adverse events.

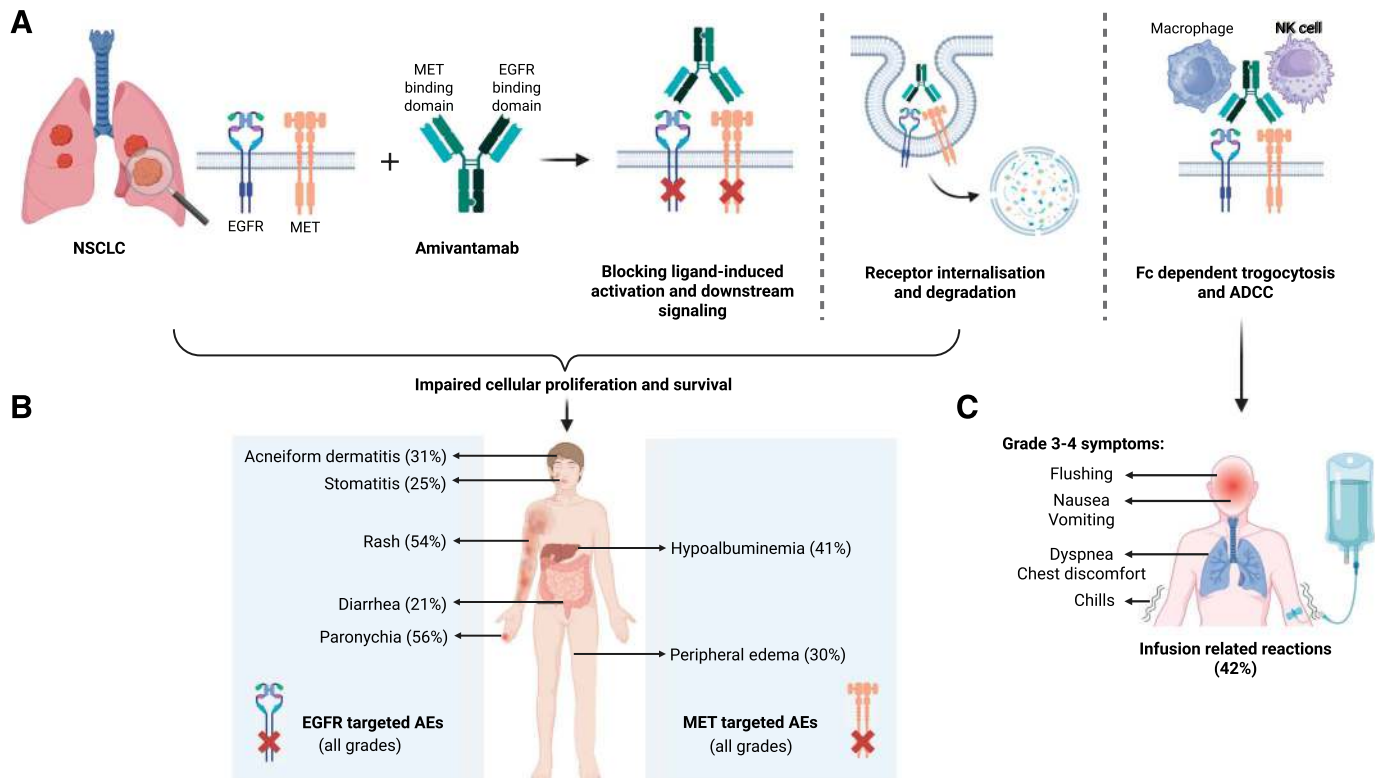


FIG 1. (A) Mechanism of action of amivantamab in NSCLC. (B) AEs attributed to EGFR inhibition and MET inhibition, with selected all-grade AEs from the PAPILLON trial. (C) Symptoms of infusion-related reactions seen with amivantamab in the PAPILLON trial. Created in BioRender. Naqash, A. (2025) BioRender.com/45lmsba. ADCC, antibody-dependent cellular cytotoxicity; AEs, adverse events; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition factor; NK, natural killer; NSCLC, non-small cell lung cancer.

isotretinoin may effectively manage this AE and allow for treatment resumption.^{16,17}

Infusion-Related Reactions With Amivantamab

Infusion-related reactions (IRRs) can occur with the infusion of a new protein and are common among monoclonal antibodies.⁴² In patients treated with amivantamab on the phase I chrysalis trial, IRR was reported in 256 of 380 (67%) patients who received the FDA-approved dose.⁴³ Signs and symptoms of IRR were generally mild, with all but eight IRRs of grade 1 to 2, and they included chills, dyspnea, flushing, nausea, chest discomfort, and vomiting. To help mitigate this risk, the infusion schedule splits the first dose into two (cycle 1 day 1: C1D1 and cycle 1 day 2: C1D2), but this adds to the chair time and scheduling burden of amivantamab. The median time to onset of IRR was 60 min, and 90% of IRRs on the chrysalis trial occurred on C1D1.

The phase III PALOMA-3 trial (ClinicalTrials.gov identifier: [NCT05388669](https://clinicaltrials.gov/ct2/show/study?term=NCT05388669)) randomly assigned patients to intravenous (IV) or subcutaneous (SC) amivantamab in combination with lazertinib and showed a significant reduction in IRRs with the SC formulation (13% v 66%).⁶ This was associated with a median administration time of 4.8 minutes with the SC formulation compared with 5 hours with the C1D1 IV dose. Surprisingly, there was significantly improved overall

survival (OS) with the SC formulation (hazard ratio [HR] for death, 0.62 [95% CI, 0.42 to 0.92]; nominal $P = .02$) and a reduced rate of venous thromboembolism (VTE; 9% v 14%). Other efforts to reduce the risk of IRR have included increasing pretreatment dexamethasone dosing. In fact, in the PAPILLON clinical trial of chemotherapy plus amivantamab, which includes premedication and postinfusion dexamethasone, the incidence of infusion reactions was lower at 42%.³ In the phase II SKIPPirr study (ClinicalTrials.gov identifier: [NCT05663866](https://clinicaltrials.gov/ct2/show/study?term=NCT05663866)), four different prophylactic tactics were tested, and oral dexamethasone 8 mg twice daily given on C1D-2, C1D-1, and the morning of C1D1 (five doses) was found to reduce the risk of IRR to 22.5%, a three-fold reduction from the rate in the chrysalis trial.⁴⁴ While the additional dexamethasone can be easily incorporated now, we anticipate a rapid transition to SC formulation when available to reduce infusion center time and steroid-associated side effects. The COPERINCUS trial (ClinicalTrials.gov identifier: [NCT06667076](https://clinicaltrials.gov/ct2/show/study?term=NCT06667076)) of SC amivantamab plus lazertinib frontline or chemo plus amivantamab in the postosimertinib setting is ongoing (Table 4).

MET-Related Toxicity With Amivantamab

Amivantamab is a more potent inhibitor of MET than EGFR and has some notable AEs attributable to on-target MET inhibition.⁴⁵ Class-related MET toxicities that are seen with

TABLE 2. Cutaneous Toxicity: Acneiform Dermatitis/Papulopustular Eruption

Grade CTCAE v 5.0	Clinical Presentation	Treatment	Level of Evidence ^a
Preventative		Topical emollients, sunscreen (SPF ≥ 30), topical steroids (class VII, ie, hydrocortisone 1%); Systemic antibiotics (doxycycline 100-200 mg/day > minocycline 100 mg/day) ¹¹	IB
Grade 1	Papules and/or pustules on <10% BSA; $\pm$ pruritus or tenderness	Topical antibiotic (clindamycin, erythromycin) ¹² ;	III
		Topical steroid (class VI, ie, hydrocortisone 2.5%) ⁷ ;	IV
		For recalcitrant disease, consider: Vitamin K1 cream ^{13,14}	III
		Colloidal oatmeal ¹⁵	III
Grade 2	Papules and/or pustules on 10%-30% BSA; $\pm$ pruritus/tenderness; psychosocial impact; limiting instrumental ADL	Oral antibiotic (doxycycline 100-200 mg/day > minocycline 100 mg/day) ¹¹	IB
Grade 3	Papules and/or pustules >30% BSA involved; moderate to severe symptoms; limiting self-care ADL	High-potency class I-II topical steroids ⁷ ;	IV
		Oral dapsone; Isotretinoin > Acitretin; Propranolol; systemic steroids ¹⁶⁻²² Pause/stop treatment; restart cautiously with dose reduction	IV
Grade 4	Any % BSA with significant burden on quality of life; life-threatening consequences	Pause/stop treatment; restart cautiously with dose reduction	
General recommendations	For extensive accumulation of fibrinopurulent debris, careful debridement should be performed Diluted sodium hypochlorite solution 0.5% compresses can be used to control bacterial colonization. ²³ Aluminum acetate compresses can be used for highly exudative reactions		

NOTE. Levels of evidence: (IA) meta-analysis of randomized controlled trials; (IB) at least 1 randomized controlled trial; (IIA) at least 1 controlled study without randomization; (IIB) at least one other type of quasi-experimental study; (III) nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and (IV) expert committee reports or opinions or clinical experience of respected authorities.

Abbreviations: ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; SPF, sun protection factor.

^aMost recommendations/evidence are extrapolated from traditional targeted therapy until additional research and data on bispecific antibodies have been accrued.

MET oral kinase inhibitors such as tepotinib, capmatinib, and salvitinib include hypoalbuminemia, peripheral edema, elevated creatinine, and gastrointestinal side effects such as nausea and diarrhea.⁴⁶ Hypoalbuminemia and the resultant peripheral edema are the two most commonly side effects seen with amivantamab and, unfortunately, are recalcitrant to many supportive measures. Diuretics are frequently ineffective, necessitating more manual edema management with compression and lymphatic massage.⁴⁷ Anecdotally, dose reduction is only mildly helpful, but treatment discontinuation resolves the edema.

Venous Thromboembolism With Amivantamab and Lazertinib

While lung cancer is a known risk of VTE, with a baseline rate of deep venous thrombosis and/or pulmonary embolism up to 12.5% in stage IV disease,⁴⁸ post hoc analysis from the CHRYSALIS (ClinicalTrials.gov identifier: [NCT02609776](#); amivantamab monotherapy and amivantamab plus lazertinib), CHRYSALIS-2 (ClinicalTrials.gov identifier: [NCT04077463](#);

amivantamab plus lazertinib), and LASER201 (ClinicalTrials.gov identifier: [NCT04075396](#); lazertinib monotherapy) trials showed a numerically higher incidence of VTE with combination amivantamab plus lazertinib (21%) than amivantamab (11%) or lazertinib (11%) monotherapy.⁴⁹ The first VTE event in the patients treated with amivantamab plus lazertinib was diagnosed at a median of 79 days, with 64% occurring within the first 4 months. These data were incorporated midway through the phase III Mariposa II trial, and either direct oral anticoagulants or low-molecular-weight heparin was recommended but not mandatory for patients receiving amivantamab-lazertinib-chemotherapy for the first 4 months.⁵ The COCOON trial included 4 months of anticoagulation prophylaxis and demonstrated a 6%-7% incidence of DVT in all patients.¹⁰

Quality of Life and Financial Toxicity With Amivantamab

Understanding how toxicity affects patients personally is imperative as we aim to ensure that patient well-being and

TABLE 3. Cutaneous Toxicity: Paronychia

Grade	Clinical	Treatment	Level of Evidence ^a
Preventative		Avoid wet work, gentle skin care, avoid nail trauma, consider nail lacquers; cushioning of affected areas; wide toe box shoes ²⁴	IV
Grade 1	Mild: Asymptomatic or mild symptoms	Warm water soaks ± dilute white vinegar OR dilute bleach ^b ; high potency class I-II topical steroids; topical antibiotics (clindamycin, erythromycin) ^{25,26}	IIB
		<i>For recalcitrant disease, consider:</i> Adapalene ²⁷	IV
Grade 2	Moderate: Limiting appropriate instrumental ADL	Oral antibiotics (if not already on therapy) ²⁸	IV
		Silver nitrate, electrodesiccation, or cryotherapy of excess granulation tissue/pyogenic granulomas ^{29,30}	IB
		<i>For procedure-adverse patients, consider:</i> Topical beta blockers (timolol gel) for granulation tissue/pyogenic granuloma ^{31,32}	IV
Grade 3	Severe: Disabling, limiting ADL	Debridement of excess granulation tissue/nail plate avulsion ³³ Pause/stop treatment; restart cautiously with dose reduction	IV

NOTE. Levels of evidence: (IA) meta-analysis of randomized controlled trials; (IB) at least 1 randomized controlled trial; (IIA) at least 1 controlled study without randomization; (IIB) at least one other type of quasi-experimental study; (III) nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and (IV) expert committee reports or opinions or clinical experience of respected authorities.

Abbreviation: ADL, activities of daily living.

^aMost recommendations/evidence are extrapolated from traditional targeted therapy until additional research and data on bispecific antibodies have been accrued.

^bVinegar soak recipe: one tablespoon of plain white vinegar:two cups of water; bleach soak recipe: 0.005% (approximately 1/4-1/8 cup of 6% bleach for 3-5 gallons water).³⁴

quality of life remain at the center of our treatment decisions. Patients frequently have questions regarding the treatment-related side effects they may face, along with the potential socioeconomic implications. Often, the overarching concern, particularly in patients with metastatic disease, is how these factors may affect overall quality of life. PROs can provide some insights into the patient experience.

Several trials studying amivantamab have included PROs as outcomes. In PAPILLON, first-line amivantamab in combination with platinum-doublet chemotherapy for NSCLC harboring the EGFR exon 20 insertion, symptomatic quality of life and function were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and PROs Measurement Information System Short Form Physical Function 8c (PROMIS-PF 8c). Adding amivantamab to chemotherapy improved global health status and overall function in physical, role, emotional, cognitive, and social domains.⁵⁰ Additionally, amivantamab plus chemotherapy lessened the burden of key NSCLC symptoms, improved the time to deterioration in physical functioning by approximately 6 months ($P = .013$), and reduced the risk of symptomatic progression by 33% ($P = .04$).⁵⁰ Later in the MARIPOSA trial investigating amivantamab and lazertinib in the frontline setting for EGFR Ex19del or L858R mutations, PROs were

evaluated in comparison to the well-tolerated standard of care, osimertinib. The EORTC-QLQ-C30 measured patient function, and symptom scores were assessed using the NSCLC-Symptom Assessment Question. While functional domains did not show significant change from baseline for amivantamab plus lazertinib or osimertinib, the global health status for patients taking osimertinib was slightly favorable to amivantamab plus lazertinib. However, it did not reach the meaningful change threshold.⁵¹ Similarly, total symptom scores trended toward improvement for both regimens; however, neither regimen outperformed the other nor reached the meaningful change threshold.⁵¹ The final analysis of time to symptomatic progression favored the amivantamab plus lazertinib regimen (not evaluable v 29.3 months; HR, 0.72; $P = .005$).⁵¹ Overall, amivantamab seems to have an acceptable quality-of-life profile compared with standard-of-care regimens among trial participants.

As previously discussed, IRRs are prominent with the IV administration of amivantamab, which can negatively affect tolerability and/or adherence to an otherwise effective therapeutic agent. To mitigate this issue, the PALOMA-3 trial reported outcomes from the SC administration of amivantamab, revealing highly promising results. IRRs decreased by 53%, and convenience scores were markedly higher among patients receiving SC administration.⁶ The



FIG 2. Clinical examples of the erosive pustular dermatosis of the scalp-like eruption after amivantamab administration. (A) Grade 1 reaction: scattered papulopustules in a folliculocentric distribution. (B) Grade 2 reaction: purulent crust and matted hair overlying an isolated ulcer with peripheral folliculocentric papulopustules. (C) Grade 3 reaction: numerous pustules coalescing into lakes of puss in a background of alopecic patches. (D) Grade 4 reaction: almost complete ulceration of the scalp with copious purulence.

time required to receive amivantamab subcutaneously is substantially shorter in the order of minutes compared with hours in the conventional setting. At the end of treatment, 85% of patients rated the SC injection as “very convenient” or “convenient” compared with only 35% of patients receiving the IV infusion.⁶ Not only were there improvements in PROs, but a clinical benefit was also recognized with a trend toward longer progression-free survival (PFS; $P = .2$) and a significant improvement in OS ($P = .02$).⁶ While the direct cause of such clinical benefit is unclear, a more tolerable and efficient drug is likely, at the very least, a contributing factor, highlighting the importance of toxicity mitigation on all fronts.

Financial toxicity is another aspect of novel drug development that affects patients. In the United States, the global mean launch price for medications increased by 19.7% per year from 2011 to 2022, with cancer drugs costing

substantially more than others.⁵² Additionally, the prices of these medications often continue to rise in the years following their launch, with a dichotomy frequently existing between price and overall clinical benefit.⁵² A recent wholesale acquisition cost of amivantamab was listed as \$3,806.68 US dollars (USD) per vial (350 mg). With doses of 1,050 mg for patients <80 kg or 1,400 mg, the wholesale acquisition cost can range from \$11,420 USD to over \$15,220 USD per treatment. Although patients do not entirely incur this cost, it can be devastating to patients who do not have adequate insurance coverage. Furthermore, these costs do not take into account the direct patient cost of copays for visits, infusions, laboratory blood draws, and multiple supportive medications necessary to allay the multitude of side effects. A cost-effectiveness analysis of amivantamab plus chemotherapy versus chemotherapy alone was performed by Yue et al on the basis of data from the PAPILLON trial. Adding amivantamab resulted in 1.904 quality-adjusted

TABLE 4. Ongoing Phase II Trials With Amivantamab

Trial	Phase	Indication	Intervention	Primary Endpoint
COPERNICUS NCT06667076	Ib	<i>EGFR</i> -mutated locally advanced or metastatic NSCLC	SC amivantamab + lazertinib as 1L treatment, or SC amivantamab + platinum-based chemotherapy (carboplatin + pemetrexed) as 2L treatment	ORR
LUNG-MAP SUB-STUDY NCT06116682	II	<i>MET</i> amplification–positive stage IV or recurrent NSCLC	Amivantamab SC weekly in cycle 1 and then every other week in subsequent cycles	ORR
PALOMA-2 NCT05498428	II	Locally advanced or metastatic NSCLC not amenable to surgical resection or chemoradiation Cohorts 1, 3, 3b, 5, 6, and 7: <i>EGFR</i> Ex19del or Exon 21 L858R mutation; Cohort 2: <i>EGFR</i> Exon 20ins mutation	Cohort 1 (1L, previously untreated): amivantamab (Q2W) + lazertinib Cohort 2 (previously untreated): amivantamab (Q3W) + chemotherapy Cohort 3 (2L, after osimertinib): amivantamab (Q3W) + lazertinib + chemotherapy Cohort 3b (2L, after osimertinib): amivantamab (Q3W) + chemotherapy Cohort 4 (previously treated with amivantamab IV): Switch from amivantamab IV to SC-CF (Q2W) Cohort 5 (1L, previously untreated): amivantamab (Q4W) + lazertinib Cohort 6 (1L, previously untreated): amivantamab (Q2W) + lazertinib + anticoagulant Cohort 7 (2L, after amivantamab + lazertinib): amivantamab (Q3W) + chemotherapy	All cohorts except Cohort 4: ORR Cohort 4: No. of participants with AEs and AEs by severity, No. of participants with abnormalities in clinical laboratory values, and abnormality by severity
NCT05845671	I/II	Locally advanced or metastatic NSCLC with a known <i>ALK</i> , <i>ROS1</i> , or <i>RET</i> fusion	Amivantamab, combined with common TKIs, is used in <i>ALK</i> , <i>ROS1</i> , and <i>RET</i> advanced NSCLC progressing on TKIs	Phase I: MTD, Recommended phase II combination dose (RP2CD) RP2CD, Phase II: ORR of amivantamab with TKIs
PolyDamas NCT05908734	I/II	Metastatic NSCLC progressed on or after standard systemic anticancer therapy	Amivantamab IV + cetrelimab IV	Phase I: RP2CD, DLTs Phase II: ORR
swalloWTail NCT06532032	I/II	Metastatic NSCLC without oncogenic driver mutations with disease progression on platinum-based chemotherapy and immune checkpoint inhibitor	Amivantamab IV + docetaxel IV	Phase I: RP2CD, No of participants with AEs by severity, DLTs Phase II: ORR
NCT06083857	I/II	Locally advanced or metastatic <i>MET</i> -altered NSCLC	Amivantamab IV + tepotinib PO	Phase I: RP2CD, DLTs Phase II: ORR
OSTARA NCT05801029	II	<i>EGFR</i> -mutated (Ex19del or L858R), locally advanced, metastatic, or recurrent non-squamous NSCLC	Osimertinib 80 mg PO daily (from day 2) + amivantamab IV 1050 mg (<80 kg) or 1400 mg (≥80 kg; in 28-day cycles: Once weekly in cycle 1 and then once every 2 weeks in subsequent cycles)	No. of participants with AEs, PFS
NEOpredict-EGF NCT06784791	II	Patients with resectable NSCLC harboring oncogenic <i>EGFR</i> mutations	Stage I: preoperative amivantamab IV monotherapy Stage II: preoperative amivantamab IV + chemotherapy (carboplatin/pemetrexed)	Feasibility of four weeks of preoperative antibody therapy with amivantamab
NCT04965090	II	Metastatic <i>EGFR</i> -mutant NSCLC with progressive/new CNS metastases on previous treatment	Amivantamab IV once weekly in cycle 1 and every other week thereafter + lazertinib PO daily	CNS ORR

(continued on following page)

TABLE 4. Ongoing Phase II Trials With Amivantamab (continued)

Trial	Phase	Indication	Intervention	Primary Endpoint
METalmark NCT05488314	I/II	Unresectable metastatic NSCLC	Capmatinib PO + amivantamab IV	Phase I: RP2CD, No. of participants with AEs by severity, DLTs Phase II: ORR
ETOP-AMAZE-lung NCT05601973	I/II	EGFR-mutant advanced NSCLC with progression on previous third-generation EGFR-TKI	Amivantamab 1,750 mg (<80 kg) or 2,100 mg (≥80 kg) IV every 3 weeks + lazertinib PO daily + bevacizumab IV every 3 weeks	ORR
AMIGO-1 NCT05299125	II	Treatment-naïve recurrent/metastatic NSCLC harboring EGFR Ex19del or Exon 21 L858R point mutations	Amivantamab 1,400 mg (<80 kg) or 1,750 mg IV (≥80 kg) once weekly in cycle 1 and on day 1 of all subsequent cycles + lazertinib PO daily + pemetrexed IV on day 1 of each cycle (21-day cycles)	PFS

Abbreviations: 1L, first line; 2L, second line; AEs, adverse events; CF, control formulation; DLTs, dose limiting toxicities; EGFR, epidermal growth factor receptor; ins, insertion; IV, intravenous; MET, mesenchymal-epithelial transition factor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression free survival; PO, per oral; Q2W, once every two weeks; Q3W, once every three weeks; Q4W, once every four weeks; RP2CD, recommended phase 2 combination dose; SC, subcutaneous; TKIs, tyrosine kinase inhibitors.

life years (QALYs) compared with 1.423 QALYs for chemotherapy alone. However, the overall cost was substantially higher at \$430,980.857 USD versus \$62,908.322 USD, respectively.⁵³ Here, cost included the drug price, subsequent treatment, routine follow-up, and cost associated with AE management. The incremental cost-effectiveness ratio of amivantamab plus chemotherapy was \$765,223.566 USD/QALY, significantly higher than the willingness-to-pay threshold set at \$150,000 USD/QALY.⁵³ These results indicate that amivantamab plus chemotherapy may not be a cost-effective regimen, and further work is needed to equalize these factors. Depending on insurance coverage and approval, it is essential that patients are afforded insight into any financial implications that may arise.

ZENOCUTUZUMAB: BRINGING NRG1 FUSIONS TO THE LIST OF ACTIONABLE ALTERATIONS

In oncogenic NRG1 fusions, the altered NRG1 binds to HER3, promoting HER2/HER3 dimerization and downstream PI3K/AKT/mammalian target of rapamycin signaling.⁵⁴ This alteration is rare, occurring in approximately 0.2% of solid tumors, including NSCLC and pancreatic adenocarcinoma.⁵⁵ NRG1 fusion-positive non-small cell lung cancer is predominately but not exclusively seen in never-smokers with mucinous adenocarcinoma histology and again is only seen in 0.2% of patients with NSCLC.⁵⁴ Historically, this has been a resistant subtype of NSCLC, with poor response to conventional chemotherapy, immunotherapy, and frontline chemoimmunotherapy combinations. For example, platinum-doublet chemotherapy in a series of 110 patients attained a low objective response rate (ORR, 13%) and modest PFS (median PFS, 5.8 months). Worse outcomes were noted in the few patients treated with chemoimmunotherapy with no objective responses and a median PFS of 3.3 months.⁵⁶

Zenocutuzumab is a humanized, full-length IgG1 bispecific antibody that docks on the HER2 receptor, optimally positioning the anti-HER3 arm to block the ligand/receptor interaction and thereby inhibiting downstream signaling.⁵⁷ The global phase II eNRGy trial and expanded access program enrolled 158 patients with a variety of solid tumor types and evaluable disease and achieved an ORR of 30% (95% CI, 23 to 37), and median duration of response (DOR) was 11.1 months (95% CI, 7.4 to 12.9). Among the 93 patients with NSCLC with measurable disease, including 12 who were treatment naïve, the ORR was 29% (95% CI, 20 to 39), with median DOR 12.7 months (95% CI, 7.4 to 20.4) and median PFS 6.8 months (95% CI, 5.3 to 7.5).

Zenocutuzumab, like amivantamab, is a humanized antibody but has a relatively low rate of IRRs, with only 12% reported in the 99 patients with NSCLC included in the trial. Infusions are once every 2 weeks. Other side effects reported in the lung cancer population include diarrhea (25%), musculoskeletal pain (23%), dyspnea (17%), decreased hemoglobin (30%), and increased liver enzymes (22%–30%), most of which were grade 1 to 2.⁵⁸

Practical Considerations With Zenocutuzumab

The biggest issue with zenocutuzumab is not toxicity management but reliably identifying patients who may benefit. DNA sequencing alone misses NRG1 fusions because of the large introns not typically included on NGS or whole-exome panels.⁵⁹ Commercial DNA and RNA NGS panels have been including NRG1 as a biomarker of interest. Still, there is not a consistent pathway to notify clinicians of prior test results that were not actionable at the time but now have an approved agent. Despite education efforts, there remains a disturbing lack of comprehensive biomarker testing among all patients with NSCLC.⁶⁰ Finally, there is room to improve

TABLE 5. Ongoing Phase II and III Trials of Immune Checkpoint Bispecific Antibodies in NSCLC

Trial	Phase	Bispecific Antibody (targets)	Eligibility	Intervention	Primary Endpoint	Interim Results
HARMONI-7 (NCT06767514)	III	Ivonescimab (PD-1 and VEGF)	First-line metastatic NSCLC with PD-L1 expression (TPS ≥50%)	Ivonescimab v pembrolizumab	PFS, OS	
HARMONI (NCT06396065)	III	Ivonescimab (PD-1 and VEGF)	<i>EGFR</i> -mutant locally advanced or metastatic NSCLC that has progressed on <i>EGFR</i> inhibitor	Ivonescimab (SMT112/AK112) + pemetrexed + carboplatin v placebo + pemetrexed + carboplatin	PFS, OS	
HARMONI-3 (NCT05899608)	III	Ivonescimab (PD-1 and VEGF)	First-line metastatic NSCLC	Ivonescimab + chemotherapy v pembrolizumab + chemotherapy	PFS, OS	
NCT06020352	II/III	KN046 (PD-1 and CTLA-4)	Neoadjuvant therapy for resectable stage IB to IIIB NSCLC	KN046 + axitinib followed by surgery	MPR and surgical resection rate	
NCT05420220	II	KN046 (PD-1 and CTLA-4)	Treatment-naïve locally advanced (unresectable and unable to receive radical chemoradiotherapy) or metastatic PD-L1–positive NSCLC who have received systemic therapy	KN046 + axitinib	ORR	ORR in PD-L1 TPS ≥1% was 54.5% (95% CI, 38.8 to 69.6) and in PD-L1 ≥50% was 66.7% (95% CI, 38.4 to 88.2) ⁶¹
LungMate-026 (NCT06837948)	II	PM8002 (PD-1 and VEGF-A)	Neoadjuvant therapy for locally advanced stage II to III NSCLC	Chemotherapy + PM8002 followed by surgery v chemotherapy + sintilimab followed by surgery	PCR rate	
NCT05756972	II/III	PM8002 (PD-1 and VEGF-A)	<i>EGFR</i> -mutant locally advanced or metastatic nonsquamous NSCLC who have failed <i>EGFR</i> -TKI treatment	PM8002 + chemotherapy v chemotherapy alone	ORR, PFS	ORR was 54.7% (35/64, 95% CI, 41.8 to 67.2) and DCR was 95.3% (61/64, 95% CI, 86.9 to 99.0) ⁶²
ABBILITY NSCLC-06 (NCT06635824)	III	Acasunlimab (PD-1 and 4-1BB)	PD-L1–positive metastatic NSCLC who have been treated with PD-1/PD-L1 inhibitor and platinum-containing chemotherapy, administered either in combination or sequentially in the metastatic setting	Acasunlimab + pembrolizumab v docetaxel	OS	
NCT05117242	II	Acasunlimab (PD-1 and 4-1BB)	Relapsed/refractory metastatic NSCLC after treatment with standard of care therapy with an immune checkpoint inhibitor	Acasunlimab v acasunlimab + pembrolizumab	ORR	Unconfirmed ORR and DCR were 31% and 50% for acasunlimab mono, 25% and 65% for arm B (100 mg + pembro 200 mg Q3W), and 30% and 75% for arm C (100 mg + pembro 400 mg Q6W), respectively ⁶³
NCT06793813	II	Cadonilimab (PD-1 and CTLA-4)	Nonsquamous and stage IV NSCLC	Cadonilimab + bevacizumab and docetaxel	6-month PFS	
NCT06617416	III	Cadonilimab (PD-1 and CTLA-4)	Unresectable locally advanced NSCLC	Cadonilimab v sugemalimab	PFS	

(continued on following page)

TABLE 5. Ongoing Phase II and III Trials of Immune Checkpoint Bispecific Antibodies in NSCLC (continued)

Trial	Phase	Bispecific Antibody (targets)	Eligibility	Intervention	Primary Endpoint	Interim Results
NCT06532591	II	Cadonilimab (PD-1 and CTLA-4)	Resectable IB (≥4 cm)—IIIB (N2) stage PD-L1–negative NSCLC	Cadonilimab + chemotherapy	MPR	
NCT06277674	II	Cadonilimab (PD-1 and CTLA-4)	T790M-negative advanced non-squamous NSCLC resistant to EGFR-TKI	Cadonilimab + pemetrexed and anlotinib	ORR	
NCT05775289	II	Tobemstomig (PD-1 and LAG-3)	Previously untreated, locally advanced, unresectable or metastatic NSCLC	Tobemstomig + platinum-based chemotherapy v pembrolizumab + platinum-based chemotherapy	ORR, PFS	Median PFS 7.6 months in tobemstomig + chemotherapy group and 7.1 in pembrolizumab + chemotherapy ($P = .9705$), ORR 41% in tobemstomig group and 42% in pembrolizumab group ⁶⁴
ARTEMIDE-Lung04 (NCT06868277)	III	Rilvegostomig (PD-1 and TIGIT)	First-line treatment of PD-L1–high metastatic NSCLC	Rilvegostomig v pembrolizumab	PFS, OS	
ARTEMIDE-Lung02 (NCT06692738)	III	Rilvegostomig (PD-1 and TIGIT)	First-line treatment of squamous metastatic NSCLC with PD-L1 ≥1%	Rilvegostomig v pembrolizumab, both in combination with platinum-based doublet chemotherapy	PFS, OS	

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; EGFR, epidermal growth factor receptor; LAG, lymphocyte activation gene; MPR, major pathological response; NSCLC, non-small cell lung cancer; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PCR, pathologic complete response; pembro, pembrolizumab; PFS, progression free survival; Q3W, once every 3 weeks; Q6W, once every 6 weeks; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domains; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score; VEGF, vascular endothelial growth factor.

response rates, durability, and salvage options for patients whose tumors harbor NRG1 fusions.

Ongoing Trials of Bispecific Antibodies in NSCLC

Many of the approaches under study target nondriver mutation pathways, such as immune checkpoints, including PD-1, cytotoxic T-cell lymphocyte-4, 4-1BB, LAG3, and TIGIT, as well as the vascular endothelial growth factor (VEGF) pathway (Table 5). Ivonescimab is a first-in-class novel humanized tetravalent bispecific antibody targeting PD-1 and VEGF-A that forms soluble complexes with VEGF-A dimers, leading to increased avidity of ivonescimab and thereby increasing its potency in blocking PD-1/PD-L1 signaling.⁶⁵ This dual-targeting mechanism allows ivonescimab to affect the tumor immune microenvironment, enhancing antitumor immune responses and reducing tumor vascularization.⁶⁶⁻⁶⁸ Cooperative VEGF-A binding with the bispecific has been shown to elevate the affinity of ivonescimab to PD-1 by more than 10-fold and vice versa, thereby increasing functional valency and potency.⁶⁹ Additionally, the Fc fragment of ivonescimab lacks effector functioning, limiting its immune toxicity effects.⁶⁵ These design characteristics of ivonescimab and its unique pharmacodynamic profile make this molecule different from existing PD-1/PD-L1 inhibitor combinations with bevacizumab.

Several clinical studies have evaluated ivonescimab's efficacy and safety. The phase Ia dose-escalation study of ivonescimab in patients with advanced solid tumors established the maximum tolerated dose was 20 mg/kg once every 2 weeks and reported the most common grade treatment-related AEs (TRAEs) included rash (29.4%), arthralgia (19.6%), and hypertension (19.6%).⁶⁷ The HARMONi-5 phase Ib study investigated ivonescimab as a first-line or second-line therapy for advanced or metastatic immunotherapy-naïve NSCLC. The study reported an ORR of 39.8% and disease control rate of 86.1% with grade ≥ 3 TRAEs observed in 22.2% of patients.⁷⁰ In cohorts that received more than 10 mg/kg, ivonescimab achieved an ORR of 56.5% in patients with PD-L1 positivity.

Randomized phase III trials have also investigated ivonescimab in various subsets of NSCLC, although these studies exclusively enrolled Asian patients. HARMONi-A was the first

double-blind, placebo-controlled, randomized phase III study to compare the efficacy of ivonescimab plus chemotherapy with chemotherapy alone for patients with advanced or metastatic EGFR-variant NSCLC who showed disease progression after EGFR-TKI treatment.⁷¹ A preplanned interim analysis of 322 patients demonstrated the median PFS was 7.06 months in the ivonescimab group versus 4.80 months in the placebo group. The grade 3 or higher treatment-related AEs were 54% in the ivonescimab versus 43% in the control arm. The results from the HARMONi study (ClinicalTrials.gov identifier: [NCT06396065](https://clinicaltrials.gov/ct2/show/study?term=NCT06396065)), a global phase III study in NSCLC that has progressed on or after EGFR-TKI treatment, are eagerly awaited with an estimated completion in 2025. In the phase III HARMONi-2 study, ivonescimab significantly improved median PFS over pembrolizumab alone (11.1 v 5.8 months) in treatment-naïve patients with locally advanced or metastatic PD-L1-positive NSCLC while maintaining a comparable safety profile (TRAEs 86% in ivonescimab v 80% in pembrolizumab group). Proteinuria (32%), laboratory abnormalities: AST increase (20%), hypercholesterolaemia (16%), and bilirubin increase (16%), and hypertension (16%) were the most common TRAEs associated with ivonescimab.⁷² Grade 3 or higher TRAEs were 29% in the ivonescimab arm versus 15% in the pembrolizumab arm. These findings suggest that ivonescimab could be a viable first-line treatment option for this patient population, pending other ongoing studies. One such study that has garnered attention is the ongoing HARMONi-3 global trial (ClinicalTrials.gov identifier: [NCT05899608](https://clinicaltrials.gov/ct2/show/study?term=NCT05899608)), which aims to further evaluate ivonescimab's potential by comparing its combination with chemotherapy against the current standard of pembrolizumab plus chemotherapy in the first-line treatment setting for metastatic NSCLC. If the results are positive, this could reshape the frontline treatment paradigm for advanced/metastatic NSCLC.

CONCLUSIONS

Bispecific antibodies are a rapidly growing class of therapeutics in NSCLC. As we move from clinical trials to real-world implementation of these therapies, management of side effects and careful consideration of PROs are essential. Ongoing research efforts are aimed at clarifying salient high-risk features and novel predictive biomarkers to optimize treatment selection.

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REFERENCES

1. Cho BC, Simi A, Sabari J, et al: Amivantamab, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) bispecific antibody, designed to enable multiple mechanisms of action and broad clinical applications. *Clin Lung Cancer* 24:89-97, 2023
2. Park K, Haura EB, Leigh NB, et al: Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: Initial results from the CHRYSALIS phase I study. *J Clin Oncol* 39:3391-3402, 2021
3. Zhou C, Tang KJ, Cho BC, et al: Amivantamab plus chemotherapy in NSCLC with EGFR exon 20 insertions. *N Engl J Med* 389:2039-2051, 2023
4. Cho BC, Lu S, Felip E, et al: Amivantamab plus lazertinib in previously untreated EGFR-mutated advanced NSCLC. *N Engl J Med* 391:1486-1498, 2024
5. Passaro A, Wang J, Wang Y, et al: Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: Primary results from the phase III MARIPOSA-2 study. *Ann Oncol* 35:77-90, 2024
6. Leigh NB, Akamatsu H, Lim SM, et al: Subcutaneous versus intravenous amivantamab, both in combination with lazertinib, in refractory epidermal growth factor receptor-mutated non-small cell lung cancer: Primary results from the phase III PALOMA-3 study. *J Clin Oncol* 42:3593-3605, 2024
7. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al: Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer* 19: 1079-1095, 2011
8. Klein C, Brinkmann U, Reichert JM, et al: The present and future of bispecific antibodies for cancer therapy. *Nat Rev Drug Discov* 23:301-319, 2024
9. Rossell R, Carcereny E, Gervais R, et al: Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EORTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 13:239-246, 2012
10. Girard NLW, Li W, Spira AI, et al: Preventing moderate to severe dermatologic adverse events in first-line EGFR-mutant advanced NSCLC treated with amivantamab plus lazertinib: Early success of the COCOON trial. Oral Presentation Presented at: European Lung Cancer Congress (ELCC); March 26-29, 2025; Paris, France, 2025
11. Lacouture ME, Mitchell EP, Piperdi B, et al: Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol* 28:1351-1357, 2010
12. Brown J, Su Y, Nellesen D, et al: Management of epidermal growth factor receptor inhibitor-associated rash: A systematic review. *J Community Support Oncol* 14:21-28, 2016
13. Gaiser MR, Lorenzen S, Mers K, et al: Vitamin K1 cream significantly reduces incidence and severity of cetuximab-related acneiform skin rash in women: A post hoc analysis of the EVITA trial. *Ann Oncol* 29:2393-2395, 2018
14. Pinto C, Barone C, Martoni A, et al: Vitamin K1 cream in the management of skin rash during anti-EGFR monoclonal antibody (mAb) treatment in patients with metastatic cancer: First analysis of an observational Italian study. *J Clin Oncol* 29, 2011 (suppl 4; abstr 594)
15. Alexandrescu DT, Vaillant JG, Dasanu CA: Effect of treatment with a colloidal oatmeal lotion on the acneiform eruption induced by epidermal growth factor receptor and multiple tyrosine-kinase inhibitors. *Clin Exp Dermatol* 32:71-74, 2007
16. George MN, Seervai RNH, Chon SY: Erosive pustular dermatosis-like eruption of the scalp secondary to amivantamab: A case series. *JAAD Case Rep* 47:72-79, 2024
17. Huang PW, Yu CJ, Yang JC, et al: Oral propranolol for the treatment of amivantamab-induced scalp ulcers with granulation tissues. *Lung Cancer* 198:108028, 2024
18. Bidoli P, Cortinovis DL, Colombo I, et al: Isotretinoin plus clindamycin seem highly effective against severe erlotinib-induced skin rash in advanced non-small cell lung cancer. *J Thorac Oncol* 5: 1662-1663, 2010
19. Gutzmer R, Werfel T, Mao R, et al: Successful treatment with oral isotretinoin of acneiform skin lesions associated with cetuximab therapy. *Br J Dermatol* 153:849-851, 2005
20. Chiang HC, Anadkat MJ: Isotretinoin for high-grade or refractory epidermal growth factor receptor inhibitor-related acneiform papulopustular eruptions. *J Am Acad Dermatol* 69:657-658, 2013
21. Bierbrier R, Lam M, Pehr K: A systematic review of oral retinoids for treatment of acneiform eruptions induced by epidermal growth factor receptor inhibitors. *Dermatol Ther* 35:e15412, 2022
22. Andrews ED, Garg N, Patel AB: A retrospective chart review on oral retinoids as a treatment for epidermal growth factor receptor inhibitor- and mitogen-activated protein kinase kinase inhibitor-induced acneiform eruptions. *J Am Acad Dermatol* 82:998-1000, 2020
23. Wilhelmi BJ, Calianos TA 2nd, Appelt EA, et al: Modified Dakin's solution for cutaneous vibrio infections. *Ann Plast Surg* 43:386-389, 1999
24. Robert C, Sibaud V, Mateus C, et al: Nail toxicities induced by systemic anticancer treatments. *Lancet Oncol* 16:e181-e189, 2015

25. Rigopoulos D, Gregoriou S, Belyayeva E, et al: Efficacy and safety of tacrolimus ointment 0.1% vs. betamethasone 17-valerate 0.1% in the treatment of chronic paronychia: An unblinded randomized study. *Br J Dermatol* 160:858-860, 2009
26. Wollina U: Acute paronychia: Comparative treatment with topical antibiotic alone or in combination with corticosteroid. *J Eur Acad Dermatol Venereol* 15:82-84, 2001
27. Hachisuka J, Yunotani S, Shidahara S, et al: Effect of adapalene on cetuximab-induced painful periungual inflammation. *J Am Acad Dermatol* 64:e20-e21, 2011
28. Shu KY, Kindler HL, Medenica M, et al: Doxycycline for the treatment of paronychia induced by the epidermal growth factor receptor inhibitor cetuximab. *Br J Dermatol* 154:191-192, 2006
29. Ghodsi SZ, Raziie M, Taheri A, et al: Comparison of cryotherapy and curettage for the treatment of pyogenic granuloma: A randomized trial. *Br J Dermatol* 154:671-675, 2006
30. Quitkin HM, Rosenwasser MP, Strauch RJ: The efficacy of silver nitrate cauterization for pyogenic granuloma of the hand. *J Hand Surg Am* 28:435-438, 2003
31. Sollena P, Mannino M, Tassone F, et al: Efficacy of topical beta-blockers in the management of EGFR-inhibitor induced paronychia and pyogenic granuloma-like lesions: Case series and review of the literature. *Drugs Context* 8:212613, 2019
32. Olamiju B, Bhullar S, Coleman EL, et al: Management of paronychia with pseudopyogenic granulomas secondary to epidermal growth factor receptor inhibitors: An assessment of topical timolol and the need for multiple medical and procedural therapies. *J Am Acad Dermatol* 84:806-808, 2021
33. Wnorowski AM, de Souza A, Chachoua A, et al: The management of EGFR inhibitor adverse events: A case series and treatment paradigm. *Int J Dermatol* 51:223-232, 2012
34. Rutala WA, Cole EC, Thomann CA, et al: Stability and bactericidal activity of chlorine solutions. *Infect Control Hosp Epidemiol* 19:323-327, 1998
35. Lacouture ME, Sibaud V, Gerber PA, et al: Prevention and management of dermatological toxicities related to anticancer agents: ESMO clinical practice Guidelines(☆). *Ann Oncol* 32:157-170, 2021
36. Brown TJ, Gupta A: Management of cancer therapy-associated oral mucositis. *JCO Oncol Pract* 16:103-109, 2020
37. Miller KK, Gorcey L, McLellan BN: Chemotherapy-induced hand-foot syndrome and nail changes: A review of clinical presentation, etiology, pathogenesis, and management. *J Am Acad Dermatol* 71:787-794, 2014
38. Basse C, Chabanol H, Bonte PE, et al: Management of cutaneous toxicities under amivantamab (anti MET and anti EGFR bispecific antibody) in patients with metastatic non-small cell lung cancer harboring EGFR Exon20ins: Towards a proactive, multidisciplinary approach. *Lung Cancer* 173:116-123, 2022
39. Nikolaou V, Gerochristou M, Sgontzou T, et al: Beneath the surface: Novel insights into amivantamab-induced acneiform rash. *Eur J Cancer* 208:114198, 2024
40. Belzer A, Nguyen MO, Talsania A, et al: Spectrum of dermatologic adverse events associated with amivantamab use. *JAMA Dermatol* 159:109-111, 2023
41. Zhou JJ, Chen LN, Lehan T, et al: Severe scalp ulcerations and granulomata during treatment with amivantamab. *Curr Probl Cancer Case Rep* 13:100273, 2024
42. Cáceres MC, Guerrero-Martín J, Pérez-Civantos D, et al: The importance of early identification of infusion-related reactions to monoclonal antibodies. *Ther Clin Risk Manag* 15:965-977, 2019
43. Park K, Sabari JK, Haura EB, et al: Management of infusion-related reactions (IRRs) in patients receiving amivantamab in the CHRYSALIS study. *Lung Cancer* 178:166-171, 2023
44. Spira AI, Paz-Ares L, Han JY, et al: Preventing infusion-related reactions with intravenous amivantamab-results from SKIPPirr, a phase 2 study: A brief report. *J Thorac Oncol* 10.1016/j.jtho.2025.01.018 [epub ahead of print on January 24, 2025]
45. Haura EB, Cho BC, Lee JS, et al: JNJ-61186372 (JNJ-372), an EGFR-cMet bispecific antibody, in EGFR-driven advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 37, 2019 (suppl 15; abstr 9009)
46. Cortot A, Le X, Smit E, et al: Safety of MET tyrosine kinase inhibitors in patients with MET exon 14 skipping non-small cell lung cancer: A clinical review. *Clin Lung Cancer* 23:195-207, 2022
47. Nishio M, Kato T, Toyozawa R, et al: Management of peripheral edema in patients with MET exon 14-mutated non-small cell lung cancer treated with small molecule MET inhibitors. *Target Oncol* 17:597-604, 2022
48. Ordning AG, Christensen TD, Skjøth F, et al: Risk of venous thromboembolism in patients with stage III and IV non-small-cell lung cancer: Nationwide descriptive cohort study. *Clin Lung Cancer* 25: 407-416 e1, 2024
49. Girard N, Cho BC, Spira AI, et al: Risk factors for venous thromboembolism (VTE) among patients with EGFR-mutated advanced non-small cell lung cancer (NSCLC) receiving amivantamab plus lazertinib versus either agent alone. *J Clin Oncol* 41, 2023 (suppl 16; abstr 9137)
50. Paz-Ares L, Veillon R, Majem M, et al: 7P Patient-relevant endpoints from PAPILLON: Amivantamab plus chemotherapy vs chemotherapy as first-line treatment of EGFR exon 20 insertion-mutated (Ex20ins) advanced NSCLC. *ESMO Open* 9:102586, 2024
51. Nguyen D, Besse B, Cho BC, et al: MA12.07 amivantamab plus lazertinib vs osimertinib in first-line, EGFR-mutant advanced NSCLC: Patient-relevant outcomes from MARIPOSA. *J Thorac Oncol* 19: S103-S104, 2024
52. Laube Y, Serra-Burriel M, Glaus CCEG, et al: Launch and postlaunch price developments of new drugs in the US, Germany, and Switzerland. *JAMA Health Forum* 5:e244461, 2024
53. Yue P, Zhang M, Feng Y, et al: Cost-effectiveness analysis of amivantamab plus chemotherapy versus chemotherapy alone in NSCLC with EGFR Exon 20 insertions. *Front Oncol* 14:1368804, 2024
54. Laskin J, Liu SV, Tolba K, et al: NRG1 fusion-driven tumors: Biology, detection, and the therapeutic role of afatinib and other ErbB-targeting agents. *Ann Oncol* 31:1693-1703, 2020
55. Jonna S, Feldman RA, Swensen J, et al: Detection of NRG1 gene fusions in solid tumors. *Clin Cancer Res* 25:4966-4972, 2019
56. Drilon A, Duruisseaux M, Han JY, et al: Clinicopathologic features and response to therapy of NRG1 fusion-driven lung cancers: The eNRGy1 global multicenter registry. *J Clin Oncol* 39:2791-2802, 2021
57. Schram AM, Goto K, Kim DW, et al: Efficacy of zenocutuzumab in NRG1 fusion-positive cancer. *N Engl J Med* 392:566-576, 2025
58. FDA package insert for zenocutuzumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761352s001lbl.pdf
59. Benayed R, Offin M, Mullaney K, et al: High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with No mitogenic driver alteration detected by DNA sequencing and low tumor mutation burden. *Clin Cancer Res* 25:4712-4722, 2019
60. Baron JM, Widatalla S, Gubens MA, et al: Real-world biomarker test ordering practices in non-small cell lung cancer: Interphysician variation and association with clinical outcomes. *JCO Precis Oncol* 10.1200/PO.24.00039
61. Zhang Yz L, Meng X, Huang Y, et al: The efficacy and safety of KN046 combined with axitinib for previously untreated and checkpoint inhibitor treated advanced non-small cell lung cancer: A single-arm, open-label, multicenter phase II clinical trial. *Ann Oncol* 24:1-26, 2024 (suppl 1)
62. Wu YL, Wang Z, Cheng Y, et al: 1255MO A phase II safety and efficacy study of PM8002/BNT327 in combination with chemotherapy in patients with EGFR-mutated non-small cell lung cancer (NSCLC). *Ann Oncol* 35:S804, 2024
63. Aerts J, Paz-Ares LG, Hellesey C, et al: Acasunlimab (DuoBody-PD-L1x4-1BB) alone or in combination with pembrolizumab (pembro) in patients (pts) with previously treated metastatic non-small cell lung cancer (mNSCLC): Initial results of a randomized, open-label, phase 2 trial. *J Clin Oncol* 42, 2024 (suppl 16; abstr 2533)
64. Nadal E, Rittmeyer A, De Marinis F, et al: 7MO: A phase II trial of tobemstomig (tobe) + platinum-based chemotherapy (chemo) vs pembrolizumab (pembro) + chemo in patients (pts) with untreated locally advanced or metastatic non-small cell lung cancer (NSCLC). *J Thorac Oncol* 20:S11-S12, 2025
65. Zhong T, Zhang L, Huang Z, et al: Design of a fragment crystallizable-engineered tetravalent bispecific antibody targeting programmed cell death-1 and vascular endothelial growth factor with cooperative biological effects. *iScience* 28:111722, 2025
66. Dhillon S: Ivonescimab: First approval. *Drugs* 84:1135-1142, 2024
67. Frentzas S, Austria Mislav AR, Lemech C, et al: Phase 1a dose escalation study of ivonescimab (AK112/SMT112), an anti-PD-1/VEGF-A bispecific antibody, in patients with advanced solid tumors. *J Immunother Cancer* 12:e008037, 2024
68. Wang F, Wei X, Zheng Y, et al: Safety, pharmacokinetics, and pharmacodynamics evaluation of ivonescimab, a novel bispecific antibody targeting PD-1 and VEGF, in Chinese patients with advanced solid tumors. *Cancer Med* 14:e70653, 2025
69. Zhong T, Huang Z, Pang X, et al: 1194 mechanism of action of ivonescimab (AK112/SMT112): A first-in-class tetravalent Fc-silent bispecific antibody with dual blockade of PD-1 and VEGF that promotes cooperative biological effects. *J Immunother Cancer* 11:A1316-A1317, 2023
70. Wang L, Luo Y, Ren S, et al: A phase 1b study of ivonescimab, a programmed cell death protein-1 and vascular endothelial growth factor bispecific antibody, as first- or second-line therapy for advanced or metastatic immunotherapy-naïve NSCLC. *J Thorac Oncol* 19:465-475, 2024
71. HARMONI-A Study Investigators, Fang W, Zhao Y, et al: Ivonescimab plus chemotherapy in non-small cell lung cancer with EGFR variant: A randomized clinical trial. *JAMA* 332:561-570, 2024
72. Xiong A, Wang L, Chen J, et al: Ivonescimab versus pembrolizumab for PD-L1-positive non-small cell lung cancer (HARMONI-2): A randomised, double-blind, phase 3 study in China. *Lancet* 405: 839-849, 2025

Broadening the Net: Overcoming Challenges and Embracing Novel Technologies in Lung Cancer Screening

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OVERVIEW

Lung cancer is one of the leading causes of cancer-related mortality worldwide, with most cases diagnosed at advanced stages where curative treatment options are limited. Low-dose computed tomography (LDCT) for lung cancer screening (LCS) of individuals selected based on age and smoking history has shown a significant reduction in lung cancer-specific mortality. The number needed to screen to prevent one death from lung cancer is lower than that for breast cancer, cervical cancer, and colorectal cancer. Despite the substantial impact on reducing lung cancer-related mortality and proof that LCS with LDCT is effective, uptake of LCS has been low and LCS eligibility criteria remain imperfect. While LCS programs have historically faced patient recruitment challenges, research suggests that there are novel opportunities to both identify and improve screening for at-risk populations. In this review, we discuss the global obstacles to implementing LCS programs and strategies to overcome barriers in resource-limited settings. We explore successful approaches to promote LCS through robust engagement with community partners. Finally, we examine opportunities to enhance LCS in at-risk populations not captured by current eligibility criteria, including never smokers and individuals with a family history of lung cancer, with a focus on early detection through novel artificial intelligence technologies.

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THINKING GLOBALLY: CHALLENGES TO IMPLEMENTATION OF SCREENING FOR LUNG CANCER IN RESOURCE-LIMITED SETTINGS

Low-dose computed tomography (LDCT) for lung cancer screening (LCS) in high-risk individuals has been associated with a significant reduction in lung cancer-specific mortality. However, implementing these programs globally remains challenging, especially in low- and middle-income countries (LMICs), where limited resources and health care infrastructure create substantial obstacles. This section explores the barriers to implementing LCS and highlights strategies to overcome these challenges in resource-limited settings.

Recruitment for LCS programs faces numerous challenges, including socioeconomic, cultural, logistical, and racial disparities. Current LCS guidelines often fail to address differences in sex, smoking history, socioeconomic status, geographic location, and ethnicity.¹ Despite widening the eligibility criteria for age and smoking pack-year history, only about 16.5% of individuals in the United States who were eligible for LCS were screened in 2022.² Underrepresentation is common among African Americans, women, never smokers, economically disadvantaged groups, minorities, and special populations, such as

individuals living with HIV. Limited awareness of the benefits of early detection, combined with misconceptions about radiation exposure and the treatability of lung cancer, further hinders participation. Fear of false positives, invasive procedures, potential cancer diagnoses, and the negative perception associated with smoking cessation counseling also deter individuals.³

Rural populations face additional barriers, such as geographic inaccessibility of urban screening centers, transportation costs, language barriers, and mistrust of health care systems.⁴ These issues increase inconvenience, loss of work time, and out-of-pocket expenses. Economic barriers are particularly pronounced in LMICs, where health care systems are often underfunded. The high costs of LDCT scans, follow-up procedures, and associated care are prohibitive for low-income populations, especially those without insurance coverage. Urban-rural disparities exacerbate these challenges, with rural regions frequently lacking the infrastructure and resources to sustain screening programs.

Sociocultural and racial disparities also play a crucial role in limiting access to LCS.⁵ Minority populations often face systemic barriers, including lower health literacy, language differences, and limited exposure to targeted educational

PRACTICAL APPLICATIONS

- Widespread implementation of low-dose computed tomography (LDCT) for lung cancer screening (LCS) in low- and middle-income countries (LMICs) is limited by manpower, infrastructure, and economic constraints.
- Performance of LDCT in LMICs is also influenced by the endemicity of pulmonary tuberculosis, differences in smoking patterns, and age of lung cancer onset compared with North America and Europe where the benefit of LDCT screening was established.
- Key steps toward influencing the community to promote LCS include maximizing screening efforts within your own system, involving all key stakeholders, and developing trusting relationships with partners who have a shared interest and community access.
- Opportunities to identify at-risk populations not captured by current eligibility criteria include evaluating methods to enhance patient selection, such as in individuals with a family history of lung cancer or a germline mutation that may increase risk for lung cancer, especially in East Asia, where the prevalence of lung cancer is high in never smokers.
- Innovative technologies such as artificial intelligence have tremendous potential to aid in precision screening and to improve the utility of digital imaging for risk stratification and early detection of lung cancer.

campaigns. Cultural beliefs and stigmas surrounding lung cancer and medical interventions further discourage screening. In addition, mistrust of health care systems, rooted in historical injustices, and implicit bias among health care providers contribute to reduced referral rates and participation among minority groups.

Gender-specific barriers further complicate LCS implementation. Women, particularly in patriarchal societies, face financial dependency and limited autonomy, which restrict access to screening services. Despite many women with lung cancer in Asia being never smokers, risk factors such as genetic predisposition, indoor air pollution, and second-hand smoke exposure are often overlooked.⁶ The misconception that lung cancer primarily affects those who smoke cigarettes delays diagnosis and screening. Men, on the other hand, may avoid screening because of societal attitudes around preventive care or a tendency to dismiss even non-cancer-related symptoms that may prompt engagement with the health care system and an opportunity to be offered screening.

LDCT screening can result in false-positive rates because of lung nodules caused by active infections, fibrosis, or intrapulmonary lymph nodes in regions endemic to tuberculosis (TB) and other granulomatous diseases.^{7,8} These false positives can lead to unnecessary investigations, increased procedure-related complications, and significant mental stress. A lack of physician referrals, driven by limited awareness of LCS guidelines and time constraints for shared decision making, further hinders the success of LCS programs.⁹ Furthermore, the aids for shared decision making and numeracy concepts may not be appropriate for individuals with low literacy levels.

Infrastructure and resource limitations present significant challenges in resource-limited settings.¹⁰ Many LMICs lack sufficient computed tomography (CT) machines, trained personnel, and specialized facilities for accurate and timely screenings. Even in urban centers with advanced diagnostic facilities, the high screening and follow-up care costs limit access for low-income populations. The cost of acquiring and maintaining CT scanners and the need for specialized training strain already limited resources.¹¹ In addition, health care systems in these regions often prioritize infectious diseases and maternal health, leaving limited room for investments in noncommunicable disease prevention like LCS. Given the competing demands of other public health priorities, questions about the cost-effectiveness of LCS programs in LMICs are particularly pertinent. Policymakers often struggle to justify allocating resources to LCS when immediate health care needs remain unmet. Furthermore, poor integration of LCS with existing health care initiatives, such as TB or noncommunicable disease programs, results in missed opportunities to optimize resources and enhance program reach.

To address these challenges, a multifaceted approach is needed. Public awareness campaigns focused on the benefits of early detection and dispelling myths about LCS are essential to improving participation rates. Using risk prediction models to identify high-risk individuals can increase the efficiency of LCS programs.¹² Screening navigators are vital for enhancing communication between participants and health care providers, addressing misconceptions, and building trust. Automated follow-up reminders can also ensure timely referrals and reduce delays in diagnosis and treatment. Reducing or subsidizing the cost of LDCT scans, especially in LMICs, can improve accessibility. Deploying mobile CT scanners can expand access to rural and underserved areas, whereas standardizing scanning protocols can ensure quality and consistency.¹³ Integrating LCS with existing health care programs, such as TB or noncommunicable disease initiatives, can enhance resource utilization and program scalability. For instance, leveraging the infrastructure and personnel of national TB programs could provide a cost-effective model for expanding LCS services in endemic regions.⁶ Sustainable financing models, including public-private partnerships and international support, are crucial for ensuring the long-term viability of

LCS programs. Developing national guidelines tailored to local epidemiologic and resource contexts can standardize practices, improve efficiency, and ensure equitable access.

Implementing LCS in resource-limited settings requires strategic investment, capacity building, and policy interventions prioritizing equity. Addressing financial constraints, infrastructure gaps, and sociocultural barriers can help overcome existing challenges. By focusing on cost-effective strategies, public awareness, and risk-based eligibility criteria, global efforts can promote equitable access to LCS and improve outcomes for populations in need. Tailored approaches, particularly in resource-limited settings, are essential to maximizing the benefits of LCS while minimizing potential harms and ensuring program sustainability.

END LUNG CANCER NOW: HOW TO ENGAGE YOUR COMMUNITY TO PROMOTE CANCER SCREENING

“Each time a person...acts to improve the lot of others...they send forth a tiny ripple of hope, and crossing each other from a million different centers of energy and daring those ripples build a current which can sweep down the mightiest walls...” —paraphrasing Sen. Robert F. Kennedy, June 6, 1966

How can one person have an influence on the health of their community, beyond the people they are directly connected to? How can one person send forth the tiny ripple that Kennedy refers to? Becoming a champion of public health initiatives to scale efforts in early detection offers this promise. Simply stated, screening saves lives. However, promoting cancer screening in your community begins with developing a model program within your own institution. You must start by looking inward before you can begin to influence outward.

Inspiring change begins with finding your why. Why have an interest in public health? Why does this matter? In the past century, the lung cancer epidemic has raged out of control. For most of this time, it has been the number one cause of cancer-related death in the United States and around the world and continues to hold that dubious distinction today. The sentinel work of Doll and colleagues and Wynder et al¹⁴ 75 years ago helped establish cigarette smoking as a major cause of lung cancer.¹⁵ While this landmark finding launched a century of activism to reduce cigarette consumption, it also inadvertently led to the stigmatization of those with lung cancer. Twenty-five years ago, cigarette smoking rates remained very high and public smoking in the workplace, hotels, restaurants, parks, and airports was still commonplace. In addition, there were no effective early detection tests for lung cancer, systemic therapy was minimally effective, sequencing of the genome was not completed yet, immunotherapy for lung cancer was still to be discovered, research funding for lung cancer lagged far behind, and advocacy was sparse. This led to a perfect storm of stigma,

guilt, shame, and hopelessness felt by many affected by lung cancer. Bearing witness to this suffering laid the foundation for action and served as the first step to leading change in communities.

Having passion and purpose is essential yet insufficient to drive transformational change. Transformational change requires leadership that applies diverse ways of thinking. Understanding how individuals and organizations process information is a key step to sustainable progress. What is the problem that needs solving? Do key stakeholders agree on the problem and the need for change? How does this change affect the community, individuals, and systems? Are your organization and partners ready to think about a problem differently? Does your team have a shared vision, mission, and values? If your team agrees on the answers to these questions, it can then begin to challenge its own thinking and develop a strategic plan.

In 2023, the End Lung Cancer Now (ELCN) team at the IU Simon Comprehensive Cancer Center decided to focus its efforts on scaling and transforming LCS rates in Indiana. This became our why and our purpose. ELCN developed a task force comprising 26 experts in various fields including radiology, pulmonary medicine, thoracic surgery, public health, systems leadership, and advocacy. The result of this work is an 85-page blueprint with 11 key recommendations (Fig 1) that any system and community can use to scale lung screening efforts for high-risk populations.

Operationalizing the recommendations in the blueprint required system buy-in. The ELCN task force used education and awareness of the problem as the foundation to influence system leadership. We emphasized the important message that lung cancer is the number one cause of cancer-related death in men and women and that LCS with LDCT reduces both lung cancer-related and all-cause-related mortalities. We highlighted that only 16% of eligible persons in Indiana undergo lung screening and that one of seven people eligible

1. Centralized structure with unified oversight	
2. Adequate resource allocation	
3. Electronic medical record improvements	
4. Improve shared decision making and tobacco treatment services	
5. Improve lung nodule management and multidisciplinary discussion	
6. Establish lung cancer screening as a quality metric	
7. Establish a mixed payer model	
8. Comprehensive education for health care professionals and patients	
9. Comprehensive community outreach and advocacy	
10. Public health awareness campaigns	
11. Implement a mobile lung cancer screening program	

Key: Implemented In progress

FIG 1. Recommendations for a comprehensive LCSP. LCSP, lung cancer screening program.

for lung screening will be diagnosed with lung cancer during their lifetime. If we scaled our efforts to screen more eligible people, their cancer will be found in an early stage with a high cure rate, and we would save lives.

After obtaining initial buy-in, we began implementing our plan. The results were immediate. In the first year, we tripled the number of screening LDCTs performed in our academic center and saw a 40% increase systemwide. This translated to a 60% increase in Lung-RADS (Lung Imaging Reporting and Data System) 4B and 4X scans, and most lung cancers were discovered at stage I. This success was rewarded with a substantial increase in personnel investments for the centralized program, growing from 0.6 full-time equivalent (FTE) to 4.2 FTE. This growth enabled us to open four new screening sites, with two additional sites scheduled to open in 2025. Wait time for a screening appointment went from months to days. A multidisciplinary review board with representation from all sites under the centralized structure meets weekly to discuss the management of all Lung-RADS 4 cases, many Lung-RADS 0 cases, and some Lung-RADS 2 and 3 cases. This meeting also serves as an opportunity to continue to build team culture and strategize for continuous growth and success.

Once a strong infrastructure for LCS is established and capacity is built within your center, it is time to start building capacity within the community. Being consistently present in your community is essential for developing trusting, authentic, and sustainable relationships. This includes understanding the priorities, resources, and challenges in these communities and identifying individuals and organizations that are most influential. ELCN forged strong partnerships with both local and national organizations including the American Lung Association, American Cancer Society, LUNGevity, Little Red Door, Indiana Tobacco Prevention and Cessation Partner Exchange, Indiana Oncology Society, The White Ribbon Project, and Indiana Rural Health Association to achieve this. Through these partnerships, ELCN engaged in community events throughout the state, including health fairs and conventions to provide education about LCS to the communities. Through this outreach, we learned that most people prefer to get medical care close to home within their own communities. Establishing a way to supporting the local infrastructure to provide care became far more important than recruiting patients to our larger system.

ELCN has partnered with the IU Simon Comprehensive Cancer Center and IU Health to launch Indiana's first and only mobile lung screening program in March 2025. This mobile program travels around the state to counties with the highest incidence of lung cancer and limited access to LCS. This program parks at trusted sites within the communities and works in partnership, not competition, with local health clinics and facilities to screen high-risk populations. The

program requires trust, transparency, and consistency, and the success of this is the key toward community influence. It lends itself as an opportunity to provide education and advocacy and become a part of the community to assist in building programs that address other social needs of those you serve.

Successfully transforming and scaling LCS is possible in the communities of those reading this. Find your why. Challenge your thinking. Develop a plan. At the end of the day, our obligation is to help one another.

In this section, we have described the efforts of ELCN as a paradigm for how community engagement can effect change and catalyze sustainable growth for LCS programs. Interested readers are invited to learn more about the work of others who are pioneering robust LCS programs in other community settings, including the studies by Gieske et al¹⁶ and Osarogiagbon et al.¹⁷

EXPANDING LCS TO NOVEL POPULATIONS

Tobacco is the leading cause of lung cancer worldwide. However, other risk factors include second-hand smoke; family history; exposure to environmental carcinogens, such as radon, air pollution, and cooking fumes; and pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) and interstitial lung diseases. Despite these known associations, the benefit of LCS is less well-elucidated in never smokers and those at risk of developing lung cancer because of family history or other risk factors.

Globally, approximately 10%-25% of lung cancer cases occur in never smokers.^{18,19} Lung cancer in individuals who never smoked was estimated to be the fifth most common cause of cancer death worldwide in 2023.²⁰ In geographic regions like Southern and East Asia, the proportion of lung cancers in never smokers is even higher, with more than 60% of women diagnosed with lung cancer having never smoked.¹⁸

The eligibility criteria associated with current screening guidelines focus on age and smoking history and may miss more than 50% of lung cancers.²¹ Risk prediction models use specific risk factors for lung cancer to enhance individual selection for screening although they have historically focused on current or former smokers. Prediction models that have incorporated nonsmoking predictors include prospective cohort models such as PLCO²²_{all2014} in an American population, NCC-LC²³_{m2021} in a Chinese population, and MD Anderson – MJ Group Integrative Risk Assessment²⁴ and Taiwanese Never Smoker Female lung cancer risk model and Simplified Questionnaire²⁵ in Taiwanese populations. However, practical application of these risk prediction models has proved to be challenging in nonsmoking populations.

SCREENING BASED ON FAMILY HISTORY AND OTHER RISK FACTORS

Individuals with family members affected by lung cancer have an increased risk of developing the disease. A meta-analysis of 28 case-control studies and 17 observational cohort studies reported a relative risk of developing lung cancer of 1.84 (95% CI, 1.64 to 2.05) for individuals with a first-degree relative with lung cancer,²⁶ enhanced when individuals had multiple affected family members or cancer diagnosed at a young age. A meta-analysis from the International Lung Cancer Consortium showed that the risk for lung cancer is 1.5-fold higher in individuals who have a first-degree relative with lung cancer, after adjustment for smoking and other potential confounders.²⁷

Several large-scale, single-arm prospective studies in Asia have evaluated broadening screening criteria to never smokers, with or without additional risk factors. One such study, The Taiwan Lung Cancer Screening in Never-Smoker Trial was a multicenter, prospective cohort study at 17 tertiary medical centers in Taiwan.²⁸ The primary outcome was lung cancer detection rate. Eligible patients age 55–75 years had either never smoked or had smoked fewer than 10 pack-years and stopped smoking for more than 15 years. In addition, inclusion required one or more of the following risk factors: family history of lung cancer, passive smoke exposure, history of TB or COPD, a cooking index (metric that quantifies exposure to cooking fumes) of 110 or higher, or cooking without ventilation. Participants underwent LDCT at baseline, then annually for two years, and then every 2 years for up to 6 years. The lung cancer detection rate was 2.6%, higher than that reported in the National Lung Screening Trial (NLST)²⁹ (1.1%) and Netherlands–Leuven Longkanker Screenings Onderzoek³⁰ (0.9%) trials. Of the diagnosed cancers, 96.5% was stage 0 or I. In multivariate analysis, female sex, a family history of lung cancer, and age older than 60 years were associated with an increased risk of lung cancer and invasive lung cancer.

Subsequently, the Taiwan Early Detection Program for Lung Cancer, a national screening program launched in 2022, targeted two screening populations: individuals with a history of heavy smoking and individuals with a family history of lung cancer.³¹ The latter group includes men between age 50 and 74 years and women between age 45 and 74 years, whose first-degree relatives were diagnosed with lung cancer. An expert consensus report on LCS implementation in Asia recommended inclusion in LCS programs with LDCT as the main screening tool for nonsmokers age 50–75 years with a family history of lung cancer in first-degree relatives.

Prospective studies of LDCT screening in never smokers with or without additional risk factors reflect a growing need to address the large global burden of lung cancers in these populations. The high rates of stage 0 and stage I cancers

highlight the importance of evaluating for overdiagnosis or diagnosis of cancers that would not become clinically apparent or lethal during an individual's life. Randomized controlled trials are needed to determine the true rates of overdiagnosis and to establish whether the higher lung cancer detection rates are associated with a decrease in lung cancer–related mortality in these populations. The implementation of randomized, controlled LDCT screening trials in never smokers has been limited by the need for large sample sizes, lengthy follow-up, and cost.

SCREENING AT-RISK INDIVIDUALS WITH GERMLINE MUTATIONS

Cancer genomics has revolutionized the management of non-small cell lung cancer, whereas understanding of inherited risk for lung cancer continues to evolve. Identifying germline pathogenic variants (PVs) that portend risk for developing lung cancer may allow for improved selection of LCS in at-risk family members. Pathogenic germline variants have been identified in families with high rates of lung cancers in never smokers. The most well-described germline PVs are in epidermal growth factor receptor (*EGFR*), particularly T790M mutations.³² Other potential germline variants implicated in lung cancer development have been described in *HER2*,³³ *ATM*,³⁴ *BRCA2*,³⁵ *CHEK2*,³⁵ and *TP53*³⁶ genes. For the latter, LCS in individuals with Li-Fraumeni syndrome typically involves annual whole-body magnetic resonance imaging to mitigate concern about radiation sensitivity.

The Investigating Hereditary Risk from T790M (INHERIT) study prospectively enrolled patients with lung cancer whose tumors harbored possible germline *EGFR* PV and their relatives.³² Of 91 confirmed or obligate carriers from 39 kindreds, 55% (50 of 91) were affected with lung cancer and 52% (34 of 65) of those were diagnosed by age 60 years. Notably, of 39 germline carriers without a cancer diagnosis, 15 had CT imaging available. Nine individuals had lung nodules, and one of these nine developed lung cancer during the follow-up period.

The role of LCS in individuals harboring germline PV associated with lung cancer needs to be explored further. As understanding of heritable risk and penetrance grows over time, unique opportunities to formally evaluate LCS in at-risk family members may arise.

NEEDLE IN THE HAYSTACK: PRECISION SCREENING FOR LUNG CANCER AND ROLE OF ARTIFICIAL INTELLIGENCE

Screening asymptomatic individuals is central to reducing lung cancer mortality because early-stage lung cancer has cure rates of up to 90%.³⁷ In the United States, however, LCS has fallen short of expectations because of incomplete eligibility criteria and low uptake of LCS among eligible individuals.^{21,38} Here, we discuss how artificial intelligence

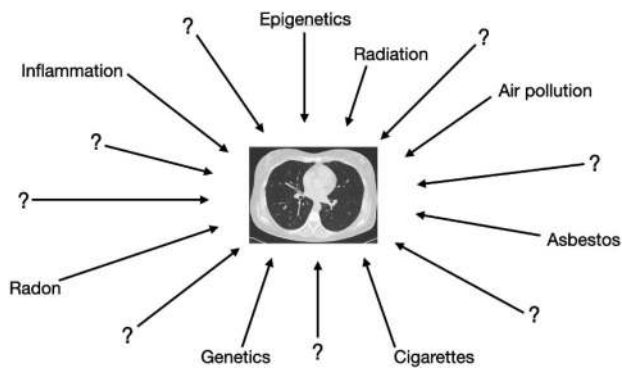


FIG 2. Imaging enables assessment of lung cancer risk. Computed tomography images could provide a downstream readout of an individual's cumulative lifetime exposure to known and unknown lung cancer risk factors.

(AI) could help refine screening criteria and expand screening access. Although exciting work is under way to develop novel bioassays for detecting existing cancers,³⁹⁻⁴³ we will focus on tools that help select individuals for screening by predicting who is likely to develop lung cancer in the future. Of note, the novel technologies discussed here remain most appropriate for the research setting rather than routine clinical practice. Nevertheless, they hold promise for a more sophisticated and accessible LCS landscape in the next decade.

THE COMPLEXITY OF LUNG CANCER RISK PREDICTION

Predicting who is at risk of lung cancer is challenging. Beyond tobacco use, many risk factors—such as air pollution and radon—are poorly understood, multifactorial, and difficult to measure or incorporate into clinical decisions.

Family history is a potent risk factor for lung cancer, yet we lack an effective genetic risk stratification tool; polygenic risk score models for lung cancer have had mixed success so far, performing well in certain populations but not generalizing to others (eg, Black populations).⁴⁴

Rather than cataloging and quantifying each exposure and predicting its interaction with germline genetics, a more practical approach would be to use a downstream readout that reflects an individual's cumulative lifetime exposures—for example, health changes documented in electronic health⁴⁵ or patterns in radiographic images (Fig 2; Table 1). LDCTs are particularly well suited to this purpose because they provide detailed images with minimal radiation exposure and they are not subject to the inaccuracies inherent to medical charting.^{46,47} However, human assessment of lung cancer risk is limited to the presence, characteristics, and change of visible lung nodules with the goal of detecting early-stage lung cancers rather than predicting future lung cancer risk. The remainder of this article will focus on challenges in developing and deploying AI tools in future cancer risk prediction, using an image-based model as an example.

MACHINE LEARNING FOR LUNG CANCER RISK PREDICTION

Machine learning (ML) is a form of AI technology that is adept at recognizing patterns in large data sets and then applying this learning to new data sets. One ML approach particularly well suited for image analysis is the convolutional neural network (CNN). CNNs use layers of filters that detect hierarchical imaging features—beginning with simple edges that can then be mixed and matched in deeper layers to build selectivity for complex textures and patterns.

TABLE 1. Chest CT–Based ML Models for Lung Cancer Risk Prediction

Model	Publication	Model Input	Model Output	Annotation Required?	Open Source?	PMID
Yang et al	2025	Single LDCT (scans with nodules ≥ 8 mm excluded)	Current lung cancer risk	No	No	39958220
Sybil	2023	Single LDCT	Future annual lung cancer risk over 6 years	No	Yes	36634294
Gao et al	2021	Single LDCT + clinical data	Current lung cancer risk	No	Yes	34957432
M3Net	2021	Single LDCT with or without clinical data with or without blood biomarkers	Current lung cancer risk	No	No	34650321
Gao et al	2020	Single LDCT	Current lung cancer risk, cancer-free progression time over 5 years	No	No	34040276
Google Health AI	2019	Single LDCT	Future lung cancer risk at 1 and 2 years	No	No	31110349
Huang et al	2019	Two sequential LDCTs with or without clinical data	Future annual lung cancer risk over 3 years	No	No	32864596

NOTE. Chest CT–based ML models for lung cancer risk prediction. Models use chest CT images as the primary input, examine global imaging features rather than focusing specifically on lung nodules, and provide an individual's current or future risk of lung cancer. Models meeting these criteria were identified in peer-reviewed publications, with priority given to studies that provided detailed methodology.

Abbreviations: CT, computed tomography; LDCT, low-dose computed tomography; ML, machine learning; PMID, PubMed Identifier.

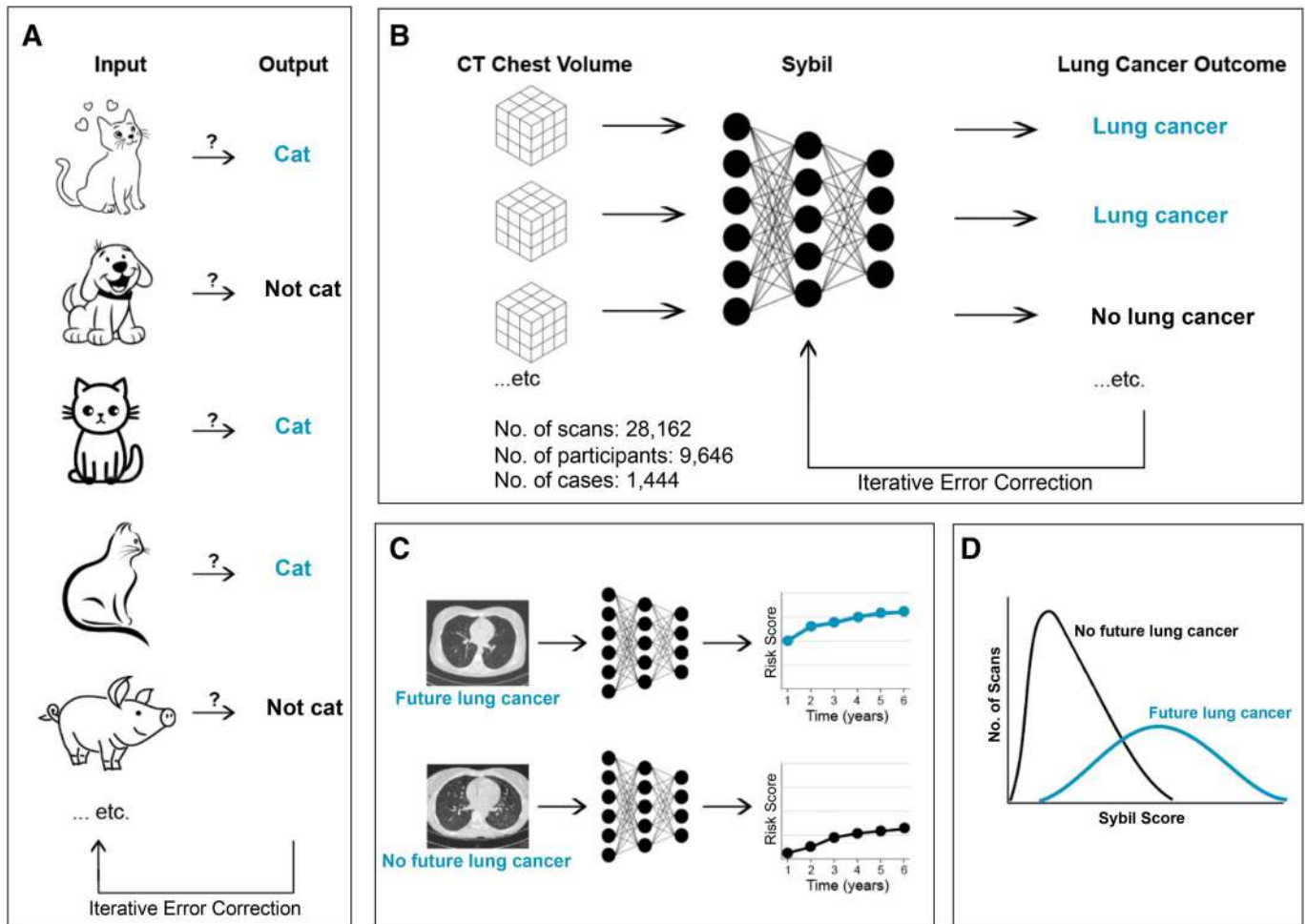


FIG 3. Training Sybil. (A) Sybil is a neural network deep learning classifier, which learned to recognize complex visual patterns by training on a series of images along with feedback regarding the correct answer (supervised learning). Supervised learning consists of providing the model with input data and a label. An intuitive analogy is teaching a child what a cat looks like by showing the child a series of animal images (Input column) along with information about which is a cat and which is not a cat (Output column). After sufficient training (ie, iterative error correction), the child will learn the patterns that are associated with a cat and can subsequently identify a cat in novel images that were not part of training. Similarly, the model will be able to assign the label “cat” to the correct animal without the ability to articulate what combinations of features are unique to cats. Importantly, everything the model knows about cats comes from the input data presented. Depending on the images included in the training data, the model could form biases or misconceptions about the unique identifying features of cats. For example, showing only images of cats on couches could lead to the misconception that couches are a key feature of cats. Sybil was trained on LDCTs from NLST participants. As a result, Sybil’s knowledge about lungs is based on individuals who are predominantly White, are 55 years and older, and have smoked ≥ 30 pack-years. (B) Sybil was trained on the volumetric data of 28,162 low-dose chest CT scans obtained from 9,646 participants in the NLST, 1,444 of whom went on to be diagnosed with lung cancer within 6 years after the chest CT. Sybil was told which scan belonged to an individual who was later diagnosed with lung cancer. During training, the model assigns numerical weights to different imaging features, with larger weights corresponding to those features that the model found to be more strongly associated with future lung cancer risk. (C) When Sybil is shown a chest CT that was not part of the training set, the output generated is a series of six risk scores corresponding to the individual’s annual cumulative lung cancer risk estimate over the subsequent six years. Since Sybil risk scores are cumulative, the score will always rise year over year for every individual. The risk scores are generally higher among those with future lung cancer and lower among those with no future lung cancer. (D) When considering a cohort or population analyzed by Sybil, most risk scores among individuals with no future lung cancer are distributed in the lower-risk range, whereas the risk scores of individuals with future lung cancer are distributed in the higher-risk range, but there is an overlap between the curves. This implies that choosing a Sybil score cutoff to inform clinical decision making will invariably result in some false positives and some false negatives. CT, computed tomography; LDCTs, low-dose computed tomographies; NLST, National Lung Screening Trial.

This enables CNNs to recognize subtleties that are not immediately apparent to even experienced radiologists.

Several ML models have been developed for risk stratification and early detection of lung cancer on imaging, with and

without consideration of blood-based biomarkers. Other differentiating features are the need for human input, either by providing clinical variables or through image annotation, and whether the model is freely available (open access; Table 1). Our group developed Sybil, an open access

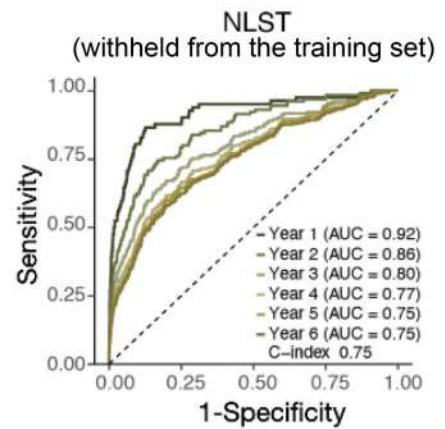
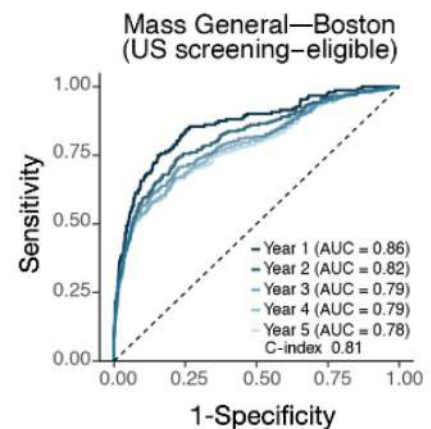
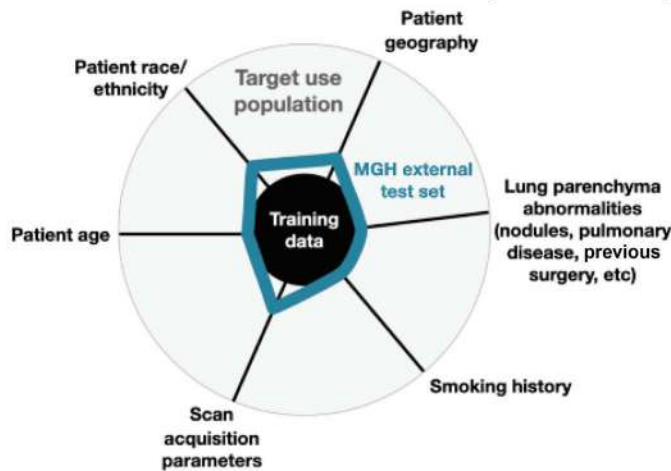
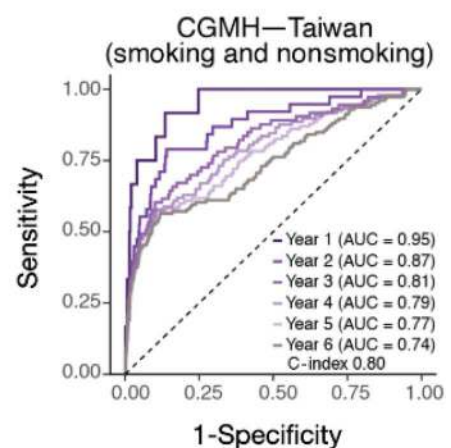
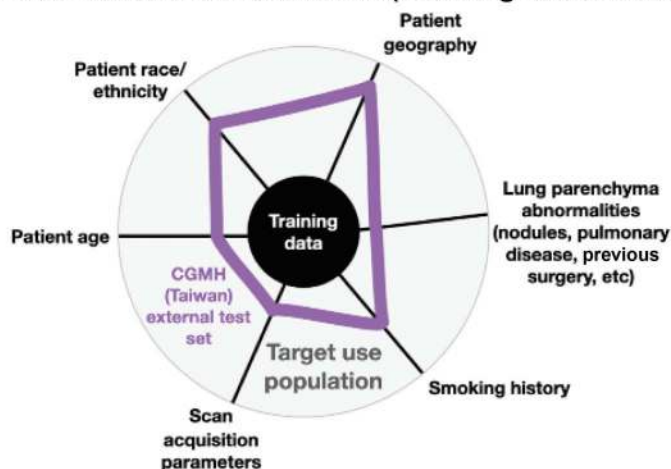
A NLST test set (withheld from the training data set)**B Mass General External Validation Set (US screening eligible)****C CGMH External Validation Set (smoking and nonsmoking; Taiwan)**

FIG 4. Validation of Sybil. Illustration of the characteristics of the three test sets used to validate the Sybil model in the 2023 JCO publication. Spider plots (left) compare the dimension of each test set with an imaginary target use population of all-comers. Comparisons shown are conceptual, not comprehensive, or quantitative. (A) The NLST test set represents a subset of data from the NLST that had not been used to train Sybil. The features of this subset used for internal validation align perfectly with the training data (spider plot), and the receiver operating curves (right) show that Sybil performs with high accuracy in this group. A well-trained model will demonstrate excellent performance during internal validation given the close alignment of the features with the data used for training. (B) The external validation set from Mass General resembles (continued on following page)

FIG 4. (Continued). the NLST training set in both demographics (predominantly White) and smoking history (USPSTF screen-eligible), but most individuals live in New England, and the CT scans were acquired more recently and in part on newer scanners. Reassuringly, the receiver operating curves (right) demonstrate that Sybil's performance is robust to the change in these features. (C) The external validation set from CGMH in Taiwan differs in additional parameters from the NLST training set in that individuals were predominantly East Asian and had a heterogeneous smoking history, including no smoking. Reassuringly, the receiver operating curves (right) demonstrate that Sybil's performance is robust to the change in these features. CGMH, Chang Gung Memorial Hospital; CT, computed tomography; MGH, Massachusetts General Hospital; NLST, National Lung Screening Trial; USPSTF, US Preventive Services Task Force.

three-dimensional CNN that predicts an individual's future risk of lung cancer based on the analysis of a single LDCT without the need for human annotation or other clinical inputs.⁴⁸

Sybil and other ML models have tremendous potential for precision LCS, even in settings where expert image interpretation is unavailable. They could support risk-adapted screening schedules—varying the frequency and intervals of LDCT scans according to individual risk—and potentially expand LCS eligibility beyond age and smoking history. Given the very low radiation dose of LDCTs using modern scanners, one could imagine a future where an LDCT is obtained at a certain age or upon the presence of certain risk factors, followed by an image-based risk assessment. We will use Sybil to discuss four concepts central to our understanding and improvement of these tools.

First, high-quality training data are crucial to developing robust AI models (Fig 3); data must be accurate, comprehensive, complete, and representative of the target population (Fig 3). Unfortunately, high-quality data sets are scarce in clinical medicine because data entry is complicated by the need to prioritize patient care and meet requirements imposed by payers. So, although data are abundant, they are rarely comprehensive or complete and are not standardized across hospitals.^{46,47} We must prioritize curating high-quality data sets to leverage the potential and promise of AI for LCS.

Second, ML models must be extensively validated before they are adopted at the bedside. All models must first pass internal validation, where they are tested on data withheld from the training set (Fig 4). Internal test sets align perfectly with the data used to train the model, and so performance should be excellent (Fig 4A). Subsequent validation should focus on external test sets that systematically assess the model's performance in cohorts that increasingly differ from the training data. Sybil performs well in a Mass General external test set that resembles the NLST training data in demographics (predominantly white) and smoking history (US Preventive Services Task Force screen eligible) but differs in geography and uses more modern CT scanners (Fig 4B). Encouragingly, Sybil's performance remains robust when tested on a cohort from Chang Gung Memorial Hospital in Taiwan, which consisted of a wide variety of smoking history, including those who never smoked (Fig 4C). Still,

Sybil remains underexplored in other key populations such as predominantly Black cohorts or those with a high prevalence of granulomatous disease. We must prioritize cultivating data sets that are representative of the wide range of patients we care for.

Third, ML models like Sybil must be calibrated to their intended population. Calibration is distinct from training because it does not modify how the model learns. Instead, it ensures that a model's predicted probabilities align with real-world outcomes. For example, if the model assigns a 30% risk of future lung cancer, calibration helps ensure that approximately 30% of individuals with that predicted risk actually develop lung cancer over time. This is important because the lessons a model has learned may not generalize to every setting, especially if the target population differs significantly from data used for training the model. In the case of Sybil, calibration requires input as LDCT scans in Digital Imaging and Communications in Medicine format of individuals representative of the population the model will be used on locally and the future lung cancer risk of these individuals. Calibrating Sybil for LCS-ineligible individuals who do not have these data available for calibration requires prospective trials.

Fourth, the successful development and deployment of ML models will require large-scale, multi-institutional collaboration to facilitate rapid and comprehensive validation, an endeavor complicated by data privacy concerns and lack of data uniformity. To facilitate this step, we opted to make Sybil available as an open-source code designed to run locally behind each institution's firewall. This design has allowed others to validate Sybil's performance.⁴⁹ We also formed a multi-institution consortium (The Sybil Implementation Consortium) to assess Sybil's performance in more geographically and racially diverse populations. Moving forward, global collaborations will be necessary to ensure that ML models deliver robust performance.

SUMMARY

LCS has been shown to save lives and to prevent deaths from lung cancer. As the global community works to implement effective and equitable access to LCS, opportunities exist to overcome barriers through public awareness, strategic investment, and cost-effective policy

interventions. Community engagement is a valuable tool to build relationships and to promote LCS at the local level. The ELCN team at the IU Simon Comprehensive Cancer Center has provided key recommendations that health care systems and communities can use to scale lung screening efforts for high-risk populations. Patient selection for screening is vital, and continuous research will inform how we can broaden the net for LCS to include high-risk

populations beyond those with a history of tobacco use, including individuals with a family history or germline mutations. Future advances may include improved risk-prediction models, DNA-based biomarkers, and other novel technologies. We predict that AI tools like Sybil will play a major role in decoding the complex landscape of lung cancer risk factors, enabling us to extend lifesaving LCS to all who are at risk.

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REFERENCES

- US Preventive Services Task Force; Krist AH, Davidson KW, et al: Screening for lung cancer: US Preventive Services Task Force recommendation statement. *JAMA* 325:962-970, 2021
- Henderson LM, Su IH, Rivera MP, et al: Prevalence of lung cancer screening in the US, 2022. *JAMA Netw Open* 7:e243190, 2024
- Gebremeskel TG, Romeo F, Shama AT, et al: Facilitators and barriers to lung cancer screening during long COVID: A global systematic review and meta-study synthesis of qualitative research. *Int J Environ Res Public Health* 21:534, 2024
- Haddad DN, Sandler KL, Henderson LM, et al: Disparities in lung cancer screening: A review. *Ann Am Thorac Soc* 17:399-405, 2020
- Castro S, Sosa E, Lozano V, et al: The impact of income and education on lung cancer screening utilization, eligibility, and outcomes: A narrative review of socioeconomic disparities in lung cancer screening. *J Thorac Dis* 13:3745-3757, 2021
- Lam DC, Liam CK, Andarini S, et al: Lung cancer screening in Asia: An expert consensus report. *J Thorac Oncol* 18:1303-1322, 2023
- Damaraju V, Karri JKK, Gandrakota G, et al: Low dose computed tomography for lung cancer screening in tuberculosis endemic countries: A systematic review and meta-analysis. *J Thorac Oncol* 20:296-310, 2025
- Damaraju V, Singh N, Garg M, et al: Effect of prior pulmonary TB on low-dose computed tomography during lung cancer screening. *Int J Tuberc Lung Dis* 27:223-225, 2023
- Coughlin JM, Zang Y, Terranella S, et al: Understanding barriers to lung cancer screening in primary care. *J Thorac Dis* 12:2536-2544, 2020
- Shankar A, Saini D, Dubey A, et al: Feasibility of lung cancer screening in developing countries: Challenges, opportunities and way forward. *Transl Lung Cancer Res* 8:S106-S121, 2019 (suppl 1)
- Hochhegger B, Camargo S, da Silva Teles GB, et al: Challenges of implementing lung cancer screening in a developing country: Results of the second Brazilian early lung cancer screening trial (BREL2). *JCO Glob Oncol* 10:1200/GO.21.00257
- Kauczor HU, Baird AM, Blum TG, et al: ESR/ERS statement paper on lung cancer screening. *Eur Radiol* 30:3277-3294, 2020
- Karanth SD, Divaker J, Blair M, et al: Rethinking how mobile units can catalyze progress on lung cancer screening: A scoping review of what we have learned. *J Thorac Dis* 16:7143-7154, 2024
- Wynder EL, Graham EA: Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of 684 proved cases. *J Am Med Assoc* 143:329-336, 1950
- Doll R, Hill AB: Smoking and carcinoma of the lung; preliminary report. *Br Med J* 2:739-748, 1950
- Gieske MR, Avery D, Bell R, et al: EP.04A.12 exploring rural Appalachian community perceptions and practices on health and lung cancer to inform screening interventions. *J Thorac Oncol* 19:S464-S465, 2024
- Osarogiabon RU, Liao W, Faris NR, et al: Lung cancer diagnosed through screening, lung nodule, and neither program: A prospective observational study of the detecting early lung cancer (DELUGE) in the Mississippi delta cohort. *J Clin Oncol* 40:2094-2105, 2022
- Sun S, Schiller JH, Gazdar AF: Lung cancer in never smokers—A different disease. *Nat Rev Cancer* 7:778-790, 2007
- de Alencar VTL, Figueiredo AB, Corassa M, et al: Lung cancer in never smokers: Tumor immunology and challenges for immunotherapy. *Front Immunol* 13:984349, 2022
- LoPiccolo J, Gusev A, Christiani DC, et al: Lung cancer in patients who have never smoked—An emerging disease. *Nat Rev Clin Oncol* 21:121-146, 2024
- Kerpel-Fronius A, Tammemägi M, Cavic M, et al: Screening for lung cancer in individuals who never smoked: An international association for the study of lung cancer early detection and screening committee report. *J Thorac Oncol* 17:56-66, 2022
- Tammemägi MC, Church TR, Hocking WG, et al: Evaluation of the lung cancer risks at which to screen ever- and never-smokers: Screening rules applied to the PLCO and NLST cohorts. *PLoS Med* 11:e1001764, 2014
- Wang F, Tan F, Shen S, et al: Risk-stratified approach for never- and ever-smokers in lung cancer screening: A prospective cohort study in China. *Am J Respir Crit Care Med* 207:77-88, 2023
- Wu X, Wen CP, Ye Y, et al: Personalized risk assessment in never, light, and heavy smokers in a prospective cohort in Taiwan. *Sci Rep* 6:36482, 2016
- Chien LH, Chen CH, Chen TY, et al: Predicting lung cancer occurrence in never-smoking females in Asia: TNSF-SQ, a prediction model. *Cancer Epidemiol Biomarkers Prev* 29:452-459, 2020

26. Matakidou A, Eisen T, Houlston RS: Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer* 93:825-833, 2005
27. Côté ML, Liu M, Bonassi S, et al: Increased risk of lung cancer in individuals with a family history of the disease: A pooled analysis from the International Lung Cancer Consortium. *Eur J Cancer* 48:1957-1968, 2012
28. Chang GC, Chiu CH, Yu CJ, et al: Low-dose CT screening among never-smokers with or without a family history of lung cancer in Taiwan: A prospective cohort study. *Lancet Respir Med* 12:141-152, 2024
29. National Lung Screening Trial Research Team; Aberle DR, Adams AM, et al: Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 365:395-409, 2011
30. de Koning HJ, van der Aalst CM, de Jong PA, et al: Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med* 382:503-513, 2020
31. Huang KP, Huang CY, Hsieh PC, et al: PL03.04 the Taiwan national lung cancer screening program. *J Thorac Oncol* 18, 2023 (suppl S35)
32. Oxnard GR, Chen R, Pharr JC, et al: Germline EGFR mutations and familial lung cancer. *J Clin Oncol* 41:5274-5284, 2023
33. Yamamoto H, Higasa K, Sakaguchi M, et al: Novel germline mutation in the transmembrane domain of HER2 in familial lung adenocarcinomas. *J Natl Cancer Inst* 106:djt338, 2014
34. Ji X, Mukherjee S, Landi MT, et al: Protein-altering germline mutations implicate novel genes related to lung cancer development. *Nat Commun* 11:2220, 2020
35. Wang Y, McKay JD, Rafnar T, et al: Rare variants of large effect in BRCA2 and CHEK2 affect risk of lung cancer. *Nat Genet* 46:736-741, 2014
36. Caron O, Frebourg T, Benusiglio PR, et al: Lung adenocarcinoma as part of the Li-fraumeni syndrome spectrum: Preliminary data of the LIFSCREEN randomized clinical trial. *JAMA Oncol* 3:1736-1737, 2017
37. Huang Z, Chen D, Hong Z, et al: Estimating the cure proportion of stage IA lung adenocarcinoma: A population-based study. *BMC Pulm Med* 23:417, 2023
38. Osarogiabon RU: Lung cancer screening, smoking cessation. Oral Presentation at Texas Lung Cancer Conference, Austin, TX, April 2024
39. Schrag D, Beer TM, McDonnell CH III, et al: Blood-based tests for multicancer early detection (PATHFINDER): A prospective cohort study. *Lancet* 402:1251-1260, 2023
40. Ulz P, Perakis S, Zhou Q, et al: Inference of transcription factor binding from cell-free DNA enables tumor subtype prediction and early detection. *Nat Commun* 10:4666, 2019
41. Mazzone PJ, Bach PB, Carey J, et al: Clinical validation of a cell-free DNA fragmentome assay for augmentation of lung cancer early detection. *Cancer Discov* 14:2224-2242, 2024
42. Chen X, Muhammad KG, Madeeha C, et al: Calculated indices of volatile organic compounds (VOCs) in exhalation for lung cancer screening and early detection. *Lung Cancer* 154:197-205, 2021
43. Tsou PH, Lin ZL, Pan YC, et al: Exploring volatile organic compounds in breath for high-accuracy prediction of lung cancer. *Cancers (Basel)* 13:1431, 2021
44. Trendowski MR, Lusk CM, Wenzlaff AS, et al: Assessing a polygenic risk score for lung cancer susceptibility in non-Hispanic White and Black populations. *Cancer Epidemiol Biomarkers Prev* 32:1558-1563, 2023
45. Placido D, Yuan B, Hjaltelin JX, et al: A deep learning algorithm to predict risk of pancreatic cancer from disease trajectories. *Nat Med* 29:1113-1122, 2023
46. Hoopes M, Voss R, Angier H, et al: Assessing cancer history accuracy in primary care electronic health records through cancer registry linkage. *J Natl Cancer Inst* 113:924-932, 2021
47. Guo LL, Morse KE, Aftandilian C, et al: Characterizing the limitations of using diagnosis codes in the context of machine learning for healthcare. *BMC Med Inform Decis Mak* 24:51, 2024
48. Mikhael PG, Wohlwend J, Yala A, et al: Sybil: A validated deep learning model to predict future lung cancer risk from a single low-dose chest computed tomography. *J Clin Oncol* 41:2191-2200, 2023
49. Phellan Aro R, Lam S, Warkentin MT, et al: MA02.11 validation of the Sybil deep learning lung cancer risk prediction model in three independent screening studies. *J Thorac Oncol* 19:S59-S60, 2024

Perioperative Therapy in Oncogene-Driven Non–Small Cell Lung Cancer: Current Strategies and Unanswered Questions

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OVERVIEW

Perioperative therapy has become a critical component in the management of resectable non–small cell lung cancer (NSCLC), particularly in the era of precision medicine. Although molecular testing is standard in metastatic NSCLC, its incorporation into early-stage disease remains essential for guiding treatment decisions. Reflex molecular testing pathways are necessary to optimize tissue utilization and ensure timely results. However, liquid biopsies, although valuable in advanced disease, have limited sensitivity in early-stage NSCLC, reinforcing the need for tissue-based next-generation sequencing. Targeted therapies have revolutionized treatment for oncogene-driven NSCLC, with adjuvant osimertinib now standard for EGFR-mutant disease and ongoing investigations into ALK tyrosine kinase inhibitors (TKIs). However, unanswered questions remain regarding the inclusion of perioperative TKI therapy, the role of molecular residual disease assessment, and whether specific TKIs offer greater benefit for high-risk subgroups. The role of immunotherapy (IO) in oncogene-driven NSCLC remains controversial. Although perioperative chemo-IO has demonstrated survival benefits in unselected NSCLC, its efficacy in EGFR, ALK, and other actionable alterations is unclear. Tumors harboring KRAS and BRAF mutations may respond better because of a more immune-inflamed microenvironment, and remains an active area of investigation. As the landscape of perioperative therapy continues to evolve, ongoing trials will help define the optimal integration of targeted therapies and IO in oncogene-driven NSCLC. Addressing these unanswered questions will be crucial in refining treatment strategies and improving patient outcomes.

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INTRODUCTION

The treatment landscape of non–small cell lung cancer (NSCLC) has evolved significantly with the integration of perioperative therapies, aimed at improving long-term outcomes for patients with resectable disease. Although platinum-based chemotherapy has historically been the foundation of adjuvant treatment, the discovery of oncogenic driver mutations—including *EGFR*, *ALK*, *MET*, *ROS1*, *RET*, among others—has redefined therapeutic strategies. Targeted therapies have demonstrated remarkable efficacy in advanced disease and are now being investigated in the perioperative setting, raising critical questions about their role in early-stage NSCLC. Simultaneously, immunotherapy (IO) has emerged as a standard of care in resectable NSCLC, but its utility in patients with actionable driver mutations remains controversial because of distinct tumor biology and concerns regarding toxicity. This chapter examines the current and emerging perioperative approaches for NSCLC with *EGFR*, *ALK*, and other targetable alterations (Fig 1), exploring the successes, challenges, and ongoing debates shaping the future of precision therapy in early-stage lung cancer.

MOLECULAR TESTING IN EARLY-STAGE NSCLC

Molecular testing has long been the standard of care in metastatic NSCLC, guiding the use of targeted therapies that improve survival outcomes. Actionable alterations in the setting of NSCLC includes the *EGFR*, *ALK*, *MET*, *KRAS*, *RET*, *ROS1*, *HER2*, *NTRK1/2/3*, and *BRAF* oncogenes. However, the incorporation of testing in the early-stage NSCLC remains inconsistent, despite its growing importance in guiding perioperative treatment decisions. In this setting, molecular results must be obtained rapidly and reliably to ensure timely therapeutic interventions, as delays could lead to missed windows for curative resection or systemic therapy initiation.

Unlike in metastatic disease, where tumor burden is often sufficient to obtain a substantial amount of tissue and to use rapid turnaround circulating tumor DNA based assays, early-stage NSCLC presents significant challenges related to tissue availability. Many patients undergo diagnostic biopsies with limited tumor material, particularly when lymph node aspirates are used for cytologic diagnosis. Additionally, the

PRACTICAL APPLICATIONS

- This chapter offers a comprehensive review of trials investigating the perioperative use of targeted therapies in early-stage non-small cell lung cancer (NSCLC) with actionable alterations.
- We highlight the importance of obtaining rapid and comprehensive molecular testing to identify oncogenic drivers and guide therapy in early-stage NSCLC.
- We explore the challenges and ongoing debates of implementing the use of precision medicine in early-stage disease.
- We provide a therapeutic algorithm for resectable NSCLC.

incidence rates of actionable oncogenic drivers in early-stage NSCLC are not well defined. There are reports suggesting similar, or perhaps lower, rates of alterations in stage I-III NSCLC compared with stage IV.^{1,2}

To overcome the challenges of delayed molecular results and ensure timely treatment initiation, reflex molecular testing at the time of NSCLC diagnosis is critical. Reflex testing—where gene alterations are assessed automatically upon pathologic confirmation of NSCLC—has been shown to be cost-effective and reduces turnaround time, and it increases the likelihood of patients receiving appropriate first-line targeted therapies.^{3,4} Although rapid molecular testing platforms have demonstrated high concordance with traditional tissue-based next-generation sequencing, they may not always match its sensitivity in detecting low-frequency variants and broader genomic alterations. Therefore, a tiered approach, integrating rapid assays for key drivers, for which alterations would dictate first-line treatment (*EGFR*, *ALK*, and *ROS1*) may be the optimal strategy to balance efficiency, accuracy, and clinical utility in early-stage NSCLC.

PERIOPERATIVE THERAPY STRATEGIES IN PATIENTS WITH *EGFR*-MUTANT NSCLC

Adjuvant Therapy: Establishing the Role of *EGFR*-Directed Tyrosine Kinase Inhibitors

The modern landscape of perioperative therapy for NSCLC was established with the publication of the Lung Adjuvant Cisplatin Evaluation meta-analysis in 2008.⁵ This study, which pooled data from five trials and included 4,584 patients with stage I-III NSCLC, demonstrated a significant improvement in 5-year overall survival (OS) with adjuvant cisplatin-based chemotherapy. The OS benefit, a 5.4% absolute increase, was primarily observed in patients with stage II and III disease.⁵ These findings cemented the role of

adjuvant chemotherapy as the standard of care after surgical resection. However, this study predated molecular profiling, which has since revolutionized treatment approaches.

With the discovery of *EGFR* mutations in NSCLC and their predictive value for response to tyrosine kinase inhibitors (TKIs),^{6,7} a new era of personalized adjuvant therapy began (Table 1). Several trials evaluated first- and second-generation *EGFR* TKIs in the adjuvant setting. The phase II EVAN trial demonstrated a significant disease-free survival (DFS) benefit with adjuvant erlotinib over chemotherapy (2-year DFS: 81.4% v 44.6%).⁸ Similarly, the phase II SELECT trial reported a promising 2-year DFS of 86% with adjuvant erlotinib after chemotherapy.⁹ However, the phase III RADIANT trial failed to demonstrate a DFS advantage for 2 years of adjuvant erlotinib versus placebo in resected stage IB-IIIa NSCLC patients with *EGFR* overexpression (hazard ratio [HR], 0.90; *P* = .324).¹⁰ The phase III ADJUVANT trial showed improved DFS with adjuvant gefitinib versus chemotherapy in stage II-IIIa NSCLC (median DFS: 28.7 v 18.0 months; HR, 0.60; *P* = .005).¹¹ However, the larger NCIC-CTG BR19 trial was prematurely closed because of toxicity concerns and a lack of OS or DFS benefit with adjuvant gefitinib.¹²

The landscape of adjuvant therapy in *EGFR*-mutant NSCLC changed dramatically with the phase III ADAURA trial, which randomly assigned patients with completely resected stage IB-IIIa NSCLC harboring *EGFR* exon 19 or L858R mutations to receive osimertinib or placebo for 3 years.¹³ The results were striking: at 24 months, 90% of patients in the osimertinib arm remained disease-free compared with 44% in the placebo group, with a HR for recurrence of 0.17 (95% CI, 0.11 to 0.26). Notably, osimertinib's superior CNS penetration translated into a markedly lower CNS recurrence rate (1% v 10%). Although adjuvant chemotherapy was recommended, it was inconsistently administered—it was received by approximately three quarters of stage II-IIIa patients and only a quarter of stage IB patients.¹³ Given the unprecedented DFS benefit, the Food and Drug Administration approved osimertinib for adjuvant use on the basis of these early results, a departure from previous regulatory precedent.¹⁴ The subsequent 5-year OS analysis confirmed osimertinib's impact, showing an OS rate of 85% in the treatment group versus 73% in the placebo group (HR, 0.49).¹⁵ This durable benefit extended beyond the 3-year treatment period, with 22% of patients continuing osimertinib after study completion. Just as the FLAURA and FLAURA2 trials established osimertinib as the preferred therapy in metastatic *EGFR*-mutant NSCLC,^{16,17} ADAURA solidified its role in early-stage disease. The upcoming ADAURA2 trial will further explore osimertinib's utility in patients with completely resected stage IA2-IA3 NSCLC.¹⁸

Neoadjuvant Therapy in *EGFR*-Mutant NSCLC

Given the established role of adjuvant targeted therapy and the potential benefits of tumor downstaging, multiple studies have explored the feasibility of *EGFR*-directed TKIs

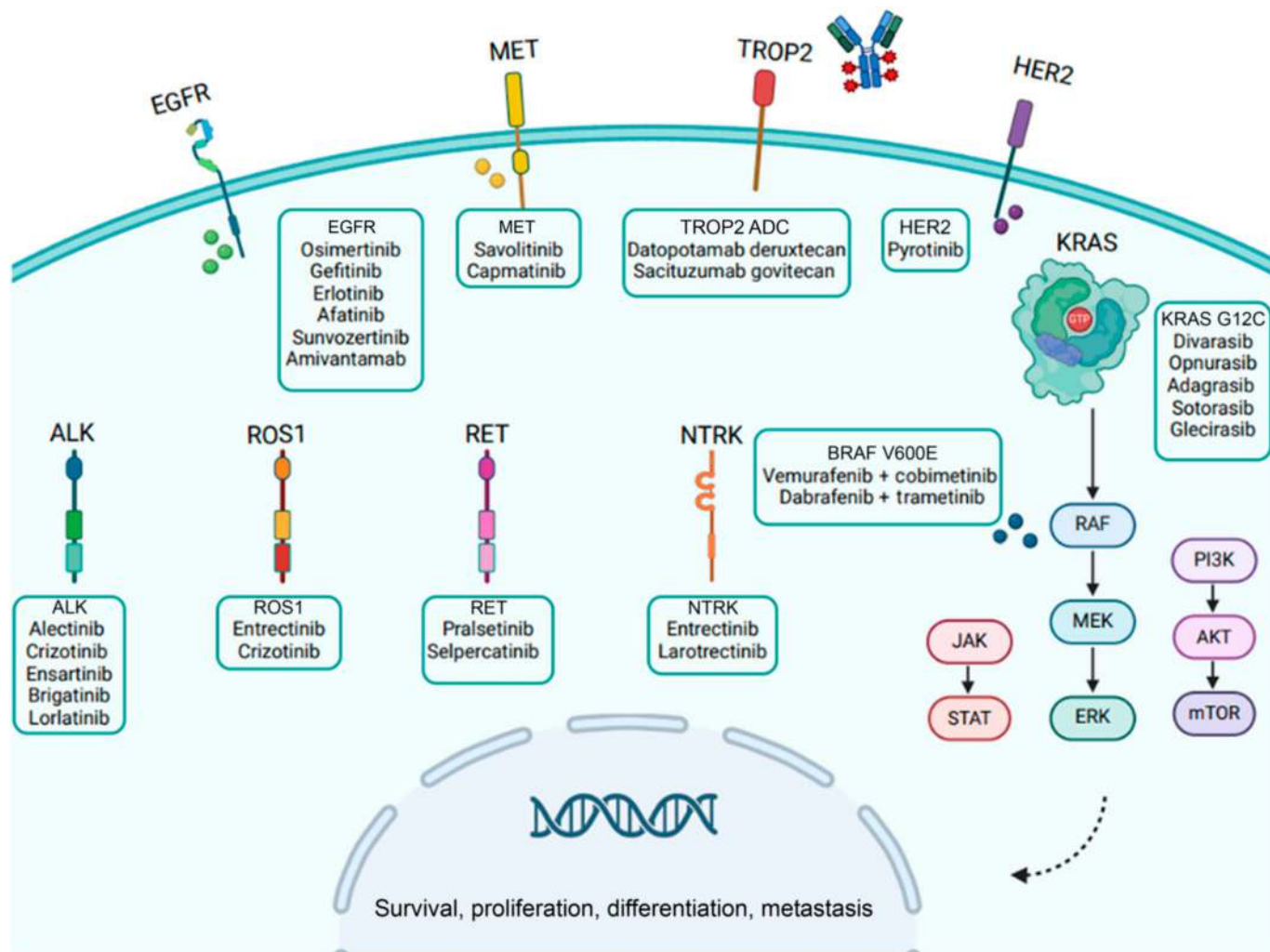


FIG 1. Targeted therapies with active clinical trials for perioperative treatment of resectable NSCLC. ADC, antibody drug conjugate; NSCLC, non-small cell lung cancer.

in the neoadjuvant setting. However, despite early enthusiasm, no neoadjuvant EGFR-TKI trial has demonstrated a substantial improvement in long-term outcomes. As a result, targeted therapy remains unapproved for perioperative use.¹⁹

Early Investigations: First- and Second-Generation TKIs

Small phase II studies investigating neoadjuvant gefitinib in patients with resectable stage II-IIIa NSCLC with EGFR mutations demonstrated moderate efficacy. Zhang et al²⁰ reported an objective response rate (ORR) of 54.5% (95% CI, 37.7 to 70.7) and a major pathologic response (MPR) rate of 24.2% (95% CI, 11.9 to 40.4). However, high toxicity rates—68.6% of patients experienced skin toxicity and 48.6% had gastrointestinal adverse effects—raised concerns about the tolerability of this approach. Notably, these trials established a correlation between MPR and prolonged DFS, highlighting a potential predictive biomarker for long-term benefit.²⁰

The signal of increased MPR with neoadjuvant gefitinib led to the exploration of second-generation EGFR inhibitors.

The ASCENT trial investigated a multistep regimen of neoadjuvant afatinib, followed by chemoradiation, surgery, and adjuvant afatinib in stage III EGFR-mutant NSCLC.²¹ This approach yielded an median progression-free survival (mPFS) of 2.6 years and an mOS of 5.8 years. However, the short median time to progression after stopping afatinib (2.8 months) and the high rate of CNS-only recurrences (38%) limited its clinical impact. Additionally, while 50% of patients who underwent surgery achieved an MPR, only 10% achieved a pathologic complete response (pCR). Similarly, the TEAM-LungMate004 trial evaluating neoadjuvant afatinib reported an MPR rate of 9.1% and a pCR rate of 3%, with high toxicity rates (78.7%).²² These findings reinforced the limitations of first- and second-generation TKIs in the perioperative setting.

Third-Generation TKIs: The Emergence of Osimertinib

The advent of third-generation EGFR TKIs, particularly osimertinib, reinvigorated interest in neoadjuvant targeted therapy. Blakely et al¹⁹ led a phase II trial evaluating neoadjuvant osimertinib monotherapy in stage I-IIIa EGFR-

TABLE 1. Summary of FDA-Approved Trials for Early-Stage NSCLC

Trial (ClinicalTrials.gov identifier: NCT)	Timing	Study Population	Patients Accrued	Intervention	Primary Outcome	Findings (intervention v comparator)	Driver Alterations
CheckMate-816 (NCT02998528)	Neoadjuvant	Stage IB-III A	358	Nivolumab + chemotherapy v chemotherapy once every 3 weeks	EFS, pCR	EFS: 31.6 v 20.8 months (HR, 0.63) pCR: 24.0% v 2.2% (OR, 13.9)	ALK and EGFR excluded
CheckMate-77T (NCT04025879)	Neoadjuvant	Stage II-III B	461	Nivolumab + chemotherapy once every 3 weeks followed by adjuvant nivolumab v chemotherapy + placebo followed by adjuvant placebo	EFS	70.2% v 50.0% (HR, 0.58)	ALK and EGFR excluded
AEGEAN (NCT03800134)	Neoadjuvant	Stage II-III B	802	Durvalumab + chemotherapy once every 3 weeks followed by adjuvant durvalumab v chemotherapy + placebo followed by adjuvant placebo	EFS, pCR	EFS: 73.4% v 64.5% (HR, 0.68) pCR: 17.2% v 4.3%	7.7% had ALK and EGFR, excluded from ITT analysis
KEYNOTE-671 (NCT03425643)	Neoadjuvant	Stage II-III B	797	Pembrolizumab + chemotherapy once every 3 weeks followed by adjuvant pembrolizumab v chemotherapy + placebo followed by adjuvant placebo	EFS, OS	EFS: 62.4% v 40.6% (HR, 0.58) OS: 80.9% v 77.6% ($P = .02$)	4.1% EGFR mutation 2.6% ALK translocation
IMpower010 (NCT02486718)	Adjuvant	Resected stage IB-III A	1,005	Atezolizumab once every 3 weeks v observation after adjuvant chemotherapy	DFS	DFS ITT at 5 years: 52.0% v 46.5% (HR, 0.85) DFS PD-L1 $\geq 1\%$: 53.2% v 42.7% (HR, 0.70)	11.6% EGFR mutation 3.3% ALK translocation
PEARLS/KEYNOTE-091 (NCT02504372)	Adjuvant	Resected stage IB-III A	1,177	Pembrolizumab once every 3 weeks v placebo	DFS	58.7 v 34.9 months (HR, 0.73)	6.2% EGFR mutation 1.2% ALK translocation
ADAURA (NCT02511106)	Adjuvant	Resected stage IB-III A	682	Osimertinib once daily $\times$ 3 years v placebo	DFS	89% v 52% (HR, 0.20)	All with EGFR mutation
ALINA (NCT03456076)	Adjuvant	Resected stage IB-III A	257	Alectinib twice daily $\times$ 2 years v chemotherapy	DFS	93.6% v 63.7% (HR, 0.24)	All with ALK rearrangement

Abbreviations: DFS, disease-free survival; EFS, event-free survival; FDA, Food and Drug Administration; HR, hazard ratio; ITT, intention to treat; NCT, National Clinical Trial; NSCLC, non–small cell lung cancer; OR, odds ratio; OS, overall survival; pCR, pathologic complete response.

mutant NSCLC. Of the 27 patients who received at least one cycle, 89% proceeded to surgery, but only 14.8% achieved an MPR, and none achieved a pCR. The trial failed to meet its prespecified MPR end point of 50%, dampening enthusiasm for osimertinib monotherapy in this setting. Although the regimen was well tolerated, with no adverse events leading to surgical delays or cancellations, exploratory analyses revealed that event-free survival (EFS) was not significantly correlated with MPR status. Moreover, the presence of co-occurring *TP53* (42%) and *RB* (21%) mutations within the study cohort raised questions about whether specific mutational subsets may derive differential benefit.¹⁹

Future Directions: NeoADAURA and the Role of Chemo-targeted Perioperative Therapy

Recognizing the limitations of single-agent neoadjuvant *EGFR* inhibition, there has been growing interest in evaluating osimertinib in combination with chemotherapy in the perioperative setting. The ongoing phase III NeoADAURA trial is comparing perioperative chemotherapy alone versus osimertinib with or without chemotherapy in patients with resectable *EGFR*-mutant NSCLC.²³ The trial's primary end point is MPR, with the potential to redefine the role of *EGFR*-targeted therapy in early-stage disease. Should NeoADAURA demonstrate a significant benefit, it will be the first study to establish targeted therapy as a standard in the perioperative setting.

The Role of IO in Patients With *EGFR*-Mutant NSCLC

The integration of IO into the perioperative treatment of NSCLC has significantly altered the treatment paradigm. Following the demonstrated DFS benefit of adjuvant IO in resectable NSCLC, attention shifted toward neoadjuvant chemo-IO approaches.^{24,25} The landmark CheckMate-816 trial established the superiority of neoadjuvant chemo-IO (nivolumab) over chemotherapy alone, demonstrating improvements in EFS (31.6 v 20.8 months; HR, 0.63; $P = .005$), pCR rates (24.0% v 2.2%; odds ratio [OR], 13.94; $P < .001$), and MPR rates (36.9% v 8.9%; OR, 5.70).²⁶ However, patients with *EGFR* alterations were specifically excluded from this study.

Encouraged by these findings, multiple trials were launched to evaluate perioperative chemo-IO regimens, comparing four cycles of neoadjuvant treatment followed by adjuvant IO versus perioperative chemotherapy followed by placebo in patients with stage II-IIIB NSCLC. These trials—CheckMate-77T (nivolumab), AEGEAN (durvalumab), and KEYNOTE-671 (pembrolizumab)—each demonstrated significant improvements in EFS and pCR rates in largely *EGFR* mutation-negative cohorts.^{27–29} Notably, KEYNOTE-671 was the first perioperative chemo-IO trial to show a statistically significant OS benefit in the intention-to-treat population (HR, 0.72; $P = .005$).³⁰

Should Patients With *EGFR*-Mutant NSCLC Receive IO?

Despite the success of perioperative chemo-IO in unselected NSCLC populations, the inclusion of patients with *EGFR* alterations remains controversial. These patients generally have tumors that exhibit lower PD-L1 expression and a lower tumor mutational burden—features associated with poor response to checkpoint inhibitors. Furthermore, concerns about the potential interaction between *EGFR* TKIs and IO, particularly the risk of immune-related adverse events that could preclude the continued use of effective targeted therapies, have made this approach controversial.

The inclusion of *EGFR*-mutant patients varied across major perioperative chemo-IO trials:

1. CheckMate-77T explicitly excluded patients with *EGFR* alterations.²⁷
2. AEGEAN enrolled and randomly assigned 51 patients with *EGFR* mutations, but they were later excluded from the study's modified intention-to-treat analysis after publication of the ADAURA trial. A per-protocol analysis of these 51 patients showed a trend toward improved EFS and pCR with perioperative durvalumab plus chemotherapy compared with chemotherapy alone (EFS HR, 0.86 [95% CI, 0.35 to 2.19]; pCR: 3.8% v 0%; OR, 3.8).²⁸ However, the findings were not statistically significant, and the small sample size limits their interpretability.
3. KEYNOTE-671 did not require *EGFR* testing before enrollment, allowing 33 patients with confirmed *EGFR* mutations to be included (14 in the pembrolizumab arm and 19 in the placebo arm). An additional 66% of patients had unknown *EGFR* status, suggesting that more patients with undetected *EGFR* alterations may have been included. Among the 33 confirmed *EGFR*-mutant patients, pembrolizumab significantly improved EFS, with only one of 14 patients in the IO arm experiencing recurrence, progression, or death compared with 10 of 19 in the placebo arm (HR, 0.09 [95% CI, 0.01 to 0.74]).²⁹ Despite this striking EFS benefit, the small cohort size and lack of OS data limit definitive conclusions.

The Challenge of Integrating Chemo-IO in *EGFR*-Mutant NSCLC

Although these findings suggest a potential role for IO in *EGFR*-mutant NSCLC, several factors argue against its widespread adoption. The well-documented increased toxicity risk when IO is followed by *EGFR* TKIs, particularly the development of severe pneumonitis, remains a major concern.³¹ Additionally, adjuvant osimertinib in ADAURA has demonstrated a clear OS benefit, making the interruption or delay of TKI therapy in favor of IO a risky trade-off.¹⁵ Given these limitations and the relatively poor response of *EGFR*-mutant tumors to immune checkpoint inhibitors, perioperative chemo-IO has not been integrated into the standard of care in this population.

PERIOPERATIVE THERAPY STRATEGIES IN EARLY-STAGE NSCLC WITH *KRAS* MUTATIONS AND OTHER RARE ONCOGENE DRIVERS

Although most NSCLCs are detected at the advanced stage, the prevalence of molecular mutations, such as *KRAS*, by stage at diagnosis appears to be similar across stages.^{32,33} In the metastatic setting, *KRAS*-mutant tumors and the majority of *BRAF* V600E-mutant NSCLCs generally respond favorably to IO potentially related to high PD-L1 expression, high tumor mutational burden, and an overall immune-inflamed tumor microenvironment.^{34,35} However, data in the early-stage NSCLC setting are limited. A recent post hoc analysis of the NEOSTAR study, a phase II trial of neo-adjuvant nivolumab ± ipilimumab, found no MPR to neo-adjuvant ICIs among three patients harboring *HER2* and/or *RET* alterations, whereas a patient with a *BRAF* V600E mutation experienced a pCR.³⁶ In addition, patients with targetable driver mutations generally had higher residual viable tumor percentages compared with wild-type patients.³⁶ These findings underscore how specific oncogenic drivers lead to varying degrees of ICI sensitivity, emphasizing the need to further refine treatment strategies on the basis of individual tumor biology.

Initial evidence from four phase II neoadjuvant trials suggests that comutations, particularly involving *STK11* and *KEAP1*, may significantly reduce pathologic response rates and are likely to affect long-term survival outcomes.³⁷⁻⁴¹ Importantly, recent findings suggest that combined PD-L1 and cytotoxic T-lymphocyte-associated protein 4 blockade may abrogate resistance to PD-1/PD-L1 monotherapy in patients with *STK11* and/or *KEAP1* mutations.⁴² A pooled analysis of two phase II neoadjuvant studies demonstrated that *KRAS* comutation with *STK11*, *KEAP1*, and/or *SMARCA4* was associated with worse EFS outcomes with nivolumab, but not nivolumab plus ipilimumab, again suggesting a potential role for dual IO for patients with early-stage lung cancer and these specific comutation patterns.⁴³

Trials With Targeted Therapy

Multiple trials are currently underway to evaluate the role of targeted therapies in the perioperative management of *KRAS*-mutant NSCLC. Several *KRAS* G12C inhibitors are being tested across different neoadjuvant and perioperative settings, either as monotherapy or in combination with immune checkpoint inhibitors. The NAUTIKA1 trial, a phase II, multicenter, umbrella study, is assessing the efficacy and safety of multiple neoadjuvant and adjuvant regimens in resectable stage IB-III NSCLC with specific molecular alterations.^{44,45} Within this trial, divarasib is being tested in the perioperative setting for patients with *KRAS* G12C-mutant NSCLC. The NAUTIKA1 trial is also investigating other perioperative strategies, including vemurafenib/cobimetinib for *BRAF* V600E mutations, pralsetinib for

RET rearrangements, and entrectinib for *ROS1* and *NTRK* fusions in patients with stage IIA to selected IIIB (T3N2) NSCLC.

Similarly, the phase II IND242 trial is investigating neo-adjuvant opnurasib in patients with resectable stage IA2 to IIIA NSCLC and *KRAS* G12C mutations.⁴⁶ Preclinical studies have demonstrated that *KRAS* G12C inhibition can remodel the tumor microenvironment, enhancing antitumor immune activity and synergizing with PD-1 inhibitors.⁴⁷ These findings provide a strong rationale for investigating combination strategies in *KRAS* G12C-mutant NSCLC.⁴⁸ Finally, the *KRAS* G12C inhibitor sotorasib is being tested as neo-adjuvant therapy in combination with chemotherapy only, in patients with stage IIA-IIIIB nonsquamous histology (ClinicalTrials.gov identifier: [NCT05118854](https://clinicaltrials.gov/ct2/show/study/NCT05118854)).

In addition to *KRAS*, other genomic alterations are being explored as potential targets for neoadjuvant and perioperative therapeutic strategies in early-stage NSCLC. The LIBRETTO-431 study evaluated seliprecatinib in patients with *RET* fusion-positive advanced NSCLC compared with chemotherapy ± pembrolizumab.⁴⁹ This showed a remarkable mPFS of 24.8 months in the intervention arm compared with 11.2 months in the control group, and led to the investigation of seliprecatinib in the perioperative setting. The LIBRETTO-001 and LIBRETTO-432 trials, which are ongoing, have been designed to determine the efficacy of neoadjuvant and adjuvant seliprecatinib in *RET*-positive early-stage NSCLC (Table 2).^{50,51} Given the notable PFS and OS benefits of TKIs for patients with rarer actionable alterations including *KRAS*, *MET*, *RET*, *ROS1*, *HER2*, *NTRK1/2/3*, and *BRAF*, there is significant enthusiasm in the field regarding their potential utility in the perioperative setting. However, at the time of this publication, the perioperative use of TKIs for patients with early-stage NSCLC and actionable alterations other than *EGFR* and *ALK* is not supported by trial data or clinical guidelines. The previously noted trials must be followed closely, as their results, if consistent with findings in *EGFR*- and *ALK*-positive NSCLCs, have the potential to transform the treatment paradigm for NSCLC patients with less common actionable genetic alterations.

PERIOPERATIVE THERAPY STRATEGIES IN PATIENTS WITH *ALK* REARRANGEMENTS

ALK rearrangements are reported to occur in 2%-7% of NSCLCs, more commonly among nonsmokers, females, and younger patients.⁵²⁻⁵⁶ Incidence of *ALK* rearrangements in early-stage NSCLC has not been well defined until recently as genomic testing was not part of routine testing in early-stage NSCLC. However, as the treatment paradigm is shifting toward the use of targeted therapies, there are emerging data demonstrating that approximately 4%-7% of early-stage NSCLCs have *ALK* fusions.^{39,53,57}

TABLE 2. Summary of Clinical Trials of Perioperative Interventions in Early-Stage NSCLC

Trial (ClinicalTrials.gov identifier: NCT)	Phase	Timing	Driver Alteration	Study Population	Patients Accrued	Intervention	Primary Outcome	Findings (intervention v comparator)	Status
EGFR									
NeoADAURA (NCT04351555)	III	Neoadjuvant	EGFR	Stage II-IIIB	358	Osimertinib daily v osimertinib daily + chemotherapy v chemotherapy once every 3 weeks	MPR	Pending	Active, not recruiting
ECTOP-1001 (NCT01833572)	II	Neoadjuvant	EGFR	Stage II-III A	36	Gefitinib once daily × 6 weeks	ORR	54.5%	Completed
NCT03433469	II	Neoadjuvant	EGFR	Stage I-III A	27	Osimertinib daily for up to two 28-day cycles	MPR	14.8% (below prespecified end point)	Active, not recruiting
NEOpredict-EGFR (NCT06784791)	II	Neoadjuvant	EGFR	Stage IB-III A	20	Chemotherapy once every 3 weeks × one cycle followed by one cycle amivantamab + carboplatin/pemetrexed	Feasibility	Pending	Recruiting
LungMate-004 (NCT04201756)	II	Perioperative	EGFR	Stage III	47	Neoadj: afatinib once daily × 8-16 weeks Adj: afatinib × 1 year	ORR	70.2%	Completed
ASCENT (NCT01553942)	II	Perioperative	EGFR	Stage III	19	Afatinib daily × 2 months then concurrent chemoradiation then surgery followed by afatinib × 2 years	ORR	63%	Active, not recruiting
EMERGING (NCT01407822)	II	Perioperative	EGFR	Stage IIIA-N2	72	Neoadj: Erlotinib daily × 6 weeks v gemcitabine/cisplatin × two cycles Adj: Erlotinib daily × 1 year v gemcitabine/cisplatin × two cycles	ORR	54.1% v 34.3% ($P = .092$)	Completed
ADAURA 2 (NCT05120349)	III	Adjuvant	EGFR	Stage IA2 or IA3	385	Osimertinib daily × 3 years v placebo	DFS in the high-risk stratum	Pending	Active, not recruiting
NCT00049543	III	Adjuvant	EGFR in 4%	Stage IB-III A	503	Gefitinib daily × 2 years v placebo	OS	No difference (HR, 1.24)	Completed
ADJUVANT-CTONG1104 (NCT01405079)	III	Adjuvant	EGFR	Stage II-III A	222	Gefitinib daily × 2 years v vinorelbine + cisplatin × four cycles	DFS	30.8 v 19.8 months (HR, 0.56)	Completed
EVAN (NCT01683175)	II	Adjuvant	EGFR	Stage III A	94	Erlotinib daily × 2 years v vinorelbine + cisplatin × four cycles	2-year DFS	81.4% v 44.6% (RR, 1.8)	Completed
SELECT (NCT00567359)	II	Adjuvant	EGFR	Stage IA-III A	100	Erlotinib daily × 2 years after adjuvant chemotherapy/radiotherapy	2-year DFS	90%	Completed
RADIANT (NCT00373425)	III	Adjuvant	EGFR expression/amplification, EGFR mutation in 16.5%	Stage IB-III A	1,252	Erlotinib daily × 2 years v placebo	DFS	50.5 v 48.2 months (HR, 0.90 [95% CI, 0.74 to 1.10])	Completed

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TABLE 2. Summary of Clinical Trials of Perioperative Interventions in Early-Stage NSCLC (continued)

Trial (ClinicalTrials.gov identifier: NCT)	Phase	Timing	Driver Alteration	Study Population	Patients Accrued	Intervention	Primary Outcome	Findings (intervention v comparator)	Status
ALK									
ARM (NCT03088930)	II	Neoadjuvant	ALK	Stage IA-IIIa	3	Crizotinib twice daily × 6 weeks	ORR	Terminated, low accrual	Completed
SAKULA (UMIN00017906)	II	Neoadjuvant	ALK	Stage II-III	7	Ceritinib daily × 12 weeks	MPR	57%	Completed
NEOLORA (NCT06682884)	II	Neoadjuvant	ALK	Stage IB-IIIB	—	Lorlatinib daily × 6-8 weeks	pCR	Pending	Not yet recruiting
LORIN (NCT05740943)	II	Neoadjuvant	ALK	Stage III	48	Lorlatinib daily × 12 weeks	pCR	Interim (n = 11): 23.1%	Recruiting
CLOG-003 (NCT06779539)	II	Neoadjuvant	ALK	Stage II-III	—	Ensartinib daily × 12 weeks	pCR	Pending	Not yet recruiting
BD-EN-IV0012 (NCT05380024)	II	Neoadjuvant	ALK	Stage II-IIIB	10	Ensartinib daily × 8 weeks	MPR	Pending	Recruiting
NCT05361564	II	Neoadjuvant	ALK	Stage I-IIIa	12	Brigatinib daily × 4-10 weeks	Molecular candidates identified by analyzing scRNA-seq	Pending	Not yet recruiting
ALNEO (NCT05015010)	II	Perioperative	ALK	Stage III	33	Neoadj: alectinib twice daily × 8 weeks Adj: alectinib twice daily × 96 weeks	MPR	Interim (n = 25): 39%	Active, not recruiting
NAUTIKA-1 (NCT04302025)	II	Perioperative	ALK	Stage 1B-III	125	Neoadj: alectinib twice daily × 8 weeks Adj: alectinib twice daily × 104 weeks	MPR	Interim (n = 7): 71%	Recruiting
ALCHEMIST (NCT02201992)	III	Adjuvant	ALK	Stage IB-IIIa	168	Crizotinib twice daily × 2 years v placebo	OS	Pending	Recruiting
BD-EN-IV006 (NCT05241028)	II	Adjuvant	ALK	Stage IB-IIIa	80	Ensartinib daily × 3 years	DFS	Pending	Recruiting
NCT05341583	III	Adjuvant	ALK	Stage IB-IIIB	202	Ensartinib daily × 2 years	DFS	Pending	Recruiting
NCT06772610	II	Adjuvant	ALK	Stage I	—	Ensartinib daily × 2 years	DFS	Pending	Not yet recruiting
Other driver mutations									
IND242 (NCT05714891)	II	Neoadjuvant	KRAS G12C	Stage IA2-IIIa	4	Opnurasib twice daily	MPR	Drug development discontinued	Active, not recruiting
Neo-KAN (NCT05472623)	II	Neoadjuvant	KRAS G12C	Stage IB-IIIa	42	Adagrasib twice daily × 6 weeks v adagrasib twice daily + nivolumab once every 3 weeks × 6 weeks	pCR	Pending	Active, not recruiting
NCT05118854	II	Neoadjuvant	KRAS G12C	Stage IIA-IIIB	27	Sotorasib daily + cisplatin/carboplatin + pemetrexed once every 3 weeks	MPR	Pending	Recruiting

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TABLE 2. Summary of Clinical Trials of Perioperative Interventions in Early-Stage NSCLC (continued)

Trial (ClinicalTrials.gov identifier: NCT)	Phase	Timing	Driver Alteration	Study Population	Patients Accrued	Intervention	Primary Outcome	Findings (intervention v comparator)	Status
NUMER (NCT06563999)	II	Neoadjuvant	<i>ALK, BRAF V600E, EGFR exon20ins, HER2, KRAS G12C, MET 14 exon, NTRK, RET, ROS1</i>	Stage III, unresectable	120	Ensartinib, dabrafenib + trametinib, sunvozertinib, pyrotinib, glecirasib, savolitinib, larotrectinib, pralsetinib, crizotinib	Resectability rate	Pending	Recruiting
NEOSTAR (NCT03158129)	II	Neoadjuvant	Any except <i>EGFR/ALK</i>	Stage I-III A	101	Nivolumab once every 3 weeks Nivolumab + ipilimumab once every 3 weeks Nivolumab + platinum doublet once every 3 weeks Nivolumab + ipilimumab + platinum doublet once every 3 weeks	MPR	No MPR in n = 3 with <i>HER2</i> and <i>RET</i> alterations; MPR in one patient with <i>BRAF V600E</i>	Completed
NAUTIKA-1 (NCT04302025)	II	Perioperative	<i>BRAF V600E, KRAS G12C, NTRK, RET, ROS1</i>	Stage IB-III	125	Vemurafenib twice daily + cobimetinib daily, divarasib, entrectinib, pralsetinib	MPR	Pending	Recruiting
GEOMETRY-N (NCT04926831)	II	Perioperative	<i>MET exon 14</i>	Stage IB-III A, N2 Select IIIB (T3N2, T4N2)	4	Neoadj: capmatinib twice daily × 8 weeks Adj: capmatinib twice daily × 3 years	MPR	—	Terminated
LUN109 (NCT06055465)	II	Perioperative	Any except <i>EGFR/ALK</i>	Stage II-III	37	Neoadj: pembrolizumab + sacituzumab govitecan on days 1 and 8 of a 21 day cycle × four cycles Adj: pembrolizumab × 13 cycles	pCR	Pending	Recruiting
NeoCOAST-2 (NCT05061550)	II	Perioperative	Any except <i>EGFR/ALK</i>	Stage II-III B	630	Combinations of durvalumab and platinum doublet chemotherapy once every 3 weeks with oleclumab, monalizumab, volrustomig, rilvegostomig, datopotamab deruxtecan, AZD0171	pCR	Durvalumab + platinum chemotherapy once every 3 weeks + Dato-DXd (n = 54): 34.1%	Recruiting
LIBRETTO-432 (NCT04819100)	III	Adjuvant	<i>RET</i>	Stage IB-III A	170	Selpercatinib twice daily × 3 years v placebo	EFS	Pending	Recruiting
ARIAN (NCT06431633)	III	Adjuvant	Any except <i>EGFR/ALK</i>	Stage IB-III A-III B (N2)	129	Observation v zimberelimab once every 3 weeks v sacituzumab govitecan on days 1 and 8 of a 21-day cycle + zimberelimab	DFS	Pending	Recruiting
TROPION-Lung12 (NCT06564844)	III	Adjuvant	Any except <i>EGFR/ALK</i>	Stage I	660	SOC v rilvegostomog once every 3 weeks v datopotamab deruxtecan + rilvegostomig once every 3 weeks	DFS	Pending	Recruiting

Abbreviations: Adj, adjuvant; Dato-DXd, datopotamab deruxtecan; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; Ins, insertion; MPR, major pathologic response; NCT, National Clinical Trial; Neoadj, neoadjuvant; NSCLC, non–small cell lung cancer; pCR, pathologic complete response; ORR, objective response rate; OS, overall survival; RR, relative risk; scRNA seq, single-cell RNA sequencing; SOC, standard of care.

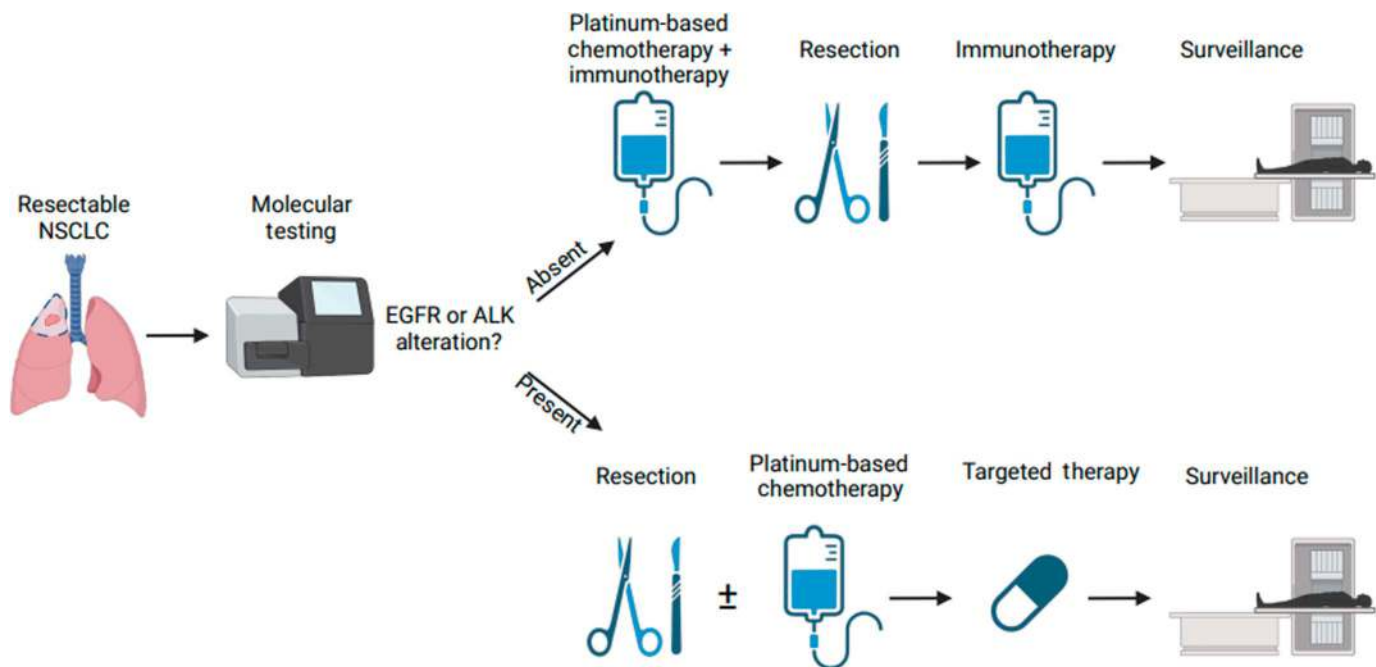


FIG 2. Current treatment algorithm for resectable NSCLC. NSCLC, non–small cell lung cancer.

Adjuvant Therapy: Establishing the Role of ALK-Directed TKIs

Adjuvant crizotinib was assessed in a small retrospective study of 59 patients with stage IB–IIIA *ALK*-positive NSCLC who underwent resection followed by adjuvant chemotherapy ($n = 29$) or crizotinib ($n = 30$).⁵⁸ Crizotinib was associated with a significant improvement in DFS (44.5 months *v* 14.0 months; $P < .001$) and OS (70.0 months *v* 45.0 months; $P = .021$).⁵⁸ Further investigations of adjuvant crizotinib were not pursued after the closure of the randomized, double-blind, placebo-controlled phase III AL-CHEMIST trial after positive results of ALINA were reported.⁵⁹

In 2024, the standard of care for the adjuvant treatment of *ALK*-positive NSCLC changed following the results of the pivotal phase III ALINA trial.⁶⁰ ALINA is an open-label trial that enrolled patients with resected stage IB–IIIA *ALK*-positive NSCLC, who were randomly assigned to receive adjuvant alectinib for 2 years ($n = 130$) versus platinum-based doublet chemotherapy for four 21-day cycles ($n = 127$). Unlike ADAURA, patients on the investigation arm did not receive adjuvant chemotherapy before random assignment. After a median follow-up of 27.8 months, adjuvant alectinib significantly prolonged DFS compared with chemotherapy at 2 years (93.8% *v* 63.0%) and 3 years (88.3% *v* 53.3%) with a HR of 0.24 (95% CI, 0.13 to 0.43; $P < .001$). This benefit with alectinib was consistent across all subgroups including stage, nodal status, age, sex, and race. Recurrent disease was seen in 11.5% of patients in the alectinib arm and 38.6% in the chemotherapy arm. At 24 months, CNS DFS was also significantly superior with alectinib compared with

chemotherapy (98.4% *v* 85.8%; HR, 0.22 [95% CI, 0.08 to 0.58]). Furthermore, fewer patients discontinued alectinib due to adverse events (5.5% *v* 12.5%). Although OS data are still pending, on the basis of the remarkable DFS results of this study, alectinib was approved in April 2024 for adjuvant treatment of early-stage IB–IIIA *ALK*-rearranged NSCLC.⁶¹

Subsequently, a real-world retrospective study assessed the efficacy of adjuvant alectinib ($n = 19$) versus platinum-based chemotherapy ($n = 49$) in patients with stage IB–IIIB *ALK*-positive NSCLC and found that 3-year DFS was improved in the alectinib group (91.7% *v* 60.7%).⁶²

Neoadjuvant Therapy in *ALK*-Rearranged NSCLC

Immune checkpoint inhibitors have limited activity in patients with actionable oncogenic drivers including *ALK* rearrangements.⁶³ Accordingly, these patients were excluded from most neoadjuvant or perioperative chemo-IO trials, with the exception of KEYNOTE-671. However, in KEYNOTE-671, only 5.2% of the cohort had an *ALK* rearrangement, which limited any insight into outcomes for this subgroup.²⁹ Although the AEGEAN trial initially included patients with *ALK* rearrangements, a subsequent amendment excluded these patients after emerging data showed limited efficacy of the regimen.²⁸ *ALK* TKIs have been evaluated in several small studies for neoadjuvant therapy (Table 2).

A retrospective review of neoadjuvant crizotinib in *ALK*-positive resectable N2 NSCLC demonstrated that 10 of 11 enrolled patients had a radiographic partial response. After a median treatment duration of 30 days (range, 28–120) before surgery, 91% of patients underwent an R0 resection, with

two patients achieving a pCR. Six patients had disease recurrence with a median DFS of 10.1 months and five of them received crizotinib at the time of disease recurrence with PFS ranging from 5 to 26 months.⁶⁴

The rarity of *ALK* alterations and the lack of standardized genetic assessment in early-stage NSCLC have led to challenges in neoadjuvant trials. The ARM phase II trial (ClinicalTrials.gov identifier: [NCT03088930](https://clinicaltrials.gov/ct2/show/study/NCT03088930)) aimed to investigate neoadjuvant crizotinib in patients with stage IA–IIIA *ALK*-rearranged NSCLC; however, only three patients were enrolled before the study was terminated for low accrual. The single-arm phase II SAKULA trial assessed the efficacy of neoadjuvant ceritinib for 12 weeks followed by surgery in patients with stage IIIA *ALK*-positive NSCLC.⁶⁵ Of the seven enrolled patients before study closure, only six completed treatment with neoadjuvant ceritinib and one withdrew because of dose-limiting toxicity. This study demonstrated an ORR of 100% and R0 resection was achieved in five patients. Of the seven patients, 57% achieved MPR and 28% achieved a pCR.⁶⁵

The ALNEO and NAUTIKA1 trials are currently ongoing to assess the efficacy of perioperative and neoadjuvant alectinib, respectively, in patients with resectable *ALK*-positive NSCLC.^{66,67} In the ALNEO trial, patients with potentially resectable stage III disease receive alectinib for 8 weeks, followed by resection and adjuvant alectinib for 96 weeks.⁶⁶ Interim analysis of 25 accrued patients reports that 21 (84%) patients underwent resection with R0 achieved in 18 patients (86%). Radiographically, objective responses were seen in 68% of patients, and pathologically, 39% achieved MPR and 17% achieved pCR.⁶⁸

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Several key questions remain regarding the optimal use of *ALK* TKIs in the perioperative setting. In neoadjuvant IO trials for NSCLC, primary end points have typically included pCR or EFS, but it is unclear whether these serve as appropriate surrogate markers for trials evaluating targeted therapies. The OS data from the ALINA trial remain immature, leaving uncertainty as to whether the observed DFS advantage will translate into a meaningful survival benefit. Additionally, the duration of perioperative TKI treatment remains an open question; although neoadjuvant TKI therapy has generally been limited to approximately 8 weeks and adjuvant alectinib was administered for 2 years in ALINA, these timeframes were largely chosen arbitrarily.

CONCLUSION

In summary, rapid and accurate molecular testing has become an essential tool to identify actionable oncogenic drivers to guide perioperative therapy for early-stage NSCLC (Fig 2). Although adjuvant osimertinib and alectinib are the new standard of care for resected early-stage *EGFR*- and *ALK*-positive NSCLCs, respectively, targeted therapies are being investigated currently in several clinical trials, with the intent of moving them into the perioperative space to replicate the successes seen with these agents in metastatic NSCLC. Additional studies are necessary to assess the utility of perioperative treatment approaches for NSCLC patients with other actionable alterations including *KRAS*, *MET*, *RET*, *ROS1*, *HER2*, *NTRK1/2/3*, and *BRAF* for which there are efficacious targeted therapies. Future studies will need to define ideal trial end points, optimal treatment durations, and the role of combinatorial strategies for these subgroups.

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REFERENCES

- Skoulidis F, Heymach JV: Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. *Nat Rev Cancer* 19:495-509, 2019
- Bruno R, Poma AM, Panozzi M, et al: Early-stage non-small cell lung cancer: Prevalence of actionable alterations in a monocentric consecutive cohort. *Cancers (Basel)* 16:1410, 2024
- Aggarwal C, Bubendorf L, Cooper WA, et al: Molecular testing in stage I-III non-small cell lung cancer: Approaches and challenges. *Lung Cancer* 162:42-53, 2021
- Gross CP, Meyer CS, Ogale S, et al: Associations between Medicaid insurance, biomarker testing, and outcomes in patients with advanced NSCLC. *J Natl Compr Canc Netw* 20:479-487.e2, 2022
- Pignon JP, Tribodet H, Scagliotti GV, et al: Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 26:3552-3559, 2008
- Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 350:2129-2139, 2004
- Paez JG, Jänne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science* 304:1497-1500, 2004
- Yue D, Xu S, Wang Q, et al: Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): A randomised, open-label, phase 2 trial. *Lancet Respir Med* 6:863-873, 2018
- Pennell NA, Neal JW, Chaff JE, et al: SELECT: A phase II trial of adjuvant erlotinib in patients with resected epidermal growth factor receptor-mutant non-small-cell lung cancer. *J Clin Oncol* 37:97-104, 2019
- Kelly K, Altorki NK, Eberhardt WE, et al: Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): A randomized, double-blind, phase III trial. *J Clin Oncol* 33:4007-4014, 2015
- Zhong WZ, Wang Q, Mao WM, et al: Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): A randomised, open-label, phase 3 study. *Lancet Oncol* 19:139-148, 2018
- Goss GD, O'Callaghan C, Lorimer I, et al: Gefitinib versus placebo in completely resected non-small-cell lung cancer: Results of the NCIC CTG BR19 study. *J Clin Oncol* 31:3320-3326, 2013
- Wu YL, Tsuboi M, He J, et al: Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 383:1711-1723, 2020
- FDA approves osimertinib as adjuvant therapy for non-small cell lung cancer with EGFR mutations, 2020; <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-osimertinib-adjuvant-therapy-non-small-cell-lung-cancer-egfr-mutations>
- Tsuboi M, Herbst RS, John T, et al: Overall survival with osimertinib in resected EGFR-mutated NSCLC. *N Engl J Med* 389:137-147, 2023
- Goss G, Tsai CM, Shepherd FA, et al: Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): A multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol* 17:1643-1652, 2016
- Mok TS, Wu YL, Ahn MJ, et al: Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* 376:629-640, 2017
- Tsutani Y, Goldman JW, Dacic S, et al: Adjuvant osimertinib vs. placebo in completely resected stage IA2-IA3 EGFR-mutated NSCLC: ADAURA2. *Clin Lung Cancer* 24:376-380, 2023
- Blakely CM, Urisman A, Gubens MA, et al: Neoadjuvant osimertinib for the treatment of stage I-IIIA epidermal growth factor receptor-mutated non-small cell lung cancer: A phase II multicenter study. *J Clin Oncol* 42:3105-3114, 2024
- Zhang Y, Fu F, Hu H, et al: Gefitinib as neoadjuvant therapy for resectable stage II-IIIA non-small cell lung cancer: A phase II study. *J Thorac Cardiovasc Surg* 161:434-442.e2, 2021
- Chang AEB, Piper-Vallillo AJ, Mak RH, et al: The ASCENT trial: A phase 2 study of induction and consolidation afatinib and chemoradiation with or without surgery in stage III EGFR-mutant NSCLC. *Oncologist* 29:609-618, 2024
- Bian D, Sun L, Hu J, et al: Neoadjuvant afatinib for stage III EGFR-mutant non-small cell lung cancer: A phase II study. *Nat Commun* 14:4655, 2023
- Tsuboi M, Weder W, Esciu C, et al: Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: NeoADAURA. *Future Oncol* 17:4045-4055, 2021
- Felip E, Altorki N, Zhou C, et al: Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (Impower010): A randomised, multicentre, open-label, phase 3 trial. *Lancet* 398:1344-1357, 2021
- O'Brien M, Paz-Ares L, Marreard S, et al: Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): An interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol* 23:1274-1286, 2022
- Forde PM, Spicer J, Lu S, et al: Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* 386:1973-1985, 2022
- Cascone T, Awad MM, Spicer JD, et al: Perioperative nivolumab in resectable lung cancer. *N Engl J Med* 390:1756-1769, 2024
- Heymach JV, Harpole D, Mitsudomi T, et al: Perioperative durvalumab for resectable non-small-cell lung cancer. *N Engl J Med* 389:1672-1684, 2023
- Wakelee H, Liberman M, Kato T, et al: Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med* 389:491-503, 2023
- Spicer JD, Garassino MC, Wakelee H, et al: Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 404:1240-1252, 2024
- Schoenfeld AJ, Arbour KC, Rizvi H, et al: Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. *Ann Oncol* 30:839-844, 2019
- Hondelink LM, Ernst SM, Atmodimedjo P, et al: Prevalence, clinical and molecular characteristics of early stage EGFR-mutated lung cancer in a real-life West-European cohort: Implications for adjuvant therapy. *Eur J Cancer* 181:53-61, 2023
- Terrenato I, Ercolani C, Di Benedetto A, et al: A real-world systematic analysis of driver mutations' prevalence in early- and advanced-stage NSCLC: Implications for targeted therapies in the adjuvant setting. *Cancers (Basel)* 14:2971, 2022
- Li H, Zhang Y, Xu Y, et al: Tumor immune microenvironment and immunotherapy efficacy in BRAF mutation non-small-cell lung cancer. *Cell Death Dis* 13:1064, 2022
- Mazieres J, Drilon A, Lusque A, et al: Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: Results from the IMMUNOTARGET registry. *Ann Oncol* 30:1321-1328, 2019
- Zhou N, Leung CH, William WN Jr, et al: Impact of select actionable genomic alterations on efficacy of neoadjuvant immunotherapy in resectable non-small cell lung cancer. *J Immunother Cancer* 12:e009677, 2024
- Cascone T, Kar G, Spicer JD, et al: Neoadjuvant durvalumab alone or combined with novel immuno-oncology agents in resectable lung cancer: The phase II NeoCOAST platform trial. *Cancer Discov* 13:2394-2411, 2023
- Cascone T, William WN Jr, Weissferdt A, et al: Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: The phase 2 randomized NEOSTAR trial. *Nat Med* 27:504-514, 2021
- Chaff JE, Oezkan F, Kris MG, et al: Neoadjuvant atezolizumab for resectable non-small cell lung cancer: An open-label, single-arm phase II trial. *Nat Med* 28:2155-2161, 2022
- Henick BS, Koch PD, Gainor JF, et al: Neoadjuvant atezolizumab + chemotherapy for resectable NSCLC: 3-year clinical update of phase II clinical trial results and translational findings. *J Immunother Cancer* 12:e009301, 2024
- Rosner S, Connor S, Sanber K, et al: Divergent clinical and immunologic outcomes based on STK11 co-mutation status in resectable KRAS-mutant lung cancers following neoadjuvant immune checkpoint blockade. *Clin Cancer Res* 31:339-351, 2025
- Skoulidis F, Araujo HA, Do MT, et al: CTLA4 blockade abrogates KEAP1/STK11-related resistance to PD-(L)1 inhibitors. *Nature* 635:462-471, 2024
- Reuss JE, Anagnostou V, Cottrell TR, et al: Neoadjuvant nivolumab plus ipilimumab in resectable non-small cell lung cancer. *J Immunother Cancer* 8:e001282, 2020
- Lee J, Toloza E, Pass HI, et al: P2.01-06 NAUTIKA1 study: Preliminary efficacy and safety data with neoadjuvant alectinib in patients with stage IB-III ALK+ NSCLC. *J Thorac Oncol* 18:S297-S298, 2023
- Lee J, Wistuba I, Ngiam C, et al: P03.04 phase II study of TKIs as neo(adjuvant) therapy in stage II-III resectable NSCLC with ALK, ROS1, NTRK or BRAFV600 alterations. *J Thorac Oncol* 16:S259-S260, 2020
- Spicer J, Blais N, Owen S, et al: A phase II study of neoadjuvant opnurasib KRAS G12C inhibitor in patients with surgically resectable non-small cell lung cancer (CCTG IND.242A): A substudy of the IND.242 platform master protocol. *Clin Lung Cancer* 26:146-151, 2025
- Canon J, Rex K, Saiki AY, et al: The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* 575:217-223, 2019
- Scott SC, Hu C, Smith KN, et al: EP02.04-007 phase 2 trial of neoadjuvant KRASG12C directed therapy with adagrasib (MRTX849) with or without nivolumab in resectable NSCLC (Neo-KAN). *J Thorac Oncol* 17:S235, 2022
- Zhou C, Solomon B, Loong HH, et al: First-line selpercatinib or chemotherapy and pembrolizumab in RET fusion-positive NSCLC. *N Engl J Med* 389:1839-1850, 2023
- Tsuboi M, Goldman JW, Wu YL, et al: LIBRETTO-432, a phase III study of adjuvant selpercatinib or placebo in stage IB-IIIA RET fusion-positive non-small-cell lung cancer. *Future Oncol* 18:3133-3141, 2022
- Drilon A, Oxnard GR, Tan DSW, et al: Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. *N Engl J Med* 383:813-824, 2020
- Allen TC, Xiao Y, Yang B, et al: Anaplastic lymphoma kinase rearrangement prevalence in patients with advanced non-small cell lung cancer in the United States: Retrospective real world data. *Oncotarget* 12:2308-2315, 2021

53. Cao H, Zhu W, Tang H, et al: Dissecting the clinicopathologic, genomic, and prognostic significance of anaplastic lymphoma kinase rearrangement in resected lung adenocarcinoma. *J Thorac Cardiovasc Surg* 169:1143-1152.e8, 2025
54. Friedlaender A, Perol M, Banna GL, et al: Oncogenic alterations in advanced NSCLC: A molecular super-highway. *Biomark Res* 12:24, 2024
55. Nana-Sinkam SP, Powell CA: Molecular biology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 143:e30S-e39S, 2013 (suppl 5)
56. Shaw AT, Yeap BY, Mino-Kenudson M, et al: Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 27:4247-4253, 2009
57. Blackhall FH, Peters S, Bubendorf L, et al: Prevalence and clinical outcomes for patients with ALK-positive resected stage I to III adenocarcinoma: Results from the European Thoracic Oncology Platform Lungscape Project. *J Clin Oncol* 32:2780-2787, 2014
58. Wang B, Song Y, Chen Z, et al: A retrospective study of postoperative targeted therapy in ALK-positive lung cancer. *Sci Rep* 13:8317, 2023
59. Sands J, Mandrekar S, Oxnard G, et al: ALCHEMIST: Adjuvant targeted therapy or immunotherapy for high-risk resected NSCLC. *J Clin Oncol* 38, 2020 (suppl 15; abstr TPS9077)
60. Wu YL, Dziadziuszko R, Ahn JS, et al: Alectinib in resected ALK-positive non-small-cell lung cancer. *N Engl J Med* 390:1265-1276, 2024
61. Tsuboi M, Goldman JW, Wu Y-L, et al: LIBRETTO-432, a phase III study of adjuvant selpercatinib or placebo in stage IB-IIIA RET fusion-positive non-small-cell lung cancer. *Future Oncol* 18:3133-3141, 2022
62. Chang ZH, Zhu TF, Ou W, et al: A real-world retrospective study to assess efficacy and safety of alectinib as adjuvant therapy in IB-IIIB NSCLC patients harboring ALK rearrangement. *Front Oncol* 14:1422035, 2024
63. Jahanzeb M, Lin HM, Pan X, et al: Immunotherapy treatment patterns and outcomes among ALK-positive patients with non-small-cell lung cancer. *Clin Lung Cancer* 22:49-57, 2021
64. Zhang C, Li SL, Nie Q, et al: Neoadjuvant crizotinib in resectable locally advanced non-small cell lung cancer with ALK rearrangement. *J Thorac Oncol* 14:726-731, 2019
65. Zenke Y, Yoh K, Sakakibara-Konishi J, et al: P1.18-04 neoadjuvant ceritinib for locally advanced non-small cell lung cancer with ALK rearrangement: SAKULA trial. *J Thorac Oncol* 14:S626-S627, 2019
66. Leonetti A, Minari R, Boni L, et al: Phase II, open-label, single-arm, multicenter study to assess the activity and safety of alectinib as neoadjuvant treatment in surgically resectable stage III ALK-positive NSCLC: ALNEO trial. *Clin Lung Cancer* 22:473-477, 2021
67. Cortinovis DL, Leonetti A, Morabito A, et al: Alectinib in early-stage anaplastic lymphoma kinase-positive non-small cell lung cancer: Current evidence and future challenges. *Cancers (Basel)* 16:2610, 2024
68. Leonetti A, Boni L, Gnetti L, et al: MA01.03 neoadjuvant alectinib in potentially resectable stage III ALK-positive NSCLC: Interim analysis of ALNEO-GOIRC-01-2020 phase II trial. *J Thorac Oncol* 19:S52, 2024

Leveling Up: Harnessing Cutting-Edge Technology to Enhance Oncology Education and Learning

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OVERVIEW

The integration and utilization of digital media, gamified learning strategies, and artificial intelligence (AI) are fundamentally transforming the landscape of oncology education and learning. These technologies collectively enhance knowledge dissemination, facilitate professional networking and mentoring, and enrich the overall educational experience for the learner. Digital formats, including social media, offer flexible and asynchronous learning modalities that provide access to the latest studies and research, expert commentary, and opportunities for professional development and collaboration. Gamification, through the application of game-based elements within educational frameworks, promotes critical thinking, supports the acquisition and reinforcement of key concepts, and fosters engagement. AI, increasingly recognized for its disruptive potential, introduces a new dimension of information exchange and novel methodologies for learner assessment and customization of educational pathways. These tools also can present potential challenges, such as the proliferation of misinformation, heightened academic and professional competition, and the imperative to critically appraise AI-generated outputs. This article examines the transformative role of these emerging technologies in oncology education, while also addressing the associated risks and underscoring the need for learners to cultivate evaluative and critical thinking skills to navigate these tools responsibly.

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INTRODUCTION

Traditional learning environments are being complemented by digital formats such as podcasts and social media, offering flexibility for learning, research updates, expert insights, and opportunities for professional growth. Gamification, the use of game-like design elements, offers a dynamic and engaging learning environment that has the potential to enhance critical thinking, skill mastery, and personal learning. Artificial intelligence (AI), often viewed as a disruptor of medical education, introduces a new dimension of information exchange and personalized learning. However, these tools also come with potential challenges, such as misinformation, competition, and need for critical evaluation of AI outputs. This article will provide an overview of digital media, gamified learning, and AI in medical education, highlighting their benefits and addressing the challenges they may present.

BEYOND THE TEXTBOOK: MEDICAL LEARNING IN THE AGE OF DIGITAL MEDIA

Digital and social media have reshaped medical education and have transformed how knowledge is shared and professional connections are made. Although digital media is not a replacement for traditional learning environments, it acts as a complement, resulting in a blended learning strategy.¹ Traditional learning focuses on modalities such as in-person

lectures, grand rounds, and meeting presentations. Such content is typically expert led and, in medical education programs, curriculum driven. This is considered synchronous learning, which is done in real time, creating active dialog and conversation between learners and experts. By contrast, digital formats such as podcasts, social media, and streaming videos are asynchronous, allowing for self-directed learning at any time. A hybrid approach that combines a structured, expert-driven curriculum with flexible, digital content can provide the most benefit for today's learner. This is especially valuable in oncology where immediate access to clinical guidelines, research updates, and expert insights can enhance training and patient care and promote lifelong learning.²

On-Demand Learning and Resources

Digital media can be used both for medical education and professional development for both trainees and faculty. It is most commonly used for on-demand learning where the learner controls what content they access and engage with, building on the foundational knowledge they have received in the traditional classroom setting. Medical professionals can access an extensive range of resources, including online courses, medical journals, mobile applications, and virtual conferences and workshops. Online platforms such as PubMed, Medscape, and specialized medical forums provide a wealth of up-to-date, evidence-based content that

PRACTICAL APPLICATIONS

- Digital media platforms, including social media, allow trainees and faculty to access an extensive range of resources, including online courses and multimedia content, which accommodate diverse learning preferences and promote knowledge sharing professional networking and collaboration.
- Gamified learning, such as escape rooms and online games, incorporates game-based design elements into learning activities, transforming learning into an interactive and engaging experience while enhancing motivation, critical thinking, and skill mastery.
- Artificial intelligence (AI) can guide a more personalized learning approach but requires that both trainees and medical professionals develop the skills to critically assess AI outputs and focus on AI literacy to leverage this tool in safe and effective ways to improve learning and patient care.

complements and enhances traditional learning. Several of these online resources, such as UpToDate, National Comprehensive Cancer Network, Epocrates, and Medscape, also have interactive mobile applications, which can be easily referenced within minutes and can aid in immediate clinical decision making. These resources expand the scope of medical education to trainees and continuing education for attending physicians. Trainees can tailor their learning experience to suit their preferences, whether through podcasts, video lectures, or interactive discussions.

Digital media also enriches learning environments through interactive platforms and multimedia content, accommodating diverse learning preferences (Table 1). All four learning styles (auditory, visual, verbal (reading/writing), and kinesthetic) can be enriched through digital media.³ Instructional videos and tutorials can reinforce evidence-based learning, while advances in virtual reality and digital simulation, such as virtual anatomy laboratories and surgical simulations, can offer a safe and controlled environment for practicing clinical procedures. This creates a dynamic and immersive learning experience that simulates real-life medical scenarios, strengthening both practical and theoretical skills. Podcasts further support flexible learning through an auditory learning experience, providing a convenient way for medical professionals to stay up to date on research and clinical updates.

Social Media for Medical Education, Professional Growth, and Community

Social media platforms such as X (formerly Twitter), Blue-sky, LinkedIn, Instagram, TikTok, and Facebook have

become tools for knowledge sharing, professional networking, and collaboration. Medical professionals can participate in online discussions and forums, share medical information and resources, stay informed on new research and advancements in the field, and collaborate with peers globally. Platforms such as X and BlueSky allow for live commentary during medical conferences, fostering global idea exchange and expanding the reach of professional dialog, and are especially valuable for those attending virtually or not attending at all. Social media facilitates mentorship opportunities, networking, and professional growth for both trainees and faculty with attending physicians and experts providing guidance and insights to trainees and early-career professionals. Interactions are not limited to one institution, which further fosters collaborative opportunities, broadening exposure to perspectives and career pathways.⁴⁻⁶ Individuals share experiences, interview tips, job opportunities, and advocacy. Virtual journal clubs, expert-led educational threads (*tweetorials*), crowdsourcing for challenging cases to help with diagnostic and management insights and infographics, and visual abstracts for research studies are only some of the ways that social media can be used for education. As previously mentioned, individuals can choose the format they are most comfortable with, such as video, audio, or text. Maintaining a professional presence on social media can enhance visibility within the oncology community, potentially leading to research collaborations, conference invitations, and academic opportunities.⁴⁻⁶

In addition to professional networking and development, social media serves as a platform for patient education and engagement. Oncology professionals can contribute to public health initiatives by sharing accurate, evidence-based medical information to counter misinformation and promote health literacy.⁷ Platforms such as Instagram, TikTok, and Facebook allow for the dissemination of complex medical concepts in an accessible and engaging manner. By observing experienced clinicians' communication strategies on these platforms, trainees can refine their ability to educate and engage with patients effectively. Furthermore, digital media provides a space to advocate for patient-centered care, advocate for access, and foster a dialog on survivorship and treatment-related concerns.⁴⁻⁶

Another way digital media affects medical education is through community and relationship building. Traditional relationships are often vertical, through models such as attending-trainee and teacher-student. These relationships are vital in the medical community but have some limitations that extend beyond geographical proximity. It is established that shared identity mentorship, among a group of people who belong to a common social group, can be beneficial, reduce imposter syndrome, and increase the sense of belonging, especially for individuals from communities that have traditionally been underrepresented in medicine. Digital media can allow someone to break through these barriers allowing for broader and more inclusive interactions and mentorship. Social media platforms can allow for a

bidirectional flow of ideas, focusing not just on content that is valued by the teacher but also what is valued by the learner. This lends itself to more horizontal relationships that have the potential to be more diverse and inclusive of both people and ideas.⁸ Physicians can engage with colleagues from different cities and countries. Positive online interactions often lead to lasting professional connections and open doors to new research and clinical opportunities.⁹ Notably, a small survey of oncology trainees and oncologists demonstrated that many did experience imposter syndrome while interacting online in a professional setting. While 62% noted positive mental health impacts from social media, 41% also experienced anxiety, loneliness, or depression.¹⁰ While active engagement online creates new avenues for mentoring, can help build a professional reputation, and can help grow as a digital opinion leader for some people, it is important to recognize and address the challenges that many people can encounter when interacting online.

Challenges of Digital Engagement

Digital media is not without its pitfalls, the greatest of which is misinformation. Misinformation is defined as information that is false, inaccurate, or misleading according to the best currently available evidence. Misinformation propagates online because of the lack of verification of credentials for social media accounts, algorithms that focus less on the quality of the content and more on engagement with the content, and fake news that often has some basis in reality and is presented as scientifically believable. Echo chambers are present online where users interact predominantly with others who share their views and beliefs. This can lead to confirmation bias, which refers to seeking information that supports a person's own hypothesis while avoiding differing information. Online health misinformation in oncology is prevalent and puts the burden of evaluating it on the user, which can be difficult, especially in the setting of limited health literacy. Health professionals can play a role in combating oncology misinformation online through sharing evidence-based information, calling out misinformation, and partnering with trusted social media creators and patient advocates to promote accurate data and sources.⁷

As digital platforms evolve, their role in shaping medical training will become increasingly prominent. To maximize these benefits, trainees must engage thoughtfully and professionally, adhere to institutional guidelines, and ensure that their online presence aligns with the highest academic integrity and medical ethics standards. Transparency and authenticity are critical. It is critical to disclose any conflicts of interest, maintain patient privacy and confidentiality at all costs, avoid providing medical advice as online engagement does not constitute a doctor-patient relationship, and remember that anything posted online should be considered permanent.¹¹ It is important to be aware and address potential imposter syndrome that may create barriers for online engagement. Through increased accessibility, flexibility, and engagement, strategic use of digital media can transform

medical education, enhance collaboration, improve patient care and prepare the next generation of medical professionals for a rapidly evolving health care landscape.

PLAY TO LEARN: GAMIFYING MEDICAL EDUCATION

Gamification is the application of game-like design elements in a nongaming field of work, including medical education and health care training that can create an interactive and dynamic learning environment. Gamification typically refers to the integration of game-like elements, such as scoring systems, leaderboards, challenges, and rewards, into nongame contexts to enhance motivation and engagement.¹²⁻¹⁴ Gamification differs from game-based learning or serious games, which use games as the primary instructional tool for non-entertainment purposes.¹²⁻¹⁴ Gamification and serious games have emerged as potential strategies and innovative tools to enhance engagement, build critical thinking, and improve learning outcomes.^{12,13,15} While there is hope that gamifying learning may reduce learner anxiety, this is complex and may vary depending on factors, such as the design of the gamified elements and learner preferences and styles.¹⁶

Educational Theories Inherent to Gamification/Serious Games

The effects of gamification/serious games on learning and behavior are based on established educational and psychology theories, including, but not exclusive to, experiential learning theory (learning experiences serve as an opportunity for reflection and improvement in behaviors), self-directed learning (learners can determine their own learning needs and autonomy promotes motivation), deliberate practice theory (learners are motivated through clear goals and immediate feedback), social comparison theory (leaderboards help learners have accurate self-evaluations compared with peers), reinforcement learning theory (learner behaviors can be influenced by rewards and punishments), and mastery learning theory (learners successfully learn a topic before advancing to a more complex one, with guidance provided as needed).¹³ Clear and relevant goals help learners stay motivated by illustrating learning objectives.¹² Immediate feedback allows learners to understand their progress and correct mistakes in real time, enhancing clinical reasoning.¹² Positive reinforcement, through leaderboards and achievement badges, encourages continuous engagement.¹⁷ Levels provide structured progression, directing learners through increasingly complex clinical scenarios, emphasizing structured knowledge acquisition. Simplified user experiences ensure that games enhance comprehension without overwhelming learners.¹⁷ Gamification may enhance personalized learning by allowing learners to set individual goals and engage with adaptive content that adjusts to their proficiency, and collaborative activities may encourage motivation, knowledge sharing, and teamwork.¹⁸ In hematology and oncology education, where trainees must navigate rapidly evolving knowledge and complex clinical decisions, gamification may provide an interactive learning approach.

Practical Applications in Medical Education

As gamification of education continues to rise in popularity, the tools and platforms that allow for gamification will continue to evolve and expand (Table 1). One of the prominent and more popular types of gamification systems currently is student response systems (SRSs). The SRS model is a way for teachers to provide a unique way for their learners to interact with educational content that rewards student engagement through gamified methodologies.¹⁹ For example, Kahoot! is an easily accessible platform that has been a successful game-based SRS. This is a tool that transforms learning into a game show where the teacher essentially becomes a game show host and the learners become competitors. It is presented in a quiz format, where learners go through rounds, answering the questions as fast as they can in real time. When combined with bright and colorful graphics, fun audio, scoreboards, and leaderboards, it becomes relatively easy to keep people engaged and motivated to learn.²⁰ Other platforms that are similar to Kahoot! are Quizizz and Gimkit, with each of them putting their own twist on the gamification of education, such as allowing learners to earn in-game currency from answering quizzes and then investing them in quirks and upgrades that keep gaming fresh and rewarding after every round.²¹ Kahoot! was demonstrated to increase final examinations in those learning radiation oncology, perhaps related to the provision of immediate feedback serving as a formative assessment tool for the learners.²²

Another example of gamifying learning is the use of escape rooms, which can be a tool for team building, research, and learning by providing educational opportunities that focus on collaborative and flexible learning.²³ Escape rooms can be delivered in multiple formats, from virtual to physical. Learners complete tasks such as solving puzzles or coded messages, to achieve the learning objectives and successfully escape the room.²⁴ Escape rooms as active learning tools have been reported to improve performance, confidence, interest, and enjoyment and are effective in teaching

complex medical topics and skills.²⁴ Escape rooms may serve as an effective alternative or complement to conventional didactic methods, reinforcing engagement and knowledge retention through immersive and interactive experiences.²⁵ An example of a virtual escape room can be found in this gastroenterology board review that focuses on educational objectives such as identifying causes of gastrointestinal bleeding, diagnosing gastrointestinal diseases from a clinical description, and evaluating hepatitis B titers.²⁶ In the oncology literature, a study of nursing students enrolled in an oncology nursing course found increased motivation, satisfaction, and confidence after playing an oncologic emergencies escape room.²⁷

Another example of gamifying learning is serious games. Serious games can be delivered in person or online with examples including board games, screen-based games, or mobile applications. Serious games are interactive, immersive, and fun and include challenges, rules, assessment, learner control, and some kind of story.²⁸ Learners receive feedback and advance through levels with increasing complexity to master skills and concepts. Serious games have been shown to improve knowledge, skills, and satisfaction across specialties and learner levels.¹⁷ Several serious games have been developed for hematology and oncology learners. An open-access blood typing game, developed by NobelPrize.org,²⁹ teaches learners about blood types and transfusions.³⁰ Other hematology games have shown increased learning motivation and knowledge gains in medical, nursing, and pharmacy students.^{31,32}

Gamification and serious games in oncology training and medical education incorporates new ways of learning to foster an active and engaging learning environment. Well-designed games can activate pleasure centers in the brain to keep learners challenged and engaged.³³ Gamification may have potential to improve well-being, by adding an element of play into learning, and allow learners to better tolerate failure through the flexible and incremental learning opportunities that create a sense of achievement and

TABLE 1. Practical Applications of Digital Media, Gamified Learning, and AI in Oncology Training and Practice

Learning Method	Description	Practical Applications	Advantages	Challenges
Traditional learning	In-person lectures, grand rounds, meeting presentations	Lectures, seminars	Real-time interaction, structured curriculum	Limited flexibility, one-size-fits-all approach, geographical constraints, passive learning
Digital media	Podcasts, social media, streaming videos	Social media journal clubs, podcasts, YouTube videos	Flexibility, on-demand learning, global collaboration	Misinformation, echo chambers, variable quality of content, privacy concerns
Gamification	Game-like design elements in learning	Kahoot!, escape rooms, serious games	Enhances engagement, critical thinking, and skill mastery	Competitive nature, cost, design complexity
AI	AI-driven tools and personalized learning	AI-based tutoring systems, real-time performance analysis	Revolutionizes information exchange, assessments, and personalized learning	Misinformation, ethical concerns, need for critical evaluation skills to assess AI outputs

Abbreviation: AI, artificial intelligence.

accomplishment.^{34,35} It is important to exercise caution that the competitive nature of gamification does not lead to discouragement and adverse effects for the learner.¹⁶ As gamification and serious games in the medical field continue to evolve, more implementations and studies in health care training are required to confirm its overall long-term benefits and impact on improving medical outcomes and well-being for trainees.

LEARNING WITH INTELLIGENCE: THE IMPACT OF AI ON MEDICAL EDUCATION

The introduction and effective integration of AI into education hold great promise of revolutionizing the information exchange combined with advances in assessments and analytics around learning, understanding, and competencies. As with many other roles, there is potential for AI to reduce educators' administrative burdens (eg, marking assignments and tests, documenting, reporting, scheduling) and to augment their abilities to connect with learners and trainees with the emphasis on human-centric education. Leveraging AI, it may be possible to generate real-time analysis of student performance to adapt and personalize the teaching approach, methods, and tools to best suit the learner. This supports extensive research that individual tutoring can significantly boost learning and addresses the limited resources we have available to provide this personalized approach for each learner. Even as digital media and gamification activities for education are being developed, the emergence of generative AI has introduced the potential to rapidly generate content to accelerate the development of such educational tools.³⁶

As AI can be used in a multitude of ways to support education (Table 1), Holmes et al suggested a typology of three categories of AI applications: (1) student-focused, (2) teacher-focused, and (3) institution-focused.³⁷ Student-focused AI applications include, but are not limited to, intelligent tutoring systems, AI-assisted educational applications, AI-assisted gamification simulations, AI to support learners with disabilities, and exploratory learning environments. Teacher-focused AI and institution-focused AI include plagiarism detection, AI teaching assistants, assistance with admissions, and e-proctoring. For medical education specifically, the history of cognitive apprenticeship has been challenged with the introduction of AI and determining the way to most effectively integrate this technology to augment the education and performance of clinicians is an ongoing journey.³⁸

AI's Influence on Medical Learning and Evaluation

Amidst this great promise and potential, AI has introduced a dramatic disruption in education as students have started to use AI in their learning, including their assignments. While there has been resistance and raised concerns by educators over the use of AI, some have approached this disruption constructively as a motivator to evaluate the educational system and methodology. For example, rather than giving

learners an assignment to generically summarize information that can be gathered from resources, developing an assignment that challenges learners to critically tackle a specific question that would require them to leverage their overall understanding of the course material would promote learning, even if they were to use AI as a supportive tool. Beyond revisiting the nature of assignments, AI had revealed limitations in how we test and evaluate knowledge. Demonstration that large language models can perform as well as physicians on multiple-choice licensing examinations has raised questions about whether AI could replace physicians. However, this may more appropriately raise the question of whether such multiple-choice examinations are evaluating the appropriate expertise and skills needed to provide safe, effective, and high-quality clinical care of patients.

As AI is influencing the approaches educators are taking to deliver and evaluate learning and knowledge, learners and trainees are also adapting how they approach their courses and training. While some are motivated to learn the content to gain deeper understanding, many may have greater motivation to just pass the tests and do well on assignments. So the question arises, how do we ensure fundamental and foundational knowledge and understanding is gained while leveraging the tools of convenience introduced by AI so that people are equipped to critically think and evaluate AI outputs when out in medical practice? Additionally, while AI policies are emerging, the importance of including the role of AI in education in these policies is being called out to ensure the public good.³⁹

AI Educational Needs for Medical Professionals

Beyond the influence AI is having on medical education, there is a pressing need to bring AI literacy to medical professionals to equip the current and future workforce to leverage this powerful tool in safe and effective ways to benefit the care of our patients. A framework for AI literacy has been proposed with four levels (Fig 1) that build upon each other while maintaining the flexibility of the breadth of content that is learned before moving to the next level, appreciating the expansive nature of each level.^{40,41}

Upskilling the Current Workforce

Recognizing that AI is being integrated into many existing devices, products, and platforms within the clinical workflow, there is a recognized need and sense of urgency to upskill the current workforce to ensure safe use of this technology as well as generating the maximal benefit from the technology. For most, the two foundational aspects, understanding AI and being able to use and apply AI, will be relevant to their roles and day-to-day activities. Understanding AI will include the general knowledge about AI, machine learning, generative AI, and large language models starting with the definition, strengths and limitations, and benefits and risks of each of these. Using and applying AI will include the ability to use the outputs of AI models for

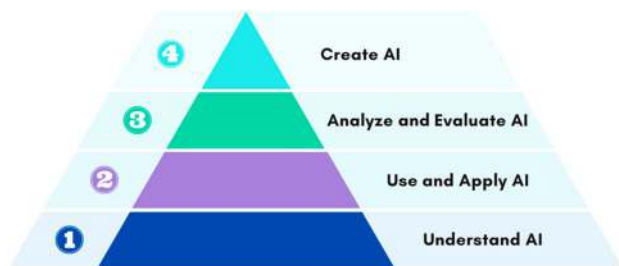


FIG 1. Proposed framework for AI literacy.⁴⁰ AI, artificial intelligence.

decisions in the workflow, serving as an informed human in the loop when needed and successfully interacting with generative AI to complete tasks while being able to discern hallucinations and inaccurate responses. These competencies are not small feats and a large gap remains for the necessary training of the current workforce to ensure safe and effective implementation of AI in health care. Building on these skills, the next tiers in the AI literacy framework are analyzing, evaluating, and creating AI which prompts even deeper engagement and a critical evaluation of AI technologies (ie, design, performance, potential biases, and limitations of AI tools). This will require an understanding of how the AI tools align with principles of accountability, transparency, fairness, ethics, and safety. At the highest level, it involves equipping learners to participate in or lead the development of AI-driven tools, as discussed below.

Training to Enable the Next Generation to Realize the Full Potential of AI

The struggle to realize impact from the rapidly evolving technology has only grown greater in recent years as the pace of new technology is seemingly increasing. Within medicine, the multidisciplinary team has been described as the team made up of clinicians from across different disciplines in medicine and interdisciplinary teams to encompass supportive care teams; however, to effectively leverage technology, this interdisciplinary team needs to be expanded. As the transition to multidisciplinary and interdisciplinary coordination required efforts to effectively communicate and ensure common understanding, this expansion of the interdisciplinary team will introduce new challenges and opportunities.⁴² By training the next generation to be able to effectively work across these cross-disciplinary and interdisciplinary teams, the ability to build AI tools with clearly defined, shared end goals will result in greater success in translation, implementation, and generation of value. This means educating future clinicians enough about the

technology for them to understand and effectively contribute to the development of future tools and even identifying the key opportunities with such technology could be useful. It also means training data scientists, software engineers, and machine learning engineers and perhaps process engineers with enough exposure to the evolving medical practices, along with exposure to the data lifecycle, so that they have an appreciation of how the AI tools could be leveraged to benefit patient care. While there are emerging certificate programs and some postgraduate training opportunities, introducing this paradigm as a part of medical education and ensuring that AI is introduced in a way that ensures core knowledge, compassion, and effective communication will be key to enabling AI augmented care in medicine.⁴³ In oncology, there is growing interest in AI tools such as scribes in patient care, diagnostic aids, prognostic models, chatbots, generative AI, and treatment recommendations. While these tools have the potential to improve clinical workflows, reduce administrative burden, and improve patient care, they require significant oversight to ensure accuracy, representation, and privacy. The balance between technological advancement and innovation with accountability and ethical stewardship is a difficult but necessary one to advance AI forward.

CONCLUSION AND FUTURE DIRECTIONS

Digital media, gamified learning, and AI have emerged as transformative tools and hold immense promise. They have and continue to reshape how knowledge is disseminated, professional connections are forged, and learning experiences are enriched. They have the opportunity to complement traditional learning environments, promote collaboration, enhance critical thinking and skill mastery, and personalize learning experiences (Table 1). It is crucial to address the challenges they present, such as misinformation, overreliance on technology, and privacy and safety risks. Online engagement and utilization of AI requires adherence to academic integrity and medical ethics standards. By fostering a culture of continuous learning and adaptability, we can ensure that these technologies are used effectively and ethically. Future research and development should focus on refining these tools, exploring their long-term impact on medical education and patient care, and developing strategies to maximize their benefits while mitigating potential risks. There is a critical need to continue to use and expand these tools in oncology education as embracing and strategically leveraging these innovations will prepare the next generation of medical professionals to navigate these evolving tools responsibly in a rapidly evolving health care landscape.

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REFERENCES

- Ruiz JG, Mintzer MJ, Leipzig RM: The impact of E-learning in medical education. *Acad Med* 81:207-212, 2006
- Ayers JW, Goodman AM, Smith DM: #MedEd: Medical education and knowledge translation on social media. *JAMA* 330:909-910, 2023
- Siddiqui NA, Khan RN, Aziz A: The evolving role of digital media in medical education. *J Pak Med Assoc* 72:958-960, 2022
- Markham MJ, Gentile D, Graham DL: Social media for networking, professional development, and patient engagement. *Am Soc Clin Oncol Educ Book* 37:782-787, 2017
- Adilman R, Rajmohan Y, Brooks E, et al: Social media use among physicians and trainees: Results of a National Medical Oncology Physician Survey. *JCO Oncol Pract* 12:79-80, 2016. e52-60
- Dizon DS, Graham D, Thompson MA, et al: Practical guidance: The use of social media in oncology practice. *JCO Oncol Pract* 8:e114-e124, 2012
- Teplinsky E, Ponce SB, Drake EK, et al: Online medical misinformation in cancer: Distinguishing fact from fiction. *JCO Oncol Pract* 18:584-589, 2022
- Das TM, Kaur G, Nematollahi S, et al: Medical education in the digital era: A new paradigm for acquiring knowledge and building communities. *JACC Adv* 1:100031, 2022
- Daneshjoui R, Adamson AS: Twitter journal clubs: Medical education in the era of social media. *JAMA Dermatol* 156:729-730, 2020
- Teplinsky E, Ponce SB, Dizon DS, et al (eds): *Characterizing Imposter Syndrome Among Oncologists on Social Media*. Chicago, IL, American Society of Clinical Oncology, 2023
- Ponce SB, M Barry M, S Dizon D, et al: Netiquette for social media engagement for oncology professionals. *Future Oncol* 18:1133-1141, 2022
- Krath J, Schurmann L, von Korfflesch HFO: Revealing the theoretical basis of gamification: A systematic review and analysis of theory in research on gamification, serious games and game-based learning. *Comput Hum Behav* 125:106963, 2021
- van Gaalen AEJ, Brouwer J, Schönrock-Adema J, et al: Gamification of health professions education: A systematic review. *Adv Health Sci Educ Theor Pract* 26:683-711, 2021
- Gentry SV, Gauthier A, L'Estrade Ehrstrom B, et al: Serious gaming and gamification education in health professions: Systematic review. *J Med Internet Res* 21:e12994, 2019
- Wolbrink TA, van Schaik SM, Turner DA, et al: Online learning and residents' acquisition of mechanical ventilation knowledge: Sequencing matters. *Crit Care Med* 48:e1-e8, 2020
- Kirsch J, Spreckelsen C: Caution with competitive gamification in medical education: Unexpected results of a randomised cross-over study. *BMC Med Educ* 23:259, 2023
- Bigdeli S, Hosseinzadeh Z, Dehnad A, et al: Underpinning learning theories of medical educational games: A scoping review. *Med J Islam Repub Iran* 37:26, 2023
- Scales CD Jr., Moin T, Fink A, et al: A randomized, controlled trial of team-based competition to increase learner participation in quality-improvement education. *Int J Qual Health Care* 28:227-232, 2016
- Barker SGL, Gribble LC: Exploring student response systems for large group teaching: A tale of engagement at scale. *J Work Appl Manag* 16:316-328, 2024
- Wang AI: The wear out effect of a game based student response system. *Comput Educ* 82:217-227, 2015
- Ayşar G, Ozan C, Aydın E: The effect of reinforcement using the Gimkit game on learning the subject in nursing students. *Nurse Educ Pract* 68:103595, 2023
- Zapata-Martinez I, Rius-Diaz F, Lorenzo-Alvarez R, et al: Radiation oncology active learning in undergraduate medical education: The usefulness of Kahoot and TikTok. *J Cancer Educ* 10.1007/s13187-025-02583-5 [epub ahead of print on February 19, 2025]
- Guckian J, Eveson L, May H: The great escape? The rise of the escape room in medical education. *Future Healthc J* 7:112-115, 2020
- Nowbuth AA, Parmar VS: Escaping the ordinary: A review of escape rooms in medical and veterinary education. *BMC Med Educ* 24:1506, 2024
- Grupel D, Wennstroem E, Moran-Gilad J: Escape room-the next generation of problem-based learning? *Clin Microbiol Infect* 28:768-770, 2022
- Gillespie M: Escape the EM boards: Interactive virtual escape room for GI board review. *J Educ Teach Emerg Med* 6:SG8-SG45, 2021
- Dönmez AA, Çalik A, Terzi K, et al: Designing and evaluating ONCOlogic EMergencies escape room game for undergraduate nursing students: The ONCEM quasi-experimental pilot study. *Educ Inf Tech* 30:1849-1872, 2025
- Gorbanev I, Agudelo-Londoño S, González RA, et al: A systematic review of serious games in medical education: Quality of evidence and pedagogical strategy. *Med Educ Online* 23:1438718, 2018
- The Nobel Prize: Nobelprize.org. <http://nobelprize.org/>
- Nobelprize.org: The Blood Typing Game, 2024. <https://educationalgames.nobelprize.org/educational/medicine/bloodtypinggame/>
- Perrin J, Mees A, Broseus J, et al: A serious game about hematology for health care workers (SUPER HEMO): Development and validation study. *JMIR Serious Games* 11:e40350, 2023
- Bianchi I, Stefani CJM, Santiago P, et al: AnemiaAR: A serious game to support teaching of haematology. *J Vis Commun Med* 45:134-153, 2022
- Kok DL, Dushyanthen S, Peters G, et al: Virtual reality and augmented reality in radiation oncology education—A review and expert commentary. *Tech Innov Patient Support Radiat Oncol* 24:25-31, 2022
- Cheng C, Ebrahimi OV: Gamification: A novel approach to mental health promotion. *Curr Psychiatry Rep* 25:577-586, 2023
- Yunyongying P: Gamification: Implications for curricular design. *J Grad Med Educ* 6:410-412, 2014
- Milberg T: The future of learning: How AI is revolutionizing education 4.0 World Economic Forum. 2024. <https://www.weforum.org/stories/2024/04/future-learning-ai-revolutionizing-education-4-0/>
- Holmes W, Holmes M, Fadel C: *Artificial Intelligence in Education: Promises and Implications for Teaching and Learning*. Boston, MA, Center for Curriculum Redesign, 2019
- Cooper A, Rodman A: AI and medical education—A 21st-century Pandora's Box. *N Engl J Med* 389:385-387, 2023
- Schiff D: Education for AI, not AI for education: The role of education and ethics in national AI policy strategies. *Int J Artif Intell Educ* 32:527-563, 2022
- Ng DTK, Leung JKL, Chu SKW, et al: Conceptualizing AI literacy: An exploratory review. *Comput Educ Artif Intell* 2:100041, 2021
- Bloom BS, Engelhart MD, Furst EJ: Taxonomy of educational objectives: The classification of educational goals, in *Handbook 1: Cognitive Domain*. New York, NY, David McKay Company, 1956, pp 10-43. <https://eclass.uoa.gr/modules/document/file.php/PPP242/Benjamin%20S.%20Bloom%20-%20Taxonomy%20of%20Educational%20Objectives%2C%20Handbook%201-%20Cognitive%20Domain-Addison%20Wesley%20Publishing%20Company%20%281956%29.pdf>
- Knopp MI, Warm EJ, Weber D, et al: AI-enabled medical education: Threads of change, promising futures, and risky realities across four potential future worlds. *JMIR Med Educ* 9:e50373, 2023
- Succi MD, Chang BS, Rao AS: Building the AI-enabled medical school of the future. *JAMA* 10.1001/jama.2025.2789 [epub ahead of print on March 31, 2025]

The Art of Oncology Education and Knowledge Sharing—It is All About the “How”

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OVERVIEW

In the rapidly evolving field of oncology, education and knowledge sharing have become essential aspects of oncology practice and must-needed tools to help patients conquer cancer. Oncology education is an art that needs to be mastered by applying scientific learning methods through structured frameworks into it, in order to have an impact. To effectively educate and share knowledge with oncology professionals, we propose following a “chain of education”. This chain consists of five links that are essential for creating a successful educational activity: “who”, “why”, “where”, “what”, and “how”. By following the “chain of education” through all links leading to the final key of how to educate, and guided by learning science principles, educators can optimize and enhance their teaching and knowledge-sharing skills and educate learners with more impact. Two common scenarios of medical education in oncology are the education of trainees and the education of community oncologists. In this article, we review them through the prism of the “chain of education”. We discuss how using effective learning science principles can guide small changes that lead to significant impacts in trainees’ education and can also leverage social media platforms in the education of community oncologists. Alongside this described framework, we briefly review some available oncology education resources, and we discuss incorporating the “chain of education” into future technologies.

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ESTABLISHING A “CHAIN OF EDUCATION” IN ONCOLOGY EDUCATION

Oncology is a rapidly evolving field. The speed and magnitude of scientific and technologic research advancements have established the foundations for an era of hope for patients with cancer, caregivers, and medical professionals. This is exemplified by the amount of oncology data published in journals or presented at major conferences and the amazingly large, yet daunting, number of new indications and approvals for cancer drugs over the past 5 years.¹ Having said that, these advancements are only relevant if those involved in patient care are educated about them. To maintain competency, oncology professionals need to know not only the fundamentals of cancer science, diagnosis, and management but also learn about new drug approvals, positive or negative results of major clinical trials, and comparison between therapies, among many other new relevant oncology information.² There is no more meaningful tagline that emphasizes the importance of oncology education than the great tagline of ASCO: “Knowledge Conquers Cancer”.³

For oncology education to have an impact and achieve its goals, there needs to be a significant focus on the know-how

of education. Any oncology knowledge-sharing activity, whether done in a traditional classroom, in-person conference environment, or through other tools such as social media and virtual settings, needs to follow scientific methods to be effective.

Adequately employing medical education science in oncology may seem difficult at first, but the deliberate use of learning science principles can streamline and enhance this process.^{4,5} Following these tools, oncology education can be appropriately and effectively applied to different learners (eg, oncology trainees and graduated oncologists), different environments (eg, lectures, social media, and podcasts), and different practice settings (eg, community and academic practices).

On the basis of the need to continue improving upon and expanding access to medical education in oncology, while making this process uncomplicated, and keeping the knowledge sharing effective, we propose following the “chain of education”, inspired by the chain of survival for cardiopulmonary resuscitation.⁶

The “chain of education” delineates the core links of any educational activity: “who”, “why”, “where”, “what”, and culminating with the key aspect of the chain which is the

PRACTICAL APPLICATIONS

- Following a “chain of education” that consists of the links “who”, “why”, “where”, “what”, and concludes with the key “how” helps deliver more effective oncology education.
- Integrating learning science principles is essential to the “how” to educate and can enhance the educational experience of trainees, community oncologists, and other learners.
- Training programs can pursue small, yet impactful, modifications that are geared toward optimizing trainees’ learning experience.
- Using interactive social media platforms and tools can tackle the diversity and complexity of community oncologists’ education needs.

“how” to educate. These links and the chain are illustrated in [Figure 1](#), and a detailed description of each link is presented below.

Who

Knowing the target learners for any educational activity is a priority, serving as the initial link for the “chain of education”. Each learner has their own background knowledge, experience, goals, and biases.⁷ For example, a first-year oncology fellow learning about metastatic lung cancer may feel overwhelmed by the large number of actionable mutations and targeted therapy options. Meanwhile, an academic thoracic oncologist may easily comprehend even more complex details about those mutations and therapies. These are two ends of a spectrum, with community oncologists in between them, exemplifying why educators must familiarize themselves with their audiences. By understanding the “who”, educators redirect themselves to what that specific group of learners needs to know, and tailor the education activity to their needs.

Why

The second link of the “chain of education” is the reason for the educational activity, or the “why”. This link may be established by educators, if the activity is their initiative, but it may also be assigned to educators by an external source, such as an invite for a specific activity. In addition to the initial reason for the teaching, “why” also encompasses objectives and goals for each learning session. By establishing the objectives and goals, teachers can lay the ground for the next links of the chain, ensuring that all efforts are tied to these general aims. Besides pointing the way for the educator, this also becomes an initial engaging step, as educators should always outline the learning objectives of each activity, guiding learners’ attention and focus.

Where

Understanding the location of the education activity is also essential. Traditional classrooms or conference rooms are different than virtual platforms. In addition, the location goes beyond the actual space, physical or virtual. A room with trainees is different than a conference room in an international society meeting. Besides that, on-demand content, through social media, videos, podcasts, and virtual settings, carry their own particularities of time allocation, audiovisual resources available, and the continuity of the activity (eg, learners may pause and split a content into smaller segments).⁸ Meanwhile, settings such as teaching hospitals or simulation centers will have their singular requirements, including environmental components that shape the learning process, especially when directly interacting with real or standardized patients.⁹ Understanding the “where” could and should drive educators to modify the education activity accordingly.

What

The next step is to determine the content to be taught or shared appropriately. It can range from an overview of the natural history of a specific cancer (ie, from the pathophysiology and diagnosis to management) to an update on the standard-of-care treatment or new data in a specific disease.

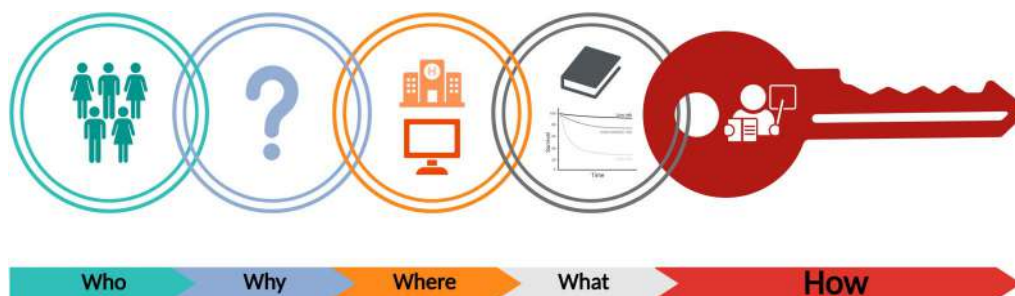


FIG 1. Chain of education.

Evidence-based, well-organized, and concise content presentation is pivotal to the success of the education activity. Due to their expertise, some educators attempt to include the vastness of data and information available, sometimes including excessive details. In doing so, they may overwhelm the learners. This is called cognitive overload. Once it ensues, learners may have difficulty focusing on the material, understanding the topics being educated, and possibly causing frustration for both learners and teachers.¹⁰ While relevant data should be discussed, embracing the notion of “less could be more” by keeping the content focused, and avoiding overload are essential to improve the efficacy and quality of the education activity. Educators could always provide the learners with more content, data, and references for self-review at a later time.

How: The Key for Successful and Effective Education

All links of the “chain of education” are important, but the “how” is ultimately the main key for a successful and effective educational activity. For oncology education to have the desired impact, it needs to be done through effective ways and methods that integrate learning science principles and tailor them based on each of the first four links of “who”, “why”, “where”, and “what”, as well as the combination of these links together. With this integration and a successful implementation of the “how”, oncology educators can transform the most overwhelming content into a pleasant and satisfactory learning experience.

The learning science principles are very effective comprehensive concepts that have been well described in the scientific educational literature.^{11,12} Table 1 lists and defines some of the principles that are most relevant to oncology education.¹¹ In this article, we briefly cover and highlight the importance of some of them, but we also cite some excellent papers that describe them with more details, and we encourage all oncology educators to check them out.

For example, by employing “analogy”, and through identifying similarities between two or more dissimilar examples, educators help learners comprehend a new concept through comparison with another known concept for them. On the other hand, by using “contrasting cases”, such as identifying differences between two or more similar oncologic cases or diagnoses, educators highlight distinctive features of a particular concept and help learners understand and analyze the distinctions by focusing on relevant differences.¹²

Other effective principles in oncology education are “elaboration” through which learners could make connections between prior knowledge and new information,¹² as well as “listening, sharing and question-driven” techniques that engage learners with opportunities to share their take-home points, discuss their doubts, and clarify some relevant key points with peers and educators, which all ultimately help enhance the learning and improve the memory.¹¹ Meanwhile,

TABLE 1. Learning Science Principles

Learning Science Principle	Definition
Analogy	Comparing examples while focusing on their similarities
Belonging	Perception of participating or belonging to a group or community
Contrasting cases	Evidencing differences between examples
Deliberate practice	Effort to further develop one's skills and knowledge
Elaboration	Connecting new information and data with previous knowledge
Feedback	Providing ongoing assessment of how one's outcome compares to their goal
Generation	Retrieving key information focusing on long-term memorization
Hands on	Participating in a learning activity with one's body
Just-in-time telling	Experiencing a new problem before discussing its concepts
Listening and sharing	Collaboration and interaction focused on problem-solving
Participation	Fostering learners' interaction with new content
Question driven	Developing new knowledge by answering questions
Reward	Motivating behavior that is progressing toward a goal
Self-explanation	Reviewing and explaining knowledge to oneself
Teaching	Learning content by educating others
Visualization	Displaying complex information in effective ways
Worked examples	Tackling a problem in a stepwise approach

figures, tables, and videos are always excellent ways of using “visualization”, a learning principle based on the creation of compelling effective ways of displaying complex information, especially for learners on digital platforms.¹³ Interactive content on digital media is based on the learning science principle of “participation”, allowing learners to directly interact and engage with the new information. Concurrently, the novelty and constantly transformative nature of the digital environment are excellent for using excitement, a principle that focuses on learner's attention and arousal.

Finally, as each educational activity should be another step forward for further sharing and expanding the knowledge, asking and motivating learners to “teach” others is a very important principle that allows learners to further develop and validate their knowledge. This can be done during a same educational activity, if time allows, or during future settings, allowing learners to expand their interest in a particular topic.¹⁴

As a framework, following the “chain of education” and its links can be used in different settings. In the following section, we discuss working examples in trainees’ education and education of community oncologists, dissecting relevant and unique educational aspects for each group and describing some effective ways (ie, the how) when it comes to educating different learners. We cite relevant educational science literature, while also sharing the author’s experiences as educators, centered on the know-how of teaching. These examples may serve as a basis for further educational developments in different and unique settings.

EDUCATION OF ONCOLOGY TRAINEES: SMALL CHANGES CAN MAKE A BIG DIFFERENCE

Applying adult learning theory and learning science principles to the day-to-day educational practices of oncology trainees can be relatively simple. This process can be further organized by following the “chain of education”. To exemplify this, we present a case inspired by a real-program scenario.

Case

Leadership of a small hematology/oncology fellowship program has received feedback from the fellows that “lectures could be better”. In addition, the program’s aggregate ASCO and American Society of Hematology (ASH) In-Training Exam (ITE) scores have been declining relative to the national average over the past several years.

The links of the “chain of education” can be followed to tackle the issues relevant to this presented case.

The “Who and Why”

For fellowship program leaders, who are responsible for the education and advancement of trainees, there are different goals of education, and it is important to be clear about your aims as you make programmatic changes.

The first step to tackle this challenge can be imported from the chain, meaning to understand the “who”, which are the hematology and oncology fellows in this scenario, and ensure the lectures are tailored to fellows’ level and needs.

The second step is to establish the “why”. The true goal for education during a training program is to guarantee that trainees are competent in providing care to patients in their subspecialties at the end of training. Experiential learning, or learning through experiences, such as patient encounters, is a mainstay of medical education and an essential piece of any training program. The increase in knowledge in the fields of hematology and oncology is exponential, and contents presented 10 years ago may no longer be relevant. Thus, most program directors feel that their main goal is to teach fellows how to think and how to tackle clinical problems rather than to teach every aspect of hematology/oncology. However, to

become board certified, fellows also need to pass the American Board of Internal Medicine (ABIM) certification examination in each specialty, adding another layer to the “why” in this case. Therefore, program leaders are faced with the duality of needing to teach learners how to think but also help them learn and retain factual knowledge needed to pass a multiple-choice test. Lectures have been the traditional way to impart that knowledge. Unfortunately, data show that after a lecture, adult learners only retain approximately 60% of the knowledge in the short term, dropping to <50% for long-term retention.¹⁵ Incorporating interactive elements to lectures can improve long-term retention by approximately 10%. Despite this relatively poor retention, medical learners value lectures as a form of teaching.¹⁶

The “Where”

Many programs transitioned to virtual learning during the COVID-19 pandemic, returning to in-person or a hybrid of in-person/virtual learning after the pandemic restrictions ended. This new model defines the “where”, bringing along new obstacles. Knowing that the addition of interactivity is important to improve retention, one needs to be mindful of how that occurs with some learners being virtually present. The program from this case continued to allow fellows to participate in a virtual format, while encouraging in-person attendance, when possible, to make it easier for teachers to include and interact with the entire audience.

The “What”

The Accreditation Council for Graduate Medical Education and the ABIM outline what topics are essential to teach trainees during their education, establishing the backbone for “what” must be taught. However, decision regarding which specific topics are formally taught in a didactic session and which are educated through other means is up to each individual program. As an example, some programs develop a 2 or even 3-year rotation of topics.

The “How”—Putting It All Together

In this described case, the goal was to help trainees get effective and efficient lectures that meet their needs, as well as improving ITE scores. Below, we describe the actions taken by this program. This is one potential way of addressing the “how” to educate. Nonetheless, different programs in different settings may have alternative ways of dealing with similar issues.

To tackle this problem, the educational structure of the program was reviewed. Previously, it consisted of a weekly lecture, a weekly case conference, and a weekly board review question session. Each experience was 1 hour long and had no relation to the other experiences during the week. Knowing that repeated exposures to the same material over time is valuable in moving information from short-term to long-

term memory,¹⁷ the program decided to structure all learning for the week around a theme. For example, if the lecture was about kidney cancer, then patient cases with kidney cancer would be discussed the following day, with board review questions about kidney cancer later that same day. The second session was initiated by asking fellows to generate their top learning points from the previous day, writing those on the board. During the board review questions, teaching points that matched the learning objectives from earlier in the week were emphasized.

Lecturers were asked to review previous lectures and make small adjustments to the format and content as follows:

1. Begin each talk with goals and objectives, limiting to four to five
2. Add at least one interactive component (ie, patient cases, board-style questions, and think/pair/share)
3. Review slides and eliminate unnecessary content
4. Provide three references for only major clinical trials that are determined essential to know

These adjustments incorporated some learning science principles as explained in [Table 2](#).

Importantly, as lectures were both in-person and virtual, a special focus was taken to avoid fatigue associated with virtual platforms, while also incorporating the learning science principles that are more relevant to virtual environments.⁸

The format change has been very well received by both the trainees and faculty. Although it is early to assess whether these changes have made any difference to standardized testing results, the simple changes of improving the structure, decreasing cognitive overload, and adding in repetition has significantly improved the fellows' satisfaction and view of their education.

This exemplifies how small changes, guided by learning science principles and the “chain of education”, may lead to meaningful and significant impact. More importantly, whether through similar action items taken by this example program or through alternative techniques other programs

may implement in relevance to their different settings or structures, focusing efforts on “how” education is delivered can put all the relevant aspects together, improving the teaching and learning experiences.

EDUCATION OF COMMUNITY ONCOLOGISTS: OPTIMIZING KNOWLEDGE SHARING THROUGH SOCIAL MEDIA

Data suggest that 55%–85% of patients with cancer diagnoses in the United States get care in community settings.^{18,19} Ensuring that community oncologists have the tools to stay up to date on all the advances happening in the cancer world is critical. While some oncologists in community settings would have a soft focus in one disease site, the majority often manage a broad spectrum of malignancies, including lung, breast, gastrointestinal, genitourinary malignancies, as well as benign and malignant hematology. Considering these challenges, many effective and easily accessible tools and strategies, such as social media and podcasts, can be leveraged by providers to stay up to date in this rapidly evolving field.

The “Who and Why”

The utilization of specific educational resources can be guided by following the “chain of education” in the process of teaching community oncologists, the “who”.

The “why” can be summarized as helping them provide top-quality care to their patients based on the latest advancements in this fast-paced specialty. Having said that, the “why” has multiple layers to it. While oncology has demonstrated faster adoption rates compared with other medical specialties, the speed of integration for these innovative treatments still varies considerably.²⁰ This is likely related to the rapid expansion of treatment possibilities presenting a significant challenge for health care professionals striving to stay abreast of the latest developments.²¹ The complexity extends beyond simply keeping pace with new approvals, such as targeted therapies, but also being up to date with their accompanying tests, such as next-generation sequencing.^{22,23}

The “Where”

In this vast ocean of data, with oncologists practicing in busy settings all over the world, how can one continue to improve, stay informed, and ensure that patients receive the best treatment close to home? In the world of media, several digital tools, including social media platforms, podcasts, and video-based Web sites, have emerged as powerful ways to disseminate scientific advances quickly so that one can integrate these new insights in clinical practice right away.²⁰ In the 2021 survey of health care professionals, 42.7% admitted using social media passively, 38.3% used it to share information infrequently, 19% used it to disseminate information daily, 66% used it to stay up to date on recent publications, and approximately 48.5% used it for networking.²¹ These

TABLE 2. Educational Measures Correlated With the Respective Learning Science Principles

Educational Measures	Learning Science Principle
Initiate a learning session by asking fellows to list the main learning points from the previous lecture	Generation
Having fellows think about a posed question, talk about it with others, and then share with the group	Listening and sharing
Having teachers eliminate unnecessary content	Avoid cognitive overload
Answering board-style questions	Question driven

figures highlight the importance of social media in daily learning, medical communication, and networking with colleagues and industry, establishing the digital setting as one of the locations “where” education occurs.

The “What”

As previously discussed, oncology is one of the medicine fields that has witnessed many new advancements in drug discovery over past decades. These updates, along with implementation of new diagnostic and monitoring tests that accompany these advancements closely, make the educational content, the “what”, even more convoluted. Importantly, as community oncologists have completed their training and are already in practice, the educational content they seek is different than the one presented to trainees. Updates and treatment modifications are more relevant for this group, which educators should be mindful of, adapting what they teach to this unique group of learners.

The “How”: Leveraging Social Media for Community Oncology Education

Social media or video-sharing tools include Twitter/X, LinkedIn, Facebook, Instagram, TikTok, and many more. These platforms have evolved into vital educational hubs for

practicing oncologists, whether in community or academic settings. [Table 3](#) lists them and their unique characteristics.

Though to interact on any social media platform, each one has its own nuances, depending on the target audience, platform-related technical specifications, and delivery mode—audio, video, figures, text, and so on. However, some key aspects for effective communication when delivering health care–related education are constant in all of them. These are summarized using the acronym “CARES”, summarized in [Table 4](#). By following the “CARES” framework, aligned with platform-specific subtleties, one can educate effectively while maintaining professionalism and audience engagement.

Examples of how this framework can be applied are reproduced on [Figure 2](#). [Figure 2A](#) reproduces a poll seeking opinion about breast cancer treatment sequencing, which led to significant virtual engagement. Similarly, [Figure 2B](#) shows another poll assessing different opinions, while tagging different social media accounts to engage experts in the discussion. Both examples maintain patient confidentiality and open space for debate of accurate scientific data. The polls are phrased respectfully, opening the space for engagement of those consuming the content. Finally, by keeping content simplicity, its consumption becomes easier and more appealing.

The diversity of approaches sets the tone for the multitude of ways to educate, once more showing the importance and relevance of “how” to teach. Additionally, social media fosters a sense of community by narrowing the gap between community and academia, offering direct access to key thought leaders who can provide insights on complex cases, and ensuring that patients continue to be treated locally.^{24–26} These platforms also promote collaboration, which encourages partnership with tertiary and quaternary centers when access to specialized treatment (chimeric antigen receptor T-cell therapy, stem cell transplantation, etc) is needed.

TABLE 3. Social Media Platforms and Their Respective Characteristics for Medical Education and Teaching

Social Media Platform	Characteristics for Medical Education and Teaching
Twitter/X	Concise Real-time information exchange Expert discussion Virtual case conferences Multidisciplinary tumor board Knowledge sharing Networking
LinkedIn	Networking Establishing collaborations Share professional achievements Communication for professional growth
Instagram/TikTok	Short video or static photo engaging presentation Stories/reels providing medical education glimpses informally Engaging trend driven patient facing education
YouTube	Video format usually for longer detailed interviews/lectures Ability to provide short videos/clips using “Shorts” Interact with the author using comments
Podcast	On the go audio/video-focused education/discussion Self-directed learning Concise learning opportunities Knowledge sharing by global leaders

TABLE 4. CARES Acronym

CARES	Application
Confidentiality	Always protect patient personal details, staying HIPAA compliant
Accuracy	Sharing articles from accurate resources, to tackle misinformation
Respect	Maintain professionalism, deliver information with respect
Engagement	Use polls, retweets, provide valuable opinion and feedback
Simplicity	Deliver information clearly, which is easy to comprehend

Abbreviation: HIPAA, Health Insurance Portability and Accountability Act.

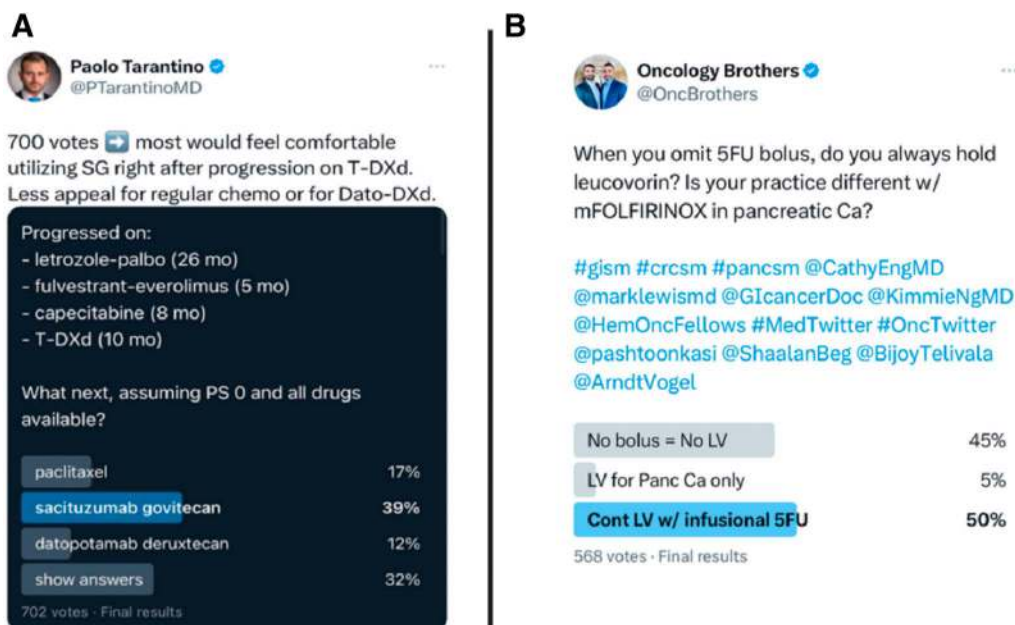


FIG 2. Twitter/X social media posts examples. (A) A poll about breast cancer treatment sequencing of new drug approvals. (B) A poll about the practice patterns of oncologists, while engaging experts. 5FU, 5-fluorouracil; Ca, cancer; Cont, continue; Dato-DXd, datopotamab deruxtecan; LV, leucovorin; mFOLFIRINOX, modified FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin); palbo, palbociclib; Panc, pancreatic; PS, performance status; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.

Podcasts or video-based Web sites are other major sources of information. Podcasts such as JCO Oncology Practice Podcast, ASCO Daily News, Research to Practice, Oncology Brothers, and others showcase expert opinions in each episode. Given busy schedules, these resources offer a time-efficient way to stay informed. They usually offer accompanying simplified visual presentations, treatment algorithms, and trial protocols, further enhancing their educational value.²⁷ One such example is highlighted in Figure 3. It depicts a treatment algorithm from the Oncology Brothers podcast about small-cell lung cancer, summarizing complex treatment paradigms into a simplified stepwise pattern which community oncologist could rely on in their practice.

Again, the learning science principles are entrenched in the examples listed above. Table 5 presents how the principles of contrasting cases, elaboration, generation, and teaching are commonly used in social media.

By leveraging social media tools, community oncologists have been staying abreast with the evolving science, bridging the gap between community and peers from academia, to provide the optimal care to their patients locally. This is achieved despite obstacles such as time constraints, large patient volume, resource limitation, and limited funding.

AVAILABLE RESOURCES AND THE FUTURE OF ONCOLOGY EDUCATION

As medicine evolved and its scientific advancements developed throughout the years, the field of medical education

also advanced and constantly renewed itself, adapting to the needs of the learners as well as the requirements of the specific point in time.²⁸ Organizations and societies were created, soon assuming a relevant role in the education of trainees and in the continuous education of physicians.

In oncology, this role was embraced by ASCO, founded in 1964.²⁹ As it developed, its presence and impact on oncology medical education increased significantly, with many effective initiatives and resources created by ASCO teams. As a matter of fact, through careful review of ASCO education activities, which have been constantly enhanced over the years, one would realize that the links of the “chain of education” have been often followed and learning science principles have been integrated to optimize the key link of “how” to educate.

From major scientific conferences covering all aspects of oncology, to many relevant educational resources and virtual materials, such as guidelines, educational book, and podcasts, ASCO always thrives to educate with impact. One additional resource to highlight is the ASCO self-evaluation program. From texts written by experts, to summarizing tables and figures, and a question bank, it has become a must-have indispensable tool that is constantly evolving and improving how education is offered for oncology trainees as well as practicing oncology professionals. Of note, considering that in the US hematology and oncology trainings are combined in most programs, it is worth mentioning that the ASH also has an effective educational resource, ASH Academy, which is a virtual hub with audiovisual materials and

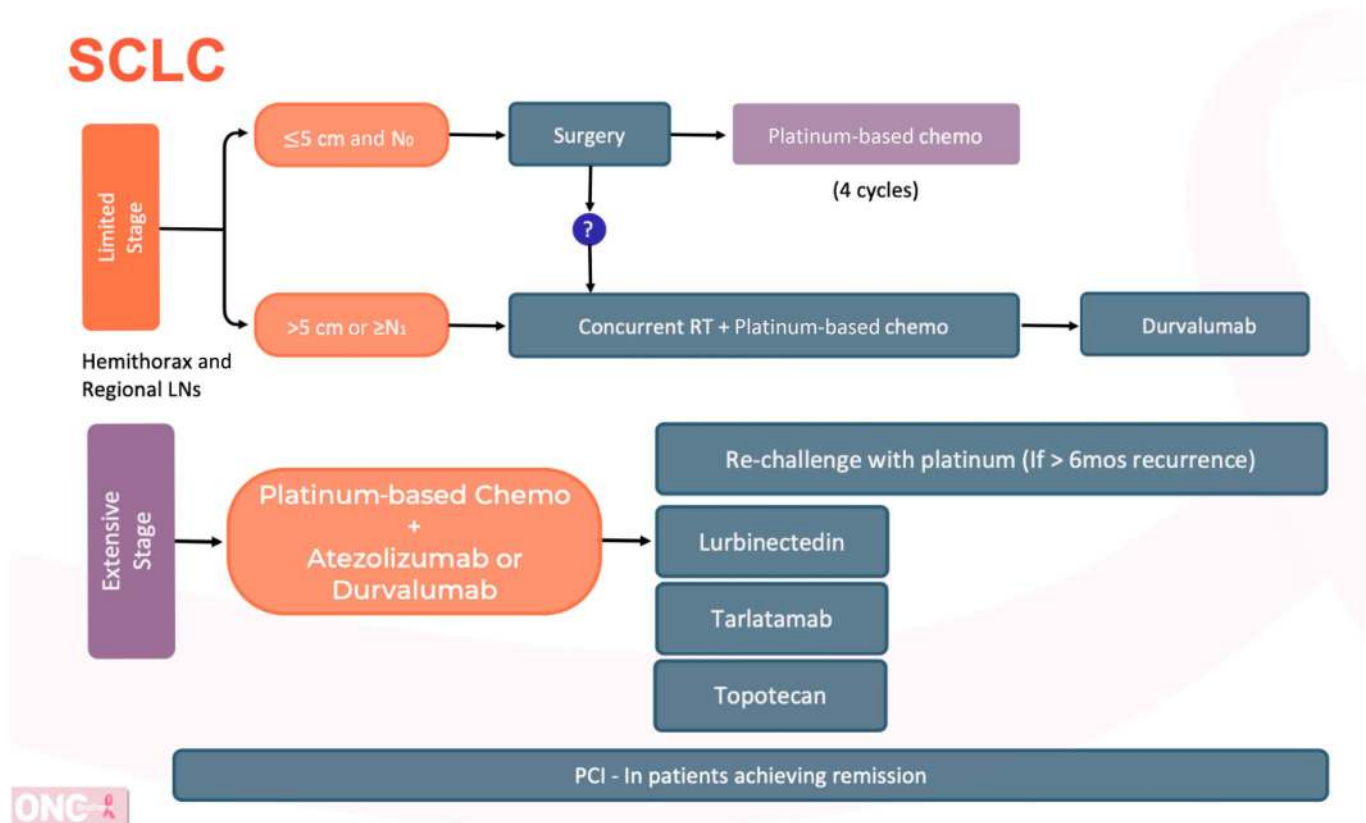


FIG 3. Treatment algorithm for SCLC presented in a podcast.²⁷ chemo, chemotherapy; LNs, lymph nodes; PCI, prophylactic cranial irradiation; RT, radiation therapy; SCLC, small-cell lung cancer.

interactive contents helping shape how to educate in hematology and hematologic malignancies.

When it comes to supporting oncology educators, ASCO also has special programs geared toward the professional development of those invested in a career in oncology

TABLE 5. Measures Used in Social Media by Community Oncologists to Stay Up to Date and the Respective Learning Science Principles

Measure	Learning Science Principle
Posting polls on X/Twitter with contrasting scenarios from daily practice to learn the management pattern of different experts	Contrasting cases
Reviewing new treatment regimens and/or new indications within the context of prior standard of care	Elaboration
Focusing on key treatment indications, outcomes, and toxicity management, providing easy to digest information	Generation
Participating on social media, allowing one to follow and learn from experts, share experiences, and educate others	Teaching

education. A major example is the ASCO Education Scholar Program, in which participants receive formal training in evidence-based education, learning science principles, and design of effective educational activities. More recently, to engage and offer a stage for educators in oncology, the International Medical Education Community of Practice (MedEd CoP) in hematology/oncology, supported by ASCO, was created. Its values of advancing careers, building connections, creating scholarship, diversifying medical education, and educating scientifically are excellent examples of goals that can guide oncology education in the present and future.³⁰ By supporting and empowering educators, it became another great resource to promote the know-how of education further.

Moving beyond presently available resources, we must acknowledge that the future of education is connected to technologic advancements. As new innovative tools develop and expand, such as the artificial intelligence (AI) revolution, they provide new virtues and possibilities in education. Having said that, while AI implementation in oncology education could allow faster development of new materials and resources and help with personalized and learner-centered educational programs,³¹ there are some uncertainties that need to be considered, such as content inaccuracies, questionable effects on critical thinking of learners and educators, as well as some other challenges. Therefore, integrating

AI in oncology education should be done cautiously and systematically.

One effective way to implement and make the most of AI's innovative tools in medical education while navigating its challenges would be to follow the recommendations we have been advocating throughout this article, which involves following the links of the "chain of education" and integrating relevant learning science principles in the final key link of how to educate.

Finally, as oncology and technologic tools evolve, oncology medical educators will become even more relevant. The role of clinician-educators is likely to keep expanding, and fostering this career pathway is essential. Their focus on effectively designing and leading educational activities, applying evidence-based learning principles, exploring new educational methods, and disseminating scholarly works on the field is essential in academic practices, especially those with training programs.³² As oncology further subspecializes in academia, clinician-educators carry their subspecialty knowledge alongside their educational expertise. However, their incorporation into community-based settings is also vital for promoting the education of the oncology workforce as a whole.

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CONCLUSION

As the great field of oncology keeps evolving in such a fast pace, oncology education should follow as one of the major pillars in conquering cancer. An effective and impactful integration of oncology education is essential, but comes with unfolding challenges. The utilization of frameworks, such as the "chain of education", is an impactful way of offering a meaningful educational experience.

In this article, we exemplified how we can educate with impact by adapting and following the "chain of education", considering how each link applies to specific education activities, and integrating learning science principles in the final key link of how to best educate.

While we focused on two major groups of learners: trainees, who will become the future of oncology, and community oncologists, who represent the bulk of the oncology workforce, this framework and these examples can be adapted and applied for any type of learners and any education setting.

Oncology education and knowledge sharing are an art. When it comes to mastering this art, it is all about the "how".

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REFERENCES

1. U.S. Food & Drug Administration: Oncology (cancer)/hematologic malignancies approval notifications. <https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancerhematologic-malignancies-approval-notifications>
2. Schrijvers D, Vermorken JB, Bokemeyer C, et al: Continuing medical education: A must for every medical oncologist. *Ann Oncol* 14:1455-1459, 2003
3. Knowledge conquers cancer: Looking to ASCO's future. ASCO Connection website. <https://connection.asco.org/do/knowledge-conquers-cancer-looking-asco-future>
4. Mayer RE: Applying the science of learning to medical education. *Med Educ* 44:543-549, 2010
5. Włodarczyk S, Dhaliwal G: The learning sciences meet the learning health system. *JAMA Netw Open* 5:e2223113, 2022
6. Cummins RO, Ornato JP, Thies WH, et al: Improving survival from sudden cardiac arrest: The "chain of survival" concept. A statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association. *Circulation* 83:1832-1847, 1991
7. Scheele F: The art of medical education. *Facts Views Vis Obgyn* 4:266-269, 2012
8. Rangachari D, Im A, Brondfield S: Moving from theory to practice in oncology education when virtual is your reality. *Am Soc Clin Oncol Educ Book* 42:1-10, 2022
9. Brondfield S, Lee K, O'Sullivan PS: The cognitive load of inpatient consults: A convergent parallel mixed methods study using the consult cognitive load instrument. *Acad Med* 96:S119-S125, 2021
10. Mancinetti M, Guttormsen S, Berendonk C: Cognitive load in internal medicine: What every clinical teacher should know about cognitive load theory. *Eur J Intern Med* 60:4-8, 2019
11. Schwartz DL, Tsang JM, Blair KP: The ABCs of How We Learn. New York, NY, Norton, 2016
12. Schwartz JE, Brondfield S, Walsh K, et al: From boring to bravo! Using learning science to create memorable presentations. *Am Soc Clin Oncol Educ Book* 43:e389392, 2023
13. Delungahawatta T, Dunne SS, Hyde S, et al: Advances in e-learning in undergraduate clinical medicine: A systematic review. *BMC Med Educ* 22:711, 2022
14. Snell L: The resident-as-teacher: It's more than just about student learning. *J Grad Med Educ* 3:440-441, 2011
15. Pamarthi V, Grimm L, Johnson K, et al: Hybrid interactive and didactic teaching format improves resident retention and attention compared to traditional lectures. *Acad Radiol* 26:1269-1273, 2019

16. Brawer J, Lener M, Chalk C: Student perspectives on the value of lectures. *Med Sci Educator* 19:84-88, 2009
17. Wollstein Y, Jabbour N: Spaced effect learning and blunting the forgetfulness curve. *Ear Nose Throat J* 101:42S-46S, 2022 (suppl 9)
18. Bringing research to the community to reduce cancer disparities. NCI website. <https://www.cancer.gov/research/areas/disparities/chanita-hughes-halbert-clinical-trials-community-access#:~:text=Approximately%2085%25%20of%20cancer%20patients,only%20NCI%2DDesignated%20Cancer%20Center>
19. What is community oncology? American Oncology Network (AON) website. <https://www.aoncology.com/2024/07/25/what-is-community-oncology/>
20. Gutzeit VA, Bhattacharya S, Wu J, et al: Speed of innovation: How quickly are different therapeutic areas adopting paradigm-shifting drugs? *Drug Discov Today* 30:104284, 2025
21. Rapid adoption of novel oncology drugs improves overall survival. *The Oncology Pharmacist*. <https://theoncologypharmacist.com/issues/2017/august-2017-vol-10-no-3/17227:rapid-adoption-of-novel-oncology-drugs-improves-overall-survival>
22. Gibbs SN, Peneva D, Cuyun Carter G, et al: Comprehensive review on the clinical impact of next-generation sequencing tests for the management of advanced cancer. *JCO Precis Oncol* 10.1200/PO.22.00715
23. Røslund GV, Engelsen AS: Novel points of attack for targeted cancer therapy. *Basic Clin Pharmacol Toxicol* 116:9-18, 2015
24. Ventola CL: Social media and health care professionals: Benefits, risks, and best practices. *P T* 39:491-520, 2014
25. Seraphine JL, Wells AF: The impact of social media and online communities of practice in rheumatology. *Explor Musculoskeletal Dis* 2:478-489, 2024
26. Social media has become an indispensable tool for disseminating health information. *UEG—United European Gastroenterology*. <https://ueg.eu/a/353>
27. Oncology Brothers: Practice-changing cancer discussions. *Oncology Brothers Podcast*. <https://podcasts.apple.com/us/podcast/oncology-brothers-practice-changing-cancer-discussions/id1653340966>
28. Custers EJFM, Cate OT: The history of medical education in Europe and the United States, with respect to time and proficiency. *Acad Med* 93:S49-S54, 2018
29. ASCO celebrates 50 years of advancing progress against cancer. *ASCO Connection website*. <https://connection.asco.org/do/asco-celebrates-50-years-advancing-progress-against-cancer>
30. Walsh K, Manochakian R, Schwartz J, et al: Launching an international community of practice in hematology/oncology medical education. *Am Soc Clin Oncol Educ Book* 44:e100046, 2024
31. Mir MM, Mir GM, Raina NT, et al: Application of artificial intelligence in medical education: Current scenario and future perspectives. *J Adv Med Educ Prof* 11:133-140, 2023
32. Meredith G: Promoting the clinician-educator career pathway in oncology. <https://dailynews.ascopubs.org/do/promoting-clinician-educator-career-pathway-oncology>

Navigating Early Career as an Oncologist: Thriving in Diverse Paths

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OVERVIEW

Early-career oncologists navigate a complex landscape of professional development, clinical responsibilities, and research endeavors. This manuscript explores key challenges and strategies for success in the early years of an oncology career, focusing on the first job after fellowship, career transitions, and practical tips for intentionality. Effective mentorship is pivotal, providing guidance in clinical decision making, research pursuits, and professional networking. Career development strategies include securing funding, building collaborative networks, and identifying opportunities for leadership. Additionally, balancing clinical duties with research and personal well-being requires time management and institutional support. This article emphasizes the importance of fostering inclusive mentorship, advocating for work-life integration, and leveraging institutional and professional resources to support career sustainability. By addressing these key aspects, early-career oncologists can build a fulfilling and impactful career while contributing meaningfully to the field of oncology.

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INTRODUCTION

The early years of your oncology career are filled with both opportunities and challenges, requiring you to navigate professional goals, career transitions, and work-life balance. This article is structured into three key sections to help you make the most of this critical phase. In *Exploring Opportunities and Finding Your Passion: The First Job*, you will learn how to choose a career path that aligns with your interests, including key considerations such as job selection, contract negotiation, and long-term career planning. *Switching Gears—Reinventing Your Career* explores how you can pivot professionally, whether by transitioning between practice settings, pursuing leadership roles, or shifting your focus in research or clinical care. Finally, *Creating Time and Space for Impact: Practical Tips for the Early Years* provides strategies for maintaining balance, prioritizing meaningful work, and maximizing your professional impact. By taking a proactive approach to your career development, you can build a fulfilling, adaptable path that supports both your personal and professional aspirations.

77.6% of physicians now employed by hospitals or health care systems, and nearly 60% of physician practices owned by hospitals or corporate entities.¹ Although private practice offers autonomy, independence, and financial incentives, these benefits are often counterbalanced by long working hours and increasing competition from hospital-based programs. Conversely, salaried positions within hospitals and health care organizations are on the rise,¹ providing greater financial security and work-life balance but with trade-offs such as increased administrative oversight and fixed compensation structures. You may find that new community oncologists are increasingly joining larger group practices as the number of independent oncology practices declines while practice sizes expand.² From 2015 to 2022, medical oncology practices have undergone significant consolidation.³ Alternative community employment models include multispecialty groups, oncology networks, and hybrid academic-community affiliations with university medical centers. Understanding these trends is crucial for you as a trainee seeking a career path that aligns with your professional and personal goals.

EXPLORING OPPORTUNITIES AND FINDING YOUR PASSION: THE FIRST JOB

Academics, Community, and Industry: First Steps

As an early-career oncologist, you face a complex and evolving employment landscape, making informed career decisions essential. In the community, the traditional solo private practice model continues to decline in the United States, with

The pharmaceutical industry has played an important role in advancing life-changing therapies for the treatment of cancer (eg, immunotherapy, antibody-drug conjugates, radioligands, and targeted therapies). From 2000 to 2020, the US Federal Drug Administration (FDA) approved 145 novel drugs to treat cancer,⁴ and in 2024, the FDA approved 50 novel drugs, of which 14 were for the treatment of cancer.⁵ The industry has also helped advance clinical research methodology and the application of biomarker-specific testing to take an individualized approach to treatment selection. Since

PRACTICAL APPLICATIONS

- **Informed career decisions:** early-career oncologists benefit from understanding different career paths, including academic, community, and industry roles, allowing them to align their first job with long-term professional and personal goals.
- **The role of mentorship:** strong mentorship relationships are essential for career development, offering guidance in clinical practice, research opportunities, and leadership pathways while also fostering professional resilience.
- **Career transitions and adaptability:** oncologists may need to pivot in their careers because of evolving interests, personal circumstances, or institutional changes, making it crucial to develop transferable skills and a growth mindset.
- **Work-life integration strategies:** balancing clinical responsibilities, research, and personal well-being requires intentional time management, institutional support, and setting professional boundaries to sustain career longevity.
- **Leading with authenticity:** staying true to personal values, embracing individuality, and fostering transparent relationships with colleagues and patients can enhance professional fulfillment and create a more inclusive, supportive oncology community.

oncology is a subspecialty attracting those interested in affecting patient care through discovery, research, and innovation, it is not surprising that the industry may appeal to you as a medical or surgical oncologist.

There are multiple different roles you could fill in the pharmaceutical industry. For example, as a medical director, you have the opportunity to learn and refine several technical and nontechnical skills: study design, clinical development strategy, how to partner with treating physicians, regulatory requirements, and leadership skills. It is essential to collaborate with interdisciplinary professionals on all cross-functional teams. If you are interested in early-phase trials, there are opportunities to learn about different dose-escalation designs, how to select a starting dose, and the complexities of dose optimization. Meanwhile, working on late-stage trials offers you the chance to learn the intricacies of statistical design and development strategy.

Job Search/Crafting

A critical component of a job search in community oncology is the concept of job crafting—the process by which you

tailor a position to align with your skills, needs, and professional goals. Effective job crafting has been shown to enhance job satisfaction, reduce stress, and improve resilience.⁶ Given the current and projected shortage of oncologists,^{7,8} you should view your future clinical practice as an asset and feel empowered to shape a role that maximizes your professional fulfillment. A recent global survey found that only 29% of oncologists reported high job satisfaction, while 20% expressed low satisfaction. Notably, those with lower satisfaction were disproportionately younger physicians with fewer years in clinical practice,⁹ highlighting the importance of you proactively defining your career priorities before entering the job market. Developing confidence in negotiating accommodations that enhance work-life balance may not come naturally to you, underscoring the need for mentorship and strategic career planning.¹⁰

Compensation and Contracts

Financial compensation is a significant factor for many physicians considering a career in community oncology. Physician salaries continue to evolve dynamically, with recent Medical Group Management Association data indicating a 4.33% increase in median compensation for hematologists and medical oncologists, reaching \$516,017 in US dollars (USD).¹¹ Compensation is largely influenced by years of experience, geographic location, and local cost of living. As many institutions transition from traditional fee-for-service models to value-based reimbursement structures, assessing physician contributions remains a shifting landscape. Additionally, factors such as medical school debt now rising over \$234,597 (USD) for the average US oncology graduate in 2024, burnout, and the extensive hours required during the transition from trainee to early-career oncologist must be carefully considered. Although private practice models often offer higher earning potential than salaried positions,¹² they also entail greater administrative and financial responsibilities beyond direct clinical care.

Early-career oncology contract negotiation can be an intimidating venture for many who are used to boilerplate language on training contracts. Many contracts have a particular term period in which salary is protected with a renewal that may be automatic or require renegotiation. It is important to understand that salary is not the only aspect of a contract to be considered. The balance of clinical time, administrative time, and research time is essential to create professional satisfaction. Many contracts still contain restrictive covenants that impair your ability to change employment within a geographic region or reach out to former patients. Despite the Federal Trade Commission in the United States proposing a national ban on noncompete contracts in April 2024, by August, there was an injunction that blocked the legislation, allowing such restrictive covenants to continue. Insurance coverage should be comprehensive and include malpractice as well as tail policies that cover you even after you have left the practice. Even if you feel you have landed a perfect position, do not hesitate to

obtain legal counsel to assist in contract review, amendment suggestions, or even to help in negotiations.

Research is often a core component of academic oncology careers, but it comes with financial and strategic challenges. As an early-career oncologist, you may struggle with the financial realities of research-focused positions. Compensation can vary widely depending on location, institution, practice model, and level of funding support. Clinical expectations can also vary widely. Understanding these financial nuances and having transparent discussions with institutional leadership is critical to your success in an academic physician-scientist career.¹³

Mentorship

To thrive in diverse practices, you must establish dynamic mentorship both within your institution and beyond.¹³ The widespread adoption of teleconferencing during the COVID-19 pandemic has created ongoing opportunities for virtual mentorship, facilitating connections with like-minded professionals across geographic boundaries.¹⁴ Mentorship provides significant personal and professional benefits, including mitigating compassion fatigue and burnout while fostering personal growth and productivity.¹⁰ In community practice, where you may serve as the sole specialist in your region, a strong professional network is essential for delivering high-quality patient care. Establishing effective mentorship begins with a self-assessment of your needs—whether in technical skills, communication, leadership, research, or work-life balance. Taking the initiative to seek out mentors, both within and outside your institution, is a critical first step toward long-term career success.

In academia, mentorship is indispensable. Identifying mentors both within and outside your institution is critical to gaining diverse perspectives, resources, and collaborative opportunities. Equally important is the act of networking.

Mentorship relationships are often diverse in their engagement and purposes. A coach may come alongside you and serve as a motivating voice, spurring you on in your career goals or keeping you accountable to project deadlines and responsibilities. Coaches may be present more during a season of your early career and may not share your specialty or role but have a greater personal or emotional connection. Coach relationships are often mutual relationships where the coach can serve as an initiating force, but just as often, you may be reaching out to find help in navigating an upcoming decision or feeling demotivated by a professional loss.¹⁵

A mentor is often someone who is further along in the oncology path than you. The mentor is often someone whom you admire for their practice or research accomplishments. The mentor can offer more concrete career advice or technical skills than the coach. Typically, you are the initiator in the relationship, seeking counsel and guidance from the mentor. The mentor is often a constant presence throughout

your career, although engagement may be more episodic depending on your needs.

A sponsor is an individual who is engaging on your behalf and leveraging their own expertise and professional relationships to bring opportunities to those who are more junior. The sponsor has influence in a community that matters to you and the opportunity to promote you into a high-visibility role. The sponsor will often see capacity in you that you may not recognize in yourself. You may not even know a sponsorship relationship took place, as you may suddenly be offered a new role in a professional society, suggested as an author for a paper, or elected to a new role within your institution, as sponsorship can come from an influential individual who has recognized your distinctive work from afar.

The coach, mentor, and sponsor roles are summarized categories of mentorship. What you may find is that there are individuals in your life who fill all of these roles at various time points. Peer mentorship is just as viable and, in certain situations, more valuable than other mentorship connections, as some early-career struggles can only be shared with an individual at a similar level of training or progress. Even as an early-career oncologist, you have opportunities to mentor others beneath you in training at the fellowship, resident, and student levels. You may feel ill-equipped as you are navigating your own challenges, but you have cherished insights to offer those still trying to finish the training process and connect with a fulfilling first position. Many mentors will attest that their mentees guide them just as much as they offer in return.¹⁶ Diversity of mentorship leads to a diversity of options. Ask trusted mentors about your strengths and drivers.

Networking

Networking is not just about professional advancement; it is about building a robust support system that can guide you through inevitable career transitions and challenges. An effective way to approach mentorship and networking is by being intentional about the relationships you cultivate. It is important to evaluate your professional network and focus on those connections that bring value, guidance, or joy. Sometimes, this may involve stepping outside your immediate institutional sphere to seek advice from individuals who are aligned with your career vision. A thriving mentorship network, including peer mentors and mentees, can help maintain balance in the demanding environment of academic oncology.

Networking in early-career oncology starts with defining and articulating your career identity and interests to colleagues. If there is a patient population that drives your work, a research interest you are exploring, or a cause you advocate for, write it out and practice how you would passionately share it with others. It will remind your colleagues of other professionals in their own networks that they can connect

with you to further your professional goals in your early career. Some networking happens as a natural process of connecting with other professionals in your institution, but much of it requires taking initiative and reaching out to individuals whose work you admire. This can happen through professional society meetings, social media platforms, or casual professional events. Intentional follow-through after a face-to-face encounter is essential to keep your network of professional contacts thriving. Reach out to your mentors to support you in growing your network, as well as connecting your own mentees to members of your network to assist in maintaining a dynamic, interconnected community.

SWITCHING GEARS—REINVENTING YOUR CAREER

Your career does not need to be a linear straight line. With your foundation as a skilled oncologist, you can choose your own adventure. Regardless of where you start your journey, you always have the option of changing the focus of your chosen role or your career path to maximize your professional fulfillment and career satisfaction.

Personal Growth, Changing Interests, and Burnout

When starting out in your first job after training, you are growing as an oncologist. Whether you have chosen a career in private practice, in academic medicine, in industry or even at the FDA, it takes time to understand what parts of your job really resonate with you and that you truly enjoy versus those that are draining and problematic. Do you like to lead teams? Do you like to ask translational or clinical questions? Do you love patient care? Do you like managing others? Does writing grants drain you? How about dealing with the administrative aspects of your job? When you first start your career, you may find that what you enjoyed as a fellow lands differently for you as an oncologist. It is important to be curious and spend time reflecting on what you like compared with what you do not like/dislike. It takes time and experience to understand what your drivers are and what makes you most fulfilled in your career and professional life. You may be exposed to challenges and opportunities that change your perspective over time as you grow in your career. Connecting with peers, mentors, and other professionals such as coaches can be beneficial in aiding in assessment of job satisfaction as well as providing feedback and tools that can support initial years in an oncologist's chosen path. There are other sources for tips regarding self-assessment including literature in journals such as *Harvard Business Review*.¹⁷

One aspect of being an oncologist that you should be aware of is the risk of burnout. Burnout is described as an occupational-related syndrome characterized by physical and emotional exhaustion, cynicism, and depersonalization (sense of detachment or disengagement), and low sense of professional accomplishment.¹⁸ Recent data report that over half (59%) of the oncologists who responded to an ASCO survey (N = 329) reported significant burnout.¹⁹ In addition, a survey of

assistant professors conducted at the University of Texas M.D. Anderson Cancer Center found that over half (54%) were experiencing burnout.²⁰ There are numerous publications that provide fantastic advice about how to identify and manage burnout.^{19,21,22} One of the strategies to address burnout is to focus on aspects of your career that are meaningful to you and that provide joy.¹⁹ Whether you are starting to face burnout or are dissatisfied with aspects of your job, reflection about what brings you happiness and fulfillment in your job can help you ask yourself the question “What kind of role or change of my current role would allow me to do more of what makes me fulfilled and happy/happy?”

Knowing Options Allows You to Choose Your Own Adventure

As an oncologist, there is flexibility in crafting your career. Each oncologist's career is a living entity that they will feed and grow. A career will naturally develop over time based upon your interests, activities, and business needs. It is important to acknowledge that your career path is unlikely to be the same as another person's career path. With career advancement, you will discover what is professionally fulfilling and where your greatest strengths exist. A change of career or focus of role is daunting—any major life change is. It is not a sign of failure to make a change. Rather, it is a sign of strength to recognize the need for change.

If you find that you need a change of role or a change of focus in your current role, there are several steps in identifying and moving to a new role.

1. Match skills and interests with potential roles: the first step is to dig into skills and experiences that are the most enjoyable and match those to potential career paths. With networking, a greater understanding of the daily work, focus, and opportunities of different career paths emerges. Talk to peers, mentors, and recruiters to understand where there may be an option that is a better match than the current role.
2. Talk with more than one potential employer: if you decide that you want to move academic centers to enable a different focus, apply to multiple positions and ask pointed questions so that the opportunities and challenges of the new role are understood in the context of career likes and dislikes. The same advice is true if you are considering a move to industry. There are multiple options in industry both in the type of company (small biotech through large pharmaceutical companies) and roles in industry (clinical development, medical affairs, translational oncology, and more). Applications to more than one company will provide you with a greater understanding of the roles and responsibilities that exist in industry. Information is power, and a comparison of opportunities provides you with confidence in the choice of the next step in your career.
3. Talk to an attorney: if you have decided on a new career path and an employer is chosen, ask an attorney that specializes in the area to review and advise on your

contract and initial offer. Note, there is more flexibility in contracts for small companies than large companies in the pharmaceutical industry. An attorney can advise about limitations such as noncompetes, timing of stock vesting, or other financial incentives that will vary depending upon the career path change that you have chosen.

4. Make the change and take comfort in knowing that any change made is not irrevocable: it can take 3 months to several years to understand if your new career choice is a right fit.²³ Give yourself time to be curious and learn as much as possible in the new role before deciding if the change meets the needs that prompted a career move. No career change permanently blocks other careers in oncology.

Recognizing that a change of role or change focus of a current role is needed acknowledges that we are complex individuals whose needs evolve over time. Knowing that options exist provides you the freedom to choose. Choose your own adventure.

CREATING TIME AND SPACE FOR IMPACT: PRACTICAL TIPS FOR THE EARLY YEARS

As an early-career oncologist, you will often juggle a multitude of responsibilities—clinical care, teaching, and research—while also contributing to your organization's or institution's broader mission through service and administrative roles. With so many competing demands on your time and attention, understanding how to allocate time to each aspect of your career is essential. This self-awareness will help you craft a balance that aligns with your personal values, professional aspirations, and the institution's needs. In this early-career phase, a well-structured approach to managing your time and responsibilities—along with an upfront investment in delegation—will be key to thriving in this dynamic environment.

Own Your Time

Balancing the demands of a career in oncology requires proactive time management.²⁴ Start by listing everything you do regularly—clinical duties, research, meetings, teaching, and service—and categorize these into blocks of time. Once you have organized your tasks, designate specific times in your weekly calendar for each category and commit to these blocks. When additional tasks or requests come in, allocate them to your next available time block, protecting sufficient time for your core responsibilities. An essential part of this process is scheduling unstructured time. The best ideas often arise when your mind is free to wander, so ensure that your calendar is not so packed that there is no room for creative thinking or accommodating unexpected opportunities. Acknowledge and proactively manage activities that drain your time and attention, for example, email. Unsubscribe from irrelevant listservs, turn off push notifications, and set an out-of-office message during focused work time to reduce distractions. A well-structured calendar, with dedicated time

for both focused work and spontaneous thought, can lead to improved productivity and greater job satisfaction.²⁵

Invest in Delegation

For early-career oncologists, delegation is key. As trainees, you are often accustomed to extreme self-sufficiency, but learning to rely on others and delegate tasks is essential to long-term success. This may include managing administrative support for scheduling, clinical staff for managing patient care logistics, or research students to maximize efficiency. To optimize support, it is important to give your team clearly defined roles and responsibilities. This approach not only frees you up to focus on your highest-priority tasks but also fosters a sense of ownership and satisfaction among your team members. When everyone works to the top of their abilities, you create a more efficient and productive work environment. Delegating tasks ensures that you are not overwhelmed by the smaller, time-consuming responsibilities that can detract from your core work.

Periodically Reassess Obligations

Adding more endeavors to your plate can be exciting, but can also quickly create overwhelming demands on your time and attention. Periodically assessing your ongoing commitments (schedule this quarterly on your calendar!) will help streamline your obligations, allowing you to conduct more impactful and timely work.²⁶ This means not only assessing where your contributions are most needed but also delivering on your promises so collaborators know they can rely on you. Over time, certain committees or other service obligations may no longer align with your evolving goals, and disengagement from these tasks can free up time and energy for new, more meaningful opportunities. Sometimes, simply recognizing when to step back and allow someone else to take over is an important part of maintaining a balanced and fulfilling career. Saying no can be challenging; one way to reframe declining an opportunity is to sponsor an engaged colleague or mentee by recommending them to replace you.

Work-Life Integration

Work-life integration involves blending professional and personal priorities in a way that aligns with your values, rather than striving for a perfect balance. Given the complexity and acuity of our work in oncology, the traditional separation of work and personal life may not always be feasible or desirable. Instead, consider how each aspect of your life—clinical practice, research, service obligations, family, and personal well-being—can support and enrich the others.²⁷ For instance, engaging in a fulfilling personal activity, such as exercise or travel, can help refresh your mind and improve focus in your professional roles. Prioritize impactful tasks that align with both your career goals and personal values, and build flexibility into your schedule to allow for spontaneity and personal connection. Establishing boundaries, both at home and work, is also critical.²⁸

Learning to recognize where you are uniquely needed will help establish priorities too. Take advantage of apps or tools that help you manage both work and personal tasks. Calendar-sharing tools, task management apps, and automated reminders can streamline communication and allow you to share the mental load. Just as you delegate work-related tasks, consider delegating personal tasks when appropriate. This frees up time and energy for both work and personal commitments that are more aligned with your strengths or goals. By integrating your work and personal life, you create a career that is sustainable long-term.²⁹

Celebrate Your Authenticity

As an early-career oncologist, you may feel pressure to conform to institutional or peer expectations or adopt certain behaviors to fit in. Although this is a normal and critical part of finding an optimal work style and approach, cultivating and celebrating your authenticity will be a cornerstone of long-term satisfaction and success.³⁰ Embracing your unique strengths, values, and perspectives can set you apart in meaningful ways. Find ways to express your individuality in your clinical practice, research, and service. For example, if you have a particular interest in patient education, focus on incorporating that passion into your clinical work or leadership roles. Celebrate your personal story—whether that includes your diverse background, your unconventional career path, or your personal interests outside of oncology.³¹ Authenticity fosters deeper connections with

colleagues and patients, and enables you to bring your full self to your work, which can enhance job satisfaction and resilience, and model inclusion for the next generation of trainees and learners. Trust that staying true to yourself will not only enrich your career but also contribute to a more supportive and inclusive work environment.

In the whirlwind of academic oncology, burnout can be a constant threat. However, by applying strategies such as strategic networking, time management, and intentional delegation, academic oncologists can create a fulfilling and balanced career. It is not about achieving perfection every day, but rather globally ensuring you are progressing in your personal and professional goals.³²

CONCLUSION

Building a rewarding oncology career requires more than just landing your first job—it is an ongoing process of reflection, adaptation, and strategic decision making. Whether you are starting out, considering a transition, or looking for ways to create impact, you have the power to shape your career in a way that aligns with your passions and values. Seeking mentorship, managing your time effectively, and staying open to new opportunities will help you navigate career transitions with confidence. By being intentional about your choices and prioritizing both professional growth and personal well-being, you can create a career that is not only successful but also deeply fulfilling.

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REFERENCES

- Physicians Advocacy Institute: PAI-Avalere report on physician employment trends and acquisitions of medical practices: 2019-2023. <https://www.physiciansadvocacyinstitute.org/PAI-Research/PAI-Avalere-Study-on-Physician-Employment-Practice-Ownership-Trends-2019-2023>
- Kirkwood MK, Hanley A, Bruinooge SS, et al: The state of oncology practice in America, 2018: Results of the ASCO practice census survey. *JCO Oncol Pract* 14:e412-e420, 2018
- Milligan M, Erfani P, Orav EJ, et al: Practice consolidation among US medical oncologists, 2015-2022. *JCO Oncol Pract* 20:827-834, 2024
- Gloy V, Schmitt AM, Dublin P, et al: The evidence base of US Food and Drug Administration approvals of novel cancer therapies from 2000 to 2020. *Int J Cancer* 152:2474-2484, 2023
- U.S. Food and Drug Administration: Novel drug approvals for 2024. <https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2024>
- Berg JM, Dutton JE, Wrzesniewski A: What is job crafting and why does it matter? University of Michigan Ross School of Business, 2008. <https://positiveorgs.bus.umich.edu/wp-content/uploads/What-is-Job-Crafting-and-Why-Does-it-Matter1.pdf>
- Schenkel C, Levit LA, Kirkwood K, et al: State of professional well-being, satisfaction, and career plans among US oncologists in 2023. *JCO Oncol Adv* 2:e2400010, 2025
- Medicus Healthcare Solutions: Examining the oncologist shortage. <https://medicusshcs.com/resources/examining-the-oncologist-shortage>

9. Raphael MJ, Fundytus A, Hopman WM, et al: Medical oncology job satisfaction: Results of a global survey. *Semin Oncol* 46:73-82, 2019
10. Thomas CA, Hirschorn AM, Tomkins JE, et al: New landscape: Physician compensation. *JCO Oncol Pract* 17:186-189, 2021
11. Medical Group Management Association: MGMA DataDive physician compensation (based on 2022 data), 2023. <https://www.mgma.com/datadive/provider-compensation>
12. Education Data Initiative: Average medical student debt. <https://educationdata.org/average-medical-school-debt>
13. Doornbos MM, Ayoola A, Topp R, et al: Conducting research with community groups. *West J Nurs Res* 37:1323-1339, 2015
14. Duska L: The crucial role of mentorship in oncology. ASCO Connection. <https://connection.asco.org/do/crucial-role-mentorship-oncology>
15. Cobell J, Munoz J, Pal S: ASCO mentoring helps early-career oncologists map career paths. ASCO Daily News, 2018. <https://dailynews.ascopubs.org/do/asco-mentoring-helps-early-career-oncologists-map-career-paths#:~:text=ASCO%20Mentoring%20Helps%20Early%2DCareer%20Oncologists%20Map%20Career%20Paths,-December%2012%2C%202018&text=ASCO's%20Diversity%20Mentoring%20and%20Virtual,career%20oncologists%20advance%20their%20careers>
16. Cooke KJ, Patt DA, Prabhu RS: The road of mentorship. *Am Soc Clin Oncol Educ Book* 37:788-792, 2017
17. Siang S: Identify—and develop—your natural strengths. *Harvard Business Review*, 2025. <https://hbr.org/2024/06/identify-and-develop-your-natural-strengths>
18. Nowakowski J, Borowiec G, Zwierz I, et al: Stress in an oncologist's life: Present but not insurmountable: (Students should not be discouraged choosing oncology as their future specialisation). *J Cancer Educ* 32:198-205, 2017
19. Hlubocky FJ, Taylor LP, Marron JM, et al: A call to action: Ethics committee roundtable recommendations for addressing burnout and moral distress in oncology. *JCO Oncol Pract* 16:191-199, 2020
20. Singh AP, Xiao L, O'Brien BJ, et al: Association of emotional exhaustion with career burnout among early-career medical oncologists: A single-institution study. *JCO Oncol Pract* 20:137-144, 2024
21. How can I avoid burnout at work? *New York Times*. <https://www.nytimes.com/2025/03/11/well/mind/how-can-i-avoid-burnout-at-work.html>
22. Hlubocky FJ, Back AL, Shanafelt TD: Addressing burnout in oncology: Why cancer care clinicians are at risk, what individuals can do, and how organizations can respond. *Am Soc Clin Oncol Educ Book* 35:271-279, 2016
23. Markman A: Give it time before deciding you hate your new job. *Harvard Business Review*, 2020. <https://hbr.org/2020/03/give-it-time-before-deciding-you-hate-your-new-job>
24. Reese S: 12 smart time management tips for doctors. *Medscape*, 2016. <https://www.medscape.com/viewarticle/860328>
25. Gordon CE, Borkan SC: Recapturing time: A practical approach to time management for physicians. *Postgrad Med J* 90:267-272, 2014
26. Vernon C: Create your personal strategic plan. The Center for Association Leadership. <https://www.asaecenter.org/en/association-careerhq/career/articles/career-management/create-your-personal-strategic-plan>
27. Abuhalmeh B, Brunton NE: Rebalancing work and life for the busy physician. *Ann Vasc Surg* 101:80-83, 2024
28. Rajput V, Hutchinson D, Mookerjee AL: Unusual advice to prevent burnout in early medical career. *MedEdPublish* (2016) 9:30, 2020
29. Pitre C, Ladd L, Welch J: Negotiating work-life integration. *MedEdPORTAL* 13:10623, 2017
30. Branzetti J, Gisondi MA, Hopson LR, et al: Physician, know thyself: Applying brand management principles to professional identity in academic medicine. *Med Educ* 10.1111/medu.15601 [epub ahead of print on December 21, 2024]
31. Talen MR, Rosenblatt J, Durchholtz C, et al: Turning the tables: Using resident physicians' experiences as patients for leveraging patient-centered care. *Int J Psychiatry Med* 53:405-414, 2018
32. Cumbler E, Yirdaw E, Kneeland P, et al: What is career success for academic hospitalists? A qualitative analysis of early-career faculty perspectives. *J Hosp Med* 13:372-377, 2018

Therapeutic Approaches to Mucosal Melanoma

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OVERVIEW

Mucosal melanoma (MM) is a rare and aggressive subtype of melanoma arising from mucosal tissues, with distinct genomic and clinical characteristics compared with cutaneous melanoma (CM). Despite therapeutic advancements, MM remains challenging to treat because of late diagnosis, high heterogeneity, and limited efficacy of conventional therapies. This review synthesizes current knowledge on the genomic landscape of MM and explores the tumor microenvironment that influences treatment resistance. Emerging therapeutic approaches, including neoadjuvant and adjuvant therapies, are critically evaluated. Targeted therapy (eg, BRAF/MEK and KIT inhibitors) demonstrated comparable efficacy in advanced MM and CM. Although immune checkpoint inhibitors show promise in CM, their efficacy in MM is modest, with antiangiogenic-based combination therapies offering potential improvements. Pre-clinical and ongoing clinical trials underscore the need for personalized treatment strategies on the basis of molecular profiling. This review emphasizes the urgency for further research to address the unmet needs in MM management and improve patient outcomes.

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INTRODUCTION

Primary mucosal melanomas (MMs) are malignant neoplasms arising from melanocytes that reside in the mucosal tissues, including the upper aerodigestive, GI, genitourinary tract, and vulvovaginal region. As a subtype of melanoma, MM is considerably outnumbered by its cutaneous counterpart, with an incidence of approximately 0.03–0.05/100,000 per year,¹ but it shows huge ethnical differences, accounting for approximately 1%–3% of all melanoma cases in Caucasian people while 20%–30% in Asian people.^{2–5} Despite the common cell of origin, MM is a clinical and pathologic entity distinct from cutaneous melanoma (CM). Ultraviolet exposure is unlikely to be implicated in MM. Because of the non-cutaneous location and nonspecific symptoms, MMs usually are diagnosed late. The etiopathogenesis, identity of precursor lesions, and biology were not fully understood. Consequently, MM has a worse prognosis and lacks effective treatment options. The management of MM is usually the same as that of CM, which lacks validation for MM. Despite numerous technological developments in surgery, radiation therapy, and advances in systemic modalities, no increased survival advantage has been seen in MM.⁶ The heterogeneity of MM in different sites also exposes management challenges.

GENOMICS

Mutation Landscape

Genetically, CM can be categorized as BRAF-mutant (50%), RAS-mutant (20%–30%), NF1-mutant (10%–15%), or triple wild-type (10%–15%).⁷ However, MM is driven by distinct

mechanisms from CM with SF3B1-mutant (15%), NF1-mutant (14%), KIT-mutant (13%), NRAS-mutant (8%), and BRAF (6%).⁸ Nassar et al⁸ aggregated 65 studies to comprehensively describe the mutational landscape of MM in 2020. On this basis, we included 11 additional studies from 2020 to 2024^{9–19} (Table 1). Subtype specific, Sun et al¹⁴ identified MUT16 (11/44, 25%) and KMD2T (8/44, 18.18%) were recurrently mutated in anorectal and gynecologic melanoma. Cui et al¹³ identified PDGFRA was most common in head and neck melanoma (23/96, 23.96%). Brandon reported that ROS1 also has a high frequency in head and neck melanomas, ranked third after NRAS and NF1 mutations. They also identified that no driver mutations provided overall survival (OS) benefits, except ROS1, which seems likely because of higher tumor burden (TMB).¹⁸ Previous studies have shown that MM has a lower TMB than CM. However, several East Asian studies have shown no significant difference in tumor burden between CM and MM.^{19–21} This may partially explain the reduced efficacy of immune checkpoint inhibitor (ICI) in CM in East Asian populations.

Mitogen-Activated Protein Kinase Pathway

Signal transduction through the mitogen-activated protein kinase (MAPK) pathway generally involves the activation of the following proteins: RAS, RAF, MEK, and ERK. Mutation in the key molecules, BRAF, NRAS, or NF1, occurs in almost all CM (94%) and only about one quarter (28%) in MM.

BRAF. BRAF oncogene has been identified in over 30 single-site missense mutations,²² of which V600 is the most common mutated codon. Only 6% of MMs are harboring BRAF V600E mutation, compared with 35%–50% in CMs.

PRACTICAL APPLICATIONS

- Molecular profiling guides treatment decisions: the distinct genomic landscape of mucosal melanoma (MM; eg, KIT and NRAS mutations) underlines the need for routine molecular testing to identify actionable targets and tailor therapies, such as KIT inhibitors for KIT-mutant tumors or MEK inhibitors for NRAS-mutant cases.
- Combination therapies show promise: antiangiogenic agents (eg, axitinib) combined with immune checkpoint inhibitors (eg, toripalimab) demonstrate improved response rates in advanced MM, suggesting this approach should be prioritized in clinical practice.
- Neoadjuvant immunotherapy for resectable MM: emerging data support the use of neoadjuvant immunotherapy plus antiangiogenic (eg, toripalimab plus axitinib) to enhance pathologic response rates and reduce recurrence risk, potentially transforming surgical outcomes for locally advanced MM.
- Adjuvant chemotherapy outperforms immunotherapy in some settings: for resected MM, adjuvant temozolomide/cisplatin may provide superior survival benefits compared with PD-1 inhibitors, highlighting the importance of selecting evidence-based regimens after surgery.
- Personalized radiation as adjuvant therapy: although adjuvant radiotherapy improves local control in head and neck MM, its limited impact on survival calls for selective use on the basis of tumor stage and anatomic risk factors, avoiding overtreatment.

However, in MM, noncanonical BRAF mutations (G469A, E501K, L505H, L597R, and T599I), especially G469A, are more frequent and result in weaker MAPK activation compared with BRAF-V600E mutations.²² Contrasting to the main previous findings, Newell et al²³ sequenced mucosal tumor tissues from 67 patients and identified a high frequency of mutations in the MAPK pathway: NRAS (12/67), BRAF (11/67), and NF1 (11/67). However, these mutations were predominantly detected in samples from recurrent or metastatic sites.²³ Besides low mutation levels, preclinical evidence suggests that function loss mutations or deletions in NF1 may lead to increased resistance to BRAF inhibitors (BRAFi).²⁴ Consequently, BRAFi, either as monotherapy or in combination with MEK inhibitors (MEKi), have been shown to provide only limited clinical benefit to the majority of patients because of low mutation prevalence.²⁵

RAS. RAS (rat sarcoma) mutations, either NRAS, KRAS, or HRAS, are also infrequent in MM, occurring in 5%–25% of primary tumors compared with 28% in CM.²⁶ In the latest

meta-analysis, NRAS mutations were detected in 40/168 (24%) Japanese patients and seem to have a preference for sinonasal melanoma (34%) and esophageal melanoma (30%).¹⁶ Brandon et al¹⁸ reported NRAS was the top mutation in head and neck melanoma (19/108, 17.6%). The common missense mutation forms were Q61R (26.3%), Q61K, G12A, and G12C.¹⁸ KRAS alterations were observed in about 8% of patients. NF1 (neurofibromatosis type 1) alterations were observed in 17% of patients. There appears to be no difference in the mutation rate of the NF1 gene in MM and CM.⁸

KIT Mutations

KIT mutations are significantly more prevalent in MM than in CM²⁷ at a rate of 13%–39% in all MMs.^{28–31} Trends in frequent mutations/amplifications of the KIT gene in anorectal and genitourinary melanomas have been noticed.³² Omholt et al³³ have reported that KIT mutation was detected 35% (eight of 23) in vulvar, 9% (two of 22) in anorectal, 7% (one of 14) in the nasal cavity, and 20% (one of five) in penile melanomas. KIT mutations are mutually exclusive with NRAS, BRAF, and NF1 mutations, suggesting they may activate the MAPK signaling pathway via different pathways.²³

GNAQ

Approximately 1%–12% of patients with MM have mutations in GNAQ (guanine nucleotide-binding protein G(q) subunit alpha), and around 1% have mutations in GNA11.^{34,35} However, Sheng et al³⁶ found an overall mutation frequency of 9.5% (27/284) for GNAQ in the Chinese MM group, with 4.6% and 4.9% for GNAQ and GNA11 mutations, respectively. They also suggest that GNAQ and GNA11 mutations may be a prognostic factor for MM. The median OS with GNAQ mutations (16.0 v 26.0 months; $P = .031$) or GNA11 mutations (15.0 v 26.0 months; $P = .039$) were significantly shorter than those for patients with wild-type GNAQ and GNA11. This may be partly attributed to the poorer prognosis of MM in Asia compared with Caucasians.

PTEN/PI3K/AKT/mTOR Pathway

PTEN (phosphatase and tensin homolog) mutation or loss is present in up to 8.5%–40% of CM and 1%–25% of MM.^{34,35,37} Patients with TP53 mutations and PTEN alteration had a worse survival rate in MM.³⁸ RICTOR regulates signaling pathways such as Akt through mTORC2, affecting cell growth and proliferation. Ichimura et al³⁹ found that RICTOR (4/10, 40%) was the most frequent genomic alteration identified in oral mucosal melanoma (OMM).

Cell Cycle-Related Mutation

Abnormal copy-number variants in CDK pathway genes are frequently found in MM. The amplification rates for CDK4 and CCND1 were 47.0% and 27.7%, respectively, and the deletion rate for P16^{INK4a} was 57.7%.⁴⁰ CDK4 amplifications were independently linked to shorter OS in acral melanoma

TABLE 1. Mutational Landscape of Mucosal Melanoma

Site	No. of cases	BRAF	NRAS	NF1	KIT	SF3B1	Method	Year
Diverse	13	0	NR	NR	NR	NR	Sanger	2004
Diverse	25	1	NR	NR	NR	NR	Sanger	2004
Diverse	38	1	2	NR	8	NR	Sanger	2005
Diverse	36	1	5	NR	NR	NR	Sanger	2005
Anorectal	20	0	1	NR	3	NR	Sanger	2007
Oral	18	NR	NR	NR	4 (3 NA)	NR	Sanger	2008
Diverse	39	3	NR	NR	6 (2 NA)	NR	Sanger	2008
Diverse	45	0	9	NR	7	NR	DHPLC/sequencing	2008
Esophageal	16	1	6	NR	1	NR	Sanger	2009
Diverse	52	NR	NR	NR	9	NR	Sanger	2009
Diverse	16	NR	NR	NR	6	NR	HRM/sequencing	2010
Diverse	71	4	7	NR	7	NR	Sanger	2011
Diverse	55	1	1		3	NR	Sanger	2011
Diverse	167	NR	NR	NR	16	NR	Sanger	2011
Diverse	93	8	11	NR	17	NR	PCR assay	2011
Diverse	5	NR	NR	NR	0	NR	PCR assay	2011
Diverse	48	NR	NR	NR	8	NR	HRM/sequencing	2011
Diverse	2	1	0	0	0	0	WES/WGS	2012
Diverse	8	0	1	1	0	0	WES	2012
Diverse	120	13	9	NR	NR	NR	Sanger	2012
Diverse	25	NR	NR	NR	7	NR	Sanger	2012
Diverse	35	NR	NR	NR	3	NR	Sanger	2012
Diverse	30	1	1	NR	5	NR	PCR assay	2012
Diverse	10	0	0	1	2	1	WGS and WES	2013
Diverse	28	2	4	NR	2	NR	Targeted NGS	2013
Sinonasal	32	0	5	NR	4	NR	Sanger	2013
Sinonasal	17	0	3	NR	1	NR	Sanger	2013
Sinonasal	56	2	8	NR	2	NR	Sanger	2013
Diverse	26	0	NR	NR	NR	NR	Pyrosequencing	2013
Vulvar and vaginal	65	0	0	NR	7 (11 NA)	NR	Sanger	2014
Vulvovaginal	24	0	4	NR	1	NR	Sanger	2014
Vulvovaginal	24	0	4	NR	4	NR	Sanger	2014
Diverse	21	NR	1	NR	NR	NR	Sanger	2014
Vulvovaginal	51	6	1	NR	10 (5 NA)	NR	Sanger/NGS	2015
Vulvovaginal	20	NR	NR	NR	3 (7 NA)	NR	Targeted NGS	2015
Anorectal	31	NR	NR	NR	11	NR	Sanger	2015
Vulvovaginal	16	1	0	NR	0	NR	Sanger	2015
Diverse	22	0	2	NR	4	NR	Sanger	2015
Diverse	23	0	1	NR	0 (7 NA)	NR	Pyrosequencing/Sanger	2015
Anorectal	15	1	1	3	5	3	Targeted NGS	2016
Oral	57	0	0	NR	4	NR	Sanger	2016
Diverse	25	0	1	NR	4 (8 NA)	NR	Sanger	2016
Diverse	31	NR	NR	NR	4	NR	Sanger	2016
Diverse	706				70		ND: from patient database	2016
Diverse	19	0	1	7	9	8	WES	2017
Diverse	8	0	2	0	2	3	WGS	2017
Diverse	71	5	6	13	5	7	Targeted NGS	2017
Diverse	45	3	7	8	10	12	Targeted NGS	2017
Diverse	46	2	6	5	3	NR	Targeted NGS	2017

(continued on following page)

TABLE 1. Mutational Landscape of Mucosal Melanoma (continued)

Site	No. of cases	BRAF	NRAS	NF1	KIT	SF3B1	Method	Year
Oral	139	NR	NR	NR	22	NR	Sanger	2017
Head and neck	42	2	2	NR	4	NR	Sanger	2017
Diverse	86	0	NR	NR	5 (43 NA)	NR	Sanger	2017
Diverse	755	66	20	NR	66	NR	Sanger	2017
Oral	14	3	4	NR	NR	NR	Pyrosequencing	2017
Diverse	62	2	NR	NR	7		Pyrosequencing/Sanger	2017
Diverse	37	NR	NR	NR	16	NR	PCR assay	2017
Oral	19	0	1	0	4	0	WES	2018
Diverse	43	3	4	6	6	5	Targeted NGS	2018
Diverse	41	0	NR	9	4	NR	Targeted NGS	2018
Head and neck	28	NR	NR	NR	7	NR	Sanger	2018
Oral	65	2	1	5	15	NR	WGS	2019
Diverse	67	3	11	11	10	8	WGS	2019
Diverse	46	0	8	NR	3	9	WES	2019
Diverse	27	NR	NR	NR	3	6	Targeted NGS	2019
Sinonasal	72	4	8	NR	16	5	Sanger	2019
Diverse	17	NR	NR	NR	7	NR	Sanger	2020
Diverse	113	7	15	19	20	30	Oncopanel	2021
Diverse	15	0	3	0	0	0	Sanger/NGS	2021
Diverse	214	25	37	NR	44	20	Sanger/NGS	2021
Head and neck	96	6	12	NR	14	NR	Sanger	2021
anorectal	44	5	3	10	10	NR	WES	2023
Diverse	112	19	17	13	17	12	Targeted NGS	2023
Diverse	168	9	40	30	14	NR	Panel/NGS	2024
Diverse	35	3	2	NR	6	NR	Custom NGS panel	2024
Head and neck	108	11	19	15	8	NR	Targeted panels	2024
Diverse	15	0	3	2	2	2	Custom panel sequencing	2024

Abbreviations: NA, not available; NR, not reported; WES, Whole-exome sequencing; WGS, Whole-Genome Sequencing.

(AM).⁴¹ However, in MM, patients with *CCND1* amplification were reported to have better outcomes.³⁸ The potential effectiveness of CDK4 inhibitors in MM is promising. *RB1* (retinoblastoma 1) mutations occur in 4%–15% of CMs and 0%–21% of MMs.^{34,35,37} *TP53* mutations are present in 15%–27% of CMs and 7%–15% of MMs.^{34,35,37} The frequency of homozygous deletions of *CDKN2A* and *CDKN2B* was high at 23% and 18%, respectively, and amplification of *MYC*, *kDR*, *KIT*, *PDGFRA*, *MITF*, *VEGFA*, and *CCND3* was also common.¹⁶

The Spliceosome Pathway

SF3B1 encodes subunit 1, the largest component of the spliceosome factor 3b (SF3B) protein complex.⁴² Mutations in *SF3B1* have been implicated in the pathogenesis of multiple cancers, including MM.⁴² Whole-genome sequencing analyses have identified *SF3B1* driver mutations as prevalent in MM.^{34,35} *SF3B1* shows a relatively high mutation frequency in MM (12%–37%). All detected mutations occur at a hotspot in codon 625, primarily in anorectal or female genital sites. Notably, all *SF3B1* mutations were found exclusively in

primary tumor samples.^{23,27,43} And Wang et al³⁸ found that *SF3B1* R625 codon mutations were unique to MMs (12.9%) compared with AMs.

Microenvironment

The tumor microenvironment (TME) consists of various cells (including immune cells, fibroblasts, endothelial cells, inflammatory cells, and lymphocytes), extracellular matrix, vasculature, and chemokines.⁴⁴ The interactions between tumor cells and the components in TME affect tumor progression and metastasis as well as the therapeutic effect.⁴⁵ myeloid-derived suppressor cells are highly enriched in the melanoma microenvironment and use multiple mechanisms to inhibit antitumor effector functions of T and NK cells.^{46,47}

The immune microenvironment of MM remains poorly understood, largely because of the distinctive and complex nature of the mucosal immune system, which differs significantly from those observed in CM.⁴⁸ A retrospective study of sinonasal melanomas reveals that the presence of melanin

in the cytoplasm of the tumor cells and immunotype B of tumor-infiltrating lymphocytes are favorable factors. The presence of NK cells, eosinophils, macrophages, and plasma cells increased the OS, while dendritic cells were correlated with unfavorable prognosis.⁴⁹ Vascular endothelial growth factor (VEGF), an angiogenic molecule, plays a critical role in the TME, regulating angiogenesis by interacting with VEGF to drive the formation and remodeling of the tumor vasculature. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is an inhibitory checkpoint receptor that suppresses T-cell activation and induces immunosuppression. Ipilimumab, an anti-CTLA-4 antibody, is the first ICI to have Food and Drug Administration approval.

PD-1 is an immune checkpoint molecule primarily expressed on the surface of T cells. Melanoma is usually characterized by high levels of PD-L1 expression, which is strongly associated with a poor prognosis. The proportion of CMs and MMJs expressing PD-L1 was comparable, at 35%⁵⁰ and 44%,⁵¹ respectively. PD-1/PD-L1 inhibitors, including nivolumab, pembrolizumab, and atezolizumab, have been successively used in melanoma. High CD73 expression has been reported to be associated with an inhibitory TME, and worse OS and disease-free survival (DFS) of melanoma in a Chinese cohort.⁵² However, we still know little about TME in MM, because of the complexity and distinctiveness of mucosal immune system.

EMERGING THERAPIES

Perioperative Treatment

Surgical intervention is the primary treatment for CM, with a 5-year survival rate exceeding 90% for early-stage melanomas after complete resection. However, MM presents significant challenges in achieving negative resection margins because of its advanced stage at diagnosis, frequent lymph node involvement, complex anatomic locations, and multifocal lesions. Consequently, the recurrence rate after surgical treatment for MM ranges from 50% to 90%. Neoadjuvant and adjuvant therapies can improve outcomes in resectable MM.

Neoadjuvant Therapy

Toripalimab and axitinib. In a single-center, open-label phase II clinical trial, patients with resectable MM received four cycles of toripalimab and axitinib as neoadjuvant therapy, followed by surgery and adjuvant toripalimab. Among the 29 treated patients, the median event-free survival (EFS) was 11.1 months, with a median recurrence-free survival (RFS) of 9.5 months and a 12-month RFS rate of 45.8%. Of the 24 patients who underwent surgery, eight (33.3%) achieved a pathologic response, including four (16.7%) with pathologic complete response (pCR) and four (16.7%) with pathologic partial response (PPR).⁵⁴

Lenvatinib and pembrolizumab. In another study, 15 patients received two cycles of neoadjuvant therapy with

lenvatinib and pembrolizumab, followed by surgery and 15 cycles of adjuvant pembrolizumab. As a result, 11 (13.3%) achieved pCR, one achieved major pathologic response, and three achieved pPR, resulting in an overall pathologic response rate of 40% (6/15).⁵⁵

Ipilimumab/nivolumab. A recent study identified 37 resectable sinonasal mucosal melanoma cases. The overall response rate to ipilimumab/nivolumab was 24%. Those who responded to ipilimumab/nivolumab ($n = 4$, 24%) exhibited improved progression-free survival (PFS; 2-year PFS: 100% v 15%; $P = .02$) and local recurrence-free survival (LRFS; 2-year LRFS: 100% v 31%; $P = .08$).⁵⁶ Besides, many cases using ipilimumab/nivolumab as neoadjuvant therapy reported achieving long-lasting remission.⁵⁷⁻⁵⁹

Adjuvant Therapy

Adjuvant postoperative treatment of MM is even more critical, as it is more likely to invade blood vessels and more likely to recur and metastasize compared with CM.

Chemotherapy. The 2012 ASCO meeting reported the first global prospective study on adjuvant therapy for MM, comparing observation, high-dose IFN- α 2b (HDI), and temozolomide plus cisplatin chemotherapy. Preliminary results indicated that patients treated with temozolomide plus cisplatin showed significant improvements in RFS ($P < .001$) and OS ($P < .01$) than those treated with either HDI or surgery alone.⁶⁰ In the 2018 ASCO congress, a Chinese multicenter, prospective, randomized phase III trial enrolled 204 patients with postoperative MM without distant metastases, assigning them 1:1 to high-dose interferon or temozolomide plus cisplatin adjuvant chemotherapy. Compared with interferon, adjuvant chemotherapy reduced recurrence risk by 44% (median RFS, 15.53 v 9.47 months; $P < .001$) and distant metastasis risk by 47% (median distant metastasis-free survival [DMFS], 16.8 v 9.57 months; $P < .001$), demonstrating its superior efficacy.⁶¹ In the 2023 ASCO congress, the latest data of chemotherapy versus toripalimab as adjuvant therapy in resected MM were further reported: adjuvant chemotherapy (temozolomide plus cisplatin) shows remarkable longer RFS, DMFS, and OS than toripalimab (anti-PD-1). It suggested that adjuvant chemotherapy may be a better option for patients with resected MM even in the present immunotherapy era.⁶²

Immunotherapy. A phase II clinical trial enrolled 145 patients with resected, nonmetastatic MM. The results showed that the median RFS was 13.9 months in the interferon group and 13.6 months in the toripalimab group, while the median DMFS was 14.6 months and 16.3 months, respectively. Both adjuvant interferon and PD-1 inhibitor therapy prolonged PFS, with PD-1 inhibition potentially offering more significant benefits in patients with positive PD-L1 expression.⁶³

A recent study retrospectively analyzed 120 patients treated with anti-PD-1 antibodies or dabrafenib plus trametinib,

including 12 patients with MM. The 3-year time to relapse for MM was 38.5%, and the 3-year OS was 33.3% (4/12).⁶⁴

An international retrospective cohort study analyzed 194 patients with stage III/IV AM or MM who received PD-1 adjuvant therapy. Unfortunately, the risk of relapse in MM remained high after PD-1 adjuvant therapy (55%, 30/55). There were no statistically significant differences in RFS (hazard ratio, 1.36 [0.69–2.68]; $P = .3799$), DMFS, or OS between the MM group and the historical cohort.⁶⁵

Targeted therapy. A retrospective study analyzed patients with metastatic or unresectable BRAF-mutant MM who received either BRAFi or chemotherapy. BRAFi has better efficacy than chemotherapy in these small samples: The median PFS was 4.4 months (95% CI, 0.8 to 12.7) and 1.1 months (95% CI, 0.1 to 3.3), respectively. The median OS was 8.2 months (95% CI, 6.6 to 19.9) and 4.7 months (95% CI, 1.0 to 9.7), respectively.⁶⁶

Radiation. Radiotherapy is mainly used as postoperative adjuvant therapy for head and neck mucosal melanoma.⁶⁷ Several retrospective studies found that adjuvant radiotherapy improved local control rates,⁶⁸ with a meta-analysis reporting a 45% reduction in local recurrence risk.⁶⁹ However, OS remains similar between surgery alone and surgery combined with radiotherapy.⁷⁰ A phase II trial noted a 92% LRFS rate with radiotherapy, although distant metastasis-free survival and OS were unaffected.⁷¹ A recent prospective study of 300 patients with nasal and paranasal sinus melanoma found that radiotherapy extended relapse-free survival (15.2 v 9.8 months) but did not significantly affect distant metastasis or OS. Notably, for stage IVA patients, radiotherapy reduced relapse risk by 0.43-fold.⁷²

To date, all studies consistently suggest that postoperative adjuvant radiotherapy primarily contributes to local control, with no evidence of a reduction in recurrence rates or improvement in OS, as distant metastases remain the leading cause of mortality in MM.⁶⁷

Systemic Treatment

Targeted Therapy

BRAF/MEK/KIT inhibitor. A phase III clinical trial enrolled 423 patients with advanced BRAF V600-mutant melanoma to evaluate the safety and efficacy of combination therapy with a BRAFi and a MEKi (dabrafenib monotherapy v dabrafenib plus trametinib). The combination therapy significantly improved PFS and OS.⁷³ MM has a BRAF V600 mutation rate of approximately 12% and may also be benefited from it. MM exhibits a higher KIT mutation rate than CM, which may contribute to its greater responsiveness to KIT inhibitors than acral or sun-damaged melanomas. Currently, to our knowledge, no clinical trials have specifically investigated KIT inhibitors in MM. However, most studies have included a substantial proportion of non-CM subtypes, with MM comprising 46% to 71% of enrolled

cases.^{30,74–76} There is a lack of effective targeted drugs for patients with NRAS mutations in melanoma. But MEKi shows acceptable tolerability and substantial clinical activity in patients with NRAS-mutated melanoma.^{77,78} The results of the phase II study showed that tunlametinib had an ORR of 34.7% and an mPFS of 4.2 months in advanced melanoma.⁷⁹ Preclinical studies have further demonstrated that phosphoinositide-dependent kinase-1 (PDPK1) loss enhances the efficacy of MEKis. The synergistic effect of PDPK1 depletion and MEKi was confirmed in NRAS-mutant melanoma cell lines using pharmacologic and molecular approaches. The combination of PDPK1 inhibitors and MEKi effectively suppressed NRAS-mutant xenograft growth, supporting the clinical development of this combinatorial strategy for melanoma treatment.⁸⁰

ICIs

The KEYNOTE-151 study reported pembrolizumab's latest 3-year follow-up results as a second-line treatment for advanced melanoma. Among the 103 enrolled patients, 15 had MM. In this subgroup, the ORR was 13.3% (2/15), and the disease control rate (DCR) was 20% (3/15). The median PFS was 2.5 months (95% CI, 1.3 to 2.8), while the median OS was 7.4 months (95% CI, 2 to 12.1).⁸¹ A post hoc analysis assessed the efficacy of pembrolizumab in patients with advanced MM in KEYNOTE-001 (ClinicalTrials.gov identifier: [NCT01295827](#)), KEYNOTE-002 (ClinicalTrials.gov identifier: [NCT01704287](#)), and KEYNOTE-006 (ClinicalTrials.gov identifier: [NCT01866319](#)). The ORR was 19% (95% CI, 11 to 29), with a median duration of response (DoR) of 27.6 months (range, 1.1 + to 27.6). Median PFS was 2.8 months (95% CI, 2.7 to 2.8), with a median OS of 11.3 months (95% CI, 7.7 to 16.6).⁸² The POLARIS-01 study reported clinical data on toripalimab as a treatment for Chinese patients with melanoma (22/128 MM). The overall ORR was 17.3%, while the ORR for the MM subgroup was 0%.⁸³ A phase II trial (HX008) assessed the safety and efficacy of pucotenlimab as second-line therapy. The IRC-assessed ORRs for MM is 8.70% (95% CI, 1.071 to 28.038), not as effective as in CM (36.36%; 95% CI, 17.198 to 59.342).⁸⁴ In another phase II trial involving 20 patients with advanced MM who received nivolumab treatment, similar outcomes were reported—ORR of 23.5%, median PFS of 1.4 months (95% CI, 1.2 to 2.8), and median OS of 12.0 months (95% CI, 3.5 to not reached).⁸⁵ However, ICIs are not as effective for clinical use in Asians as they are in Caucasians⁸⁶ (Table 2).

Combined anti-CTLA-4 and anti-PD-1 checkpoint inhibition achieves the highest 5-year OS rate among therapies for advanced melanoma but is also associated with the highest incidence of immune-related adverse events.⁸⁷ A pooled analysis collected data from 889 patients (86 MM and 665 CM) who received nivolumab monotherapy in clinical studies, 305 patients (36 MM and 269 CM) who received ipilimumab monotherapy, and 360 patients (35 MM and 325 CM) who received nivolumab combined with ipilimumab. For patients receiving nivolumab monotherapy, the median PFS was 3.0 months for MM and 6.2 months for CM, with ORRs of

TABLE 2. ICIs' Efficacy in Different Races

Race	Pembrolizumab	Nivolumab	Pemb or Nivo	Ipilimumab	Ipi and Nivo	Toripalimab	ICI (retrospective)
Asian	ORR: 13.3%	ORR: 23.5% ⁸⁵ PFS: 1.4 months mOS: 12 months			ORR: 40.0% PFS: 4.3 months mOS: 33.1 months	ORR: 0% OS: 10.3 months PFS: 1.9 months	PFS: 14 months
Caucasian	ORR: 19% PFS: 2.8 months OS: 11.3 months	ORR: 23.3% PFS: 3 months	ORR: 23% PFS: 3.9 months OS: 12.4 months (American)	ORR: 12.5% (German)			ORR: 11.9% OS: 15.97 months (French)

Abbreviations: ICI, immune checkpoint inhibitor; Ipi, ipilimumab; mOS, median overall survival; Nivo, nivolumab; ORR, objective response rate; OS, overall survival; Pemb, pembrolizumab; PFS, progression-free survival.

23.3% and 40.9%, respectively. For patients receiving ipilimumab monotherapy, the median PFS was 2.7 months for MM and 3.9 months for CM. In those treated with nivolumab plus ipilimumab, the median PFS was 5.9 months for MM and 11.7 months for CM, with ORRs of 37.1% and 60.4%, respectively.⁸⁸ However, the median time to response was similar for both melanoma subtypes, regardless of treatment.⁸⁸ Moreover, a current retrospective study by Horisaki et al⁸⁹ analyzing 57 patients with advanced or recurrent MM receiving ICIs as first-line systemic therapy found no significant differences in ORR (40.0% v 27.7%; $P = .176$), median PFS (4.3 v 9.9 months; $P = .578$), or median OS (33.1 v 22.8 months; $P = .697$) between patients treated with combined anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) therapy and those receiving anti-PD-1 monotherapy.⁸⁹ Despite observable responses to ICIs in mucosal melanoma, their efficacy is consistently suboptimal relative to cutaneous and acral subtypes under current standard-of-care (SOC) regimens for melanoma (Table 3).

Antiangiogenic-Based Combination Therapy

MM exhibits a high propensity for vascular invasion, which may contribute to its relative sensitivity to antiangiogenic agents.⁹⁰ The antiangiogenic-based combination therapy may offer a therapeutic opportunity.

Toripalimab plus axitinib. A phase Ib study evaluated toripalimab, a humanized anti-PD-1 monoclonal antibody, in combination with the VEGF receptor inhibitor axitinib for advanced melanoma. Among 29 treatment-naïve patients with MM, 14 achieved partial response and 11 had stable disease, resulting in an ORR of 48.3% and a DCR of 86.2%. The median DoR was 13.7 months, with a median PFS of 7.5 months and a median OS of 20.7 months.^{91,92}

Atezolizumab plus bevacizumab. A phase II trial evaluated atezolizumab (anti-PD-1 monoclonal antibody) combined with bevacizumab (VEGF monoclonal antibody) in advanced MM, enrolling 22 patients. The best ORR was 36.4%, with a median PFS of 5.2 months and the best DCR of 59.1%.⁹³ The latest three-year follow-up results of this study indicated that, among 43 intent-to-treat patients, the median overall survival was 23.7 months (95% CI, 15.1 to 34), with a 3-year OS rate of 28.7% (95% CI, 17.6 to 46.8).⁹⁴

Camrelizumab plus apatinib. Zhao et al⁹⁵ evaluated the efficacy and safety of camrelizumab (humanized anti-PD-1 antibody), in combination with apatinib (a VEGFR tyrosine kinase inhibitor), for advanced MM. Among 28 evaluable patients, the confirmed ORR was 42.9%, with a DCR of 82.1% and a median PFS of 8.05 months. Notably, the median PFS was 11.89 months in treatment-naïve patients and 6.47 months in those who had received previous therapy.⁹⁵

Antiangiogenic agents plus chemotherapy. A Chinese retrospective study presented at the 2018 European Society for Medical Oncology Congress reported a PFS of 4 months for first-line therapy (dacarbazine + cisplatin + endostar) and 2 months for second-line treatment (paclitaxel + carboplatin + bevacizumab). These findings suggest that chemotherapy combined with antiangiogenic agents may be viable for unresectable or advanced MM.⁹⁶

ONGOING CLINICAL TRIALS AND FUTURE PERSPECTIVES

Preclinical Research

Whole-genome sequencing study for MM identifies genomic alterations, informing promising targeted therapy options for MM. Many preclinical trials provide ideas for new drugs and combinations. A PDX trial demonstrates potent anti-tumor effects of palbociclib in CDK4-amplified MM.⁹⁷ Transcriptome analyses revealed significant upregulation of receptor tyrosine kinase (RTK) signaling, particularly the nerve growth factor receptor (NGFR), in OMMs and organoids from patients resistant to anti-PD-1 therapy. Combining anti-PD-1 with amlotinib (a phase II multitargeted RTK inhibitor for OMMs) or NGFR knockdown enhances the practical activity of immune cells in organoid-immune cell coculture systems.⁹⁸ Freiburger et al⁹⁹ found through next-generation sequencing that the combinational expression of tumor testis antigens NY-ESO-1, MAGE-A3, and MAGE-A4 predicts response to immunotherapy in patients with MM.

Ongoing Clinical Trials

While new therapies continue to emerge, MM still shows limited long-term clinical benefit from current targeted therapies. ICIs and targeted drugs are the two main trends in

TABLE 3. SOC for Melanoma (including mucosal melanoma)

Region	Trial Name	Subtype	No.	Regimen	ORR	PFS (month)	OS (month)
CN	KEYNOTE-151	Acral: 37.9%, mucosal: 14.6% Cutaneous: 39.8%, unknown: 7.8%	103	Pembrolizumab	Mucosal: 13.3% Cutaneous: 19.5%	Acral: 2.8 Mucosal: 2.6 Cutaneous: 2.8	Acral: 14.8 Mucosal: 7.4 Cutaneous: 13.5
	POLARIS-01	Acral: 39.4%, mucosal: 17.3% Cutaneous: 22.8%, unknown: 20.5%	127	Toripalimab	Mucosal: 0% Cutaneous: 31%	Acral: 3.2 Mucosal: 1.9 Cutaneous: 5.5	Acral: 16.9 Mucosal: 10.3 Cutaneous: NE
	HX008	Acral: 52.1%, mucosal: 19.3% Cutaneous: 18.5%, unknown: 10.1%	119	HX008	Mucosal: 8.7% Cutaneous: 36%	Acral: 3.3 Mucosal: 2.0 Cutaneous: 4.2	Acral: 17.9 Mucosal: 9.4 Cutaneous: NE
Global	KEYNOTE-006	Not reported	277 v 278	Pembro (once every 3 weeks) v Ipi	Overall: 32.9% v 11.9%	4.1 v 2.8	32.7 v 15.9
	RELATIVITY-047	Cutaneous: 70.4%, acral: 11.5%, mucosal: 7.1%	355 v 359	Nivo + Rela v Nivo	Overall: 43.1% v 32.6% Cutaneous: 47.2% v 38.3%, mucosal: 30.4% v 25.0%	Overall: 10.2 v 4.6 Cutaneous HR: 0.78 Acral HR: 0.84 Mucosal HR: 0.64	Not reported
	CheckMate 067	Not reported	313 v 313	Nivo + Ipi v Nivo	57.6% v 43.7%	11.5 v 6.5	72.1 v 36.9
	Pooled analysis	Mucosal and cutaneous	35 and 326	Nivo + Ipi	Mucosal: 23.3% Cutaneous: 40.9%	Mucosal: 5.9 Cutaneous: 11.7	Not reported

Abbreviations: CN, China; HR, hazard ratio; Ipi, ipilimumab; NE, not evaluable; Nivo, nivolumab; ORR, objective response rate; OS, overall survival; Pembro, pembrolizumab; PFS, progression-free survival; Rela, relatlimab; SOC, standard of care.

TABLE 4. Ongoing Phase III Studies of IO-Naïve Melanoma (including mucosal)

NCT Number	Region	Company	Regimen	Subtype	No.	Study Time	Primary End Point	Existing Efficacy Data	Safety Data
NCT05727904	Global	Iovance	Lifileucel + Pembro v Pembro	Uveal excluded	670	March 2023-March 2028	ORR, PFS	1L (cutaneous 65.2%) 1: ORR: 65.2% (15/23), DCR: 91.3% (21/23), 12-month DoR: 53.3%, 6-month DoR: 73.3%	≥G3 hematologic AE 100%, ≥G3 nonhematologic AE 13%
NCT06112314	Global	Immunocore	IMC-F106C (PRAME/CD3) + Nivo v Nivo ± Rela	—	680	December 2023-December 2026	PFS	Only released data of mono IMC-F106C for IO treated 2: ORR 11%, DCR: 56%	
NCT05352672	Global	Regeneron	Fianlimab (LAG-3) + cemiplimab v Pembro + placebo v cemiplimab + placebo	Arcal + mucosal <10%	1,590	July 2022-March 2026	PFS	1-2L PD-1-naïve 3: ORR 61%, PFS 15 months	≥Grade 3 TEAE 44% SAE 30% AE-discontinuation 16%
NCT05625399 -RELATIV-ITY-127	Global	BMS	rHuPH20 (PD-1/LAG-3) SC v Nivo + Rela IV	Ocular excluded	570	March 2023-February 2025	PK indicators		
NCT06054555	Global	Amgen	ABP206 (Nivo-biosimilar) v Nivo	Uveal excluded	620	November 2023-January 2027	ORR, PFS, OS, DoR		

Abbreviations: 1L, first-line therapy; 2L, second-line therapy; AE, adverse event; DCR, disease control rate; DoR, duration of response; G, global; IO, immuno-oncology; IV, intravenous; LAG-3, lymphocyte-activation gene 3; NCT, national clinical trial; Nivo, nivolumab; ORR, objective response rate; OS, overall survival; Pembro, pembrolizumab; PFS, progression-free survival; PK, pharmacokinetics; rela, relatlimab; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event.

future treatment strategies. ICI monotherapy is less effective in patients with MM. This may be partly attributed to the high heterogeneity of MMs, including TMB differences and immune microenvironments. Combination therapy may exert synergistic antitumor effects. Many ongoing trials investigate the efficacy and safety of novel or combination therapies in patients with MM (Table 4). The complex

molecular landscape of MM contributes to its poor prognosis and limits the development of effective targeted therapies. Therefore, comprehensive whole genome sequencing/whole exome sequencing studies are essential to identify actionable targets. However, given the low prevalence of the disease, accumulating sufficient data will require time.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. RARECARENet—On line analysis. <https://seer.cancer.gov/statfacts/html/melan.html>
2. Lee HY, Chay WY, Tang MB, et al: Melanoma: Differences between Asian and Caucasian patients. *Ann Acad Med Singap* 41:17-20, 2012
3. Wang Y, Zhao Y, Ma S: Racial differences in six major subtypes of melanoma: Descriptive epidemiology. *BMC Cancer* 16:691, 2016
4. Bai X, Mao L, Guo J: Comments on Chinese guidelines for diagnosis and treatment of melanoma 2018 (English version). *Chin J Cancer Res* 31:740-741, 2019
5. Bai X, Kong Y, Chi Z, et al: *MAPK* pathway and *TERT* promoter gene mutation pattern and its prognostic value in melanoma patients: A retrospective study of 2,793 cases. *Clin Cancer Res* 23: 6120-6127, 2017
6. Lazarev S, Gupta V, Hu K, et al: Mucosal melanoma of the head and neck: A systematic review of the literature. *Int J Radiat Oncol Biol Phys* 90:1108-1118, 2014
7. Cancer Genome Atlas Network: Genomic classification of cutaneous melanoma. *Cell* 161:1681-1696, 2015
8. Nassar KW, Tan AC: The mutational landscape of mucosal melanoma. *Semin Cancer Biol* 61:139-148, 2020
9. Doma V, Barbai T, Bealeau MA, et al: KIT mutation incidence and pattern of melanoma in central Europe. *Pathol Oncol Res* 26:17-22, 2020
10. Riobello C, Casanueva Muruais R, Suárez-Fernández L, et al: Intragenic NF1 deletions in sinonasal mucosal malignant melanoma. *Pigment Cell Melanoma Res* 35:88-96, 2022
11. Buchbinder EI, Weirather JL, Manos M, et al: Characterization of genetics in patients with mucosal melanoma treated with immune checkpoint blockade. *Cancer Med* 10:2627-2635, 2021
12. Wróblewska JP, Dias-Santagata D, Ustaszewski A, et al: Prognostic roles of BRAF, KIT, NRAS, IGF2R and SF3B1 mutations in mucosal melanomas. *Cells* 10:2216, 2021
13. Guo W, Yin G, Cui C, et al: Gene mutations and clinical prognosis of mucosal melanoma in different locations of head and neck. *Acta Otolaryngol* 142:94-99, 2022
14. Sun W, Liu K, Zhou H, et al: Whole-exome sequencing reveals mutational profiles of anorectal and gynecological melanoma. *Med Oncol* 40:330, 2023
15. Wang H-Y, Liu Y, Deng L, et al: Clinical significance of genetic profiling based on different anatomic sites in patients with mucosal melanoma who received or did not receive immune checkpoint inhibitors. *Cancer Cell Int* 23:187, 2023
16. Hida T, Kato J, Idogawa M, et al: Genomic landscape of cutaneous, acral, mucosal, and uveal melanoma in Japan: Analysis of clinical comprehensive genomic profiling data. *Int J Clin Oncol* 29: 1984-1998, 2024
17. Clavero-Rovira L, Gómez-Tomás Á, Bassas-Freixas P, et al: Mucosal melanoma clinical management and prognostic implications: A retrospective cohort study. *Cancers* 16:227, 2024
18. Leirich BM, Abiri A, Nguyen TV, et al: Mutational landscape and predictors of survival in head and neck mucosal melanoma. *Int Forum Allergy Rhinol* 14:858-861, 2024
19. Hida T, Idogawa M, Kato J, et al: Genetic characteristics of cutaneous, acral, and mucosal melanoma in Japan. *Cancer Med* 13:e70360, 2024
20. Zou Z, Ou Q, Ren Y, et al: Distinct genomic traits of acral and mucosal melanomas revealed by targeted mutational profiling. *Pigment Cell Melanoma Res* 33:601-611, 2020
21. Lyu J, Wu Y, Li C, et al: Next-generation sequencing in advanced Chinese melanoma reveals therapeutic targets and prognostic biomarkers for immunotherapy. *Sci Rep* 12:9559, 2022
22. Wan PTC, Garnett MJ, Roe SM, et al: Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell* 116:855-867, 2004
23. Newell F, Kong Y, Wilmott JS, et al: Whole-genome landscape of mucosal melanoma reveals diverse drivers and therapeutic targets. *Nat Commun* 10:3163, 2019
24. Cirenajwis H, Lauss M, Ekedahl H, et al: *NF1*-mutated melanoma tumors harbor distinct clinical and biological characteristics. *Mol Oncol* 11:438-451, 2017
25. Alicea GM, Rebecca VW: Emerging strategies to treat rare and intractable subtypes of melanoma. *Pigment Cell Melanoma Res* 34:44-58, 2021
26. Fortuna A, Amaral T: Multidisciplinary approach and treatment of acral and mucosal melanoma. *Front Oncol* 14:1340408, 2024
27. Hintsche JD, Gordon NT, Amato CM, et al: Whole-exome sequencing identifies recurrent SF3B1 R625 mutation and comutation of NF1 and KIT in mucosal melanoma. *Melanoma Res* 27:189-199, 2017
28. Curtin JA, Busam K, Pinkel D, et al: Somatic activation of KIT in distinct subtypes of melanoma. *J Clin Oncol* 24:4340-4346, 2006
29. Beadling C, Jacobson-Dunlop E, Hodi FS, et al: *KIT* gene mutations and copy number in melanoma subtypes. *Clin Cancer Res* 14:6821-6828, 2008
30. Carvajal RD, Antonescu CR, Wolchok JD, et al: KIT as a therapeutic target in metastatic melanoma. *JAMA* 305:2327-2334, 2011
31. Lyu J, Wu Y, Li C, et al: Mutation scanning of *BRAF*, *NRAS*, *KIT*, and *GNAQ/GNA11* in oral mucosal melanoma: A study of 57 cases. *J Oral Pathol Med* 45:295-301, 2016
32. Indini A, Roila F, Grossi F, et al: Molecular profiling and novel therapeutic strategies for mucosal melanoma: A comprehensive review. *Int J Mol Sci* 23:147, 2021
33. Omholt K, Grafström E, Kanter-Lewensohn L, et al: KIT pathway alterations in mucosal melanomas of the vulva and other sites. *Clin Cancer Res* 17:3933-3942, 2011
34. Hayward NK, Wilmott JS, Waddell N, et al: Whole-genome landscapes of major melanoma subtypes. *Nature* 545:175-180, 2017
35. Rabbie R, Ferguson P, Molina-Aguilar C, et al: Melanoma subtypes: Genomic profiles, prognostic molecular markers and therapeutic possibilities. *J Pathol* 247:539-551, 2019
36. Sheng X, Kong Y, Li Y, et al: *GNAQ* and *GNA11* mutations occur in 9.5% of mucosal melanoma and are associated with poor prognosis. *Eur J Cancer* 65:156-163, 2016
37. Newell F, Johansson PA, Wilmott JS, et al: Comparative genomics provides etiologic and biological insight into melanoma subtypes. *Cancer Discov* 12:2856-2879, 2022
38. Wang M, Banik I, Shain AH, et al: Integrated genomic analyses of acral and mucosal melanomas nominate novel driver genes. *Genome Med* 14:65, 2022
39. Ichimura N, Urata Y, Kobayashi T, et al: Mutational landscape of oral mucosal melanoma based on comprehensive cancer genomic profiling tests in a Japanese cohort. *Oral Oncol* 152:106807, 2024
40. Xu L, Cheng Z, Cui C, et al: Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. *J Transl Med* 17:245, 2019
41. Huang R, Shen G, Ren Y, et al: Prognostic value of genetic aberrations and tumor immune microenvironment in primary acral melanoma. *J Transl Med* 21:78, 2023
42. Zhou Z, Gong Q, Wang Y, et al: The biological function and clinical significance of SF3B1 mutations in cancer. *Biomark Res* 8:38, 2020

43. Yavuzytigotlu S, Koopmans AE, Verdijk RM, et al: Uveal melanomas with SF3B1 mutations: A distinct subclass associated with late-onset metastases. *Ophthalmology* 123:1118-1128, 2016
44. Denton AE, Roberts EW, Fearon DT: Stromal cells in the tumor microenvironment, in Owens BMJ, Lakins MA (eds): *Stromal Immunology*, Volume 1060. Cham, Switzerland, Springer International Publishing, 2018, pp 99-114
45. Hirata E, Sahai E: Tumor microenvironment and differential responses to therapy. *Cold Spring Harb Perspect Med* 7:a026781, 2017
46. Umansky V, Sevko A, Gebhardt C, et al: Myeloid-derived suppressor cells in malignant melanoma. *J Dtsch Dermatol Ges* 12:1021-1027, 2014
47. Bitsch R, Kurzay A, Özbay Kurt F, et al: STAT3 inhibitor napabucasin abrogates MDSC immunosuppressive capacity and prolongs survival of melanoma-bearing mice. *J Immunother Cancer* 10:e004384, 2022
48. Lerner BA, Stewart LA, Horowitz DP, et al: Mucosal melanoma: New insights and therapeutic options for a unique and aggressive disease. *Oncology (Williston Park)* 31:23-32, 2017
49. Trandafir CM, Closca RM, Poenaru M, et al: Morphological and immunohistochemical aspects with prognostic implications and therapeutic targets of primary sinonasal mucosal melanoma: A retrospective study. *Cancers* 16:2863, 2024
50. Taube JM, Anders RA, Young GD, et al: Colocalization of inflammatory response with B7-H1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med* 4:127ra37, 2012
51. Kaunitz GJ, Cottrell TR, Lilo M, et al: Melanoma subtypes demonstrate distinct PD-L1 expression profiles. *Lab Invest* 97:1063-1071, 2017
52. Gao Z, Wang L, Song Z, et al: Intratumoral CD73: An immune checkpoint shaping an inhibitory tumor microenvironment and implicating poor prognosis in Chinese melanoma cohorts. *Front Immunol* 13:954039, 2022
53. Ho J, Mattei J, Tetzlaff M, et al: Neoadjuvant checkpoint inhibitor immunotherapy for resectable mucosal melanoma. *Front Oncol* 12:1001150, 2022
54. Lian B, Li Z, Wu N, et al: Phase II clinical trial of neoadjuvant anti-PD-1 (toripalimab) combined with axitinib in resectable mucosal melanoma. *Ann Oncol* 35:211-220, 2024
55. Mao L, Si L, Dai J, et al: NeoPlus: A phase II study of neoadjuvant lenvatinib and pembrolizumab in resectable mucosal melanoma. *J Clin Oncol* 41, 2023 (suppl 16; abstr 9514)
56. Salem AF, Chen MM, Williams MD, et al: Resectable sinonasal mucosal melanoma in the immunotherapy era: Upfront surgery vs. neoadjuvant therapy. *Head Neck* 10.1002/hed.28098 [pub ahead of print on February 5, 2025]
57. Ong CV, Samlowski W: Neoadjuvant ipilimumab plus nivolumab therapy as a potential organ preservation strategy in mucosal melanoma: Case report. *Front Oncol* 14:1301424, 2024
58. Krueger O, Eisenburger R, Tasdogan A, et al: Case report: Durable complete response of a mucosal melanoma of the rectum after neoadjuvant immunotherapy with ipilimumab plus nivolumab. *Front Immunol* 15:1369190, 2024
59. Papanikolaou GE, Tsimogiannis K, Kampletsas E, et al: Combined neoadjuvant-adjuvant immunotherapy and abdominoperineal resection for a primary anorectal melanoma: A case report. *Cureus* 16:e73931, 2024
60. Lian B, Si L, Cui C, et al: Phase II randomized trial comparing high-dose IFN- α 2b with temozolomide plus cisplatin as systemic adjuvant therapy for resected mucosal melanoma. *Clin Cancer Res* 19:4488-4498, 2013
61. Lian B, Cui C, Song X, et al: Phase 3 randomized, multicenter trial comparing high-dose IFN- α 2b with temozolomide plus cisplatin as adjuvant therapy for resected mucosal melanoma. *J Clin Oncol* 36, 2018 (suppl 15; abstr 9589)
62. Lian B, Tian H, Si L, et al: Temozolomide plus cisplatin versus toripalimab (anti-PD-1) as adjuvant therapy in resected mucosal melanoma. *J Clin Oncol* 41, 2023 (suppl 16; abstr 9508)
63. Lian B, Si L, Chi ZH, et al: Toripalimab (anti-PD-1) versus high-dose interferon- α 2b as adjuvant therapy in resected mucosal melanoma: A phase II randomized trial. *Ann Oncol* 33:1061-1070, 2022
64. Muto Y, Kambayashi Y, Kato H, et al: Three-year analysis of adjuvant therapy in postoperative melanoma including acral and mucosal subtypes. *Cancers* 16:2755, 2024
65. Jacques SK, McKeown J, Grover P, et al: Outcomes of patients with resected stage III/IV acral or mucosal melanoma, treated with adjuvant anti-PD-1 based therapy. *Eur J Cancer* 199:113563, 2024
66. Bai X, Mao LL, Chi ZH, et al: BRAF inhibitors: Efficacious and tolerable in BRAF-mutant acral and mucosal melanoma. *Neoplasia* 64:626-632, 2017
67. Azem O, Nabulsi O, Jelinek M, et al: Radiation therapy in the management of head and neck mucosal melanoma. *Cancers* 16:3304, 2024
68. Caspers CJ, Dronkers EAC, Monserez D, et al: Adjuvant radiotherapy in sinonasal mucosal melanoma: A retrospective analysis. *Clin Otolaryngol* 43:617-623, 2018
69. Li W, Yu Y, Wang H, et al: Evaluation of the prognostic impact of postoperative adjuvant radiotherapy on head and neck mucosal melanoma: A meta-analysis. *BMC Cancer* 15:758, 2015
70. Tsushima N, Kano S, Yasuda K, et al: Treatment outcomes of the patient with sinonasal mucosal melanoma: The role of endoscopic resection and postoperative radiotherapy. *Int J Clin Oncol* 28: 1218-1226, 2023
71. Yao J-J, Zhang F, Zhang GS, et al: Efficacy and safety of primary surgery with postoperative radiotherapy in head and neck mucosal melanoma: A single-arm phase II study. *Cancer Manag Res* 10: 6985-6996, 2018
72. Lian B, Yang Y, Zheng B, et al: Efficacy and safety of postoperative adjuvant radiation therapy in resected nasal cavity and paranasal sinus mucosal melanoma: A combined analysis. *Int J Radiat Oncol Biol Phys* 120:528-536, 2024
73. Long GV, Stroyakovskiy D, Gogas H, et al: Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 386:444-451, 2015
74. Guo J, Carvajal RD, Dummer R, et al: Efficacy and safety of nilotinib in patients with KIT-mutated metastatic or inoperable melanoma: Final results from the global, single-arm, phase II TEAM trial. *Ann Oncol* 28:1380-1387, 2017
75. Hodi FS, Corless CL, Giobbie-Hurder A, et al: Imatinib for melanomas harboring mutationally activated or amplified *KIT* arising on mucosal, acral, and chronically sun-damaged skin. *J Clin Oncol* 31: 3182-3190, 2013
76. Guo J, Si L, Kong Y, et al: Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring *c-kit* mutation or amplification. *J Clin Oncol* 29:2904-2909, 2011
77. Wang X, Luo Z, Chen J, et al: First-in-human phase I dose-escalation and dose-expansion trial of the selective MEK inhibitor HL-085 in patients with advanced melanoma harboring NRAS mutations. *BMC Med* 21:2, 2023
78. Ascierto PA, Schadendorf D, Berking C, et al: MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: A non-randomised, open-label phase 2 study. *Lancet Oncol* 14:249-256, 2013
79. Wei X, Zou Z, Zhang W, et al: A phase II study of efficacy and safety of the MEK inhibitor tunlametinib in patients with advanced NRAS-mutant melanoma. *Eur J Cancer* 202:114008, 2024
80. Cai W, Nguyen MQ, Wilski NA, et al: A genome-wide screen identifies PDPK1 as a target to enhance the efficacy of MEK1/2 inhibitors in NRAS mutant melanoma. *Cancer Res* 82:2625-2639, 2022
81. Si L, Zhang X, Shu Y, et al: Pembrolizumab in Chinese patients with advanced melanoma: 3-year follow-up of the KEYNOTE-151 study. *Front Immunol* 13:882471, 2022
82. Hamid O, Robert C, Ribas A, et al: Antitumour activity of pembrolizumab in advanced mucosal melanoma: A post-hoc analysis of KEYNOTE-001, 002, 006. *Br J Cancer* 119:670-674, 2018
83. Tang B, Chi Z, Chen Y, et al: Correction: Safety, efficacy, and biomarker analysis of toripalimab in previously treated advanced melanoma: Results of the POLARIS-01 multicenter phase II trial. *Clin Cancer Res* 26:5048, 2020
84. Cui C, Chen Y, Luo Z, et al: Safety and efficacy of pucotenlimab (HX008)—A humanized immunoglobulin G4 monoclonal antibody in patients with locally advanced or metastatic melanoma: A single-arm, multicenter, phase II study. *BMC Cancer* 23:121, 2023
85. Nomura M, Oze I, Masuishi T, et al: Multicenter prospective phase II trial of nivolumab in patients with unresectable or metastatic mucosal melanoma. *Int J Clin Oncol* 25:972-977, 2020
86. Mao L, Qi Z, Zhang L, et al: Immunotherapy in acral and mucosal melanoma: Current status and future directions. *Front Immunol* 12:680407, 2021
87. Carlino MS, Larkin J, Long GV: Immune checkpoint inhibitors in melanoma. *Lancet* 398:1002-1014, 2021
88. D'Angelo SP, Larkin J, Sosman JA, et al: Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: A pooled analysis. *J Clin Oncol* 35:226-235, 2017
89. Horisaki K, Yoshikawa S, Omata W, et al: Comparison of efficacy between anti-PD-1 antibody monotherapy and nivolumab plus ipilimumab therapy as first-line immunotherapy for advanced mucosal melanoma in Japanese patients: A single-center, retrospective cohort study. *J Dermatol* 51:1425-1433, 2024
90. Cui C, Mao L, Chi Z, et al: A phase II, randomized, double-blind, placebo-controlled multicenter trial of endostar in patients with metastatic melanoma. *Mol Ther* 21:1456-1463, 2013
91. Sheng X, Yan X, Chi Z, et al: Axitinib in combination with toripalimab, a humanized immunoglobulin G4 monoclonal antibody against programmed cell death-1, in patients with metastatic mucosal melanoma: An open-label phase IB trial. *J Clin Oncol* 37:2987-2999, 2019
92. Sheng X, Yan X, Chi Z: Overall survival and biomarker analysis of a phase Ib combination study of toripalimab, a humanized IgG4 mAb against programmed death-1 (PD-1) with axitinib in patients with metastatic mucosal melanoma. *J Clin Oncol* 38:10007, 2020
93. Si L, Fang M, Chen Y: Atezolizumab in combination with bevacizumab in patients with unresectable locally advanced or metastatic mucosal melanoma: Interim analysis of an open-label phase II trial. *J Clin Oncol* 39:9511-9511, 2021

94. Dai J, Xu T, Li L, et al: Atezolizumab plus bevacizumab in patients with unresectable or metastatic mucosal melanoma: 3-year survival update and multi-omics analysis. *Clin Transl Med* 15:e70169, 2025
 95. Zhao L, Ren Y, Zhang G, et al: Single-arm study of camrelizumab plus apatinib for patients with advanced mucosal melanoma. *J Immunother Cancer* 12:e008611, 2024
 96. Cui C, Yan X, Liu S, et al: Real-world clinical outcomes of anticancer treatments in patients with advanced melanoma in China: Retrospective, observational study. *Int J Surg Oncol* 4:e76, 2019
 97. Zhou R, Shi C, Tao W, et al: Analysis of mucosal melanoma whole-genome landscapes reveals clinically relevant genomic aberrations. *Clin Cancer Res* 25:3548-3560, 2019
 98. Sun L, Kang X, Ju H, et al: A human mucosal melanoma organoid platform for modeling tumor heterogeneity and exploring immunotherapy combination options. *Sci Adv* 9:eadg6686, 2023
 99. Freiburger SN, Holzmann D, Morand GB, et al: Combinational expression of tumor testis antigens NY-ESO-1, MAGE-A3, and MAGE-A4 predicts response to immunotherapy in mucosal melanoma patients. *J Cancer Res Clin Oncol* 149:5645-5653, 2023
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Beyond Checkpoint Inhibition: Keeping Therapeutic Options Open

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OVERVIEW

Combination immune checkpoint inhibitor therapy (ICI) with ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4) + nivolumab (anti-PD-1) in untreated, metastatic melanoma has achieved a ten-year melanoma-specific survival of 52%. However, approximately 40%–55% of patients with metastatic melanoma have primary resistance and do not initially respond to anti-PD-1, and an additional 25% of patients develop secondary resistance, exhibiting an initial response followed by disease progression. In PD-1-refractory melanoma, treatment options are limited. Addition of ipilimumab, relatlimab (anti-LAG3), or lenvatinib (VEGFR TKI) has minimal to modest efficacy. Switching to targeted BRAF/MEK inhibition improves survival for BRAF-mutant disease. MEK and KIT inhibitors have limited activity in NRAS- and KIT-mutant metastatic melanoma, respectively. Recently, personalized, autologous tumor-infiltrating lymphocyte therapy has become a US Food and Drug Administration–approved second-line option; lifileucel demonstrates durable response (approximately 30%) in heavily pretreated, metastatic melanoma. Emerging therapeutics that show promising clinical benefit in ongoing clinical trials include novel engineered oncolytic viral and human leukocyte antigen (HLA)–restricted immune-mediated T-cell therapies. As a therapy which is limited to patients who are HLA-A*02:01, T-cell receptor (TCR) engineered T cells (TCR-T) iterates on personalized adoptive cell transfer, and immune mobilizing monoclonal TCRs against cancer are CD3 bispecifics that bind glycoprotein 100 (tebentafusp, approved for metastatic uveal melanoma) or PRAME to activate T cells. Finally, in patients at high risk for immune-related adverse events (irAEs), ICI should still be considered. ICI may be given with modified immunosuppression in patients with autoimmune disease or previous organ transplantation. Cumulative data support safe administration in older patients and in ICI rechallenge for patients with previous irAE.

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INTRODUCTION

The emergence of immune checkpoint inhibitors (ICIs), including PD-1 inhibitors such as pembrolizumab and nivolumab, marked a paradigm shift in the treatment of melanoma. Anti-PD-1 therapy enables tumor-reactive T cells to overcome innate and acquired regulatory mechanisms in the tumor microenvironment to help facilitate antitumor response. Several landmark trials have demonstrated the efficacy of anti-PD-1 therapy in melanoma, with superior outcomes compared with previous standard-of-care treatments, including anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monotherapy or chemotherapy.^{1–4}

Despite the success of anti-PD-1 therapy, which is now standard-of-care for melanoma in both the adjuvant and metastatic settings, >50% of patients with advanced melanoma do not experience a tumor response to anti-PD-1 monotherapy (ie, primary resistance).⁵ Of those who do

experience tumor regression, many will develop resistance over time (ie, secondary resistance) with a reported approximately 23% progression-free survival (PFS) at 10 years among patients receiving anti-PD-1 monotherapy.⁴ Several mechanisms have been implicated in resistance, including loss of antigen presentation, oncogenic pathway activation, upregulation of alternate immune checkpoints, tumor microenvironment factors, and genetic influences.⁶

Leveraging understanding of these resistance mechanisms, there are now several established treatment strategies that offer hope for patients with anti-PD-1-refractory melanoma including TIL therapy. Additionally, emerging next-generation therapeutics in melanoma include oncolytic viruses, CD3 bispecific immune-mobilizing monoclonal TCR against cancer (ImmTAC), and T-cell receptor (TCR) engineered T-cell (TCR-T) therapy.

Finally, concern for immune-related adverse events (irAEs) has limited the use of ICI in those with autoimmune diseases,

PRACTICAL APPLICATIONS

- The development of immune checkpoint inhibition and BRAF-targeted therapies for metastatic melanoma was revolutionary in producing durable responses that dramatically improved overall survival for approximately half of the patients. However, for the nearly 50% of patients who do not benefit from checkpoint inhibition because of primary or secondary resistance, effective treatment options are limited, and survival remains poor.
- A new generation of therapeutics, notably including adoptive cell transfer with tumor-infiltrating lymphocyte and T-cell receptor (TCR) engineered T cells, oncolytic virus therapy, and CD3 bispecific immunomobilizing monoclonal TCRs against cancer, are poised to be the next breakthrough in therapeutics for metastatic melanoma. These novel therapies provide the potential for long-term survival, even in patients with checkpoint inhibitor-resistant and BRAF-targeted refractory disease.
- Patients with a high risk of immune-related adverse events (irAEs), such as individuals with autoimmune diseases, transplant recipients, history of severe irAE, and elderly patients, have traditionally been considered ineligible for immune checkpoint inhibition. Newer emerging treatment strategies for irAE allow ICIs to be safely administered and cautiously challenged in these populations to improve survival, with close monitoring and modified immunosuppression regimens as necessary.

transplant recipients, individuals with previous irAE, and elderly patients. Strategies to dampen the toxicity of irAE without sacrificing efficacy can expand the number of people who experience durable ICI response.

TREATMENT APPROACHES FOR PATIENTS WITH ANTI-PD-1-REFRACTORY MELANOMA

Immunotherapy

With the differential and complementary effects of CTLA-4 and PD-1 blockade, combined administration of therapies directed at these immune checkpoints has been tested in the anti-PD-1-refractory metastatic melanoma, with comparison with either agent alone in metastatic melanoma. The addition of ipilimumab to pembrolizumab after disease progression on an anti-PD-1 therapy led to responses in 29% of patients, with a median duration of response (DOR) of 16.6 months, a median PFS of 5 months, and a median overall survival (OS) of 24.7 months.⁷ These encouraging findings are coupled with the toxicity risk of combination ICI

therapy, with 27% of patients experiencing grade 3 to 4 drug-related adverse events.⁷ Additionally, the SWOG S1616 trial evaluated combination ipilimumab + nivolumab versus ipilimumab alone in metastatic melanoma refractory to previous anti-PD-(L)1 therapy. This combination therapy significantly improved PFS (hazard ratio [HR], 0.63) with a 28% objective response rate (ORR) and 40.9-month median DOR compared with a 9% response rate in the ipilimumab monotherapy arm.⁸ Of note, grade 3 to 4 treatment-related toxicity in the ipilimumab + nivolumab arm was approximately 56%, similar to historically reported toxicity rates in patients receiving this combination at standard dosing of ipilimumab at 3 mg/kg + nivolumab at 1 mg/kg.⁸ Consideration should be given to this toxicity profile when considering this approach for higher-risk patient populations (eg, patients with underlying autoimmune disorders, previous ICI toxicities, and the elderly).

The Checkmate 511 trial investigated flipped-dose ipilimumab and nivolumab at 1 and 3 mg/kg every 3 weeks for 4 cycles, respectively, among patients with previously untreated unresectable stage IV melanoma compared against more traditional dosing and demonstrated significantly lower grade 3/4 toxicities seen with the former regimen, 34% versus 48% ($P = .006$).⁹ Although flipped-dose ipilimumab + nivolumab has not been tested prospectively in the anti-PD-1-refractory population, this approach may be considered when concerns surrounding potential ICI toxicity is a barrier to a patient receiving combination immunotherapy.

Patients with anti-PD-1-refractory melanoma progression in the CNS can be a particularly difficult subset of patients to treat. Tawbi et al¹⁰ reported approximately 50% intracranial response rate with first-line ipilimumab + nivolumab in patients with asymptomatic melanoma brain metastases with durable responses seen in 42% of patients at 7 years.¹¹ BRAF/MEK inhibitors (MEKi) have also demonstrated intracranial activity but with relatively short (approximately 6 months) intracranial PFS.¹² Based upon these data, ipilimumab + nivolumab is established as first-line therapy for patients with brain metastases, when possible, and typically recommended for anti-PD-(L)1 relapsed or refractory melanoma in the CNS.

The combination of relatlimab, an anti-LAG-3 therapy, with nivolumab is another treatment option for anti-PD-1-refractory melanoma. Early-phase studies tested nivolumab + relatlimab in heavily pretreated patients with melanoma refractory to anti-PD-1 ± anti-CTLA-4, and demonstrated response rates between 9% and 12%.¹³ In the phase II/III RELATIVITY-047 trial, nivolumab plus relatlimab significantly improved PFS (10.1 v 4.6 months) compared with nivolumab alone for patients with untreated metastatic melanoma, highlighting potential benefits of dual PD-1/LAG-3 blockade.¹⁴ Nivolumab + relatlimab appears to be better tolerated, with grade 3-4 treatment-related adverse events seen in approximately 20% of patients, compared with the higher likelihood of high-

grade treatment-related adverse events seen with standard ipilimumab + nivolumab dosing.

Lifileucel, an autologous TIL therapy, is an emerging treatment modality for patients with disease progression after anti-PD-1 therapy and BRAF/MEK inhibitor therapy. In the phase II C-144-01 trial, lifileucel demonstrated a 31.4% ORR in patients with heavily pretreated metastatic melanoma including those with high baseline disease burden and previous exposure to anti-PD-1 and BRAF/MEK inhibitors.¹⁵ These durable responses led to the US Food and Drug Administration (FDA) accelerated approval for lifileucel, offering a new therapeutic option for patients with progressive unresectable or advanced melanoma previously treated with PD-1-based therapy, and if BRAF V600-positive, a BRAF inhibitor with or without a MEK inhibitor.

Talimogene laherparepvec (T-VEC), an oncolytic virus therapy derived from genetically modified herpes simplex virus type 1, is designed to selectively replicate within and lyse tumor cells while stimulating an antitumor response. T-VEC may be considered in a select population of anti-PD-1-refractory melanoma tumors, including stage IIIB to IVM1a melanoma with tumors amenable for direct injection. The phase II MASTERKEY-115 study evaluated efficacy of T-VEC plus pembrolizumab in patients with unresectable/metastatic melanoma that previously progressed on anti-PD-1 therapy and in patients with resected melanoma who experienced recurrence despite adjuvant anti-PD-1 therapy. Among patients with recurrent melanoma occurring <6 months and ≥6 months after starting adjuvant anti-PD-1 therapy, ORR was 40% and 46.7%, respectively. Among patients with unresectable/metastatic melanoma who had primary and acquired resistance, ORR was 0% and 6%, respectively.¹⁶ Patient selection is critical for patients under consideration for T-VEC, and those with small volume, injectable tumors may be better served compared with patients with high tumor burden.

There is a paucity of data on the best approach to locoregional resectable recurrence after receiving adjuvant anti-PD-1 therapy. Historically, in patients who had not previously undergone a complete lymph node dissection (CLND), a CLND was recommended at the time of locoregional lymph node recurrence.¹⁷ Systemic therapy is now routinely recommended in these patients and, in addition to the therapies discussed throughout this chapter, neoadjuvant sequencing of immunotherapy may also be considered for patients. This consideration is based on data extrapolated from the NADINA trial, which showed improved event-free survival in patients with macroscopic stage III melanoma who received neoadjuvant ipilimumab + nivolumab followed by surgery and response-driven adjuvant therapy compared with patients who received surgery followed by adjuvant therapy (HR, 0.32).¹⁸

Finally, among patients who recur off, or after completion of, adjuvant anti-PD-1 therapy, re-treatment with anti-PD-1 monotherapy therapy may be considered.¹⁹

Targeted Therapy

Melanoma is a genetically heterogeneous disease with distinct mutational profiles that influence tumor behavior, treatment response, and resistance mechanisms. Next-generation sequencing (NGS) can play a critical role in determining treatment options for both treatment-naïve and anti-PD-1-refractory advanced melanoma. Specifically, through comprehensive genomic profile of the tumor, NGS can identify actionable mutations such as BRAF, KIT, and NRAS, which may be targeted with specific inhibitors to improve outcomes for patients.

Mutations in BRAF are present in approximately 40%–50% of cutaneous melanoma, with the most common alterations including BRAF V600E and V600K. These mutations lead to the constitutive activation of the MAPK/ERK signaling pathway and act as drivers facilitating unregulated growth of melanoma cells. BRAF inhibitors (BRAFi) and MEKi can offer relatively robust and expedient benefit to patients with BRAF-mutated melanoma. There are three FDA-approved BRAFi/MEKi combinations for treatment of advanced BRAFV600 E/K melanoma; dabrafenib + trametinib, encorafenib + binimetinib, and vemurafenib + cobimetinib. Efficacy is similar across all three combinations, with reported median PFS of 11.4, 12.9, and 12.3 months, respectively.^{10,20,21} Patients should be counseled on what is often a limited DOR with these agents owing to the development of resistance. Side effects between the three combinatorial agents vary and should also be taken into consideration for an individual patient.

Key data for patients with PD-1-refractory, BRAF-mutated disease stem from KEYNOTE-006, in which patients with progression of melanoma on pembrolizumab received BRAFi with or without MEKi. The response rate for all comers was 30%, and rose to 43% for patients naïve to BRAFi/MEKi. Median OS from the time of BRAF/MEK initiation was 16 months without previous BRAFi/MEKi and 12 months for patients previously treated with targeted agents.²² The DREAMseq (EA6134) trial established the preferred sequencing of BRAFi/MEKi was after combination ipilimumab + nivolumab and also yielded lessons on expected outcomes with targeted therapy both in this context, and more generally for anti-PD-1-refractory disease. In this study, combination dabrafenib and trametinib after previous ipilimumab + nivolumab therapy led to a superior 2-year OS rate of 72% compared with 52% for those who began with targeted therapy and then switched to combination immunotherapy at the time of progression.²³

KIT inhibitors may be considered in patients whose melanoma harbors activating KIT mutations. Of note, these mutations are more frequently identified in acral and mucosal subtypes of melanomas. A small study was published showing activity of imatinib in patients with KIT-mutant metastatic melanoma with an ORR of 29% and a median follow-up of 10.9 months (range, 3.6–27 months).²⁴ Similar

efficacy, and DOR, was seen for ripretinib in a small phase I study studying efficacy and safety of this approach for patients with KIT-altered metastatic melanoma.²⁵ Targeted therapy options for patients with NRAS-mutant metastatic melanoma are limited, with MEK inhibition demonstrating limited success. Binimetinib, a MEKi, was compared with dacarbazine in patients with NRAS-mutant metastatic melanoma with a median PFS of 2.8 months and 1.5 months, respectively (HR, 0.62).²⁶ Additional targeted therapy considerations are listed in the National Comprehensive Cancer Network guidelines for less common actionable mutations and fusions (eg, NTRK, ROS1) seen in melanoma tumors.

Combinatorial Immunotherapy + Targeted Therapy

The phase II LEAP-004 trial investigated the efficacy of pembrolizumab and lenvatinib for patients with PD-(L)1-refractory advanced melanoma. In this study, combination pembrolizumab and lenvatinib demonstrated an ORR of 21.4% with a median DOR of 8.3 months.²⁶ Median PFS was 4.2 months with a median OS of 14 months.²⁶ Toxicity of this combination needs to be considered, given reported grade 3–5 treatment-related adverse events were seen in approximately 45% of patients. Given the modest efficacy and higher rate of side effects, this treatment approach is generally considered after a patient experiences progressive disease after other combinatorial ICI approaches and BRAF-/MEK-targeted therapy.

Chemotherapy

Conventional chemotherapy can be considered for all patients with anti-PD-1-refractory melanoma, but is generally reserved for those who are refractory to, or ineligible for, all other targeted or immunotherapy options. Chemotherapeutic agents commonly used for melanoma include temozolomide (particularly for melanoma with CNS involvement), with previous studies showing a median PFS of 1.9 months²⁷ and carboplatin/paclitaxel with a median PFS of 4.1.²⁸

NEXT-GENERATION THERAPEUTICS

Oncolytic Viruses

Oncolytic viruses leverage multiple mechanisms to directly kill tumor cells and to amplify immunogenic cell death toward a broader expansion of antitumor immunity. Vusolimogene oderparepvec (previously known as RP1) is a genetically engineered HSV-1 platform (strain RH018A) designed to be nonpathogenic (deletion of genes encoding neurovirulence factors ICP34.5 and ICP47) and to have augmented tumor cell killing (insertion of gene encoding fusogenic protein GALV-GP-R⁻ and human GM-CSF).²⁹ Murine modeling with the agent demonstrated both injected and noninjected lesion response as well as activity of RP1 with anti-PD-1 in an anti-PD-1-resistant model.²⁹ The phase I/II IGNYTE study (ClinicalTrials.gov identifier:

NCT03767348) enrolled patients with locally advanced or metastatic cutaneous melanoma who had progressive disease on previous anti-PD-1 ± anti-CTLA-4 and had at least one measurable, injectable tumor (≥1 cm).³⁰ Patients received an initial dose of intratumoral RP1 at 1×10^6 plaque-forming units (PFU) followed by RP1 at 1×10^7 PFU combined with nivolumab 240 mg intravenously every two weeks for up to eight total cycles, followed by maintenance nivolumab for up to 2 years. In a registration-intent phase II cohort (FDA PDUFA date July 22, 2025), 140 patients were included, notably including 65.7% with primary anti-PD-1 resistance and 43% who had received both anti-PD-1 and anti-CTLA-4.³¹ The ORR was 33.6% with complete response (CR) occurring in 15.0% and 3-year OS of 54.8%. Responses were durable with 85.1% ongoing response 1 year after treatment initiation and a median DOR of 21.6 months.³¹ Tumor response was seen in both injected and noninjected lesions. Treatment-related adverse events (TRAEs) were predominantly low-grade and constitutional or associated with injection, including fatigue, chills, pyrexia, nausea, injection site pain, and/or known safety profile of nivolumab. The subsequent phase III, randomized controlled multicenter trial IGNYTE-3 (ClinicalTrials.gov identifier: NCT06264180) will investigate RP1 + nivolumab versus physician's choice.³²

CD3 Bispecifics

ImmTACs are immune-mobilizing monoclonal TCRs against cancer engineered by fusing a tumor-associated, epitope-specific TCR to a humanized anti-CD3 antibody fragment with the intent of inducing tumor targeted T-cell responses.³³ Tebentafusp is an ImmTAC that recognizes glycoprotein 100 (gp100), which is a peptide presented by human leukocyte antigen (HLA)-A*02:01 and is highly expressed in uveal melanoma.³⁴ Approximately 45% of people in the United States and Europe are HLA-A*02:01-positive.³⁵ Notably, HLA testing is obtained from a peripheral blood sample and serves as an important patient-derived biomarker that guides treatment selection.

Tebentafusp, a gp100 targeting ImmTAC, is approved for treatment of HLA-A*02:01+ patients with unresectable or metastatic uveal melanoma, based upon results from a phase III randomized trial (ClinicalTrials.gov identifier: NCT03070392) with 378 treatment-naïve patients reporting a 1-year OS of 73% with tebentafusp versus 59% investigator's choice (HR, 0.51 [95% CI, 0.37 to 0.71]).³⁵ The most common toxicities were cytokine release syndrome (CRS; 89%), rash (83%), and pyrexia (76%), with G3–G4 events notably including CRS and rash. Tebentafusp has also shown promise beyond uveal melanoma, with early-phase data demonstrating preliminary efficacy alone and in combination with immune checkpoint inhibition in metastatic cutaneous melanoma.³⁶ The TEBE-AM trial (ClinicalTrials.gov identifier: NCT05549297) is an ongoing phase II/III trial investigating tebentafusp as monotherapy and in combination with pembrolizumab in HLA-A*02:01+ patients with previously treated advanced nonuveal melanoma.³⁷

Brenetafusp is a novel CD3 bispecific immTAC targeting PRAME. A phase I trial (ClinicalTrials.gov identifier: [NCT04262466](#)) including 56 HLA-A*02:01+ patients with pretreated cutaneous melanoma reported brenetafusp achieved a disease control rate of 58% in PRAME+ patients.³⁸ The toxicity profile of brenetafusp was similar to tebentafusp, with most frequently reported TRAEs of CRS, rash, pyrexia, and chills; G3-G4 events were notable for transient lymphocyte decrease. A subsequent phase III randomized trial PRISM-MEL-301 (ClinicalTrials.gov identifier: [NCT06112314](#)) comparing combination brenetafusp + nivolumab to either nivolumab or nivolumab + relatlimab is in progress.³⁹ Notably, baseline T-cell fitness may be predictive of immTAC clinical benefit. A novel T-cell fitness gene expression signature (correlating with naïve and stem cell memory T-cell genes) has been identified to be strongly associated with OS in patients with metastatic uveal melanoma treated with tebentafusp and brenetafusp.⁴⁰

Tumor-Infiltrating Lymphocyte Therapy

Autologous TIL cell therapy is a personalized adoptive T-cell therapy that leverages preexistent tumor immunity with the potential to recognize the spectrum of patient-specific neoantigens.¹⁵ To pursue TIL therapy, tumor-resident T cells are first surgically harvested from a patient's tumor tissue and expanded ex vivo, then administered back to the patient as a therapeutic agent.⁴¹ TIL product reinfusion is preceded by nonmyeloablative, lymphodepleting chemotherapy, and is followed by high-dose aldesleukin (alias interleukin-2 [IL-2]) for enhanced immune stimulation.

In a phase III trial (ClinicalTrials.gov identifier: [NCT02278887](#)), 168 patients with unresectable or metastatic melanoma were randomly assigned to receive TIL versus ipilimumab.⁴¹ The primary end point of the study was reached with statistically significant improvement in median PFS (7.2 v 3.1 months; HR, 0.50) as well as OS (25.8 v 18.9 months). Notable TRAEs were predominately because of chemotherapy or IL-2 including febrile neutropenia (85%, any grade) and capillary leak syndrome (30%, any grade). Lifileucel is a TIL cell therapy that received FDA Accelerated Approval in 2024 for people with advanced melanoma that progressed after ICI and targeted therapy (if BRAF V600-mutated). The approval was based on C-144-01 (ClinicalTrials.gov identifier: [NCT02360579](#)), a phase II multicenter study of 153 patients with advanced, anti-PD-1-refractory melanoma and ≥1 resectable tumor lesion (≥1.5 cm diameter).⁴² Patients were heavily pretreated (median three lines of previous therapy) with 71.2% demonstrating primary anti-PD-1 resistance. The ORR was 31.4%, with eight patients achieving CR. Responses were durable, with a median 1.5-month time to best response and median DOR was not reached (95% CI, 8.3 to NR). Long-term survival outcomes were favorable, with OS rates of 54.0%, 33.9%, and 21.9% at 1, 2, and 4 years, respectively.⁴² Toxicity was similar to that seen in other TIL clinical trials, with most frequently reported TRAEs of thrombocytopenia, chills, anemia, and fever

with G3-G4 events notable for thrombocytopenia, anemia, and febrile neutropenia.

One issue limiting broad relevance of TIL is the use of high-dose IL-2. Emerging strategies are attempting to provide alternative cytokine stimulation and support after cell infusion. OBX-115 is an autologous TIL therapy engineered with inducible expression of membrane bound IL-15 (regulated by acetazolamide).⁴³ Acetazolamide is administered after TIL infusion with optional redosing at week 6. A first-in-human study (ClinicalTrials.gov identifier: [NCT05470283](#)) of OBX-115 to date reported in 10 patients, with advanced, ICI refractory melanoma demonstrated an ORR of 44.4% and elimination of IL-2 associated toxicity.⁴³ A phase I/II multicenter study of OBX-115, Agni-01 (ClinicalTrials.gov identifier: [NCT06060613](#)), is ongoing.

TCR Engineered T-Cell Therapy

TCR-T therapy is a personalized, adoptive cell therapy approach for treatment of solid tumors through targeting both extracellular and intracellular tumor-associated antigens.⁴⁴ Notably, TCR-T differs from chimeric antigen receptor T cells (CAR-T). In TCR-T, both intracellular and extracellular antigen recognition occurs via major histocompatibility complex presentation and is HLA-restricted, whereas in CAR-T, extracellular antigen recognition occurs via a single-chain fragment variable antibody at the cell surface and is not HLA-restricted.

ACTengine IMA203 is a novel autologous TCR-T engineered to express a high affinity and high specificity TCR targeting PRAME.⁴⁵ After identification of HLA-A*02:01+ status, patients undergo leukapheresis, then TCR-T is manufactured and expanded ex vivo. Patients receive lymphodepleting chemotherapy before TCR-T infusion, followed by optional low-dose IL-2. A phase I trial (ClinicalTrials.gov identifier: [NCT03686124](#)) evaluated IMA203 in patients with HLA-A*02:01 and PRAME expressing solid tumors who were refractory to standard therapy.⁴⁵ Among 28 patients with melanoma treated above the recommended phase II dose, IMA203 demonstrated an ORR of 62%, median progression-free survival of 6.0 months, and median duration of response of 12.1 months. TRAE were most notable for cytopenias related to lymphodepletion and CRS associated with IMA203, but rapidly reversible with tocilizumab. A phase III randomized trial SUPRAME-ACTengine (ClinicalTrials.gov identifier: [NCT06743126](#)) is open to accrual evaluating IMA203 versus investigator's choice.

Conclusion: Next-Generation Therapeutics

The development of BRAF and immune checkpoint inhibition for melanoma was a revolution in solid tumor oncology as they ushered in an era of durable responses and dramatically improved OS for approximately half of the patients facing metastatic disease. A new generation of therapeutics, notably including oncolytic virus, CD3 bispecifics, TIL, and

TCR T cells, are positioned to be the next major steps forward in melanoma therapeutics providing the potential for long-term survival even in patients with BRAF and ICI refractory disease.

RETHINKING CONTRAINDICATIONS TO CHECKPOINT BLOCKADE

Preexisting Autoimmune Disease

Retrospective data suggest that ICIs can induce autoimmune flares in patients with autoimmune disorders but can be safely used with careful monitoring and immunosuppressive treatment. Johnson et al⁴⁶ found that autoimmune exacerbations occurred in only 27% treated with ipilimumab and 30% receiving anti-PD-1 therapy for melanoma. Notably, tumor response rates remained consistent with those seen in clinical trials. When treated with anti-PD-1 therapy, Menzies et al⁴⁷ observed that 38% of patients with preexisting autoimmune conditions experienced toxicities, and these were manageable with immunosuppression. Leonardi et al⁴⁸ reported that, among patients with non-small cell lung cancer (NSCLC) and autoimmune disease treated with PD-L1 inhibitor, 55% developed irAEs, of which 38% were mild and managed without systemic immunosuppression. The AIM-Nivo trial (ClinicalTrials.gov identifier: [NCT03816345](#)) is a phase Ib study assessing the safety of nivolumab in patients with advanced malignancies and preexisting autoimmune disorders, and it will provide key insights into the feasibility of ICIs in these high-risk populations.⁴⁹

Patients with preexisting autoimmune disease receiving ICI have similar OS outcomes. A meta-analysis by Zhao et al⁵⁰ found no significant difference in ORRs and disease control rates between initial and rechallenged ICI patients, suggesting that ICI rechallenge does not compromise cancer-related outcomes. Similarly, Sleiman et al⁵¹ reported that patients with preexisting inflammatory bowel disease (IBD) had a higher incidence of immune-mediated diarrhea and colitis but similar OS to non-IBD controls (HR, 0.89 [95% CI, 0.54 to 1.48]). These data cumulatively suggest at least equal efficacy of ICI in patients with preexisting autoimmune disease.

Concurrent use of targeted biologics with checkpoint inhibition may improve safety without compromising efficacy. Combining pembrolizumab with tocilizumab in the treatment of advanced melanoma in the context of Crohn's disease achieved a durable antitumor response without disease exacerbation.⁵² Multiple prospective trials testing concurrent biologic therapy with ICIs are ongoing. The TICIMEL phase Ib trial (ClinicalTrials.gov identifier: [NCT03293784](#)) in advanced melanoma showed that adding TNF inhibitors with ipilimumab (3mg/kg) and nivolumab (1mg/kg) every 3 weeks for 4 cycles was safe. Grade 3/4 adverse events occurred in 52% (13/25) of the certolizumab cohort and 31% (4/13) of the infliximab cohort.⁵³ Ongoing phase II trials further explore the role of IL-6 blockade in mitigating immune-related toxicities while maintaining the

efficacy of checkpoint inhibitors (ClinicalTrials.gov identifiers: [NCT04940299](#), [NCT03999749](#)).^{54,55} Early findings suggest that tocilizumab reduces the incidence of grade 3/4 irAEs and improves tolerability of ipilimumab/nivolumab, with fewer treatment discontinuations.

Although patients with preexisting autoimmune disease face a higher risk of autoimmune flares, evidence demonstrates low rates of treatment discontinuation and favorable on-cologic outcomes. Emerging data suggest concurrent use of biologic agents with ICI may lower risk of irAE with equal oncologic efficacy. These findings reinforce the use of ICIs for this patient population. Close monitoring and a multidisciplinary approach, including pretreatment clinical and biological assessments, are recommended.^{56,57}

Rechallenging Patients With Previous Immune-Related Adverse Events

The decision to rechallenge patients with ICI after irAEs is complex because of the risk of recurrent toxicity. Current guidelines recommend that rechallenge be considered when symptoms and laboratory values revert to grade 1 or less, and permanent discontinuation is advised for grade 4 irAEs.^{50,56,58} By contrast, a retrospective study by Simonaggio et al⁵⁹ reported 55% recurrence rate of grade 2 or higher irAEs among retreated patients with anti-PD-1 or anti-PD-L1 therapy after previous irAEs. Although this rate is high, the data emphasize that only half of the patients who are rechallenged experience recurrent irAEs. Similarly, a multinational analysis by Dolladille et al⁶⁰ found a 28.8% recurrence rate of the initial irAE, with colitis, hepatitis, and pneumonitis being the most common. In particular, continuing maintenance anti-PD-1 monotherapy after a combination of CTLA-4/PD-1 may have a lower irAE risk. Pollack et al⁶¹ found that, among patients who discontinued CTLA-4/PD-1 combination therapy because of severe irAEs, only 18% experienced recurrent toxicity upon resumption of anti-PD-1 monotherapy, suggesting that rechallenge with PD-1 inhibitors is relatively safe, particularly in those with previous colitis.

irAE data from patients with NSCLC demonstrate similar risks of recurrent irAE and improved cancer-related outcomes after rechallenge. In this study, 52% developed recurrent or new irAE after ICI rechallenge.⁶² However, the majority (58%) were mild (grade 1 to 2) and 84% resolved or improved to grade 1.⁶² In patients without an objective response before irAE onset, retreatment was associated with significantly improved PFS (HR, 0.46 [95% CI, 0.21 to 1.0]; $P = .049$) and OS (HR, 0.24 [95% CI, 0.093 to 0.61]; $P = .0026$).⁶² By contrast, among patients with partial responses before an irAE, PFS and OS were similar between the retreatment and discontinuation cohorts, demonstrating the need for individualized decision making.⁶²

Rechallenge has shown efficacy comparable to initial treatment, with objective response and disease control rates

in melanoma, renal cell carcinoma, and NSCLC.⁵⁰ Prospective clinical trials are needed to identify predictive biomarkers for both toxicity and immunotherapy efficacy upon rechallenge. A multidisciplinary discussion is recommended for each case, and referrals to academic centers with expertise in ICI rechallenge should be considered.^{50,60}

Organ Transplant

Patients undergoing solid organ or hematopoietic stem-cell transplant (HSCT) require immunosuppression to maintain graft tolerance, and the PD-1/PD-L1 pathway is crucial for graft survival. Transplant recipients are excluded from clinical trials because of chronic use of steroids and immunosuppressive agents.

Data regarding the safety of ICI in transplant rejection are mixed. A systematic review by Rossi et al⁶³ found that 14 of 34 patients with melanoma experienced graft rejection, particularly with anti-PD-1 agents, with a median rejection time of 21 days. By contrast, a phase I study of cemiplimab in renal transplant recipients with advanced cutaneous squamous cell carcinoma demonstrated that an immunosuppressive regimen incorporating an mammalian target of rapamycin inhibitor, rapamycin, and corticosteroids allowed for durable antitumor responses without kidney rejection.⁶⁴ Among 11 patients, 46% responded to treatment, with no observed graft loss, suggesting that modifying immunosuppression may allow for safe ICI use in transplant recipients.⁶⁴

In HSCT recipients, graft-versus-tumor activity is critical for cancer control, particularly in relapse because cancer cells can escape detection by suppressing checkpoint pathways.⁶⁵ A clinical trial evaluating ipilimumab in patients with relapsed hematologic malignancies postallogeic HSCT found no cases of acute or chronic graft-versus-host disease (GVHD) induction or exacerbation.⁶⁶ Although 14% of patients experienced irAE, these were manageable with immunosuppressive therapy, and 17% of patients achieved objective responses, including durable complete remissions in Hodgkin lymphoma cases.⁶⁶ These data suggest that ICI enhances the immune response and increases the risk of irAEs and GVHD, which can be managed with immunosuppressive therapy.^{46,65,66}

Patients with a renal allograft appear to be at highest risk of rejection when treated with ICI. Data suggest that anti-CTLA-4 antibodies are associated with a lower rejection risk than PD-1 antibodies, but rejection remains a significant concern.^{46,56} Adjusting immunosuppressive therapy during the ICI treatment can help preserve the allograft, but multidisciplinary coordination with the renal transplant nephrology team is required.⁴⁶ Renal function should be closely monitored, with serum creatinine checked before each dose of ICI therapy.⁴⁷ If no alternative for kidney injury, such as intravenous contrast, dehydration, medication, or infections, is identified, immune-related renal toxicity should be

presumed.⁴⁷ Establishing institutional protocols for managing ICI use in transplant patients could reduce morbidity mortality.

Despite the higher rejection risk, response rates to ICIs remain comparable between patients with and without rejection. The benefits of tumor control, reduced cancer-related morbidity and mortality, and the risk of graft rejection should be weighed through a multidisciplinary discussion with the patient.⁶³ Further studies are needed to refine the balance of efficacy and toxicity.

Elderly Patients

Older patients, defined as adults age 70 years or older, are often underrepresented in clinical trials despite representing a significant proportion of those receiving immunotherapy.⁶⁷ Functional status, frailty, and comorbidities are key concerns, but age-related immune changes could also affect responses to ICI.^{46,68} Key immunologic changes include thymic involution, reduced naïve T-cell populations, increased memory T cells, broader antigen recognition diversity, greater T-cell exhaustion, and anergy due to chronic antigen exposure. These changes can weaken the anti-tumor immune responses.⁶⁸⁻⁷¹

Retrospective analyses and meta-analyses suggest that ICIs can be used safely in elderly patients. Betof et al and De Glas et al demonstrated that ICI are effective across all age groups, including older adults with metastatic melanoma.^{67,72} No significant differences in OS or PFS were observed between younger and older patients.^{67,72} In terms of toxicity, all age groups had similar rates of irAEs. Elderly patients had slightly higher rates of arthritis and endocrinopathies and were more likely to discontinue treatment because of low-grade toxicities compared with younger patients.^{67,72}

Low-grade irAEs can significantly affect the quality of life in older patients. In addition to OS and PFS, it is important to consider avoiding toxicity, preserving autonomy, cognitive and functional abilities, and quality of life.⁶⁸ Geriatric assessments should incorporate frailty, functional independence, falls risk, mobility, cognitive, emotional, nutritional status, polypharmacy, social support, and comorbidities to better predict treatment tolerability and outcomes than only relying on chronological age.⁶⁸ A multidisciplinary team ideally includes a geriatrician or geriatric oncologist, a geriatric nurse, a physical therapist, an occupational therapist, a social worker, a dietitian, and a pharmacist.⁶⁸

CONCLUSIONS

Anti-PD-1-refractory melanoma remains a challenging clinical scenario and an area of active investigation owing to the critical need for better treatment strategies. In recent years, several established treatment strategies offer hope for improving outcomes. Both combination immunotherapy approaches and targeted therapies for driver mutations

remain viable options. NGS testing and fusion panel testing should always be considered for patients in this context to uncover any other potentially actionable mutations that might offer therapeutic avenues. Adoptive cell therapy with lifileucel has demonstrated durable responses in heavily pretreated patients. Oncolytic virus therapy has shown benefit in select patient populations with limited, unresectable disease and continue to evolve with greater potential for abscopal effect. Novel emerging T-cell therapies such as TCR-T and immTACs show preliminary benefit in refractory settings. In high-risk populations, multiple new approaches to irAE treatment and prophylaxis have expanded the number of patients for ICI is no longer an absolute contraindication. ICI challenge for high-risk

individuals and rechallenge after an irAE can be safe and requires a multidisciplinary with careful patient selection, close monitoring, and immunosuppressive adjustments. The future of treating anti-PD-1-refractory melanoma will likely involve personalized, multimodal therapeutic strategies that build upon, and integrate, the diverse treatment options described herein.

SUMMARY

Limited options exist for melanoma beyond checkpoint inhibition. We review available and emerging strategies for checkpoint refractory disease and for expanding access to checkpoint therapies.

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REFERENCES

- Leach DR, Krummel MF, Allison JP: Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 271:1734-1736, 1996
- Hodi FS, O'Day SJ, McDermott DF, et al: Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 363:711-723, 2010
- Robert C, Thomas L, Bondarenko I, et al: Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 364:2517-2526, 2011
- Wolchok JD, Chiarion-Sileni V, Rutkowski P, et al: CheckMate 067 Investigators: Final, 10-year outcomes with nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 392:11-22, 2025
- Robert C, Long GV, Brady B, et al: Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 372:320-330, 2015
- Lim SY, Shklovskaya E, Lee JH, et al: The molecular and functional landscape of resistance to immune checkpoint blockade in melanoma. *Nat Commun* 14:1516, 2023
- Olson DJ, Eroglu Z, Brockstein B, et al: Pembrolizumab plus ipilimumab following anti-PD-1/L1 failure in melanoma. *J Clin Oncol* 39:2647-2655, 2021
- VanderWalde A, Bellasea SL, Kendra KL, et al: Ipilimumab with or without nivolumab in PD-1 or PD-L1 blockade refractory metastatic melanoma: A randomized phase 2 trial. *Nat Med* 29:2278-2285, 2023
- Lebbé C, Meyer N, Mortier L, et al: Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: Results from the phase IIIb/IV CheckMate 511 trial. *J Clin Oncol* 37:867-875, 2019
- Tawbi HA, Forsyth PA, Algazi A, et al: Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med* 379:722-730, 2018

11. Long GV, Atkinson V, Lo SN, et al: Ipilimumab plus nivolumab versus nivolumab alone in patients with melanoma brain metastases (ABC): 7-year follow-up of a multicentre, open-label, randomised, phase 2 study. *Lancet Oncol* 26:320-330, 2025
12. Davies MA, Saiaj P, Robert C, et al: Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): A multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol* 18:863-873, 2017
13. Ascierto PA, Lipson EJ, Dummer R, et al: Nivolumab and relatlimab in patients with advanced melanoma that had progressed on anti-programmed death-1/programmed death ligand 1 therapy: Results from the phase I/IIa RELATIVITY-020 trial. *J Clin Oncol* 41:2724-2735, 2023
14. Tawbi HA, Schadendorf D, Lipson EJ, et al: Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med* 386:24-34, 2022
15. Chesney J, Lewis KD, Kluger H, et al: Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: Pooled analysis of consecutive cohorts of the C-144-01 study. *J Immunother Cancer* 10:e005755, 2022
16. Robert C, Gastman B, Gogas H, et al: Open-label, phase II study of talimogene laherparepvec plus pembrolizumab for the treatment of advanced melanoma that progressed on prior anti-PD-1 therapy: MASTERKEY-115. *Eur J Cancer* 207:114120, 2024
17. Faries MB, Thompson JF, Cochran AJ, et al: Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med* 376:2211-2222, 2017
18. Blank CU, Lucas MW, Scolyer RA, et al: Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. *N Engl J Med* 391:1696-1708, 2024
19. Owen CN, Shoushtari AN, Chauhan D, et al: Management of early melanoma recurrence despite adjuvant anti-PD-1 antibody therapy. *Ann Oncol* 31:1075-1082, 2020
20. Ascierto PA, Dummer R, Gogas HJ, et al: Contribution of MEK inhibition to BRAF/MEK inhibitor combination treatment of BRAF-mutant melanoma: Part 2 of the randomized, open-label, phase III COLUMBUS trial. *J Clin Oncol* 41:4621-4631, 2023
21. Long GV, Arance A, Mortier L, et al: Antitumor activity of ipilimumab or BRAF ± MEK inhibition after pembrolizumab treatment in patients with advanced melanoma: Analysis from KEYNOTE-006. *Ann Oncol* 33:204-215, 2022
22. Atkins M, Lee SJ, Chmielewski B, et al: Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: The DREAMseq trial—ECOG-ACRIN EA6134. *J Clin Oncol* 41:186-197, 2023
23. Hodi FS, Corless CL, Giobbie-Hurder A, et al: Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. *J Clin Oncol* 31:3182-3190, 2013
24. Janku F, Bauer S, Shoumariyeh K, et al: Efficacy and safety of ripretinib in patients with KIT-altered metastatic melanoma. *ESMO Open* 7:100520, 2022
25. Dummer R, Schadendorf D, Ascierto PA, et al: Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 18:435-445, 2017
26. Arance A, de La Cruz-Merino L, Petrella TM, et al: Phase II LEAP-004 study of lenvatinib plus pembrolizumab for melanoma with confirmed progression on a programmed cell death protein-1 or programmed death ligand 1 inhibitor given as monotherapy or in combination. *J Clin Oncol* 41:75-85, 2023
27. Middleton MR, Grob JJ, Aaronson N, et al: Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 18:158-166, 2000
28. Flaherty KT, Lee SJ, Schuchter LM, et al: Final results of E2603: A double-blind, randomized phase III trial comparing carboplatin (C)/paclitaxel (P) with or without sorafenib (S) in metastatic melanoma. *J Clin Oncol* 28, 2010 (suppl 15; abstr 8511)
29. Thomas S, Kuncheria L, Roulstone V, et al: Development of a new fusion-enhanced oncolytic immunotherapy platform based on herpes simplex virus type 1. *J Immunother Cancer* 7:214, 2019
30. Wong MKK, Sacco JJ, Robert C, et al: Efficacy and safety of RP1 combined with nivolumab in patients with anti-PD-1–failed melanoma from the IGYTE clinical trial. *J Clin Oncol* 42, 2024 (suppl 16; abstr 9517)
31. Robert C, Milhem MM, Sacco JJ, et al: Primary efficacy, safety, and survival data from the registration-intended cohort of patients with anti-PD-1–failed melanoma from the IGYTE clinical trial with RP1 combined with nivolumab. *Ann Oncol* 35:1-72, 2024 (suppl 2)
32. Luke JJ, Kong G, Gullo G, et al: A randomized, controlled, multicenter, phase 3 study of vosilomogene oderparepvec (VO) combined with nivolumab vs treatment of physician's choice in patients with advanced melanoma that has progressed on anti-PD-1 and anti-CTLA-4 therapy (IGYTE-3). *J Clin Oncol* 42, 2024 (suppl 16; abstr TPS9604)
33. Oates J, Jakobsen BK: ImmTACs: Novel bi-specific agents for targeted cancer therapy. *Oncoimmunology* 2:e22891, 2013
34. Liddy N, Bossi G, Adams KJ, et al: Monoclonal TCR-redirected tumor cell killing. *Nat Med* 18:980-987, 2012
35. Nathan P, Hassel JC, Rutkowski P, et al: Overall survival benefit with tebentafusp in metastatic uveal melanoma. *N Engl J Med* 385:1196-1206, 2021
36. Hamid O, Hassel JC, Shoushtari AN, et al: Tebentafusp in combination with durvalumab and/or tremelimumab in patients with metastatic cutaneous melanoma: A phase 1 study. *J Immunother Cancer* 11:e006747, 2023
37. Davar D, Ikeguchi A, Buchbinder EI, et al: A phase 2/3 trial in progress on tebentafusp as monotherapy and in combination with pembrolizumab in HLA-A*02:01+ patients with previously treated advanced non-uveal melanoma (TEBE-AM). *J Clin Oncol* 41, 2023 (suppl 16; abstr TPS9594)
38. Hamid O, Williams A, Lopez JS, et al: Phase 1 safety and efficacy of IMC-F106C, a PRAME × CD3 ImmTAC bispecific, in post-checkpoint cutaneous melanoma (CM). *J Clin Oncol* 42, 2024 (suppl 16; abstr 9507)
39. Long GV, Atkinson V, Ascierto PA, et al: A phase 3 trial of IMC-F106C (PRAME x CD3) plus nivolumab versus standard nivolumab regimens in HLA-A*02:01+ patients with previously untreated advanced melanoma (PRISM-MEL-301). *J Clin Oncol* 42, 2024 (suppl 16; abstr TPS9602)
40. Sacco JJ, Carvajal RD, Hamid O, et al: Association of a blood T cell fitness gene signature with clinical benefit from ImmTAC bispecific T cell engagers. *Ann Oncol* 35:S238-S308, 2024 (suppl 2)
41. Rohaan MW, Borch TH, van den Berg JH, et al: Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. *N Engl J Med* 387:2113-2125, 2022
42. Wermke M, Chesney JA, Whitman E, et al: Long-term efficacy and patterns of response of lifileucel tumor-infiltrating lymphocyte (TIL) cell therapy in patients with advanced melanoma: A 4-year analysis of the C-144-01 study. *Ann Oncol* 20:100589, 2023 (suppl 1)
43. Amaria RN, McQuade JL, Davies MA, et al: OBX-115, an interleukin 2 (IL2)-sparing engineered tumor-infiltrating lymphocyte (TIL) cell therapy, in patients (pts) with immune checkpoint inhibitor (ICI)-resistant unresectable or metastatic melanoma. *J Clin Oncol* 42, 2024 (suppl 16; abstr 9515)
44. Klebanoff CA, Chandran SS, Baker BM, et al: T cell receptor therapeutics: Immunological targeting of the intracellular cancer proteome. *Nat Rev Drug Discov* 22:996-1017, 2023
45. Wermke M, Alsdorf W, Araujo DM, et al: 687 ACTengine IMA203 TCR-T targeting PRAME shows deep and durable anti-tumor activity in heavily pretreated solid cancer patients. *J Immunother Cancer* 12, 2024 (suppl 2)
46. Johnson DB, Sullivan RJ, Menzies AM: Immune checkpoint inhibitors in challenging populations. *Cancer* 123:1904-1911, 2017
47. Menzies AM, Johnson DB, Ramanujam S, et al: Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol* 28:368-376, 2017
48. Leonardi GC, Gainor JF, Altan M, et al: Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. *J Clin Oncol* 36:1905-1912, 2018
49. Ileana Dumbrava EE, Suarez-Almazor ME, Painter J, et al: A phase Ib study of nivolumab in patients with autoimmune disorders and advanced malignancies (AIM-NIVO). *J Clin Oncol* 38, 2020 (suppl 15; abstr TPS3158)
50. Zhao Y, He R, Oerther S, et al: Cardiovascular complications in hematopoietic stem cell transplanted patients. *J Pers Med* 12:1797, 2022
51. Sleiman J, Wei W, Shah R, et al: Incidence of immune checkpoint inhibitor-mediated diarrhea and colitis (imDC) in patients with cancer and preexisting inflammatory bowel disease: A propensity score-matched retrospective study. *J Immunother Cancer* 9:e002567, 2021
52. Uemura M, Trinh VA, Haymaker C, et al: Selective inhibition of autoimmune exacerbation while preserving the anti-tumor clinical benefit using IL-6 blockade in a patient with advanced melanoma and Crohn's disease: A case report. *J Hematol Oncol* 9:81, 2016
53. Meyer N, Lusque A, Virazels M, et al: 846P Triple combination of ipilimumab + nivolumab + anti-TNF in treatment naive melanoma patients: Final analysis of TICIMEL, a phase Ib prospective clinical trial. *Ann Oncol* 33:S936-S937, 2022
54. Anouti B, McVay K, Abraham M, et al: Phase II trial of weekly or bi-weekly tocilizumab with ipilimumab and nivolumab in advanced melanoma: Clinical outcomes and biomarker analysis. *J Clin Oncol* 42, 2024 (suppl 16; abstr 9553)
55. Weber JS, Puranik A, Mitzutani T, et al: Interleukin-6 receptor blockade with tocilizumab to reduce immune-related toxicity with ipilimumab and nivolumab in metastatic melanoma. *J Clin Oncol* 42, 2024 (suppl 16; abstr 9538)
56. Brahmer JR, Lacchetti C, Schneider BJ, et al: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice guideline. *J Clin Oncol* 36:1714-1768, 2018
57. Martin M, Villar A, Sole-Calvo A, et al: Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1, 21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: A study by the GEICAM group. *Ann Oncol* 14:833-842, 2003
58. Thompson JA, Schneider BJ, Brahmer J, et al: NCCN guidelines insights: Management of immunotherapy-related toxicities, version 1.2020. *J Natl Compr Cancer Netw* 18:230-241, 2020

59. Simonaggio A, Michot JM, Voisin AL, et al: Evaluation of readministration of immune checkpoint inhibitors after immune-related adverse events in patients with cancer. *JAMA Oncol* 5:1310-1317, 2019
 60. Dolladille C, Ederhy S, Sassier M, et al: Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. *JAMA Oncol* 6:865-871, 2020
 61. Pollack MH, Beto A, Dearden H, et al: Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. *Ann Oncol* 29:250-255, 2018
 62. Santini FC, Rizvi H, Plodkowski AJ, et al: Safety and efficacy of Re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res* 6:1093-1099, 2018
 63. Rossi E, Schinzari G, Maiorano BA, et al: Immune-checkpoint inhibitors in renal transplanted patients affected by melanoma: A systematic review. *Immunotherapy* 14:65-75, 2022
 64. Hanna GJ, Dharanesswaran H, Giobbie-Hurder A, et al: Cemiplimab for kidney transplant recipients with advanced cutaneous squamous cell carcinoma. *J Clin Oncol* 42:1021-1030, 2024
 65. Merryman RW, Armand P: Immune checkpoint blockade and hematopoietic stem cell transplant. *Curr Hematol Malig Rep* 12:44-50, 2017
 66. Bashey A, Medina B, Corringham S, et al: CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. *Blood* 113:1581-1588, 2009
 67. de Glas NA, Bastiaannet E, van den Bos F, et al: Toxicity, response and survival in older patients with metastatic melanoma treated with checkpoint inhibitors. *Cancers (Basel)* 13:2826, 2021
 68. Eochagain CM, Neuendorff NR, Gente K, et al: Management of immune checkpoint inhibitor-associated toxicities in older adults with cancer: Recommendations from the International Society of Geriatric Oncology (SIOG). *Lancet Oncol* 26:e90-e102, 2025
 69. Thomas R, Wang W, Su DM: Contributions of age-related thymic involution to immunosenescence and inflammaging. *Immun Ageing* 17:2, 2020
 70. Fang M, Roscoe F, Sigal LJ: Age-dependent susceptibility to a viral disease due to decreased natural killer cell numbers and trafficking. *J Exp Med* 207:2369-2381, 2010
 71. Manser AR, Uhrberg M: Age-related changes in natural killer cell repertoires: Impact on NK cell function and immune surveillance. *Cancer Immunol Immunother* 65:417-426, 2016
 72. Beto AS, Nipp RD, Giobbie-Hurder A, et al: Impact of age on outcomes with immunotherapy for patients with melanoma. *Oncologist* 22:963-971, 2017
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Navigating B-ALL in the Era of Blinatumomab

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OVERVIEW

Blinatumomab has rapidly emerged as a cornerstone in the treatment of B-cell ALL (B-ALL) across age and risk groups. Initially approved for minimal residual disease (MRD)-positive adult B-ALL in 2018, its indications have since expanded after pivotal trials demonstrating significant efficacy. The BLAST and E1910 trials highlighted the benefit of blinatumomab in adults in MRD-positive and MRD-negative remission, respectively, with notable improvements in overall survival and relapse-free survival. In pediatric populations, studies such as the AALL1731 and a landmark trial in infants with *KMT2A*-rearranged B-ALL demonstrated striking reductions in relapse when blinatumomab was added to standard regimens. Similarly, in Philadelphia chromosome-positive B-ALL, blinatumomab-based regimens have enabled chemotherapy minimization while achieving durable remissions. Despite these advances, the rapid integration of blinatumomab into standard care poses challenges related to administration, toxicity management, and equitable access. Variability in inpatient observation durations, infusion bag sizes, home health availability, and handling of infusion-related complications underscore the need for standardized delivery models. Additionally, low-grade and long-term toxicities—such as neurotoxicity, cytokine release syndrome, and hypogammaglobulinemia—remain undercharacterized. Looking forward, research is focusing on optimizing the use of blinatumomab, including its integration into reduced-intensity or chemotherapy-free regimens, alternative dosing schedules, and subcutaneous administration. As clinical use expands, emphasis must shift toward developing equitable, patient-centered delivery strategies and understanding the full spectrum of toxicities to ensure optimal and accessible care for all patients with B-ALL.

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INTRODUCTION

Blinatumomab is a bispecific antibody molecule that binds the B-cell antigen, CD19, and the T-cell antigen, CD3. In B-cell ALL (B-ALL), blinatumomab binds the B lymphoblasts and engages the patient's own T cells resulting in redirected cell lysis. The first-in-human study of blinatumomab, a dose-finding study in relapsed/refractory (r/r) non-Hodgkin lymphoma, was reported in 2008.¹ In 2011, the results of the first B-ALL trial were published, followed by several early-phase, single-arm studies in patients with r/r B-ALL.²⁻⁵ These trials demonstrated that blinatumomab had a favorable safety profile and efficacy exceeding expectations in heavily pretreated r/r patients. Overall, these studies led to US Food and Drug Administration (FDA) approval of blinatumomab for r/r Ph-negative B-ALL adult and pediatric patients in 2014 and 2016, respectively, then r/r Philadelphia chromosome-positive (Ph+) B-ALL in 2017. This remarkable and rapid progress in r/r patients supported several ensuing seminal investigations of blinatumomab in newly diagnosed patients.

Here, we will review data from these trials that have culminated in the establishment of blinatumomab as a key

therapy component for most patients with newly diagnosed B-ALL. This rapid rise from investigational agent to standard of care has resulted in dramatically increased use of blinatumomab for B-ALL over a short span of time. Thus, here we also review challenges related to delivery and care practices, including supportive care, and consider opportunities for development of corresponding clinical practice guidelines. Finally, we will speculate on what comes next for blinatumomab in the management of patients with newly diagnosed B-ALL.

EVIDENCE TO SUPPORT USE IN PATIENTS WITH NEWLY DIAGNOSED ADULT B-ALL

Minimal Residual Disease-Positive B-ALL

After dose-establishing data from adult patients with r/r lymphoma, blinatumomab was first explored in a small, single-arm study of adults with B-ALL with minimal residual disease (MRD) after induction and consolidation chemotherapy. A single cycle of blinatumomab was administered, and 16 of 20 evaluable patients cleared their MRD.⁴ Subsequently, the BLAST trial enrolled 144 adults in morphologic remission with MRD $\geq 0.1\%$. Enrolled patients

PRACTICAL APPLICATIONS

- Based on recently emerging clinical trial data, blinatumomab is now a standard-of-care component of therapy for most patients with relapsed/refractory B-cell ALL (B-ALL) as well as a majority of pediatric and essentially all adult patients with newly diagnosed B-ALL.
- Although overall blinatumomab is well tolerated, it is associated with the unique toxicities of cytokine release syndrome and neurotoxicity, including seizures and encephalopathy, which tend to be rare and low grade in newly diagnosed patients.
- Important gaps in knowledge regarding blinatumomab-associated short- and long-term toxicities and their management exist.
- The rapidly expanding use of blinatumomab has exposed challenges in administration and variability in care delivery practices, which may contribute to inequitable access and important clinical and quality-of-life outcomes.
- Future initiatives related to blinatumomab include exploration of reducing chemotherapy intensity while maintaining excellent outcomes, effective yet less burdensome dosing strategies and modes of administration, filling gaps in toxicity and administration data, and prevention of and mitigation of access inequities.

could receive up to four cycles of blinatumomab. Although therapy after blinatumomab was not dictated by the study, most patients achieving complete remission (CR) underwent hematopoietic stem-cell transplant (HSCT). Overall, 78% achieved MRD negativity after one blinatumomab cycle.⁶ For those receiving blinatumomab in first CR, the median overall survival (OS) was 41.2 months and was not reached in those with a complete MRD response.⁷ Importantly, 7 of 36 patients who received blinatumomab in CR1 and achieved a complete MRD response and did not undergo HSCT were alive and in remission after 5 years of follow-up.⁷ The results of this pivotal trial led to the expansion of the FDA label in 2018 to include patients with MRD-positive, Ph-negative, B-ALL.

MRD-Negative Remission

The randomized phase III trial, E1910, was recently completed by the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network. Adults (age 30–70 years) with MRD-negative Ph-negative B-ALL were randomly assigned after induction and intensification therapy to receive either standard consolidation

chemotherapy alone (cycle 1, 2, and 4: cytarabine, etoposide, pegaspargase [pegaspargase in cycle 1 only], intrathecal [IT] methotrexate $\pm$ rituximab; cycle 3: daunorubicin, vincristine, dexamethasone, cyclophosphamide, cytarabine, mercaptopurine, IT methotrexate, $\pm$ rituximab) or this same chemotherapy plus four cycles of blinatumomab.⁸ At an interim efficacy analysis, blinatumomab demonstrated a significant clinical benefit with improved 3-year OS (85% v 68%) and relapse-free survival (80% v 64%) compared with chemotherapy alone. This result prompted the study's data and safety monitoring committee to recommend early termination of the randomization. In a post hoc subgroup analysis, hazard ratios favored the incorporation of blinatumomab across all age groups, patients of all molecular risk groups, and regardless of HSCT. In 2024, based on the results of the E1910 trial, the FDA expanded blinatumomab approval to include all patients with B-ALL in consolidation phases of therapy.

Ph+ B-ALL

Although the introduction of tyrosine kinase inhibitors to therapy has significantly improved outcomes in patients with Ph+ B-ALL, this subtype is still associated with high rates of relapse.^{9–13} For adults with Ph+ B-ALL, HSCT in first CR is largely considered standard of care.⁹ The suboptimal outcomes in this group of patients led to the design of Ph+ trials incorporating blinatumomab and minimizing traditional chemotherapy. The first such study, a single-arm phase II trial (GIMEMA LAL216, D-ALBA), enrolled 63 newly diagnosed Ph+ B-ALL (median age 54 years). Eligible patients began therapy with a steroid prophase then received induction therapy with dexamethasone and dasatinib. Patients then received two to four cycles of blinatumomab with concomitant dasatinib. After these blinatumomab/dasatinib cycles, most patients underwent HSCT.¹⁴ Overall, the 53-month disease-free survival (DFS)/OS was 75.8%/80.7%.¹⁵ There were 29 patients in molecular remission after blinatumomab/dasatinib who continued only dasatinib without any further chemotherapy, and did not undergo HSCT. Of these, 28 remained alive and in remission after 4 years of follow-up.¹⁵ A single-center, phase II study combining blinatumomab with ponatinib has also reported promising rates of molecular response.¹⁶

EVIDENCE TO SUPPORT USE IN PATIENTS WITH NEWLY DIAGNOSED PEDIATRIC B-ALL

Infants

Infants with B-ALL, a majority of whom have a *KMT2A*-rearrangement (*KMT2Ar*), are a chemotherapy-refractory group with historically dismal outcomes.¹⁷ A phase II, single-arm, international trial was conducted to investigate whether one postinduction cycle of blinatumomab added to the Interfant-06 chemotherapy regimen would be tolerable and effective. The study enrolled 30 infants younger than <1 year with newly diagnosed *KMT2Ar* B-ALL. After

induction, patients with <25% marrow blasts were given a 28-day cycle of blinatumomab, before proceeding through the remainder of Interfant-06 therapy (protocol 1B, MARMA, OCTADAD, and maintenance therapy)⁸ with high-risk infants (age <6 months at diagnosis with WBC $\geq 300 \times 10^9$ per liter at diagnosis or a poor response to prednisone) allocated to HSCT in CR1. All patients completed the course of blinatumomab with no adverse effects attributable to blinatumomab reported. The results compared with historical controls treated with Interfant-06 therapy alone were striking. The two-year DFS/OS was 81.6%/93.3% compared with 49.4%/65.8% on the original Interfant-06 trial. Overall, the cumulative incidence of relapse was 13% with no reported CD19 loss nor lineage switch.¹⁸ Despite the non-randomized design and the small sample size, the marked difference in outcomes compared with those previously reported have led most to consider blinatumomab a standard component of therapy for infant B-ALL.

National Cancer Institute Standard-Risk B-ALL

The Children's Oncology Group (COG) AALL1731 trial was a randomized phase III study evaluating the addition of blinatumomab to chemotherapy in children with National Cancer Institute (NCI) standard-risk (SR) B-ALL (<10 years, WBC <50,000/ μ L at diagnosis). After three-drug induction and risk-adapted consolidation chemotherapy, 835 patients with average relapse risk (SR-Average [SR-Avg]) and 605 with higher relapse risk (SR-High) were randomly assigned to receive either chemotherapy alone or chemotherapy with two, nonsequential cycles of blinatumomab. SR-Avg patients received standard-intensity chemotherapy as was given to average-risk patients on arm C of COG study AALL0932.¹⁹ SR-High patients received a modified augmented Berlin-Frankfurt-Munster chemotherapy backbone similar to the control arm of AALL1131.²⁰ Randomization was stopped at the first interim analysis because of observed

significant benefit from blinatumomab. With a median 2.5 years of follow-up, 3-year DFS was 96.0% with blinatumomab versus 87.9% with chemotherapy alone. Blinatumomab improved DFS in both SR-Avg (97.5% v 90.2%) and SR-High (94.1% v 84.8%) patients, reducing the 3-year relapse rate from 11.8% to 3.3%. Although blinatumomab reduced marrow-involving relapses, it did not affect isolated CNS relapses—a finding consistent with blinatumomab's known lack of CNS activity. All patients with marrow-involving relapses after blinatumomab maintained CD19 expression. Subgroup analyses indicated benefit across all cytogenetic, racial, ethnic, and MRD status groups as well as among those with and without Down syndrome.²¹ The results of this trial indicate that most children with NCI SR B-ALL should receive blinatumomab as part of their postinduction/premaintenance therapy.

NCI High-Risk B-ALL

To date, a trial comparing therapy with versus without blinatumomab has not been conducted among patients with NCI high-risk (HR) B-ALL (≥ 10 years and/or WBC $\geq 50,000/\mu$ L at diagnosis). However, given that the predicted outcomes and treatment approach for NCI HR patients are largely overlapping with both the higher-risk NCI SR patients treated on AALL1731, and the younger adults treated on the E1910 trial, most agree that it is reasonable to extrapolate that they too will benefit from blinatumomab. Thus, based on several recent trials with overwhelmingly positive results, blinatumomab has been widely incorporated into therapy for most patients with B-ALL (Fig 1).

BARRIERS TO BLINATUMOMAB ADMINISTRATION AND ACCESS

As blinatumomab is now standard of care for most patients with B-ALL, we must ensure that all patients likely to derive

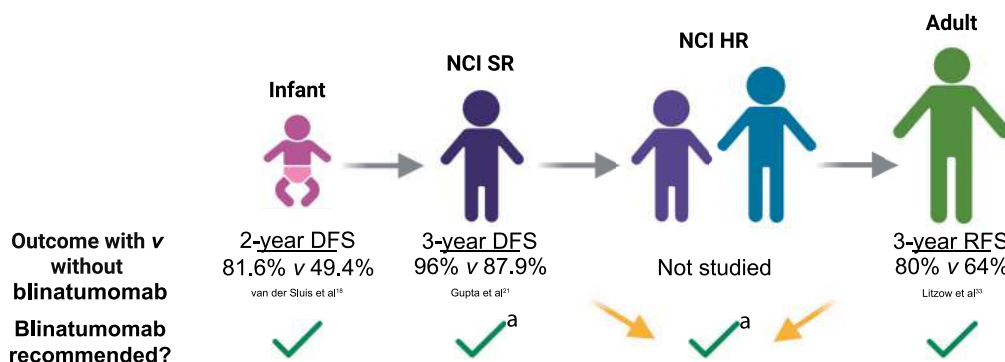


FIG 1. Blinatumomab outcomes and recommended use by age and risk group. Summary of recent seminal trials in newly diagnosed B-ALL supporting its inclusion in standard therapy. ^aBlinatumomab recommended for all except those with excellent outcomes with chemotherapy alone namely NCI SR patients with favorable cytogenetics (*ETV6::RUNX1* fusion or trisomies of chromosomes 4 and 10), CNS 1 or 2 status, day 8 peripheral blood MRD <1%, and end-of-induction marrow MRD <0.01%, and NCI HR patients younger than 10 years, CNS 1, favorable cytogenetics, and end-of-induction marrow MRD <0.01%. B-ALL, B-cell ALL; DFS, disease-free survival; HR, high-risk; MRD, minimal residual disease; NCI, National Cancer Institute; RFS, relapse-free survival; SR, standard-risk.

benefit have equal access. We reviewed available data regarding administration practices and reported challenges with access and uptake of blinatumomab, considering varied levels of quality evidence. Evidence is strongest from clinical trials with targeted toxicity reporting; however, providers with real-world experience administering and caring for patients receiving blinatumomab provide experiential data that are of lower-quality evidence but still valuable, especially as the need to deliver this drug expands rapidly. We also consider care delivery through a multilevel framework with a goal that the translation of recent clinical trial evidence into clinical practice considers access equity and aims to minimize adverse clinical and quality-of-life outcomes. We leverage experience conducting and caring for patients on pediatric trials, but the themes reviewed here are applicable to patients of all ages (Table 1).

Building on Clinical Trial Toxicity Reporting to Guide Care Delivery

Toxicity reporting in clinical trial consortia is a required and critical component of scientific research. Toxicity reporting has historically relied solely on clinician reports using the Common Terminology Criteria for Adverse Events (CTCAE) grading system.²² CTACE reporting in clinical trials is most often limited to higher grades of toxicity (ie, grade 3 or higher) except where unique toxicity data capture is relevant and important to the primary or secondary outcomes of a trial. For example, in pediatric ALL trials investigating blinatumomab, toxicity reporting required cytokine release syndrome (CRS) and neurotoxicity as unique and important for reporting to determine the safety and tolerability of these regimens.

The low rates of reported blinatumomab-related toxicity support care delivery practices such as outpatient administration after an initial period of inpatient observation. Currently, the US Prescribing Information (USPI) from the FDA recommends that patients with MRD-negative B-ALL receiving blinatumomab in consolidative phases are monitored for a minimum of 72 hours after first blinatumomab exposure.²³ However, there is variation of institutional-reported inpatient observation requirements, ranging from 1 to 9 days and with one third of COG institutions reporting ≤ 72 hours of observation required.^{24–26} Longer hospital stays for initiation of blinatumomab cycles increase health care utilization and affects patient and family quality of life. Hospitalization is also associated with increased financial burden because of increased out-of-pocket costs and lost work or income, especially during extended hospitalizations.^{27,28} Patients who remain hospitalized are also at increased risk of exposure to or acquisition of hospital-acquired infections, including central-line associated bloodstream infections.²⁹

However, a limitation and potential risk of clinical management based on the clinical trial-reported toxicities related to blinatumomab is the omission of low-grade clinical and patient-reported toxicities. For example, lower grades of CRS may have been undercaptured in clinical trial data sets.

Currently, to our knowledge, there are no guidelines for management of low-grade CRS (often manifest as fever alone) for patients with B-ALL receiving blinatumomab, and clinical intervention is varied, ranging from obtaining blood cultures and observation to a more aggressive approach with broad-spectrum antibiotics and increased hospitalization duration. A similar scenario exists for low-grade blinatumomab-associated neurotoxicity, in the uncertainty regarding clinical management of grade 1 and 2 neurotoxicity. Recently, the FDA USPI label for blinatumomab was revised to recommend interruption of infusion and dose modification for pediatric patients with grade 2 immune effector cell-associated neurotoxicity syndrome; previously, this was limited to grade 3 and higher.²³ This raises important questions about recommendations for frequency of monitoring, the tools by which to monitor and assess neurotoxicity, and anticipatory guidance for patients/families. Another gap in knowledge of lower-grade toxicities is optimal management of hypogammaglobulinemia. Current monitoring of immunoglobulin levels and subsequent administration of intravenous immunoglobulin G (IVIG), an intervention that is costly and often restricted to specific, but variable, populations across hospital systems, varies widely. Thus, collection of evidence to support clinical management guidance for low-grade blinatumomab toxicities is needed.

Adapting to New Care Delivery Challenges With Limited Evidence-Based Data and Recommendation

Although COG trial AALL1731 was open and accruing, members of the COG study team received frequent questions from nurses, pharmacists, and providers related to blinatumomab administration. It became evident that there were common and concerning questions around navigating administration, care of the continuous infusion both inpatient and outpatient, and patient monitoring during blinatumomab cycles. Many of these frequently asked questions (FAQs) stemmed from discordance between the USPI drug label for blinatumomab, protocol-specific guidance, local institutional policies and procedures, and the reality of blinatumomab treatment in real-world settings. For example, the drug label and protocol guidance recommend avoiding flushing during blinatumomab cycles, but this is not practical as the infusion may be interrupted for clinical reasons (ie, administration of supportive medications, central line access issues). During such flushes, providers, mostly nurses, have reported significant discomfort because of administration of a bolus dose of blinatumomab, especially in contrast to the drug label and protocol guidance. For example, a common infusion rate for blinatumomab is 5 mL/h; a 3-mL volume required for a flush result in a significant dose administered over 1–2 minutes. The COG study team therefore developed a FAQs resource document to provide recommendations and practice examples to concerned providers. The team included COG nurses with expertise in clinical trials and the care of children and adolescents with a leukemia diagnosis, pharmacists, and the study chairs; the resource document was subsequently shared and updated on the COG study website. This FAQ document is

TABLE 1. Special Considerations With Blinatumomab

Treatment-Related Adverse Effect	Practice Variation or Gap in Knowledge	Potential Implications
CRS (low-grade CRS with isolated fever relatively common with first exposure)	Duration of inpatient observation at initiation of cycles Staffing ratios/utilization (nurse:patient) Fever management variability	Hospital resource utilization Family separation/stress Patient isolation related to hospitalization affecting mood Lost work hours/days (patient/parent/caregiver) Financial costs related to hospitalization Exposure to unnecessary antibiotics Unnecessary infusion interruption
Neurotoxicity (severe toxicity such as seizure, encephalopathy is rare in upfront setting, but low-grade adverse events such as hand tremors, headache, and mild cognitive changes likely more frequent)	Frequency of neurologic assessment Type of neurologic assessment (ie, handwriting, finger-to-nose testing) Variability in approach to low-grade neurotoxicity	Provider uncertainty regarding management May impact trust between health care team and patient/family Patient and family distress Unnecessary infusion interruptions
Hypogammaglobulinemia (expected side effect of blinatumomab, duration and time to resolution unknown)	Timepoints and frequency of screening IgG levels IVIg replacement practices Insurance coverage Provider/practice variability	Increased infectious toxicities IVIg-related reactions/toxicities Disproportionate access to IVIg
Blinatumomab administration		
Selection of bag size (24-, 48-, 72-, and 96-hour, and 7-day options)	Limited 7-day bag experience Hesitation to move to 7-day bags because of lower infusion rate Comfort with current bag size options (72- and 96-hour bags used in context of trials, but only recently FDA-approved) Variability of site-level support for frequent bag change, home care support, especially with increase in demand for blinatumomab administration Insurance v institution influence options available to a patient/setting Limited availability of home care nursing and home care pharmacies Weight differences with 7-day bags more concentrated (typically 120 mL with overflow compared with 500 mL for the other prescriptions)	Variable numbers of hospital or clinic visits Treatment-related financial hardship related to travel, childcare costs for siblings, and loss of work Interruption of school and other family activities Family comfort with home care workers (culture, language, other considerations) Geographic location (patients in rural locations with fewer options for home care) 7-day bags lighter weight on day 1 and could improve function, comfort, and independence particularly for younger children
Selection of equipment	Port-a-cath needle (may crack or become dislodged) IV tubing (some reported to leak) Closed system transfer devices (regulatory requirement of CSTD, which may cause more frequent disconnections) Pump alarms such as air in line—some have reported safely turning off this pump alarm	Infusion disconnections Infusion interruptions Unplanned hospital visits Need for new blinatumomab bag with some drug waste Possible need for readmission to hospital for longer infusion interruptions (more likely for families who live far from hospital)
Patient and family education	Importance of treatment recommendations inclusive of blinatumomab Potential clinical, psychosocial, and financial implications of blinatumomab as a part of ALL therapy	Development of standardized patient- and family-centered guidance/education Home monitoring of symptoms or other reportable events with clear instructions for reporting/obtaining support from health care team Resource support or navigation to address needs during treatment (eg, travel, lodging, home care, and pharmacy)

Abbreviations: CRS, cytokine release syndrome; CSTD, closed system transfer devices; FDA, US Food and Drug Administration; IgG, immunoglobulin G; IV, intravenous; IVIg, intravenous immunoglobulin G.

iteratively updated, as experience and expertise with administering blinatumomab has evolved, and new information related to administration is updated.

As more experiences were shared and integrated into the FAQ, a COG institutional-wide survey was conducted in 2021 to understand variations in practice and to collate institutional examples of care delivery approaches for

blinatumomab.²⁴ This survey was done during the period when blinatumomab was still being tested during AALL1731. There were 150 respondents (78%) from 192 eligible COG sites; most respondents were nurses (95%). The survey identified key practice variations affecting optimal care delivery, including access and choice of infusion pumps for inpatient and outpatient blinatumomab delivery, access to home health resources, placement of secondary intravenous

(IV) access devices such as peripherally inserted central catheters during blinatumomab cycles, flushing practices, and time of hospitalization for blinatumomab cycles.

Drug Delivery Considerations to Support a Patient- and Family-Centered Approach

Most institutions reported the use of 72-hour and 96-hour bags for blinatumomab administration,²⁴ consistent with the trial-designated investigational blinatumomab available at the time of the survey completion. Currently, there is wide variation in the bag size for outpatient administration, including options for 24-, 48-, 72-, 96-, and 168-hour (7-day) bags. Choice of blinatumomab bag size is determined by institutions, often considering formulation available, selection of pharmacy for preparation, and availability of home care for bag changes. Until recently, 72 and 96-hour bag options were not approved by the FDA for commercial supply of blinatumomab. The bag size has implications from a clinical perspective (eg, number of times the central line is accessed, which affects risk for infection) and care delivery perspective (eg, frequency of home care visits, number of clinic visits required, home care coverage requirements). The care delivery considerations include multiple levels of care, and, in the case of bag size, this system-level determination influences a patient and family's logistical, financial, and psychosocial experiences during treatment. Home care was available to a minority of institutions (34%), and most patients were required to return to the treating hospital for blinatumomab bag changes.²⁴ These additional clinic visits generate additional costs for families to cover (eg, gas, public or private transportation, parking costs, purchasing food, lost work hours for parent(s), and childcare costs for siblings). From the patient and family perspective, the bag size that allows the least number of hospital visits or health care visits is the ideal state. However, there are challenges associated with the larger bag size; providers reported discomfort with 7-day bags because of the lower infusion rate and subsequent risk for line malfunction. Readiness for change was not a priority, especially when the current process (keeping patients hospitalized or using smaller bag sizes) was working and would require change efforts directed toward many system levels (pharmacy workflows, electronic medical records, standard-of-care protocols and treatment delivery maps, provider education). There may also be an undercurrent of expectation from the institution and providers on families to do anything to access therapy that will improve survival outcomes. Striking a balance between minimizing the patient/family burden with clinical and safety considerations is critical to ensuring the appropriate delivery of a standard-of-care treatment that requires a complex coordination for effective delivery.

Anticipating Gaps in Equitable Care Delivery and Minimizing Worsening of Disparities

Increased expectation of families is an area of concern, given our knowledge that blinatumomab should be offered to

nearly all patients with B-ALL. The literature increasingly demonstrates the alarming inequities in access and outcomes that are largely influenced by adverse determinants of health that are often out of the control of the patient/family (ie, economic stability, reliable transportation, social support).^{30,31} Access to novel therapies such as blinatumomab must be a constant consideration as we not only measure the clinical success of its addition to treatment regimens, but also as we develop and tailor models of care delivery that prioritize equitable access.³²

Encouragingly, outpatient infusion for patients for most of the blinatumomab cycles is possible; in the 2021 survey, 9% of respondents reported that patients remained in hospital for the entire 28-day cycle.²⁴ Given the projected expansion of prescription and delivery of blinatumomab in B-ALL, a priority is understanding how best to support clinical settings, patients, and families to coordinate and deliver outpatient administration of blinatumomab.

An effective care delivery model must consider best practices to mitigate infusion-related complications. During outpatient blinatumomab delivery, minimizing infusion interruptions is a primary goal. This supports optimal drug administration but also mitigates patient/family burden for unplanned medical visits for infusion-related concerns. Most institutions reported at least one infusion complication that resulted in an infusion interruption including air-in-line pump alarm, blood backing up in the line, line leak or break, and line disconnections.²⁴ Understanding contributing factors or antecedents to these interruptions is critical to developing recommendations to mitigate infusion interruptions. Sharing care practices and experiences with equipment choices through the oncology community can lead to improvements in rates of infusion interruptions. Anecdotally, oncology nurses may use discussion boards or email listservs to discuss which equipment, such as port needle or IV tubing, has been associated with line leaks and breaks during blinatumomab cycles. After an assessment of risk and benefits, some institutions have reported turning off the air-in-line pump alarm and removing add-on devices such as closed system transfer devices to IV tubing to minimize infusion-related complications during outpatient blinatumomab delivery despite this being in contradiction with institutional policy.

From the patient perspective, receiving a continuous infusion for 28 days has implications for activities of daily life; however, there is no guidance related to activity recommendations for patients receiving outpatient blinatumomab. Given the very low toxicity rate, and the clinical observation that patients generally tolerate the drug well with minimal side effects, these 28-day cycles offer an important time to engage patients in physical, social, and developmentally appropriate activities. Blinatumomab treatment should be considered as processes and recommendations for school and work attendance, and other developmentally appropriate activities are developed and evaluated. Balancing

patient/family comfort and preferences with emerging data on safety, specifically considering activity limitations, is yet another important care delivery consideration.

WHAT IS LIKELY NEXT FOR BLINATUMOMAB IN THE UPFRONT SETTING?

Blinatumomab in Combination With Reduced-Intensity Chemotherapy

The infant trial, E1910, and AALL1731 all added blinatumomab to existing standard treatment regimens without removal of any chemotherapy.^{18,21,33} This has left many wondering if the entire chemotherapy backbone is now necessary. In the relapse setting, trials testing blinatumomab as a replacement for some or all components of therapy have demonstrated improved safety and efficacy.^{34–36} In the upfront setting, in Ph+ B-ALL as discussed above, many studies have successfully removed most standard cytotoxic components of therapy—although these data are confounded by the frequent use of HSCT.^{14–16} Data from the pediatric UKALL group recently demonstrated that in patients with excess toxicity precluding receipt of standard chemotherapy, replacement with blinatumomab was well tolerated and resulted in outcomes similar to matched patients receiving the entirety of planned chemotherapy.³⁷ Similarly, the UKALL group recently described replacement of two intense blocks of chemotherapy with a block of blinatumomab for medium-risk infant KMT2Ar B-ALL, demonstrating excellent outcomes.³⁷ Furthermore, several adult studies in the upfront setting and a small study in pediatric r/r patients have demonstrated the feasibility and efficacy of chemo-lite to chemo-free regimens incorporating blinatumomab plus the CD22-targeted antibody-drug conjugate, inotuzumab ozogamicin.^{38–40} Combined, these data support that deintensification of standard chemotherapy is likely feasible in the era of blinatumomab. Carefully designed trials are necessary to compare outcomes in patients receiving these reduced-intensity regimens to establish if this results in improved tolerability while maintaining outcomes. Blinatumomab's limited CNS activity must be taken into consideration when deciding which components of therapy to reduce/omit. Patient-/family-reported toxicities and time points during therapy that are associated with increased burden and symptom distress, collected during and adjacent to the recently completed trials,⁴¹ will be used to inform trial designs where blinatumomab is poised to replace parts of standard chemotherapy. Additionally, patient-reported toxicities, quality of life, and financial and social needs should be prospectively captured in these trials to ensure tolerability includes both clinician and patient report.

Alternative Dosing and Delivery of Blinatumomab

An open question in the field is how many courses of blinatumomab is optimal for efficacy. The pivotal infant trial gave one cycle,¹⁸ AALL1731 gave NCI-defined SR pediatric

patients two,²¹ the E1910 trial gave up to four for MRD-negative adult patients,³³ and some immunotherapy-heavy trials are giving several courses.³⁸ Dedicated studies will need to evaluate the optimal number of cycles for various patient populations. Balanced against efficacy will have to be the burden and cost of administration of increasing numbers of cycles.

Additionally, while effective, continuously infused blinatumomab is cumbersome to administer. A subcutaneous (SQ) formulation of blinatumomab, which can be dosed intermittently, is currently being evaluated in clinical trials. A study in adults with heavily pretreated r/r B-ALL tested two 28-day dosing strategies, 250 µg/dose once daily for the first week and 500 µg/dose once daily 3 days per week for the remainder of the course or 500 µg/dose once daily for a week followed by 1,000 µg/dose once daily 3 days per week. Both dosing strategies demonstrated efficacy with 12 of 14 in the lower-dose group and 12 of 13 in the higher-dose group achieving CR, with most CRs being MRD-negative. Although grade ≥3 events including CRS (23% of all patients) and neurotoxicity (34.6% of all patients) were common, most resolved after paused dosing. Such rates indicate the possible need for inpatient observation for some period of administration.⁴² Overall, there were no deaths attributable to blinatumomab. Three patients discontinued treatment due to an adverse event (one CRS, one neurotoxicity, and one other). Clinical trials of SQ blinatumomab in children are currently in development.

Another potential means to reduce the burden of blinatumomab administration is a shorter infusion time. Some small studies have already demonstrated that courses as short as even 6–10 days may be as efficacious as the full 28-day course.^{43,44} Additionally, a retrospective study of the initial pediatric phase I/II trial revealed that by day 15, most patients who would achieved an MRD-negative CR had already done so, suggesting that most of the efficacy of blinatumomab is achieved within the first several days of the infusion.⁴⁵ Additionally, there is emerging evidence to suggest that the 28-day continuous exposure to bispecific T-cell engagers may be associated with T-cell exhaustion, potentially affecting efficacy.⁴⁶ Shorter infusions with rest intervals could overcome such exhaustion.⁴⁶ Therefore, clinical trials of shorter-duration infusions could determine whether this is as or potentially more efficacious compared with the standard 28-day cycles currently used for treatment. Such studies could also deepen our understanding of the nature and extent of T-cell exhaustion in the context of blinatumomab treatment.

More Granular Delineation of Blinatumomab-Related Complications

Although toxicity data have been collected across numerous clinical trials testing blinatumomab, several uncertainties remain. For example, B-cell aplasia and resultant hypogammaglobulinemia are expected, but their duration is

undefined. One small study in adult patients suggests hypogammaglobulinemia can last up to a year after blinatumomab.⁴⁷ Such findings must be confirmed and importantly, we must also pursue dedicated exploration in pediatric populations. Given well-known age-associated differences in basal B-cell repertoire,⁴⁸ it is plausible that the impact of blinatumomab on normal B cells in children is distinct from adults. Other questions remain, such as whether blinatumomab-associated hypogammaglobulinemia is associated with increased infectious complications as was seen in blinatumomab-treated patients on AALL1731,²¹ and if so, whether empiric IVIG repletion may lessen those risks. Additionally, given the recent incorporation as standard of care, we will need detailed studies to understand potential for and actual long-term complications. Such investigations among larger populations will be crucial to inform patient anticipatory guidance and standardized follow-up health surveillance guidelines.

Beyond blinatumomab-associated systemic effects, it is expected that trends in infusion-related complications, interruptions, or other challenges with care delivery will emerge and vary across practice settings. As with any clinical question, we must ensure that we are capturing the data that are necessary to answer and address a current challenge. In the context of a 28-day continuous infusion medication that significantly improves survival among patients with B-ALL, data on how the drug is prescribed, obtained, coordinated, delivered, and monitored are all critical, especially as patients transition between the clinic and home.

Next Steps to Promote Equity in Access

Ensuring access to blinatumomab must be a preemptive consideration of any care delivery initiatives. Efforts to collect data (eg, state registry data, institutional cancer registries, or other cohort mechanisms) should focus on identification of patients who meet criteria to receive blinatumomab, track institutional-level prescribing patterns and gaps, and identify patient-level challenges to initiating and completing the prescribed treatment. For example, data collected during the AALL1731 trial to measure household material hardship and caregiver burden will be critical to our understanding of patient-, parent-, and household-level challenges that may influence ability to receive recommended treatment regimens. Further adjacent research, such as a COG Cancer Care Delivery observational study of parental financial distress during a child's treatment for ALL,⁴¹ will provide rich data (quantitative and qualitative) that may provide additional insights as strategies and interventions to promote evidence-based care delivery for ALL are developed and tested. Such data can be leveraged to improve ongoing processes at local institutions through quality improvement projects, as well as inform larger-scale trials that aim to address multilevel challenges in access, uptake, and outcomes regarding blinatumomab administration or broadly guideline-recommended care for ALL. We must ensure populations known to experience access and

outcome disparities are not excluded, such as adolescents and young adults,^{49,50} patients who live far from a treating center, patients identifying from historically underserved groups by race, ethnicity, or language preference,⁵¹ and patients facing or at risk for financial hardship.⁵²

One institutional-level approach to avoid inequities in access and subsequent worsening of outcome disparities might use a centralized model to distribute information and consultative guidance from institutions or groups of individuals with expertise in blinatumomab prescribing, administration, and management. Certain institutions and clinical teams have longer and higher volumes of experience with blinatumomab; thus, one might consider the opportunity of sharing expertise with health care teams that are newer to blinatumomab prescribing or that manage pediatric ALL less frequently. A centralized consultation model, such as has been developed and tested with other novel cancer treatment-related decision making and management,^{53,54} might support institutions to adapt and implement successful care delivery strategies to their own local settings.

Certainly, another approach might focus on supportive care for the patient and family that meets their needs, recognizing that some families may require additional support to meet the demands of a continuous infusion therapy. This may include provision of additional clinical resources (home care nursing), psychosocial support services, or tailored navigation to address financial needs. Regardless, situating the family and patient at the center of the care delivery plan is necessary to ensure successful treatment delivery.

CONCLUSION

In 2018, blinatumomab picked up its first indication in newly diagnosed patients when gained approval in adults with MRD-positive disease. From there, the indication rapidly expanded, culminating in its approval for all patients with newly diagnosed B-ALL in June 2024 in the context of the impressive outcomes in infants,¹⁸ adults,³³ and NCI SR children²¹ with B-ALL, all reported between the years of 2023–2024. The addition of blinatumomab to the standard of care for most patients with newly diagnosed B-ALL because of these studies will undoubtedly lead to the first substantial leap in the improvement of patient outcomes achieved over recent years.

The field is now poised to address the next generation of questions related to incorporation of blinatumomab into standard upfront B-ALL therapy. Perhaps the most pressing question is how much traditional chemotherapy is now necessary for cure. Emerging data suggest deintensification of chemotherapy is possible,^{14–16,37,38,55} but how much and which agents can be removed, while preserving outcomes, must be determined in the context of clinical trials including patients across age and risk groups. Additionally, work to evaluate less cumbersome means of blinatumomab administration, including shorter cycles of continuously infused blinatumomab and a SQ formulation, is promising. As

we optimize the use of blinatumomab in terms of efficacy, we must also ensure we are gaining a complete understanding of short- and long-term complications and devising standard approaches to managing them.

Finally, although there is cause for excitement, the rapid expansion of blinatumomab's indications has left many

centers contending with a sudden increase in the number of blinatumomab infusions. As the acute period of figuring out delivery and access to exponentially more blinatumomab settles, we must shift our focus to assessment of local processes and the development of standards of blinatumomab care delivery to ensure equitable access for all patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Bargou R, Leo E, Zugmaier G, et al: Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science* 321:974-977, 2008
- Kantarjian HM, Stein AS, Bargou RC, et al: Blinatumomab treatment of older adults with relapsed/refractory B-precursor acute lymphoblastic leukemia: Results from 2 phase 2 studies. *Cancer* 122: 2178-2185, 2016
- Topp MS, Gökbuget N, Stein AS, et al: Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: A multicentre, single-arm, phase 2 study. *Lancet Oncol* 16:57-66, 2015
- Topp MS, Kufer P, Gökbuget N, et al: Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol* 29:2493-2498, 2011
- von Stackelberg A, Locatelli F, Zugmaier G, et al: Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol* 34:4381-4389, 2016
- Gökbuget N, Dombret H, Bonifacio M, et al: Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood* 131:1522-1531, 2018
- Gökbuget N, Zugmaier G, Dombret H, et al: Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia. *Leuk Lymphoma* 61: 2665-2673, 2020
- Pieters R, De Lorenzo P, Ancliffe P, et al: Outcome of infants younger than 1 year with acute lymphoblastic leukemia treated with the Interfant-06 protocol: Results from an international phase III randomized study. *J Clin Oncol* 37:2246-2256, 2019
- Ravandi F: How I treat Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 133:130-136, 2019
- Schultz KR, Bowman WP, Aledo A, et al: Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: A Children's Oncology Group study. *J Clin Oncol* 27:5175-5181, 2009
- Schultz KR, Carroll A, Heerema NA, et al: Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia* 28:1467-1471, 2014
- Hunger SP, Tran TH, Saha V, et al: Dasatinib with intensive chemotherapy in de novo paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (CA180-372/COG AALL1122): A single-arm, multicentre, phase 2 trial. *Lancet Haematol* 10:e510-e520, 2023
- Biondi A, Schrappe M, De Lorenzo P, et al: Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): A randomised, open-label, intergroup study. *Lancet Oncol* 13:936-945, 2012
- Foà R, Bassan R, Vitale A, et al: Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. *N Engl J Med* 383:1613-1623, 2020
- Foà R, Bassan R, Elia L, et al: Long-term results of the dasatinib-blinatumomab protocol for adult Philadelphia-positive ALL. *J Clin Oncol* 42:881-885, 2024
- Jabbour E, Short NJ, Jain N, et al: Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: A US, single-centre, single-arm, phase 2 trial. *Lancet Haematol* 10:e24-e34, 2023
- Brown P, Pieters R, Biondi A: How I treat infant leukemia. *Blood* 133:205-214, 2019
- van der Sluis IM, de Lorenzo P, Kotecha RS, et al: Blinatumomab added to chemotherapy in infant lymphoblastic leukemia. *N Engl J Med* 388:1572-1581, 2023
- Angiolillo AL, Schore RJ, Kairalla JA, et al: Excellent outcomes with reduced frequency of vincristine and dexamethasone pulses in standard-risk B-lymphoblastic leukemia: Results from Children's Oncology Group AALL0932. *J Clin Oncol* 39:1437-1447, 2021
- Salzer WL, Burke MJ, Devidas M, et al: Toxicity associated with intensive postinduction therapy incorporating clofarabine in the very high-risk stratum of patients with newly diagnosed high-risk B-lymphoblastic leukemia: A report from the Children's Oncology Group study AALL1131. *Cancer* 124:1150-1159, 2018
- Gupta S, Rau RE, Kairalla JA, et al: Blinatumomab in standard-risk B-cell acute lymphoblastic leukemia in children. *N Engl J Med* 392:875-891, 2025
- Common Terminology Criteria for Adverse Events (CTCAE). Bethesda, MD, National Cancer Institute, Division of Cancer Treatment & Diagnosis, 2025
- Amgen: Blincyto (blinatumomab). Bethesda, MD, US Food & Drug Administration, 2024
- Withycombe JS, Kubaney HR, Okada M, et al: Delivery of care for pediatric patients receiving blinatumomab: A Children's Oncology Group study. *Cancer Nurs* 47:451-459, 2024
- Oranges K, Windawi S, Powell S, et al: How we infuse blinatumomab. *Pediatr Blood Cancer* 67:e28541, 2020
- Moody J, Barker PJ, Sciasci J, et al: Blinatumomab infusion interruptions in pediatric patients rarely lead to readmission. *Pediatr Blood Cancer* 71:e31223, 2024
- Bassett HK, Collier RJ, Beck J, et al: Financial difficulties in families of hospitalized children. *J Hosp Med* 15:652-658, 2020
- Santacrose SJ, Kneipp SM: Influence of pediatric cancer-related financial burden on parent distress and other stress-related symptoms. *Pediatr Blood Cancer* 67:e28093, 2020
- Kelada AS, Foster TB, Gagliano GC, et al: Central-line-associated bloodstream infections and central-line-associated non-CLABSI complications among pediatric oncology patients. *Infect Control Hosp Epidemiol* 44:377-383, 2023

30. Bona K, Blonquist TM, Neuberg DS, et al: Impact of socioeconomic status on timing of relapse and overall survival for children treated on Dana-Farber Cancer Institute ALL Consortium Protocols (2000-2010). *Pediatr Blood Cancer* 63:1012-1018, 2016
31. Wadhwa A, Chen Y, Hageman L, et al: Poverty and relapse risk in children with acute lymphoblastic leukemia: Children's Oncology Group study AALL03N1 report. *Blood J* 142:221-229, 2023
32. Parsons SK, Beauchemin MP, Dupuis L, et al: Children's Oncology Group 2023 blueprint for research: Cancer care delivery research. *Pediatr Blood Cancer* 70:e30579, 2023 (suppl 6)
33. Litzow MR, Sun Z, Mattison RJ, et al: Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. *N Engl J Med* 391:320-333, 2024
34. Brown PA, Ji L, Xu X, et al: Effect of postinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: A randomized clinical trial. *JAMA* 325:833-842, 2021
35. Locatelli F, Zugmaier G, Rizzari C, et al: Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: A randomized clinical trial. *JAMA* 325:843-854, 2021
36. Kantarjian H, Stein A, Gökbüget N, et al: Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 376:836-847, 2017
37. Hodder A, Mishra AK, Enshaei A, et al: Blinatumomab for first-line treatment of children and young persons with B-ALL. *J Clin Oncol* 42:907-914, 2024
38. Jabbour E, Short NJ, Senapati J, et al: Mini-hyper-CVD plus inotuzumab ozogamicin, with or without blinatumomab, in the subgroup of older patients with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: Long-term results of an open-label phase 2 trial. *Lancet Haematol* 10:e433-e444, 2023
39. Wieduwilt MJ, Yin J, Kour O, et al: Chemotherapy-free treatment with inotuzumab ozogamicin and blinatumomab for older adults with newly diagnosed, Ph-negative, CD22-positive, B-cell acute lymphoblastic leukemia: Alliance A041703. *J Clin Oncol* 41, 2023 (suppl 16; abstr 7006)
40. Gibson A, Nunez C, Robusto L, et al: Combination low-intensity chemotherapy plus inotuzumab ozogamicin, blinatumomab and rituximab for pediatric patients with relapsed/refractory B-cell acute lymphoblastic leukemia. *Haematologica* 109:3042-3047, 2024
41. Beauchemin M, Santacroce SJ, Bona K, et al: Rationale and design of Children's Oncology Group (COG) study ACCL20N1CD: Financial distress during treatment of acute lymphoblastic leukemia in the United States. *BMC Health Serv Res* 22:832, 2022
42. Jabbour E, Zugmaier G, Agrawal V, et al: Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia. *Am J Hematol* 99:586-595, 2024
43. Xie J, Liu S, Zhou M, et al: Short-course blinatumomab for refractory/relapse precursor B acute lymphoblastic leukemia in children. *Front Pediatr* 11:1187607, 2023
44. Yin J, Cai X, Qian B, et al: Short-course blinatumomab treatment as a bridge to further salvage therapy for relapsed/refractory B-cell acute lymphoblastic leukemia: A retrospective single-center study. *Cancer Med* 13:e70515, 2024
45. Brown P, Zugmaier G, Gore L, et al: Day 15 bone marrow minimal residual disease predicts response to blinatumomab in relapsed/refractory paediatric B-ALL. *Br J Haematol* 188:e36-e39, 2020
46. Philipp N, Kazerani M, Nicholls A, et al: T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals. *Blood* 140:1104-1118, 2022
47. Zugmaier G, Topp MS, Alekar S, et al: Long-term follow-up of serum immunoglobulin levels in blinatumomab-treated patients with minimal residual disease-positive B-precursor acute lymphoblastic leukemia. *Blood Cancer J* 4:e244, 2014
48. Morbach H, Eichhorn EM, Liese JG, et al: Reference values for B cell subpopulations from infancy to adulthood. *Clin Exp Immunol* 162:271-279, 2010
49. Wolfson JA, Grimes AC, Nuno M, et al: Characteristics of health care settings where adolescents and young adults receive care for ALL. *JCO Oncol Pract* 20:491-502, 2024
50. Beauchemin MP, Roth ME, Parsons SK: Reducing adolescent and young adult cancer outcome disparities through optimized care delivery: A blueprint from the Children's Oncology Group. *J Adolesc Young Adult Oncol* 12:314-323, 2023
51. Kahn JM, Keegan TH, Tao L, et al: Racial disparities in the survival of American children, adolescents, and young adults with acute lymphoblastic leukemia, acute myelogenous leukemia, and Hodgkin lymphoma. *Cancer* 122:2723-2730, 2016
52. Winestone LE, Aplenc R: Disparities in survival and health outcomes in childhood leukemia. *Curr Hematol Malig Rep* 14:179-186, 2019
53. Jillella AP, Lee SJ, Altman JK, et al: A simplified patient care strategy to decrease early deaths in acute promyelocytic leukemia (APL): Results of the ECOG-ACRIN EA9131 trial. *Blood* 140:1011-1013, 2022 (suppl 1)
54. Elia G, Skelton MR, Sweeney A, et al: Impact and cost-effectiveness of synergy between embedded palliative care and quality improvement teams on EOL quality metrics and resources utilization in a community-based oncology practice. *JCO Oncol Pract* 20:32, 2024 (suppl 10)
55. Hodder A, Mishra AK, Connor P, et al: Blinatumomab with de-escalated chemotherapy for infant KMT2A-rearranged B-cell acute lymphoblastic leukemia. *Blood* 144:2816, 2024 (suppl 1)

Redefining Survivorship in Pediatric Oncology: A Fresh Look at a Long-Term Problem

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OVERVIEW

Therapeutic advances have resulted in a growing population of childhood cancer survivors. Unfortunately, this success comes at a price. A substantial proportion of the survivors develop life-threatening chronic health conditions such as subsequent neoplasms and cardiovascular diseases. These conditions are likely initiated by exposure to chemotherapy and radiation used to treat the underlying childhood cancer and potentiated by additional accumulation of comorbidities. These conditions can cause premature death, resulting in significantly shorter lifespans. Previous research using large cohorts of childhood cancer survivors has described the magnitude of the burden or morbidity and the association between key therapeutic exposures and specific chronic health conditions. These findings have resulted in the creation of risk-based guidelines for surveillance and early detection of the complications. Now, research is increasingly focused on understanding the pathogenesis of treatment-related complications, identifying survivors at risk for these complications, developing targeted interventions, determining where and how to provide life-long risk-based care, and finally, whether providing risk-based surveillance will mitigate the burden of morbidity and mortality among childhood cancer survivors. We address these topics in this manuscript.

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INTRODUCTION

Substantial improvements in childhood cancer survival rates have resulted in a growing population of survivors who are living longer. Unfortunately, these survivors carry a substantial burden of morbidity.¹ Some of the most prevalent long-term and late-occurring life-threatening conditions include subsequent neoplasms and cardiovascular diseases. These conditions are directly related to the chemotherapy and radiation used to treat the underlying childhood cancer.¹ These conditions can cause premature death, resulting in significantly shorter lifespans. Studies in the United States and Europe have shown that childhood cancer survivors have up to 17-fold higher mortality rates compared with the general population, even decades after completing treatment.²⁻⁵ Within the first 10-15 years after diagnosis, recurrence or progression of the primary malignancy is the main contributor to late deaths. However, mortality due to causes other than the primary cancer such as subsequent neoplasms and cardiovascular disease increases from 10 years after diagnosis onwards.^{5,6}

Previous research using large cohorts of childhood cancer survivors has described the magnitude of the burden or morbidity and the association between key therapeutic exposures and specific chronic health conditions. These findings have resulted in the creation of risk-based surveillance recommendations.^{7,8} As illustrated in [Figure 1](#), the

research focus has increasingly turned to understand the pathogenesis of the treatment-related complications, identifying survivors at risk for complications, developing targeted interventions, determining where and how to provide life-long risk-based care, and finally, whether providing risk-based surveillance has mitigated the burden of morbidity and mortality among childhood cancer survivors. We address these topics in this manuscript.

MOLECULAR UNDERPINNINGS OF TREATMENT-RELATED COMPLICATIONS IN CHILDHOOD CANCER SURVIVORS

In this section, we use anthracycline-related cardiomyopathy among childhood cancer survivors to illustrate how the genetic makeup of an individual can modify the treatment-complication relationship. Anthracyclines form the backbone of chemotherapy regimens used to treat childhood cancer; 60% of patients receive anthracycline-based regimens.⁹⁻¹¹ The clinical utility of anthracyclines is compromised by cardiac dysfunction that may progress to heart failure. Compared with the general population, childhood cancer survivors are at a 5- to 15-fold higher risk of cardiac dysfunction.¹⁰⁻¹³ Once diagnosed with heart failure, the 5-year survival is <50%.¹⁴ The dose-dependent risk of cardiac dysfunction^{15,16} is modified by young age at exposure to anthracyclines, female sex, chest radiation, and presence of cardiovascular risk factors (diabetes and hypertension).¹⁷ Interpatient variability in cardiac dysfunction risk suggests

PRACTICAL APPLICATIONS

- An understanding of the pathogenesis of treatment-related complications can inform therapeutic strategies.
- Strategies to prevent or mitigate the risk of key treatment-related complications outlined in this manuscript can serve as paradigms for application in other scenarios.
- Examples of survivorship care delivery models can serve as a framework for providing risk-based care to survivors within the context of the available resources.

the role of genetic susceptibility.^{18–20} Here, we summarize the current knowledge regarding the molecular underpinning of anthracycline-related cardiomyopathy, drawing from studies that have focused on survivor populations that are either primarily childhood cancer survivors or include survivors of both childhood and adult-onset cancer (Table 1).

Drug Biotransformation Genes

Glutathione S-transferases (GSTs) facilitate elimination of anthracyclines, suggesting that a lack of function of GSTs could play a role in oxidative damage-induced cardiomyopathy. Singh et al²¹ observed a 2.7-fold greater odds of anthracycline-induced cardiomyopathy among childhood cancer survivors with *GSTM1* null genotype. Carbonyl reductases (CBRs) catalyze reduction of anthracyclines to cardiotoxic alcohol metabolites. Polymorphisms in *CBR3* influence synthesis of these metabolites. Blanco et al²²

showed that childhood cancer survivors with *CBR3* V244M homozygous G genotypes (*CBR3*:GG) exposed to low- to moderate-dose anthracyclines (1–250 mg/m²) carried a 3.3-fold greater odds of cardiomyopathy when compared with *CBR3*:GA/AA genotypes exposed to low- to moderate-dose anthracyclines. Visscher et al²³ identified genes relevant in drug pharmacokinetics/dynamics and transport (*SLC28A3*, *SLC22A17*, *SLC22A17*, and *UGT1A6*) to be associated with anthracycline-induced cardiomyopathy.

Antioxidant Mechanisms

Wang et al³² identified a single-nucleotide polymorphism (SNP), rs2232228, in *HAS3* that exerted a modifying effect on anthracycline-induced cardiomyopathy risk. Hyaluronan produced by *HAS3* reduces reactive oxygen species (ROS)–induced cardiac injury. *HAS3* mRNA levels in healthy hearts were lower among individuals with AA genotypes, suggesting that the cardiomyopathy risk could be due to inadequate protection of the heart from ROS-mediated injury.

TOP2B-Mediated DNA Damage

Aminkeng et al³³ identified a nonsynonymous variant (rs2229774) in *RARG* associated with anthracycline-induced cardiomyopathy. This variant leads to derepression of Top2b; Top2b plays a role in the development of cardiomyopathy in a murine model.^{38,39}

Alternative Splicing of TNNT2

Wang et al³⁴ identified a SNP rs1786814 on *CELF4* to be associated with cardiomyopathy. Among survivors exposed to >300 mg/m² of anthracyclines, the rs1786814 GG genotype conferred a 10.2-fold increased risk of cardiomyopathy compared with those with GA/AA genotypes and anthracycline exposure of ≤300 mg/m². *CELF4* protein controls

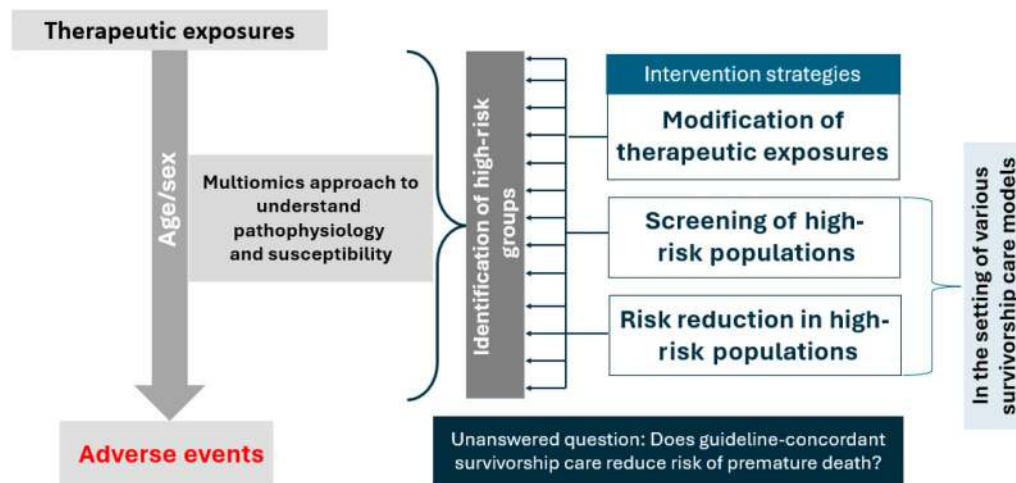


FIG 1. Emerging strategies to improve the survival and well-being of childhood cancer survivors.

TABLE 1. Genetic Variants Associated With Anthracycline-Related Cardiomyopathy in Childhood Cancer Survivors

First Author (year)	Study Design	Age at Anthracycline Exposure (years)	Type of Cancer	Definition of Cardiotoxicity	Results	Replication
Drug biotransformation						
Singh et al (2020) ²¹	Case-control Patients with cardiomyopathy: n = 75 Patients without cardiomyopathy: n = 92	Patients with cardiomyopathy: 7.8 (3.8-11.5) Patients without cardiomyopathy: 9.6 (3.3-14.8)	ALL, AML, HL, NHL, bone tumors, kidney tumor, sarcoma, neuroblastoma	LVEF <40% and/or FS <28%	GSTM1 null genotype: (OR, 2.7 [95% CI, 1.3 to 5.9]; <i>P</i> = .007)	No replication performed
Blanco et al (2012) ²²	Case-control Patients with cardiomyopathy: n = 170 Patients without cardiomyopathy: n = 317	Patients with cardiomyopathy: 7.3 (0-20.7) Patients without cardiomyopathy: 7.6 (0-21.1)	HL, NHL, bone tumors, soft tissue sarcoma, ALL, AML, other	(1) Signs/symptoms of cardiac compromise (2) LVEF ≤40%; FS ≤28%	CBR3 V244M homozygous G genotypes (<i>CBR3</i> :GG), exposure to low- to moderate-dose anthracyclines increased cardiomyopathy risk compared with individuals with <i>CBR3</i> :GA/AA genotypes unexposed to anthracyclines (OR, 5.48; <i>P</i> = .003), and exposed to low- to moderate-dose anthracyclines (OR, 3.30; <i>P</i> = .006)	No replication performed
Visscher et al (2012) ²³	Cohort Discovery: n = 156; 38 patients with cardiomyopathy Replication: (1) n = 188; 40 patients with cardiomyopathy (2) n = 96; 43 patients with cardiomyopathy	Discovery Patients with cardiomyopathy: 5.5 (0-17) Patients without cardiomyopathy: 3.9 (0-16.5) Replication 1 Patients with cardiomyopathy: 6.2 (0.4-17.6) Patients without cardiomyopathy: 3.7 (0.05-16.9) Replication 2 Patients with cardiomyopathy: 9.0 (0.5-16.8) Patients without cardiomyopathy: 10.6 (2.1-17.7)	ALL, AML, other leukemia, HL, NHL osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, other sarcoma, Wilms tumor, hepatoblastoma, neuroblastoma, carcinoma	(1) FS ≤26% (2) Signs and symptoms of cardiac compromise indicating need for intervention	SLC28A3 rs7853758 (OR, 0.20; <i>P</i> = 7.1×10^{-6}) SLC28A3 rs4877847 (OR, 0.54; <i>P</i> = .009) UGT1A6 rs6759892 (OR, 2.93; <i>P</i> = 2.2×10^{-5})	Replication in a second cohort of 188 children from across Canada and further replication of the top SNP in a third cohort of 96 patients from the Netherlands
Visscher et al (2013) ²⁴	Replication: (1) n = 128 (2) n = 90	Replication 1 Patients with cardiomyopathy: 9.1 (0.5-16.8) Patients without cardiomyopathy: 11.2 (1.8-17.7) Replication 2 Patients with cardiomyopathy: 12.6 (0.9-17.0) Patients without cardiomyopathy: 4.9 (0.5-16.0)	ALL, AML, HL, NHL osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, Wilms tumor, germ cell tumor, carcinoma, hepatoblastoma, neuroblastoma	(1) FS ≤26% (2) Signs/symptoms of cardiac compromise indicating need for intervention	UGT1A6 rs17863783 (<i>P</i> = 1.6×10^{-5}) SLC8A3 rs885004 (<i>P</i> = 3.0×10^{-5}) were replicated in this analysis	

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TABLE 1. Genetic Variants Associated With Anthracycline-Related Cardiomyopathy in Childhood Cancer Survivors (continued)

First Author (year)	Study Design	Age at Anthracycline Exposure (years)	Type of Cancer	Definition of Cardiotoxicity	Results	Replication
Visscher et al (2015) ²⁵	<i>Cohort</i> Discovery: n = 335; 78 patients with cardiomyopathy Replication: n = 185; 44 patients with cardiomyopathy	Patients with cardiomyopathy: 7.4 (0.04-17.6) Patients without cardiomyopathy: 4.9 (0.1-17.7)	Leukemia, lymphoma, sarcoma, and others	(1) FS <26% (2) Signs/symptoms of cardiac compromise indicating need for intervention	SLC22A17 rs4982753 (P = .0078) SLC22A7 rs4149178 (P = .003)	SLC22A17 and SLC22A7 were replicated (P = .0071 and P = .047, respectively)
Leger et al (2016) ²⁶	<i>Nested case cohort</i> Patients with cardiomyopathy: n = 79 Comparison cohort: n = 267	Adult and pediatric patients	BMT recipients for acute leukemia/MDS, chronic leukemia, lymphoma, multiple myeloma, solid tumors, nonmalignant disorder	Administrative data sources (National Death Index; state hospital discharge and death registry records) and self-report	Identified association with previously reported genetic associations among early-onset cardiomyopathy cases, including rs17863783 (UGT1A6)	No replication performed
Gándara-Mireles et al (2021) ²⁷	<i>Cohort</i> N = 67	2-18	ALL	A decrease of between 10% and 5% in LVEF	There was a significant association between heterozygous CBR3 rs1056892 genotype status and anthracycline-cardiotoxicity risk (OR, 9.91 [95% CI, 1.07 to 91.47]; P = .04)	No replication performed
Drug transport						
Visscher et al (2012) ²³	<i>Cohort</i> Discovery: n = 156; 38 patients with cardiomyopathy Replication: (1) n = 188; 40 patients with cardiomyopathy (2) n = 96; 43 patients with cardiomyopathy	<i>Discovery</i> Patients with cardiomyopathy: 5.5 (0-17) Patients without cardiomyopathy: 3.9 (0-16.5) <i>Replication 1</i> Patients with cardiomyopathy: 6.2 (0.4-17.6) Patients without cardiomyopathy: 3.7 (0.05-16.9) <i>Replication 2</i> Patients with cardiomyopathy: 9.0 (0.5-16.8) Patients without cardiomyopathy: 10.6 (2.1-17.7)	ALL, AML, other leukemia, HL, NHL osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, other sarcoma, Wilms tumor, hepatoblastoma, neuroblastoma, carcinoma	(1) FS ≤26% (2) Signs and symptoms of cardiac compromise indicating need for intervention	ABCB4 rs1149222 (OR, 2.31; P = .002) ABCC1 rs4148350 (OR, 3.77; P = .005)	Replication in a second cohort of 188 children from across Canada and further replication of the top SNP in a third cohort of 96 patients from the Netherlands
Krajinovic et al (2016) ²⁸	<i>Cohort</i> Discovery: n = 251 Replication: n = 44	<i>Mean age</i> Discovery cohort: 6.16 (1-18) Replication cohort: 5.27 (1-17)	ALL	Reduction in FS and EF	ABCC5 TT-1629 genotype associated with an average of 8% to 12% reduction of EF and FS (EF: P < .0001, FS: P = .001)	An additional cohort of 44 patients with ALL replicated the association
Armenian et al (2013) ²⁹	<i>Case-control</i> Patients with cardiomyopathy: n = 77 Patients without cardiomyopathy: n = 178	Patients with cardiomyopathy: 49.2 (16-68.8) Patients without cardiomyopathy: 51.0 (6.4-72.6)	Leukemia, myeloma, lymphoma status after hematopoietic cell transplantation	Sign/symptoms of cardiac compromise indicating need for intervention	ABCC2 rs8187710 (OR, 4.3; P < .01)	No replication performed

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TABLE 1. Genetic Variants Associated With Anthracycline-Related Cardiomyopathy in Childhood Cancer Survivors (continued)

First Author (year)	Study Design	Age at Anthracycline Exposure (years)	Type of Cancer	Definition of Cardiotoxicity	Results	Replication
Gándara-Mireles et al (2021) ²⁷	Cohort N = 67	2-18	ALL	A decrease of between 10% and 5% in LVEF	Heterozygosis for the ABCC1 rs3743527 allele was associated with protection from anthracycline cardiotoxicity (OR, 0.30 [95% CI, 0.09 to 0.91]; <i>P</i> = .03)	No replication performed
Iron homeostasis						
Armenian et al (2013) ²⁹	Case-control Patients with cardiomyopathy: n = 77 Patients without cardiomyopathy: n = 178	Patients with cardiomyopathy: 49.2 (16-68.8) Patients without cardiomyopathy: 51.0 (6.4-72.6)	Leukemia, myeloma, lymphoma status after hematopoietic cell transplantation	Sign/symptoms of cardiac compromise indicating need for intervention	HFE rs1799945 (OR, 2.5; <i>P</i> = .05)	No replication performed
Lipshultz et al (2013) ³⁰	Cohort n = 184	15.2 (3.1-31.4)	ALL	(1) cTnT >0.01 ng/mL (2) NT-proBNP >150 pg/mL (<1 year) (3) NT-proBNP >100 pg/mL (≥1 year)	HFE C282Y carriers associated with myocardial injury	No replication performed
Singh et al (2023) ³¹	Case-control Patients with cardiomyopathy: n = 40 Patients without cardiomyopathy: n = 64	Patients with cardiomyopathy: 8.2 (3.6-13.9) Patients without cardiomyopathy: 9.7 (3.3-14.4)	ALL, AML, Ewing sarcoma, Hodgkin lymphoma, kidney tumors, neuroblastoma, non-Hodgkin lymphoma, osteosarcoma, soft tissue sarcoma	(1) Signs/symptoms of cardiac compromise (2) EF ≤40% and/or FS ≤28%	HP was identified as the top differentially expressed gene. Participants with high HP gene expression had 6-fold greater odds of developing cardiomyopathy (OR, 6.4 [95% CI, 1.4 to 28.6]). The HP1-2 and HP2-2 genotypes combined with the G/G genotype for rs35283911 and/or rs2000999 placed the survivors at 4-fold greater risk (OR, 3.9 [95% CI, 1.0 to 14.5]) for developing cardiomyopathy	No replication performed
Antioxidant mechanisms						
Wang et al (2014) ³²	Discovery Case-control: n = 287; 93 patients with cardiomyopathy Replication Patients with cardiomyopathy only: n = 76	Discovery Patients with cardiomyopathy: 19.4 (0.4-41.7) Patients without cardiomyopathy: 18.5 (3.5-49.2) Replication Patients with cardiomyopathy: 48 (13-68)	Discovery: HL, NHL bone tumors, soft tissue sarcoma, ALL, AML, other Replication: HL, NHL, ALL, AML, other	(1) Symptoms/signs of cardiac compromise (2) LVEF ≤40% and/or FS ≤28%	HAS3 rs2232228 exerted a modifying effect on anthracycline dose-dependent cardiomyopathy risk (<i>P</i> = 5.3 × 10 ⁻⁷)	Gene-environment interaction successfully replicated in 76 patients
Leger et al (2016) ²⁶	Nested case cohort Patients with cardiomyopathy: n = 79 Comparison cohort: n = 267	Adult and pediatric patients	BMT recipients for acute leukemia/MDS, chronic leukemia, lymphoma, multiple myeloma, solid tumors, nonmalignant disorder	Administrative data sources (National Death Index; state hospital discharge and death registry records) and self-report	Identified association with previously reported genetic associations among early-onset cardiomyopathy cases, including rs2232228 (HAS3)	No replication performed

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TABLE 1. Genetic Variants Associated With Anthracycline-Related Cardiomyopathy in Childhood Cancer Survivors (continued)

First Author (year)	Study Design	Age at Anthracycline Exposure (years)	Type of Cancer	Definition of Cardiotoxicity	Results	Replication
TOP2B-mediated DNA damage						
Aminkeng et al (2015) ³³	<i>Cohort</i> Discovery: n = 280; 32 patients with cardiomyopathy Replication European patients: n = 96; 22 patients with cardiomyopathy Non-European patients: n = 80; 19 patients with cardiomyopathy	<i>Discovery</i> Patients with cardiomyopathy: 9.0 (2.5-14) Patients without cardiomyopathy: 4 (2-7.5) <i>Replication (Dutch population):</i> Patients with cardiomyopathy: 7.5 (5-12) Patients without cardiomyopathy: 11 (6-14)	ALL, AML, HL, NHL, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, hepatoblastoma, neuroblastoma, Wilms tumor	FS ≤24% or signs/symptoms of cardiac compromise indicating need for intervention	Nonsynonymous variant (rs2229774, p.Ser427Leu) in RARG (OR, 4.7 [95% CI, 2.7 to 8.3]; $P = 5.90 \times 10^{-8}$)	Replication in similarly treated cohorts of 96 European and 80 non-European patients
Alternative splicing of TNNT2						
Wang et al (2016) ³⁴	<i>Discovery</i> Case-control Patients with cardiomyopathy: n = 112 Patients without cardiomyopathy: n = 219 <i>Replication</i> Patients with cardiomyopathy only: n = 54	<i>Discovery</i> : Cases: 7.5 (0-20); Patients without cardiomyopathy: 7.9 (0-21) <i>Replication</i> : Patients with cardiomyopathy: 5.6 (1.1-17.3)	<i>Discovery</i> : HL, NHL, sarcoma, AML, ALL, and others <i>Replication</i> : HL, NHL, sarcoma, AML, ALL, and others	(1) Signs/symptoms of cardiac compromise (2) EF ≤40% and/or FS ≤28%	Anthracyclines >300 mg/m ² , CELF4 rs1786814 GG genotype conferred a 10.2-fold ($P < .001$) increased risk of cardiomyopathy compared with those who had GA/AA genotypes and anthracycline exposure ≥300 mg/m ²	Gene-environment interaction was successfully replicated in an independent set of patients with anthracycline-related cardiomyopathy
Leger et al (2016) ²⁶	<i>Nested case cohort</i> Patients with cardiomyopathy: n = 79 Comparison cohort: n = 267	Adult and pediatric patients	BMT recipients for acute leukemia/MDS, chronic leukemia, lymphoma, multiple myeloma, solid tumors, nonmalignant disorder	Administrative data sources (National Death Index; state hospital discharge and death registry records) and self-report	Identified association with previously reported genetic associations among early-onset cardiomyopathy cases, including rs1786814 (CELF4)	No replication performed
Profibrotic Slit-Robo signaling pathway						
Wang et al (2022) ³⁵	<i>Discovery</i> Cohort (n = 1,866; patients with cardiomyopathy: n = 126) <i>Replication</i> Case-control Patients with cardiomyopathy: n = 105 Patients without cardiomyopathy: n = 160	<i>Discovery</i> Patients with cardiomyopathy: 7 (0-20) Patients without cardiomyopathy: 11 (0-20) <i>Replication</i> Patients with cardiomyopathy: 6.6 (0-20.6) Patients without cardiomyopathy: 8.6 (0.3-21.7)	<i>Discovery and replication</i> : ALL, AML, HL, NHL, bone tumors, soft tissue sarcoma, other	<i>Discovery</i> : Self-report of CTCAE grade 3 to 5 congestive heart failure <i>Replication</i> : (1) Signs/symptoms of cardiac compromise (2) EF ≤40% and/or FS ≤28%	ROBO2 rs17736312: Compared with GG/AG genotypes and low-dose anthracyclines, the AA genotype and high-dose anthracyclines conferred a 2.2-fold and 8.2-fold higher risk of cardiomyopathy in the discovery and validation data sets, respectively Significant gene-level associations with heart failure: main effect (TGF- β 1, $P = .007$); gene*anthracycline interaction (ROBO2*anthracycline, $P = .0003$); and gene*gene*anthracycline interaction (SLIT2*TGF- β 1*anthracycline, $P = .009$)	Successfully replicated

(continued on following page)

TABLE 1. Genetic Variants Associated With Anthracycline-Related Cardiomyopathy in Childhood Cancer Survivors (continued)

First Author (year)	Study Design	Age at Anthracycline Exposure (years)	Type of Cancer	Definition of Cardiotoxicity	Results	Replication
Cardiac conduction disorders						
Sapkota et al (2022) ³⁶	<i>Cohort</i> Discovery: n = 1,870 non-Hispanic White individuals Replication 1: 301 African American survivors Replication 2: 4,020 non-Hispanic White individuals	<i>Discovery</i> Patients with cardiomyopathy: 10.5 (0-20.5) Patients without cardiomyopathy: 6.9 (0-23.6)	Discovery and replication 1: all childhood cancers Replication 2: ALL, AML, HL, NHL, bone tumors, soft tissue sarcoma, other	(1) Reduction in EF and (2) Clinically assessed cardiac dysfunction	Discovery: A variant near KCNK17 showed genome-wide significant association with EF (rs2815063-A: LVEF reduction = 1.6%; $P = 2.1 \times 10^{-8}$) rs2815063-A showed a 1.80-fold ($P = .008$) risk of severe or disabling or life-threatening cardiac dysfunction Replication 1: LVEF reduction 1.5%; $P = .004$ Replication 2: 1.4-fold greater odds of cardiac dysfunction ($P = .04$)	Successfully replicated
Cardiomyocyte apoptosis						
Sharafeldin et al (2023) ³⁷	<i>Discovery</i> Case-control Patients with cardiomyopathy: n = 129 Patients without cardiomyopathy: n = 149 Replication cohort	<i>Discovery</i> Patients with cardiomyopathy: 7 (0-21) Patients without cardiomyopathy: 7 (0-20) <i>Replication</i> Patients with cardiomyopathy: 13 (0-20) Patients without cardiomyopathy: 6.0 (0-20)	ALL, AML, brain tumors, Ewing sarcoma, HL, NHL, neuroblastoma, osteosarcoma, soft tissue sarcoma, Wilms tumor, other	Discovery: (1) Signs/symptoms of cardiac compromise (2) EF $\leq 40\%$ and/or FS $\leq 28\%$ Replication: Self-report of CTCAE grade 3 to 5 congestive heart failure	Gene-level association for P2RX7 (OR, 0.10 [95% CI, 0.04 to 0.27]; $P = 2.19 \times 10^{-6}$) was successfully replicated (HR, 0.65 [95% CI, 0.47 to 0.90]; $P = .009$)	Successfully replicated

Abbreviations: BMT, bone marrow transplantation; CTCAE, Common Terminology Criteria for Adverse Events; cTnT, cardiac troponin T; EF, ejection fraction; FS, fractional shortening; HL, Hodgkin lymphoma; HP, haptoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; OR, odds ratio; SNP, single-nucleotide polymorphism.

developmentally regulated splicing of *TNNT2*, the gene that encodes for cardiac troponin T (cTnT), a biomarker of myocardial injury. Coexistence of >1 cTnT variant results in a temporally split myofilament response to calcium impairing contractility. Analysis of healthy human hearts showed an association between rs1786814 GG genotype and coexistence of >1 *TNNT2* splicing variants.

Profibrotic Slit-Robo Signaling Pathway

Wang et al³⁵ identified a SNP (rs17736312 [*ROBO2*]) that modified the anthracycline dose-cardiomyopathy relationship. Compared with GG/AG genotypes and low-dose anthracyclines, the AA genotype and high-dose anthracyclines conferred a higher risk of cardiomyopathy. *ROBO2* encodes transmembrane Robo receptors that bind Slit ligands. Slit-Robo signaling pathway promotes cardiac fibrosis by interfering with the *TGF- β 1*/Smad pathway, resulting in disordered remodeling of the extracellular matrix and potentiating heart failure.

Cardiac Conduction Disorders

Sapkota et al³⁶ identified a variant near *KCNK17* (rs2815063-A) to be associated with cardiac dysfunction. Whole-blood DNA methylation showed significant correlation between rs2815063-A and dysregulation of *KCNK17* enhancers. Furthermore, rs2815063-A was associated with *KCNK17* downregulation on the basis of RNA sequencing. *KCNK17* is associated with cardiac conduction disorders in the general population.

Cardiomyocyte Apoptosis

Sharafeldin et al³⁷ identified the protective effect of *P2RX7* such that SNP sets having ≤ 1 copies of *P2RX7* variant alleles were associated with reduced risk of cardiomyopathy. *P2RX7* activation leads to cardiomyocyte apoptosis and cardiac dysfunction.

Aberrant DNA Methylation

Singh et al³¹ identified 32 differentially methylated probes and 354 differentially methylated regions associated with anthracycline-induced cardiomyopathy. Several of the associated genes were linked to cardiac dysfunction. Knockout of genes *EXO6CB*, *FCHSD2*, *NIPAL2*, and *SYNPO2* in hiPSC-CMs increased sensitivity to doxorubicin. EWAS analysis identified hypomethylation of probe cg15939386 in gene *RORA* to be associated with anthracycline-induced cardiomyopathy. *RORA* protects against angiotensin II-induced cardiac hypertrophy and heart failure.

Differentially Expressed Genes

Singh et al^{40,41} identified differential mRNA expression profiles in the peripheral blood of anthracycline-exposed childhood cancer survivors with and without

cardiomyopathy. Haptoglobin (HP) was identified as the top differentially expressed gene (DEG). Participants with higher HP gene expression had 6-fold greater odds of developing cardiomyopathy. HP binds to free hemoglobin to form an HP-hemoglobin complex, thereby preventing oxidative damage from free heme iron. Additional DEGs included upregulation of *LDHA* and *CD36* genes, suggesting metabolic perturbations in a failing heart, and dysregulation of proinflammatory cytokine receptors *IL1R1* and *IL1R2* and matrix metalloproteinases *MMP8* and *MMP9* indicating structural remodeling.

Metabolomics

Armenian et al⁴² performed plasma metabolomic analyses (eight pathways; 354 metabolites) in anthracycline-exposed childhood cancer survivors. Individuals with cardiac dysfunction had significantly lower plasma carnitine levels. Clinically, both primary and secondary carnitine deficiency can result in cardiomyopathy and cardiac arrhythmias, due in part to the accumulation of long-chain fatty acids and acylcarnitines that are unable to be oxidized in the mitochondria and are unavailable for energy production.

Prediction of Anthracycline-Induced Cardiomyopathy

The poor prognosis coupled with the interindividual variability in risk has resulted in an increasing interest in developing prediction tools to identify patients at highest risk of cardiomyopathy.^{20,43,44} Such a risk prediction tool could inform personalized decisions regarding risk-mitigating interventions. Clinical risk prediction models have yielded modest predictive power,^{44,45} resulting in some initial studies that have added genetic variants to improve the ability to discriminate anthracycline-exposed survivors by their risk of developing cardiomyopathy.^{24,29,46} In 2016, Aminkeng et al⁴⁶ followed a standard guideline development process and developed clinical practice recommendations with an international expert group. They identified *RARG* rs2229774, *SLC28A3* rs7853758, and *UGT1A6* rs17863783 variants to have the strongest and the most consistent evidence for association with anthracycline-related cardiomyopathy. They recommended pharmacogenomic testing for the *RARG* rs2229774 (S427L), *SLC28A3* rs7853758 (L461L), and *UGT1A6**4 rs17863783 (V209V) variants in childhood cancer patients with an indication for doxorubicin or daunorubicin therapy (Level B—moderate). However, since this publication almost a decade ago, several additional genetic associations have been discovered. There is a need to collate all candidate genes that have demonstrated robust, biologically plausible associations, and develop risk-prediction models (and externally validate them) to identify childhood cancer survivors at high risk for anthracycline-related cardiomyopathy, thus setting the stage for targeted interventions. Such efforts are currently underway. As of now, the Children's Oncology Group (COG) or the International Group Harmonization guidelines do not recommend

the clinical use of the genetic variants in identifying patients at increased risk of anthracycline-related cardiomyopathy.

ROLE OF PERSONALIZED INTERVENTIONS TO REDUCE MORBIDITY IN CHILDHOOD CANCER SURVIVORS

There is evidence to suggest that interventions to reduce treatment-related morbidity can be integrated into frontline cancer treatment (primary prevention) or delivered to asymptomatic cancer survivors at risk for late-occurring health complications (secondary prevention). For certain cancers where cancer-free survival rates are high (eg, Hodgkin lymphoma [HL], ALL), there are ongoing efforts to de-escalate treatment or consider biological alternatives to conventional chemotherapy or radiation (primordial prevention). However, clinical trials to mitigate treatment-related morbidity across the cancer continuum are not without challenges. They often require long-term follow-up to document clinically meaningful impact, multidisciplinary and multicenter collaborations, and real-time engagement of key stakeholders such as clinicians and survivors who may not be regularly engaged in survivorship-focused care. Here, we provide examples of recent pharmacologic trials that have leveraged information about the pathogenesis of the chronic health condition to strategize risk mitigation.

Primary Prevention

Some of the earliest organized efforts to mitigate long-term toxicities of chemotherapy focused on dose-dependent cardiotoxicity associated with anthracyclines.⁴⁷ Although prolonged infusion to decrease peak doxorubicin plasma concentration did not lower cardiotoxicity risk in children,^{47,48} concomitant administration of the cardioprotectant dexrazoxane did show early promise by reducing blood biomarkers of acute cardiac injury (eg, cardiac troponin levels), without compromising the antitumor effect of anthracyclines.^{47,49,50} Concerns for higher rates of subsequent neoplasms in dexrazoxane-treated patients initially limited its use,⁴⁷ but these concerns were largely alleviated with the recently completed multicenter study of very long-term survivors (median 18 years since cancer diagnosis) previously randomly assigned to anthracyclines $\pm$ dexrazoxane, confirming the safety and efficacy of the cardioprotectant in those treated with high-dose (≥ 250 mg/m²) cumulative doxorubicin equivalents of anthracyclines.^{51,52} As a result, the recent international consensus guidelines recommend administration of dexrazoxane in children expected to receive ≥ 250 mg/m² cumulative doxorubicin equivalent dose of anthracyclines.⁵³ Other cardioprotective approaches, including liposomal encapsulation of doxorubicin or anthracycline derivatives such as aclarubicin and diMe-doxorubicin^{54,55} are also being considered in the frontline setting, with promising signals that will need to be evaluated in longer-term survivors of childhood cancer.

Platinum compounds (cisplatin and carboplatin) have contributed to improvement in survival in children with cancer,

especially germ cell tumors, hepatoblastoma, neuroblastoma, and medulloblastoma.⁵⁶ However, ototoxicity develops shortly after platinum exposure and results in delayed speech and language development, reduced academic performance, and long-term cognitive impairment.^{56,57} Randomized trials have assessed the efficacy of systemic otoprotective drugs such as amifostine, sodium diethyldithiocarbamate or disulfiram, and sodium thiosulfate (STS); only STS demonstrated efficacy.⁵⁷ Studies in patients with hepatoblastoma (SIOPEL 6)⁵⁸ and a variety of solid tumors (ACCL0431)⁵⁹ receiving cisplatin confirmed the otoprotective effect of STS in patients with localized disease, without compromise of antitumor efficacy. However, a post hoc analysis of ACCL0431 showed inferior overall survival among patients with disseminated disease on the STS arm.⁵⁹ As such, this compound is currently licensed only for children who have nonmetastatic solid tumors.⁵⁷ As with dexrazoxane, long-term follow-up is needed to demonstrate the continued benefits of STS in childhood cancer survivors.

Secondary Prevention

Secondary pharmacologic prevention trials are especially challenging because of the need to (1) enroll asymptomatic survivors who may no longer be engaged in cancer survivorship care; (2) have a clear understanding of the pathophysiology and long-term trajectory of asymptomatic disease; (3) rely on intermediate (preclinical) end points to demonstrate efficacy; and (4) identify a robust infrastructure that includes multidisciplinary teams (eg, pediatric and adult medicine, subspecialty services) for long-term monitoring and care. Despite these challenges, recent randomized trials provide promising insights.

Radiation-Related Breast Cancer

Adolescent and young adult females treated with chest radiation for a primary cancer (eg, HL) are at a high risk for developing breast cancer; the cumulative incidence ranges from 13% to 20% by age 40–45 years, similar to that observed in BRCA mutation carriers.^{1,60,61} Breast cancer survival in childhood cancer survivors is worse than survival after de novo breast cancer,⁶² emphasizing the need for breast cancer risk reduction. A phase IIb randomized placebo-controlled trial showed that low-dose tamoxifen administered for two years was safe and well tolerated in chest-irradiated female cancer survivors, and resulted in significantly lower mammographic breast density and blood IGF1 levels (established biomarkers of breast cancer risk), compared with placebo.⁶³ This study will serve as a building block for future phase III trials to evaluate reduction in breast cancer risk.

Anthracycline-Induced Cardiomyopathy

Low-dose antihypertensives (eg, angiotensin-converting enzyme inhibitors [enalapril] or beta blockers [carvedilol]) showed early promise because of their ability to reduce systemic vascular resistance and improve cardiac

remodeling.⁶⁴ However, a recently completed phase IIb randomized placebo-controlled trial of carvedilol in childhood cancer survivors treated with high-dose (≥ 250 mg/m²) anthracyclines did not show a significant improvement in the primary end point (standardized left ventricular wall thickness-dimension ratio Z-score).⁶⁵ A subanalysis of participants with elevated blood NT-N-terminal pro-hormone of brain natriuretic peptide (an established blood biomarker of cardiac injury) at baseline showed a significant improvement in primary and secondary end points compared with placebo.⁶⁶ This may provide the impetus to consider more personalized clinical and biomarker-based (imaging, blood) approaches to screen survivors who may derive the most benefit from secondary prevention.

Future Considerations

Ultimately, the most effective strategies to reduce the burden of morbidity will be those that focus on eliminating or reducing exposures to cancer treatments with known late effects, without compromising gains made in cancer-related survival. There are several childhood cancers where primordial prevention will likely result in a lower burden of late effects, including near elimination of cranial radiation for childhood ALL and chest radiation for HL, further reduction of cumulative anthracycline dose in ALL and Wilms tumor, improved surgical approaches (eg, limb salvage for bone tumors), and more precise delivery of radiation for brain tumors. The emergence of biological therapies has provided new hope for previously incurable cancers, and these agents are increasingly being considered in the frontline setting. Ongoing vigilance will be required to examine the short- and longer-term benefits associated with these novel strategies.

CARE DELIVERY MODELS FOR SURVIVORS

Survivorship Care in the United States

Providing risk-based survivorship care to cancer survivors in the United States is a difficult and uncoordinated set of tasks. The term *care delivery models* encompasses type and elements of care being delivered as well as providers and the setting. In survivorship, models of care are often categorized into oncology-led, primary care-led, shared care, and multidisciplinary models. For two unique populations of cancer survivors, those diagnosed as children, and adolescents or young adults (AYA), survivorship care delivery is especially challenging.⁶⁷ For these populations, designing or evaluating models of care requires a thorough understanding of the needs of these populations as well as the barriers and facilitators for receipt of care. Available evidence indicates that children and those diagnosed in the AYA period are treated in heterogeneous settings. For those diagnosed during childhood, the majority are treated at COG institutions, and many are treated on COG trials.⁶⁸ Those diagnosed in the AYA period are more likely to be treated in community settings and may be less likely to enroll on clinical trials.⁶⁹

Regardless of the age at diagnosis, models of care for these survivors must accommodate the transition from oncology to survivorship care, as well as the overlapping transition from pediatric to adult-oriented care, complicated by social, economic, geographic, and organizational factors.⁷⁰ Among children with special health care needs, poor transition from pediatric to adult-oriented care can result in gaps in care, patient and family frustration, and adverse health outcomes.⁷¹ A recent systematic review of barriers to transition from pediatric to adult care found 57 relevant articles.⁷² The most commonly cited barriers to transition included those related to patient-provider relationships (eg, difficulty letting go of pediatric providers), followed by access or insurance barriers, barriers related to patient beliefs or expectations, and barriers related to provider knowledge and skills. In a survey of childhood cancer survivors nearing transition, most survivors indicated willingness to transition to adult-oriented care.⁷³ Notably, insurance coverage and provider expertise in childhood cancer survivorship were considered very important transition facilitators. Therefore, individual factors related to the knowledge and skills of the adult-oriented provider and the insurance coverage of the survivor are important to address. At the same time, pediatric providers and organizations have the opportunity to facilitate coordinated transition but may not have the infrastructure in place to do so. A recent survey of transition practices, barriers, and implementation at COG institutions found that although transfer to primary care was a common practice, few institutions offered formal transition processes.⁷⁴

A recent publication using data from the National Health Interview Survey⁷⁵ reported on measures of medical financial hardship including problems paying bills, worry about paying bills, and foregoing care because of cost among cancer survivors. Cancer survivors younger than 50 years were more likely to report measures of medical financial hardship, compared with older cancer survivors and the general population. Furthermore, high-deductible private insurance was associated with greater hardship. These findings likely affect the ability of survivors to access or attend survivorship care. A separate study of childhood cancer survivors in Connecticut found that insurance status was an important predictor of attendance in a survivorship clinic.⁷⁶ Besides cost, other individual factors likely influence receipt of risk-based survivorship care.⁷⁷ A retrospective analysis of a Canadian provincial pediatric cancer registry found that attendance at a survivorship clinic was associated with female sex, higher treatment intensity, higher socioeconomic status, an annual examination by a PCP, and living within 10 km of the clinic.⁷⁸

Yet, barriers to receipt of risk-based survivorship care for childhood and AYA cancer survivors are not only individual factors such as insurance status and distance to care. Funded by the Survivorship, Treatment, Access, and Research Act (STAR Act) of 2018, the National Cancer Institute (NCI) commissioned three evidence reports from the Agency for Healthcare Research and Quality (AHRQ). The first of these

provided an overview of the existing evidence on disparities and barriers for childhood cancer survivorship care.⁷⁹ This report found 47 studies of barriers to survivorship care. The most frequently studied barriers were at the level of the patient or provider. No intervention studies addressed barriers in policy, organization, health care system, or payer levels. After this report, the NCI funded administrative supplements to evaluate organizational barriers to childhood cancer survivorship care and published a Notice of Special Interest to encourage research into these questions. The second STAR Act–funded AHRQ report was a comparative effectiveness review of interventions or implementation strategies for transitions of care from pediatric- to adult-oriented services for children with special health care needs, including childhood cancer survivors. Unfortunately, little rigorous evidence was identified, and assessment or evaluation of strategies and practices for transition could not be conducted. The third report was a realist review of care models that include primary care for adult survivors of childhood cancer.⁸⁰ A definition of effective care emerged: survivors living longer and feeling better through high-value care. An intermediate step to effectiveness, degree of understanding cancer history, risk, symptoms, needs, and resources, was also identified. Overall, the result of these reports was an acknowledgment of the substantial lack of evidence for childhood cancer survivor care delivery, including evidence regarding higher-level barriers to care, care transitions, or models of care delivery. Not surprisingly, this lack of evidence is reflected in the haphazard and uncoordinated delivery of survivorship care to childhood cancer survivors.⁸¹ Recent workshops and funded grants from the NCI and other institutes and centers of the National Institutes of Health are intended to spur research to better understand and address these gaps.

For childhood cancer survivors, care in a specialized survivor clinic may be the preferable model. Evidence from Ontario (where specialty childhood cancer survivorship clinics are available) suggests that attendance at one of these clinics is associated with better adherence to COG Long-Term Follow-Up Guidelines⁷ and fewer emergency department visits.⁸² However, whether adherence to guidelines translates to better health was not reported.⁸³ In addition, whether these findings from the Canadian health care system translate to the United States is unknown.

Care delivery models for those diagnosed in the AYA period are even less frequently assessed. One review of published models for AYA cancer survivors found only 25 studies, with the majority promoting shared or multidisciplinary care; the lack of evidence on efficacy or outcomes was highlighted.⁸⁴ Most survivors diagnosed in the AYA period are not aware of survivorship services at their treating institution or in the community, and do not feel that their health care team is in touch with AYA concerns.⁸⁵ A recent review noted that this population may experience two health care transitions: oncology to primary care, and pediatric to adult providers.⁸⁶ At the same time, risk of poor care coordination and loss to

follow-up is high. Because no single model of survivorship care has emerged as superior, local resources and individual factors (such as insurance status and late effects from treatment) are driving care.

Opportunities for research to inform models of care for childhood and AYA cancer survivors are important. The National Childhood Cancer Registry (NCCR), part of the NCI Childhood Cancer Data Initiative, has been established as a resource for this work.⁸⁷ The NCCR is a central platform that links 28 NCCR participating cancer registries, representing 75% of the US population age 0–39 years, to other sources of data including electronic health records, research institutions, health care administration databases, and elsewhere. The recently published National Standards for Cancer Survivorship Care, which includes health care policy, process, and assessment measures, provides a scaffold for evaluation of survivorship care quality.⁸⁸ After the publication of the Standards, the NCI funded 18 administrative supplements to support research to assess and inform the alignment of survivorship care with the Standards.⁸⁹ Having a tool to facilitate the evaluation the effectiveness of survivorship care delivery models is essential to the promotion and adoption of risk-based survivorship care.

Survivorship Care in Europe

In many European countries, there is a lack of survivorship care for pediatric and especially adult survivors of childhood and adolescent cancer.⁹⁰ In 2006 and 2016, pediatric oncologists, psychologists, nurses, epidemiologists, survivors, and their parents agreed on the Erice Statement, stating that survivorship care should be available and accessible for all childhood and adolescent cancer survivors throughout their lifespan.⁹¹ The European collaboration for survivorship care and research, PanCare, developed a guideline for models of survivorship care.⁹² The guideline recommends that survivorship care should be provided in or under the guidance of a survivorship expert service or cancer center and that the survivor and health provider should make a joint decision for the optimal model of survivorship care on the basis of previous cancer treatment, health condition, and survivor preferences. Different models of care are described: (1) self-management with primary care support, (2) follow-up at primary care level or by a nurse experienced in management of late effects and followed by supported self-management, (3) follow-up at cancer survivorship center, or (4) shared care between survivorship center and primary care or pediatric centers.⁹²

In 2019, the EU funded the PanCareFollowUp project.⁹³ Within this project, the European-wide harmonized surveillance guidelines on the basis of the available International Guideline Harmonization Group (IGHG) guidelines, existing guidelines, and experts opinions was developed.⁹⁴ Furthermore, to improve the survivorship care for adult survivors of childhood cancer across Europe, PanCareFollowUp developed the PanCareFollowUp Care

intervention, a person-centered approach to survivorship care on the basis of the European guideline for surveillance of late effects and the follow-up care model used in the Netherlands.⁹⁵ The structured follow-up model is designed to support personalized survivorship care first through a clinical visit and follow-up call, and includes a survivor questionnaire, and individualized care plans on the basis of previous treatment exposure-based guideline recommendations. The intervention was implemented in a prospective cohort study at clinical sites in Belgium, the Czech Republic, Italy, and Sweden. These countries represented different levels of implementation of survivorship care after childhood cancer in Europe. The main lessons for future implementation of survivorship care are the need for dedicated staff, a multidisciplinary expert team, a coordinator for care, a digital care plan, and a transition plan from pediatric to adult care. Analyses on empowerment of survivors, cost-effectiveness, and yield of screening are underway. All the materials developed in this project, including lay language summaries of the guidelines and policy recommendations, are available at the PanCare website.⁹⁶

In Europe, the EU-CAYAS-NET project has developed an evidence-based clinical guideline aimed at improving the transition process for childhood and young adult cancer survivors in Europe.⁹⁷ This evidence-based guideline focuses on a structured and personalized approach, increasing the chance of a successful transition to long-term follow-up care 5 years after diagnosis and from pediatric to adult-oriented survivorship care. The guideline integrates scientific research, clinical experience, and patient feedback to ensure that survivors receive ongoing, age-appropriate care addressing both their medical and psychosocial needs. The guideline recommends that pediatric cancer centers should appoint a transition coordinator—such as a nurse practitioner—who works with the survivor, their parents or caregivers, and other health care professionals to create an individualized transition plan. It also recommends that centers provide clear, age-appropriate, and developmentally appropriate informational materials (both digital and printed) that explain the importance of the transition process, what it entails, what to expect during and after the transition, and how the roles of survivors and their caregivers will evolve.

DOES EARLY DETECTION OF TREATMENT-RELATED CHRONIC HEALTH CONDITIONS REDUCE MORTALITY IN CHILDHOOD CANCER SURVIVORS?

Risk-based long-term follow-up care of cancer survivors facilitates early detection and timely intervention of treatment-related chronic health conditions and ultimately aims to prevent premature death. The global International Late Effects of Childhood Cancer Guideline Harmonization Group, IGHG, is a worldwide endeavor initiated by several guideline groups to collaborate in guideline development for survivorship care.⁸ The main goal is to develop surveillance recommendations to detect chronic health conditions early

in survivors of cancer diagnosed during childhood, adolescence, and young adulthood. IGHG guidelines emphasize targeting high-risk individuals (on the basis of treatment exposures) for more intensive or earlier screening. Evidence- and consensus-based recommendations have been published on 20 topics thus far.⁸ The key questions in every guideline include (1) Which survivors are at increased risk? (2) When and how frequently should screening be performed? (3) Which screening methods or tests should be used? (4) What interventions are advised if screening reveals abnormalities? Surveillance for a specific chronic health condition is recommended in IGHG guidelines only if there is evidence or consensus that identifying the complication at an asymptomatic or early stage will allow for less-invasive treatments, improved quality of life, and potentially better survival.⁸ Four examples where early detection and early treatment can reduce mortality in childhood cancer survivors are presented here and include surveillance for breast cancer, colorectal cancer, cardiomyopathy, and modifiable cardiovascular risk factors.

Breast Cancer Surveillance

Female survivors of childhood cancer treated with chest radiation are at increased risk of developing breast cancer at a young age.⁹⁸⁻¹⁰⁰ The cumulative incidence for developing breast cancer ranges from 13% to 20% by age 40-45 years. Long-term surveillance with mammography and breast magnetic resonance imaging has been recommended for female survivors treated with chest radiation at doses >10 Gy.¹⁰¹ These recommendations were informed by the magnitude of risk of radiation-related breast cancer in childhood cancer survivors, and the value of screening in the general population. Although studies investigating whether early detection of breast cancer in childhood cancer survivors improves survival are lacking, simulation studies in childhood cancer survivors¹⁰² and research in the general population^{103,104} show that mammographic screening lowers breast cancer mortality.

Colorectal Cancer Surveillance

Childhood cancer survivors treated with abdominal or pelvic radiation are at approximately 11-fold increased risk of colorectal cancer when compared with unirradiated survivors.^{105,106} The COG guidelines⁷ recommend initiating colorectal cancer screening, such as colonoscopy, and/or multitarget stool DNA test for survivors exposed to abdominal or pelvic radiation at an earlier age than the general population. One simulation study showed that early initiation of colorectal cancer screening in childhood cancer treated with abdominal radiation is cost-effective and can prevent colorectal cancer deaths expected.¹⁰⁷

Surveillance for Cardiomyopathy

The IGHG guidelines recommend screening echocardiograms for survivors treated with anthracyclines >100 mg/m²

and/or chest radiation at doses >15 Gy.¹⁰⁸ Although direct evidence supporting the benefits of surveillance is limited, several simulation studies have demonstrated improved survival rates among survivors who participated in surveillance programs, assuming treatment effectiveness similar to the effects in the general population with asymptomatic cardiomyopathy.^{109–111} These findings suggest a gain in life-years through early intervention for cardiomyopathy detected via surveillance echocardiograms in childhood cancer survivors.

Screening for Modifiable Cardiovascular Risk Factors

Childhood cancer survivors are at an increased risk of developing cardiovascular risk factors, such as hypertension, dyslipidemia, obesity, and diabetes.¹¹² Healthy lifestyle and absence of hypertension and diabetes are each associated with a 20%–30% reduction in health-related mortality independent of other factors.⁶ As a result, surveillance and treatment of modifiable cardiovascular risk factors should decrease the risk of health-related mortality. The COG and IGHG guidelines recommend surveillance of modifiable risk factors for survivors at risk for treatment-associated coronary artery disease and cardiomyopathy.^{108,113} Currently, to our knowledge, no studies have investigated the effect of screening for these risk factors on survival. Indirect evidence from studies focusing on an association between these risk

factors and increased risk of mortality are used to formulate these recommendations.^{108,113}

Summary

Surveillance for treatment-related chronic health conditions in childhood cancer survivors is important for early detection to improve quality of life and potentially survival. Evidence to support that early surveillance reduces mortality is lacking. However, simulation studies in childhood cancer survivors and evidence extrapolated from other populations suggest that such benefit is achievable in the childhood survivor cancer population as well.

CONCLUSION

As the population of childhood cancer survivors continues to grow and age, there is a critical need to accelerate our pace in attempting to understand the mechanistic basis for treatment-related morbidity, identify those at highest risk, and develop, test, and implement personalized interventions to mitigate the burden of this morbidity. Furthermore, we need to examine how to develop effective models of survivorship care delivery, while remaining very focused on our understanding whether the surveillance guidelines truly benefit the childhood cancer survivors.

are those of the authors and do not necessarily represent the official position of the National Cancer Institute.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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DISCLAIMER

The article was prepared as part of EST's official duties as employee of the US Federal Government. The findings and conclusions in this report

REFERENCES

- Bhatia S, Tonorez ES, Landier W: Clinical care for people who survive childhood cancer: A review. *JAMA* 330:1175–1186, 2023
- Armstrong GT, Chen Y, Yasui Y, et al: Reduction in late mortality among 5-year survivors of childhood cancer. *N Engl J Med* 374:833–842, 2016
- Byrne J, Schmidtmann I, Rashid H, et al: Impact of era of diagnosis on cause-specific late mortality among 77 423 five-year European survivors of childhood and adolescent cancer: The PanCareSurFup consortium. *Int J Cancer* 150:406–419, 2022
- Fidler MM, Reulen RC, Henson K, et al: Population-based long-term cardiac-specific mortality among 34 489 five-year survivors of childhood cancer in Great Britain. *Circulation* 135:951–963, 2017
- Kilsdonk E, van Dulmen-den Broeder E, van Leeuwen FE, et al: Late mortality in childhood cancer survivors according to pediatric cancer diagnosis and treatment era in the Dutch LATER cohort. *Cancer Invest* 40:413–424, 2022
- Dixon SB, Liu Q, Chow EJ, et al: Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: A report from the childhood cancer survivor study cohort. *Lancet* 401:1447–1457, 2023
- Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Version 6.0, 2024. <http://www.survivorshipguidelines.org/>
- Kremer LC, Mulder RL, Oeffinger KC, et al: A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer* 60:543–549, 2013
- Baech J, Hansen SM, Lund PE, et al: Cumulative anthracycline exposure and risk of cardiotoxicity; a Danish nationwide cohort study of 2440 lymphoma patients treated with or without anthracyclines. *Br J Haematol* 183:717–726, 2018

10. van Dalen EC, van der Pal HJ, Kok WE, et al: Clinical heart failure in a cohort of children treated with anthracyclines: A long-term follow-up study. *Eur J Cancer* 42:3191-3198, 2006
11. Krischer JP, Epstein S, Cuthbertson DD, et al: Clinical cardiotoxicity following anthracycline treatment for childhood cancer: The Pediatric Oncology Group experience. *J Clin Oncol* 15:1544-1552, 1997
12. Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 355:1572-1582, 2006
13. Tukenova M, Guibout C, Oberlin O, et al: Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol* 28:1308-1315, 2010
14. Felker GM, Thompson RE, Hare JM, et al: Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 342:1077-1084, 2000
15. Lipshultz SE, Lipsitz SR, Sallan SE, et al: Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol* 23:2629-2636, 2005
16. van der Pal HJ, van Dalen EC, Hauptmann M, et al: Cardiac function in 5-year survivors of childhood cancer: A long-term follow-up study. *Arch Intern Med* 170:1247-1255, 2010
17. Armstrong GT, Oeffinger KC, Chen Y, et al: Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol* 31:3673-3680, 2013
18. Leong SL, Chaiyakunapruk N, Lee SW: Candidate gene association studies of anthracycline-induced cardiotoxicity: A systematic review and meta-analysis. *Sci Rep* 7:39, 2017
19. Linschoten M, Teske AJ, Cramer MJ, et al: Chemotherapy-related cardiac dysfunction: A systematic review of genetic variants modulating individual risk. *Circ Genom Precis Med* 11:e001753, 2018
20. Bhatia S: Genetics of anthracycline cardiomyopathy in cancer survivors: JACC: CardioOncology State-of-the-Art review. *JACC CardioOncol* 2:539-552, 2020
21. Singh P, Wang X, Hageman L, et al: Association of GSTM1 null variant with anthracycline-related cardiomyopathy after childhood cancer-A Children's Oncology Group ALTE03N1 report. *Cancer* 126:4051-4058, 2020
22. Blanco JG, Sun CL, Landier W, et al: Anthracycline-related cardiomyopathy after childhood cancer: Role of polymorphisms in carbonyl reductase genes—A report from the Children's Oncology Group. *J Clin Oncol* 30:1415-1421, 2012
23. Visscher H, Ross CJ, Rassekh SR, et al: Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *J Clin Oncol* 30:1422-1428, 2012
24. Visscher H, Ross CJ, Rassekh SR, et al: Validation of variants in SLC28A3 and UGT1A6 as genetic markers predictive of anthracycline-induced cardiotoxicity in children. *Pediatr Blood Cancer* 60:1375-1381, 2013
25. Visscher H, Rassekh SR, Sandor GS, et al: Genetic variants in SLC22A17 and SLC22A7 are associated with anthracycline-induced cardiotoxicity in children. *Pharmacogenomics* 16:1065-1076, 2015
26. Leger KJ, Cushing-Haugen K, Hansen JA, et al: Clinical and genetic determinants of cardiomyopathy risk among hematopoietic cell transplantation survivors. *Biol Blood Marrow Transpl* 22:1094-1101, 2016
27. Gándara-Mireles JA, Lares-Asseff I, Reyes Espinoza EA, et al: Association of genetic polymorphisms NCF4 rs1883112, CBR3 rs1056892, and ABCB1 rs3743527 with the cardiotoxic effects of doxorubicin in children with acute lymphoblastic leukemia. *Pharmacogenet Genomics* 31:108-115, 2021
28. Krajcinovic M, Elbared J, Drouin S, et al: Polymorphisms of ABCB5 and NOS3 genes influence doxorubicin cardiotoxicity in survivors of childhood acute lymphoblastic leukemia. *Pharmacogenomics* 16:530-535, 2016
29. Armenian SH, Ding Y, Mills G, et al: Genetic susceptibility to anthracycline-related congestive heart failure in survivors of haematopoietic cell transplantation. *Br J Haematol* 163:205-213, 2013
30. Lipshultz SE, Lipsitz SR, Kutok JL, et al: Impact of hemochromatosis gene mutations on cardiac status in doxorubicin-treated survivors of childhood high-risk leukemia. *Cancer* 119:3555-3562, 2013
31. Singh P, Zhou L, Shah DA, et al: Identification of novel hypermethylated or hypomethylated CpG sites and genes associated with anthracycline-induced cardiomyopathy. *Sci Rep* 13:12683, 2023
32. Wang X, Liu W, Sun CL, et al: Hyaluronan synthase 3 variant and anthracycline-related cardiomyopathy: A report from the Children's Oncology Group. *J Clin Oncol* 32:647-653, 2014
33. Aminkeng F, Bhavsar AP, Visscher H, et al: A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. *Nat Genet* 47:1079-1084, 2015
34. Wang X, Sun CL, Quiñones-Lombraña A, et al: CELF4 variant and anthracycline-related cardiomyopathy: A Children's Oncology Group genome-wide association study. *J Clin Oncol* 34:863-870, 2016
35. Wang X, Singh P, Zhou L, et al: Genome-wide association study identifies ROBO2 as a novel susceptibility gene for anthracycline-related cardiomyopathy in childhood cancer survivors. *J Clin Oncol* 41:1758-1769, 2023
36. Sapkota Y, Ehrhardt MJ, Qin N, et al: A novel locus on 6p21.2 for cancer treatment-induced cardiac dysfunction among childhood cancer survivors. *J Natl Cancer Inst* 114:1109-1116, 2022
37. Sharafeldin N, Zhou L, Singh P, et al: Gene-level analysis of anthracycline-induced cardiomyopathy in cancer survivors: A report from COG-ALTE03N1, BMTSS, and CCSS. *JACC CardioOncol* 5:807-818, 2023
38. Zhang S, Liu X, Bawa-Khalife T, et al: Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med* 18:1639-1642, 2012
39. Lyu YL, Kerrigan JE, Lin CP, et al: Topoisomerase IIbeta mediated DNA double-strand breaks: Implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. *Cancer Res* 67:8839-8846, 2007
40. Singh P, Shah DA, Jouni M, et al: Altered peripheral blood gene expression in childhood cancer survivors with anthracycline-induced cardiomyopathy—A COG-ALTE03N1 report. *J Am Heart Assoc* 12:e029954, 2023
41. Singh P, Crossman DK, Zhou L, et al: Haptoglobin gene expression and anthracycline-related cardiomyopathy in childhood cancer survivors: A COG-ALTE03N1 report. *JACC CardioOncol* 5:392-401, 2023
42. Armenian SH, Gelehrter SK, Vase T, et al: Carnitine and cardiac dysfunction in childhood cancer survivors treated with anthracyclines. *Cancer Epidemiol Biomarkers Prev* 23:1109-1114, 2014
43. Armenian S, Bhatia S: Predicting and preventing anthracycline-related cardiotoxicity. *Am Soc Clin Oncol Educ Book* 38:3-12, 2018
44. Chow EJ, Chen Y, Kremer LC, et al: Individual prediction of heart failure among childhood cancer survivors. *J Clin Oncol* 33:394-402, 2015
45. Armenian SH, Yang D, Teh JB, et al: Prediction of cardiovascular disease among hematopoietic cell transplantation survivors. *Blood Adv* 2:1756-1764, 2018
46. Aminkeng F, Ross CJ, Rassekh SR, et al: Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity. *Br J Clin Pharmacol* 82:683-695, 2016
47. Leerink JM, de Baat EC, Feijen EAM, et al: Cardiac disease in childhood cancer survivors: Risk prediction, prevention, and surveillance: JACC CardioOncology State-of-the-Art review. *JACC CardioOncol* 2:363-378, 2020
48. Lipshultz SE, Miller TL, Lipsitz SR, et al: Continuous versus bolus infusion of doxorubicin in children with ALL: Long-term cardiac outcomes. *Pediatrics* 130:1003-1011, 2012
49. Lipshultz SE, Scully RE, Lipsitz SR, et al: Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: Long-term follow-up of a prospective, randomised, multicentre trial. *Lancet Oncol* 11:950-961, 2010
50. Lipshultz SE, Rifai N, Dalton VM, et al: The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med* 351:145-153, 2004
51. Chow EJ, Asselin BL, Schwartz CL, et al: Late mortality after dexrazoxane treatment: A report from the Children's Oncology Group. *J Clin Oncol* 33:2639-2645, 2015
52. Chow EJ, Aggarwal S, Doody DR, et al: Dexrazoxane and long-term heart function in survivors of childhood cancer. *J Clin Oncol* 41:2248-2257, 2023
53. de Baat EC, Mulder RL, Armenian S, et al: Dexrazoxane for preventing or reducing cardiotoxicity in adults and children with cancer receiving anthracyclines. *Cochrane Database Syst Rev* 9:CD014638, 2022
54. Waterhouse DN, Tardi PG, Mayer LD, et al: A comparison of liposomal formulations of doxorubicin with drug administered in free form: Changing toxicity profiles. *Drug Saf* 24:903-920, 2001
55. Piska K, Koczurkiewicz P, Bucki A, et al: Metabolic carbonyl reduction of anthracyclines - role in cardiotoxicity and cancer resistance. Reducing enzymes as putative targets for novel cardioprotective and chemosensitizing agents. *Invest New Drugs* 35:375-385, 2017
56. van As JW, van den Berg H, van Dalen EC: Platinum-induced hearing loss after treatment for childhood cancer. *Cochrane Database Syst Rev* 2016:CD010181, 2016
57. Meijer AJM, Diepstraten FA, Ansari M, et al: Use of sodium thiosulfate as an otoprotectant in patients with cancer treated with platinum compounds: A review of the literature. *J Clin Oncol* 42:2219-2232, 2024
58. Brock PR, Maibach R, Childs M, et al: Sodium thiosulfate for protection from cisplatin-induced hearing loss. *N Engl J Med* 378:2376-2385, 2018
59. Freyer DR, Chen L, Krailo MD, et al: Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): A multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 18:63-74, 2017
60. Ehrhardt MJ, Krull KR, Bhakta N, et al: Improving quality and quantity of life for childhood cancer survivors globally in the twenty-first century. *Nat Rev Clin Oncol* 20:678-696, 2023
61. Henderson TD, Liu Q, Turcotte LM, et al: Association of changes in cancer therapy over 3 decades with risk of subsequent breast cancer among female childhood cancer survivors: A report from the Childhood Cancer Survivor Study (CCSS). *JAMA Oncol* 8:1765-1774, 2022
62. Turcotte LM, Hasan H, Stene E, et al: Treatment modifications and mortality among female patients with subsequent breast cancer: A report from the childhood cancer survivor study (CCSS). *J Clin Oncol* 42, 2024 (suppl 16; abstr 10026)
63. Bhatia S, Palomares MR, Hageman L, et al: A randomized phase IIb study of low-dose tamoxifen in chest-irradiated cancer survivors at risk for breast cancer. *Clin Cancer Res* 27:967-974, 2021
64. Lipshultz SE, Adams MJ, Colan SD, et al: Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: Pathophysiology, course, monitoring, management, prevention, and research directions: A scientific statement from the American heart association. *Circulation* 128:1927-1995, 2013

65. Armenian SH, Hudson MM, Lindenfeld L, et al: Effect of carvedilol versus placebo on cardiac function in anthracycline-exposed survivors of childhood cancer (PREVENT-HF): A randomised, controlled, phase 2b trial. *Lancet Oncol* 25:235-245, 2024
66. Armenian SH, Hudson MM, Lindenfeld L, et al: Carvedilol to improve cardiac remodeling in anthracycline-exposed childhood cancer survivors: Subgroup analysis of COG ALTE1621. *JACC CardioOncol* 6:791-793, 2024
67. Oeffinger KC, Hudson MM: Long-term complications following childhood and adolescent cancer: Foundations for providing risk-based health care for survivors. *CA Cancer J Clin* 54:208-236, 2004
68. O'Leary M, Kralio M, Anderson JR, et al: Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group. *Semin Oncol* 35:484-493, 2008
69. Collins CL, Malvar J, Hamilton AS, et al: Case-linked analysis of clinical trial enrollment among adolescents and young adults at a National Cancer Institute-designated comprehensive cancer center. *Cancer* 121:4398-4406, 2015
70. Parsons HM, Abdi HI, Nelson VA, et al: Transitions of care from pediatric to adult services for children with special healthcare needs, in *Comparative Effectiveness Reviews*. Rockville, MD, AHRQ, 2022
71. McManus MA, Pollack LR, Cooley WC, et al: Current status of transition preparation among youth with special needs in the United States. *Pediatrics* 131:1090-1097, 2013
72. Gray WN, Schaefer MR, Resmini-Rowlinson A, et al: Barriers to transition from pediatric to adult care: A systematic review. *J Pediatr Psychol* 43:488-502, 2018
73. Sadak KT, Dinofia A, Reaman G: Patient-perceived facilitators in the transition of care for young adult survivors of childhood cancer. *Pediatr Blood Cancer* 60:1365-1368, 2013
74. Marchak JG, Sadak KT, Effinger KE, et al: Transition practices for survivors of childhood cancer: A report from the Children's Oncology Group. *J Cancer Surviv* 17:342-350, 2023
75. Zheng Z, Jemal A, Han X, et al: Medical financial hardship among cancer survivors in the United States. *Cancer* 125:1737-1747, 2019
76. Zheng DJ, Sint K, Mitchell HR, et al: Patterns and predictors of survivorship clinic attendance in a population-based sample of pediatric and young adult childhood cancer survivors. *J Cancer Surviv* 10:505-513, 2016
77. Robison LL, Hudson MM: Survivors of childhood and adolescent cancer: Life-long risks and responsibilities. *Nat Rev Cancer* 14:61-70, 2014
78. Nathan PC, Agha M, Pole JD, et al: Predictors of attendance at specialized survivor clinics in a population-based cohort of adult survivors of childhood cancer. *J Cancer Surviv* 10:611-618, 2016
79. Mobley EM, Moke DJ, Milam J, et al: Disparities and barriers to pediatric cancer survivorship care, in *Comparative Effectiveness Technical Briefs*. Rockville, MD, AHRQ, 2021
80. Snyder C, Yuan CT, Wilson RF, et al: Models of Care that Include Primary Care for Adult Survivors of Childhood Cancer: A Realist Review. Rockville, MD, Agency for Healthcare Research and Quality, 2022
81. Snyder C, Smith KC, Leisenring WM, et al: Continuity and coordination of care for childhood cancer survivors with multiple chronic conditions: Results from the Childhood Cancer Survivor Study. *Cancer* 130:4347-4359, 2024
82. Sutradhar R, Agha M, Pole JD, et al: Specialized survivor clinic attendance is associated with decreased rates of emergency department visits in adult survivors of childhood cancer. *Cancer* 121:4389-4397, 2015
83. Kagramanov D, Sutradhar R, Lau C, et al: Impact of the model of long-term follow-up care on adherence to guideline-recommended surveillance among survivors of adolescent and young adult cancers. *Cancer Med* 10:5078-5087, 2021
84. Ke Y, Ng T, Chan A: Survivorship care models for breast cancer, colorectal cancer, and adolescent and young adult (AYA) cancer survivors: A systematic review. *Support Care Cancer* 26:2125-2141, 2018
85. Jacobsen RL, Macpherson CF, Pflugeisen BM, et al: Care experience, by site of care, for adolescents and young adults with cancer. *JCO Oncol Pract* 17:e817-e826, 2021
86. Ehrhardt MJ, Friedman DN, Hudson MM: Health care transitions among adolescents and young adults with cancer. *J Clin Oncol* 42:743-754, 2024
87. National Childhood Cancer Registry Explorer. <https://nccrexplorer.ccdi.cancer.gov/>
88. Mollica MA, McWhirter G, Tonorez E, et al: Developing national cancer survivorship standards to inform quality of care in the United States using a consensus approach. *J Cancer Surviv* 18:1190-1199, 2024
89. Mollica MA, McWhirter G, Tonorez E, et al: Developing national cancer survivorship standards to inform quality of care in the United States using a consensus approach. *J Cancer Surviv* 18:1190-99, 2024.
90. WHO Model List of Essential Medicines - 23rd list, 2023. [who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02](https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02)
91. Jankovic M, Haupt R, Spinetta JJ, et al: Long-term survivors of childhood cancer: Cure and care-the Erice statement (2006) revised after 10 years (2016). *J Cancer Surviv* 12:647-650, 2018
92. Michel G, Mulder RL, van der Pal HJH, et al: Evidence-based recommendations for the organization of long-term follow-up care for childhood and adolescent cancer survivors: A report from the PanCareSurFup Guidelines Working Group. *J Cancer Surviv* 13:759-772, 2019
93. van Kalsbeek RJ, van der Pal HJH, Hjorth L, et al: The European multistakeholder PanCareFollowUp project: Novel, person-centred survivorship care to improve care quality, effectiveness, cost-effectiveness and accessibility for cancer survivors and caregivers. *Eur J Cancer* 153:74-85, 2021
94. van Kalsbeek RJ, van der Pal HJH, Kremer LCM, et al: European PanCareFollowUp recommendations for surveillance of late effects of childhood, adolescent, and young adult cancer. *Eur J Cancer* 154:316-328, 2021
95. van Kalsbeek RJ, Mulder RL, Haupt R, et al: The PanCareFollowUp care intervention: A European harmonised approach to person-centred guideline-based survivorship care after childhood, adolescent and young adult cancer. *Eur J Cancer* 162:34-44, 2022
96. PanCare: <https://www.pancare.eu>
97. European Network of Youth Cancer Survivors: Recommendations for transition of care for childhood and adolescent cancer survivors. <https://beatcancer.eu/wp-content/uploads/2024/08/Summaries-of-Transition-Guideline-EN.pdf>
98. Bhatia S, Yasui Y, Robison LL, et al: High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the late effects study group. *J Clin Oncol* 21:4386-4394, 2003
99. Kenney LB, Yasui Y, Inskip PD, et al: Breast cancer after childhood cancer: A report from the childhood cancer survivor study. *Ann Intern Med* 141:590-597, 2004
100. Taylor AJ, Winter DL, Stiller CA, et al: Risk of breast cancer in female survivors of childhood Hodgkin's disease in Britain: A population-based study. *Int J Cancer* 120:384-391, 2007
101. Mulder RL, Hudson MM, Bhatia S, et al: Updated breast cancer surveillance recommendations for female survivors of childhood, adolescent, and young adult cancer from the International Guideline Harmonization Group. *J Clin Oncol* 38:4194-4207, 2020
102. Wong FL, Lee JM, Leisenring WM, et al: Health benefits and cost-effectiveness of Children's Oncology Group breast cancer screening guidelines for chest-irradiated Hodgkin lymphoma survivors. *J Clin Oncol* 41:1046-1058, 2023
103. Nelson HD, Cantor A, Humphrey L, et al: Screening for breast cancer: A systematic review to update the 2009 U.S. Preventive Services task force recommendation, in U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Rockville, MD, Agency for Healthcare Research and Quality, 2016
104. Oeffinger KC, Fontham ET, Etzioni R, et al: Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. *JAMA* 314:1599-1614, 2015
105. Henderson TQ, Oeffinger KC, Whitton J, et al: Secondary gastrointestinal cancer in childhood cancer survivors: A cohort study. *Ann Intern Med* 156:757-766, 2012. W-260
106. Nottage K, McFarlane J, Krasin MJ, et al: Secondary colorectal cancer after childhood cancer. *J Clin Oncol* 30:2552-2558, 2012
107. Gini A, Meester RGS, Keshavarz H, et al: Cost-effectiveness of colonoscopy-based colorectal cancer screening in childhood cancer survivors. *J Natl Cancer Inst* 111:1161-1169, 2019
108. Ehrhardt MJ, Leerink JM, Mulder RL, et al: Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 24:e108-e120, 2023
109. Yeh JM, Nohria A, Diller L: Routine echocardiography screening for asymptomatic left ventricular dysfunction in childhood cancer survivors: A model-based estimation of the clinical and economic effects. *Ann Intern Med* 160:661-671, 2014
110. Wong FL, Bhatia S, Landier W, et al: Cost-effectiveness of the Children's Oncology Group long-term follow-up screening guidelines for childhood cancer survivors at risk for treatment-related heart failure. *Ann Intern Med* 160:672-683, 2014
111. Ehrhardt MJ, Ward ZJ, Liu Q, et al: Cost-effectiveness of the international late effects of Childhood Cancer Guideline Harmonization Group screening guidelines to prevent heart failure in survivors of childhood cancer. *J Clin Oncol* 38:3851-3862, 2020
112. Bolier M, de Winter DTC, Pluimakers VG, et al: Prevalence and determinants of metabolic syndrome in 2338 childhood cancer survivors: A Dutch childhood cancer survivor LATER 2 study. *Cancer* 131:e35681, 2025
113. van Dalen EC, Mulder RL, Suh E, et al: Coronary artery disease surveillance among childhood, adolescent and young adult cancer survivors: A systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Eur J Cancer* 156:127-137, 2021

Emerging Strategies for Drug-Based Cancer Risk Reduction

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OVERVIEW

Chemoprevention has emerged as a promising strategy to reduce cancer incidence by using pharmacologic agents that interrupt the carcinogenesis process. This review discusses emerging insights and recent advancements in chemoprevention, emphasizing novel approaches in several cancer types. Specifically, we examine breast cancer prevention, focusing on optimized endocrine therapy dosing to enhance adherence and minimize adverse effects while maintaining efficacy. Additionally, the potential of glucagon-like peptide-1 receptor agonists to mitigate obesity-related cancer risks is evaluated, highlighting their role in addressing an increasingly prevalent risk factor in the general population. The review further explores strategies targeting colorectal cancer (CRC), specifically in familial adenomatous polyposis, a hereditary CRC syndrome that exemplifies the complex interplay between chemoprevention, genetic risk, and patient management. In prostate cancer, we highlight the evidence supporting the use of 5- α reductase inhibitors, detailing their effectiveness in reducing cancer incidence as well as their safety profile. Across these areas, this review underscores the importance of precision medicine, advocating for personalized approaches that balance efficacy, safety, and quality-of-life considerations. Ultimately, advancing chemopreventive strategies through targeted research and clinical trials is essential for reducing cancer burden and improving patient outcomes.

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INTRODUCTION

Cancer prevention has evolved beyond traditional screening modalities to encompass pharmacologic interventions aimed at mitigating cancer risk in high-risk populations. Although early detection remains a cornerstone of cancer control, chemoprevention offers a complementary strategy with the potential to substantially reduce both the incidence and mortality of several common malignancies. A growing body of evidence supports the efficacy of diverse agents—including low-dose endocrine therapies, glucagon-like peptide-1 receptor agonists (GLP-1RAs), nonsteroidal anti-inflammatory drugs (NSAIDs), and 5- α reductase inhibitors (ARIs)—in lowering the risk of breast, obesity-related, gastrointestinal, and prostate (PC) cancers. Recent advances in dose-optimization strategies have underscored the importance of tailoring regimens to enhance tolerability and adherence, thereby facilitating broader implementation of preventive therapies. In this review, we examine emerging approaches to dose refinement, highlight opportunities for drug repositioning, and summarize key developments in cancer chemoprevention across multiple tumor types.

SELECTING THE RIGHT DOSE: THE CASE OF LOW-DOSE ENDOCRINE BREAST CANCER PREVENTION

The incidence of breast cancer continues to rise, maintaining its rank as the most common cancer diagnosis among

women globally. While early detection through screening remains critical, there is an urgent need for effective and acceptable prevention strategies. Statistical modeling has recently highlighted that integrating risk-reducing medications with early detection through screening could further lower the incidence of invasive breast cancer and associated mortality in high-risk populations. These findings emphasize the need to consider the role of preventive therapies in minimizing the overall burden of breast cancer.¹

Preventive approaches using selective estrogen receptor modulators (eg, tamoxifen and raloxifene) or aromatase inhibitors (eg, exemestane and anastrozole) at therapeutic doses have demonstrated a 40%–50% reduction in breast cancer incidence among high-risk women, as evidenced in large phase III randomized trials. However, real-world adoption of these therapies remains low, ranging from less than 5% to 25% depending on risk profile, age, and treatment center. Women diagnosed with high-risk lesions (HRLs) or estrogen receptor-positive (ER+) ductal carcinoma in situ (DCIS) exhibit the highest uptake rates.² Limited adoption is largely attributable to concerns about serious adverse effects, such as endometrial cancer, deep vein thrombosis, and fractures. Additionally, poor adherence to treatment is often due to menopausal symptoms, including hot flashes, night sweats, vaginal dryness, dyspareunia, and musculoskeletal discomfort.

PRACTICAL APPLICATIONS

- Prevention through pharmacologic innovation, large clinical trials, and long follow-up is essential for an effective reduction in cancer incidence and mortality.
- Managing drug effects, side effects, and willingness of the patient is essential to ensure effectiveness and adherence in preventive therapy.
- Surrogate biomarkers are actively being developed to further select at-risk patients and predict early response to preventive therapy.
- Chemoprevention is not currently recommended for most cancer types, except for breast cancer. Further studies are necessary to strengthen evidence and guide future clinical recommendations.

A critical question in breast cancer prevention is the widespread assumption that therapeutic doses used in adjuvant and advanced disease settings should also be applied in prevention. Recognizing an issue of dose optimization in clinical oncology, the US Food and Drug Administration (FDA) has recently initiated a dose optimization project aimed at identifying the right dose, or the minimum effective dose, to mitigate both clinical and financial toxicities associated with oncology treatments.³ This is particularly relevant in breast cancer as up to 40% of patients in adjuvant settings discontinue endocrine therapy prematurely and 30% fail to adhere fully to prescribed dosing, resulting in a 49% increase in all-cause mortality.⁴

Although not explicitly focused on prevention, the FDA's dose optimization strategy is highly relevant to this field for two key reasons: (1) precancerous or at-risk breast tissues exhibit fewer genomic alterations, potentially requiring lower drug doses, and (2) minimizing harm is an obvious principle of prevention, in as much as reducing toxicity could enhance tolerability, uptake, and adherence.^{5,6} Lower doses and modified schedules of tamoxifen have been evaluated in previous studies to maintain efficacy while minimizing adverse effects. Biomarker-based studies demonstrated that a 5 mg once daily dose of tamoxifen ("babytam") effectively reduced mammographic breast density in high-risk premenopausal women^{5,6} and achieved a comparable reduction in Ki-67 levels to the standard 20 mg once daily dose during a 4-week presurgical treatment trial.⁶ Moreover, a prospective cohort study in postmenopausal women with clinically detected DCIS found that tamoxifen administered at a dose of 10 mg taken once every other day significantly reduced any breast event and ipsilateral DCIS recurrence.⁷ Finally, a phase III randomized trial (Tam01) comparing 5 mg once daily of tamoxifen with placebo in women with ER+ DCIS or HRLs

showed a 40% reduction in recurrence risk after 5 years of follow-up, with minimal adverse effects.⁸ A 10-year follow-up analysis showed that low-dose tamoxifen significantly prevents recurrence from noninvasive breast cancer after 7 years from treatment cessation without long-term adverse events.⁹ For instance, the cumulative incidence of hot flashes, the commonest adverse event, in the low-dose tamoxifen group was not higher than the placebo group during the 3-year intervention period (Fig 1).

Interestingly, Bhatia et al¹⁰ demonstrated that low-dose tamoxifen effectively reduces mammographic density and circulating insulin-like growth factor 1 levels, two established biomarkers of breast cancer risk, without increasing severe adverse events in chest-irradiated cancer survivors. As advancements in imaging and computational modeling evolve, measuring breast cancer risk through artificial intelligence-based models that analyze mammographic features and capture tissue changes after therapy initiation may improve the identification of women who would benefit most from antiestrogen treatment in a precision prevention approach. In this context, low-dose tamoxifen has demonstrated its potential in reducing mammographic density, a crucial factor in breast cancer risk assessment and prevention. The KARISMA trial showed that a 5 mg once daily dose of tamoxifen resulted in a nearly 20% reduction in mammographic density after 6 months in premenopausal women, an effect comparable with that of the standard 20 mg once daily dose but with significantly fewer vasomotor and gynecologic side effects. These findings suggest that lower dose regimens may improve adherence while maintaining efficacy in modulating breast tissue composition.¹¹ Moreover, a $\geq 20\%$ reduction in relative breast density was associated with a 24% decrease in interval cancers, underscoring the dual role of low-dose tamoxifen in both risk reduction and improved early detection.¹²

These findings have led to the inclusion of low-dose tamoxifen as a management option for DCIS and HRLs in several clinical guidelines. For example, the ASCO Clinical Practice Guideline Update on Endocrine Therapy for Breast Cancer Risk Reduction discusses the utility of low-dose tamoxifen for both premenopausal and postmenopausal women with intraepithelial neoplasia.¹³ Similarly, the National Comprehensive Cancer Network guidelines for DCIS acknowledge low-dose tamoxifen (5 mg once daily or 10 mg once every other day for 3 years) as a viable alternative for patients unwilling or unable to tolerate the standard 20 mg once daily regimen.¹⁴

Recent studies in relevant US centers have consistently shown that low-dose tamoxifen has gained popularity as a preventive therapy for HRLs and at-risk women.^{2,15-17} Notably, 1-year discontinuation rates were markedly lower compared with those for standard endocrine agents, including tamoxifen at 20 mg once daily, raloxifene, exemestane, and anastrozole.² In real-world practice, Patel et al¹⁷ observed that more than 75% of patients preferred

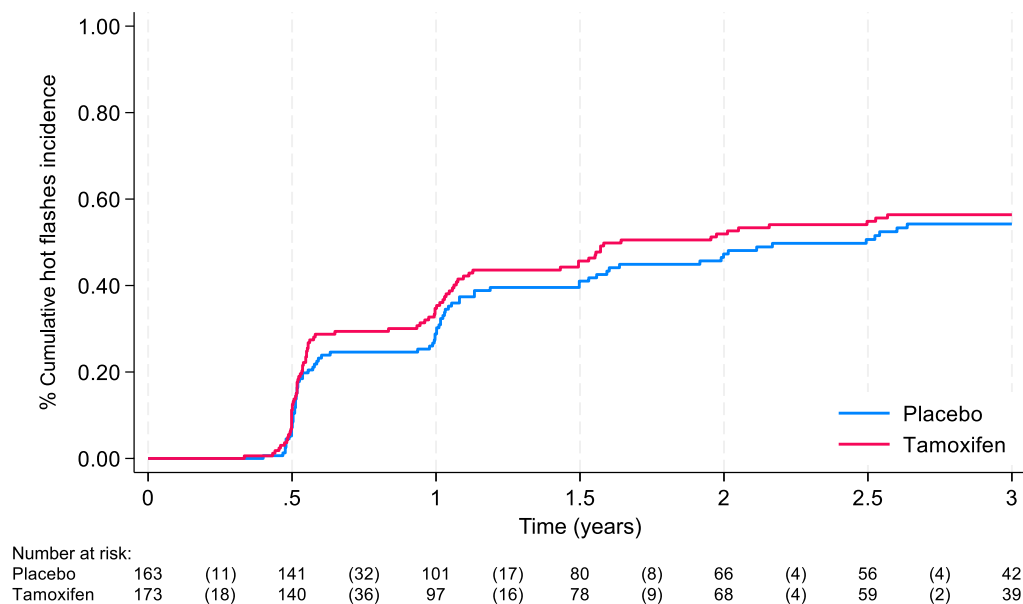


FIG 1. Time to first hot flash among women without hot flash at baseline in the Tam01 trial (n = 336).

low-dose tamoxifen when both standard and low-dose regimens were offered, particularly among those with atypical lesions such as atypical ductal hyperplasia and lobular carcinoma in situ. Many patients cited concerns about the side effects of standard-dose tamoxifen as a reason for their preference. These results highlight the potential of low-dose tamoxifen to improve breast cancer prevention by addressing common barriers to treatment, such as tolerability and adherence.¹⁸

The optimal dosing for aromatase inhibitors has also been investigated through a randomized biomarker study of exemestane,¹⁹ evaluating this effective preventive agent with limited clinical uptake. In a presurgical window trial involving patients with ER+ breast cancer, a regimen of exemestane 25 mg three times a week (babyexe) for 4–6 weeks before surgery was shown to be noninferior to daily dosing in achieving estradiol suppression—a key surrogate marker for aromatase inhibitor activity. Additionally, no significant differences were observed in Ki-67 changes or toxicity between the two doses. However, the short intervention period limits definitive conclusions on long-term tolerability.

To further evaluate the long-term tolerability of babyexe, the Baby Tamoxifen or Baby Exemestane Assessment Randomized Study (BabyTEARS) was recently launched. This double-blinded phase IIb trial compares low-dose tamoxifen and low-dose exemestane administered on alternate days, focusing on their effects on patient-reported outcomes and surrogate biomarkers (ClinicalTrials.gov identifier: [NCT06364267](https://clinicaltrials.gov/ct2/show/study/NCT06364267)). The study involves postmenopausal women at increased risk because of a diagnosis of HRL or ER+ DCIS, germline variants associated with ER+ breast cancer, or a 5-year breast cancer risk of $\geq 3\%$ as estimated by validated risk models. Given

concerns over adverse events and menopausal symptoms are significant barriers to the uptake and adherence of preventive medications, quality of life, adherence, and reasons for acceptance or refusal are pivotal end points for advancing precision prevention efforts. The primary end point is the change in the overall score of the Menopause-Specific Quality of Life Questionnaire (MENQOL) from baseline to 12 months, comparing low-dose exemestane (babyexe) versus low-dose tamoxifen (babytam). Allowing for a 10% dropout rate, an overall sample size of 140 patients will be enrolled to detect a clinically significant mean difference of at least 0.9 points in the MENQOL overall score. If both treatments demonstrate good tolerability in terms of patient-reported outcomes, quality of life, and adherence, a phase III vis-a-vis comparison will be launched. Importantly, use of low-dose tamoxifen will also be tested in the adjuvant setting in the LoTam trial (ClinicalTrials.gov identifier: [NCT06671912](https://clinicaltrials.gov/ct2/show/study/NCT06671912)), a phase III study comparing low-dose tamoxifen with standard hormonal therapies, such as aromatase inhibitors, in treating postmenopausal women with low-risk hormone receptor-positive, human epidermal growth factor receptor 2-negative early-stage breast cancer.

In conclusion, emerging evidence highlights increased uptake, adherence, and tolerability of low-dose tamoxifen (babytam) in women at elevated breast cancer risk. While multiple studies validate the benefits of babytam, growing evidence also supports the potential of a reduced exemestane dose. Together, these findings suggest that approved dosing schedules for endocrine agents may not represent the optimal approach for breast cancer prevention and adjuvant treatment. This realization provides an opportunity to refine dosing strategies to enhance drug uptake, safety, and adherence. Such a paradigm shift could significantly advance breast cancer prevention and treatment of low-risk breast

cancer, reducing both incidence and mortality rates and treatment withdrawals. A summary of preventive endocrine agents evaluated at low doses for breast cancer risk reduction is presented in [Table 1](#).

DRUG REPOSITIONING: GLP1 INHIBITION AND CANCER RISK REDUCTION—WHAT ARE WE WAITING FOR?

The Impact of Obesity on Cancer

Excess body size and obesity are linked to several major chronic diseases and associated mortality.²⁰ For the past 20 years, a considerable evidence base has established excess body weight as a significant contributor to cancer risk at the population level.^{21,22} Large, population-based studies from multiple countries and across ethnic populations have established that having excess body weight is associated with a higher risk of developing at least 13 distinct cancers, including breast (postmenopausal), colorectal, endometrial, esophageal (adenocarcinoma), kidney, stomach (cardia), gallbladder, liver, ovarian, multiple myeloma, meningioma, thyroid, and pancreatic cancers ([Fig 2](#)) with others potentially associated.^{21,23,24}

Despite the strong and consistent associations between excess body size and cancer, the rates of overweight and obesity continue to rise in many populations. A recent global study suggests that the number of people with poor health and early death as a result of metabolism-related risk factors, such as hypertension, hyperglycemia, and elevated BMI, has risen by 50% since 2000. Data from the 2017 to 2018 National Health and Nutrition Examination Survey shows that 73% of US adults aged 20 years and older are classified as either overweight (with a BMI of 25.0–29.9) or obese (with a BMI of 30 or

higher).²⁵ In 2018, 36% of Canadian adults aged 18 years and older were classified as overweight, while 27% were classified as obese, based on their BMI.²⁶ Moreover, the prevalence of class II (BMI, 35.0–39.9) and class III (BMI, 40.0–49.9) obesity is rising across all age groups.²⁷ Meanwhile, western populations are seeing an increase in common cancers linked to excess body size, such as colorectal, postmenopausal breast, endometrial, and several others.^{22,28} Incidence rates of colorectal cancer (CRC) are three to four times higher in western populations, compared with countries in developmental transition.²⁸ Rising incidence rates have also been observed for postmenopausal breast cancer in several high-income countries and in North America.²⁸

Like the impact on cancer risk, excess body size has shown consistent, strong increases in cancer-related mortality. A recent systematic review and meta-analysis of 203 studies with 6,320,365 participants reported that obesity was associated with reduced overall survival (hazard ratio [HR], 1.14), cancer-specific survival (HR, 1.17), and disease-free survival (HR, 1.13) after a cancer diagnosis.²⁹ Patients with breast or CRC and obesity had higher overall mortality (breast: HR, 1.26 [95% CI, 1.2 to 1.33]; $P < .001$; colorectal: HR, 1.22 [95% CI, 1.14 to 1.31]; $P < .001$), reduced cancer-specific survival (breast: 1.23 [95% CI, 1.15 to 1.32]; $P < .001$; colorectal: HR, 1.24 [95% CI, 1.16 to 1.32]; $P < .001$), and reduced disease-free survival (breast: HR, 1.14 [95% CI, 1.1 to 1.19]; $P < .001$; colorectal: HR, 1.15 [95% CI, 1.01 to 1.3]; $P = .01$) than those without obesity.

Can GLP-1RA Use Reduce the Impact of Excess Body Size on Cancer Incidence and Mortality?

GLP-1RAs have been widely studied for their effects on weight loss and diabetes management with more recent

TABLE 1. Preventive Endocrine Agents at Low Dose for Breast Cancer Risk Reduction

Agent	Patient Population	Endpoint	Relative Risk Reduction/Effect	References
Tamoxifen 5 mg once daily	Women with HRLs or ER+ DCIS	Breast cancer recurrence, including contralateral	Approximately 40% significant reduction in recurrence at 5 and 10 years	^{8,9}
Tamoxifen 10 mg once every other day	Postmenopausal women with DCIS	Ipsilateral DCIS recurrence	34% reduction in ipsilateral DCIS recurrence (HR, 0.66 [95% CI, 0.49 to 0.88])	⁷
Tamoxifen 1, 2.5, 5, 10, 20 mg once daily	Premenopausal women	Mammographic density	2.5, 5, and 10 mg: noninferior to 20 mg in reducing breast density in premenopausal women; 1 mg: no efficacy; dose-dependent AEs	¹¹
Tamoxifen 5 mg once daily	Chest-irradiated cancer survivors	Mammographic density, IGF-1	Decrease in mammographic density and IGF-1; no severe AEs	¹⁰
Exemestane 25 mg three times a week	Postmenopausal women, ER+ breast cancer (presurgical window trial)	Estradiol suppression, Ki-67	Noninferior to daily dose in 4-6 week intervention	¹⁹
Tamoxifen or exemestane (low dose)	Women with HRLs, ER+ DCIS, high risk per model	Quality of life, adherence, biomarker changes	Ongoing phase IIb BabyTEARS trial	NCT06364267

Abbreviations: AEs, adverse events; DCIS, ductal carcinoma in situ; ER+, estrogen receptor–positive; HR, hazard ratio; HRL, high-risk lesion; IGF-1, insulin-like growth factor 1

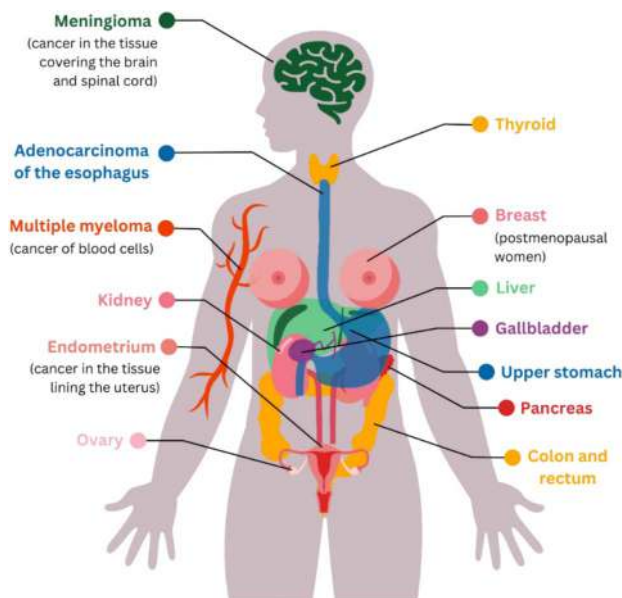


FIG 2. Cancers consistently associated with overweight and obesity.

evidence for cardiovascular disease prevention. Emerging evidence suggests that GLP-1RAs could also play a role in relenting the increasing impact of obesity-related cancer incidence and mortality.³⁰ GLP-1RAs, such as semaglutide, liraglutide, and tirzepatide, have demonstrated considerable, clinically relevant weight reduction, with participants achieving 5.7%–21% weight loss over several months and long term—up to 80 weeks—in clinical trials. These effects are in stark contrast to the modest to null benefits seen in placebo and diet/exercise-only groups.³⁰ The substantial weight loss facilitated by GLP-1RAs could potentially reduce the risk of developing obesity-related cancers and improve survival outcomes.

Cancer incidence outcomes have been challenging to address in randomized control trials to date given the long-term follow-up that would be required. Early data from observational studies among patients receiving GLP-1RAs for diabetes suggest a potential role for therapeutic reduction/prevention. For example, a retrospective cohort study including over 1.6 million patients with type 2 diabetes who had no prior diagnosis of cancer observed that those treated with GLP-1RAs had a significantly reduced risk of developing 10 out of 13 types of obesity-associated cancers compared with those treated with insulin. These cancers included esophageal, colorectal, endometrial, gallbladder, kidney, liver, ovarian, and pancreatic cancers, as well as meningioma and multiple myeloma.³¹ Another large-scale cohort study of 1.1 million individuals with obesity reported reductions in cancer risk across multiple cancer types among those treated with GLP-1RAs compared with matched controls, including gastrointestinal (HR, 0.67 [95% CI, 0.59 to 0.75]), skin (HR, 0.62 [95% CI, 0.55 to 0.70]), breast (HR, 0.72 [95% CI, 0.64 to 0.82]), female genital (HR, 0.61 [95% CI, 0.53 to 0.71]), prostate (HR, 0.68 [95% CI, 0.58 to 0.80]), and lymphoid/

hematopoietic (HR, 0.69 [95% CI, 0.60 to 0.80]) cancers.³² Several other real-world cohort studies have reported associations between GLP-1RA use and reduced risk of hepatocellular carcinoma,^{33,34} PC,³⁵ and pancreatic cancer among those with high BMI.^{36,37}

Given the relatively recent nature of more widespread GLP-1RA use, there is less comparatively existing evidence on the impact of GLP-1RA use on survival outcomes for patients already diagnosed with cancer. One observational, retrospective cohort study examined the associations between the use of GLP-1RAs, cancer recurrence, and all-cause mortality among 67,591 cancer survivors versus the noncancer population and reported a significant association between ever use of GLP-1RAs and lower risk (64%) of all-cause mortality among cancer survivors but not among the population without cancer diagnoses.³⁸ Similar associations were observed for obesity-related cancers.³⁸

Evidence Gaps Remaining for Cancer Risk Reduction

Although GLP-1RAs show promise for reducing obesity-related cancer incidence and mortality, long-term effectiveness and safety remain uncertain. Despite impressive short-term weight loss results, there are concerns about gastrointestinal side effects^{39–42} and potential risks, such as pancreatitis and potential increases in risk of some cancers, although recent studies have not observed increased risk.⁴³ Additionally, the challenge of weight maintenance after discontinuation of these drugs is notable, as many individuals experience weight rebound, underscoring the need for ongoing lifestyle interventions or potentially long-term use to sustain benefits.^{44–46} Although pharmacologic interventions offer a valuable tool for rapid weight reduction, further research is necessary to address prevention and long-term weight management. Recent expansion of indications for GLP-1RAs into cardiovascular disease risk reduction is likely to considerably increase the number of people on longer term courses of GLP-1RA therapy, which will consequentially result in larger sample sizes and higher numbers of studies of observational studies. This additional observational and real-world evidence will continue to fuel the discussion around repurposing GLP-1RAs for cancer prevention.

Large Phase III Prevention Trial Is Needed

While observational data for cancer prevention with GLP-1RAs have been quite promising among those with high BMIs and diabetes, observational data may not be sufficient to meaningfully alter practice in the coming years. Large phase III randomized trials were needed to more rigorously evaluate previously promising candidates for chemoprevention such as hormone replacement therapy,⁴⁷ alpha-tocopherol, beta-carotene,⁴⁸ and NSAIDs.⁴⁹ Given the overwhelming impact of obesity on cancer and the growing impact projected over the coming decades in North America and other westernized populations, investment in a large phase III trial

may be warranted. Despite the potential cost and complexity of a sufficiently powered phase III trial, the potential cost of inaction could be much higher. Without meaningful intervention, the number of obesity-related cancers will rise considerably over the coming decades. To stem this rising tide, all tools should be considered, including the potential repurposing of GLP-1RAs for cancer prevention.

PREVENTIVE AGENTS FOR GI CANCERS

CRC prevention through chemoprevention using aspirin and NSAIDs has shown promise in reducing colorectal neoplasia risk in the general population. Aspirin's role, primarily through cyclooxygenase-2 (COX-2) inhibition, highlights its potential in broader preventive strategies. In this section, we will focus on familial adenomatous polyposis (FAP), a high-risk hereditary syndrome serving as a paradigm for the targeted use of chemoprevention in the gastrointestinal tract. FAP is a hereditary CRC syndrome caused by inactivating mutations in the *adenomatous polyposis coli* (APC) gene. This condition leads to the development of hundreds to thousands of adenomas in the colon and rectum, with an inevitable progression to CRC if left untreated. The current standard of care involves prophylactic colectomy and rigorous endoscopic surveillance.⁵⁰⁻⁵² Although these approaches effectively reduce CRC risk, their frequent and invasive nature can substantially affect patients' quality of life.⁵³

Chemoprevention—using drugs to block or slow down the process of carcinogenesis—has emerged as a promising complement to traditional FAP management. Researchers have investigated a wide spectrum of agents, ranging from NSAIDs and selective COX-2 inhibitors to compounds targeting key molecular pathways such as mammalian target of

rapamycin (mTOR), with the goal of developing accessible, cost-effective, and well-tolerated therapies. These treatments aim to slow polyp progression and potentially delay or reduce the need for prophylactic surgery. Despite encouraging preliminary findings, no single agent or combination has yet been shown to definitively alter the natural history of FAP, in part, because of issues with adverse effects, long-term safety, and individual variability in response. In this review, we update recent advances in chemoprevention, highlighting both its potential benefits and the current challenges that remain in optimizing its use for FAP (Table 2).

Anti-inflammatory Drugs

NSAIDs such as sulindac, celecoxib, rofecoxib, and aspirin have shown effectiveness in promoting polyp regression in patients with FAP. These agents work, in part, by inhibiting cyclooxygenase enzymes—especially COX-2, which is pivotal in colorectal carcinogenesis. Elevated COX-2 expression in adenomatous polyps drives tumor growth and angiogenesis and impedes apoptosis, underscoring its critical role in cancer progression. Thus, NSAID-mediated COX-2 inhibition represents a promising chemopreventive strategy in FAP, aiming to reduce polyp burden and potentially delay the development of CRC.

Sulindac, the most extensively studied NSAID in FAP, works by inhibiting both COX-1 and COX-2. Daily doses of 150–300 mg once daily have been shown to reduce the size and number of colorectal adenomas.⁵⁴ Prolonged treatment can maintain this effect: One small series reported no advanced adenomas at 64 months,⁵⁵ and larger trials with over seven years of follow-up confirmed rapid polyp reduction in most

TABLE 2. Summary of Challenges of Chemoprevention in FAP

Topic Area	Key Points	Clinical Implications/Recommendations
FAP background	FAP is a hereditary CRC syndrome caused by APC mutations that leads to hundreds/thousands of adenomas and inevitable progression to CRC if untreated	Prophylactic colectomy and strict endoscopic surveillance remain the standard, despite their invasiveness and impact on quality of life
Overview of chemoprevention	Uses drugs to block or slow carcinogenesis Aims to reduce polyp burden and delay or decrease the need for surgery Wide range of agents evaluated (NSAIDs, COX-2 inhibitors, mTOR inhibitors, etc)	Offers a potential complement to standard management; however, no agent has yet definitively changed FAP's natural history due to safety and response variability
Trial design challenges	End points: Reduction in polyp burden must correlate with delayed surgery, prevention of advanced neoplasia, or reduced CRC incidence Patient heterogeneity: Wide age range and surgical status complicate data interpretation Assessment variability: Inconsistent endoscopic techniques may undermine surrogate end points	Focus on composite and long-term clinical outcomes Stratify patients by disease stage and surgical history Standardize imaging protocols and use centralized review
Patient selection for chemoprevention	Ideal candidates are those who decline surgery, have high surgical risk (extensive polyposis), or are young with early-stage disease under regular surveillance	Individualized treatment decisions and participation in clinical trials are crucial to optimize chemopreventive strategies

Abbreviations: APC, *adenomatous polyposis coli*; CRC, colorectal cancer; COX-2, cyclooxygenase-2; FAP, familial adenomatous polyposis; mTOR, mammalian target of rapamycin; NSAIDs, nonsteroidal anti-inflammatory drugs.

patients.⁵⁶ Sulindac may also delay the need for colectomy in attenuated polyposis⁵⁷; for instance, when used as suppositories, one study found complete adenoma reversion without relapse in 87% of 15 colectomized patients after 33 months.^{58,59} However, the benefits of sulindac are temporary, as adenomas quickly regrow once treatment stops,⁵⁸ and rectal cancers have still been reported despite its use.^{55,60} Moreover, a randomized, double-blind, placebo-controlled study in 41 young patients with FAP showed no benefit in preventing new colorectal adenoma formation.⁶¹

Studies have shown that APC inactivation and epidermal growth factor receptor (EGFR) signaling can increase COX-2 expression, thereby promoting intestinal neoplasia. Erlotinib, an EGFR inhibitor, disrupts these signaling pathways that drive cell proliferation and survival. As a single agent, erlotinib has demonstrated promising chemopreventive effects in FAP. In a multicenter phase II trial, once a week administration of 350 mg of erlotinib for 6 months led to a significant 29.6% reduction in duodenal polyp burden, with modest reductions observed in lower gastrointestinal polyps.⁶² Although 71.7% of participants experienced grade 2 to 3 adverse events, these were generally well tolerated, suggesting that a weekly dosing regimen strikes a reasonable balance between efficacy and safety. Moreover, when erlotinib is combined with sulindac, the chemopreventive effects are even more pronounced. In a double-blind, placebo-controlled trial involving 92 patients with FAP, daily treatment with sulindac (300 mg once daily) and erlotinib (75 mg once daily) for 6 months resulted in a 70% reduction in colorectal polyp burden, with only mild skin-related side effects.^{63,64} By simultaneously inhibiting both the EGFR and COX-2 pathways, this combination therapy seems to achieve superior suppression of neoplastic progression in FAP.

Preclinical studies indicate that reducing colorectal mucosal polyamines—key regulators of cell growth—may help prevent CRC. In this context, inhibiting ornithine decarboxylase (ODC) with low-dose eflornithine (DFMO or CPP-1X) in combination with sulindac has shown promise.^{58,65} In a randomized trial involving 171 patients, researchers evaluated eflornithine (750 mg once daily) and sulindac (150 mg once daily), administered alone or together for 48 months, to delay disease progression in FAP.^{58,66} Although the composite outcome of upper and lower gastrointestinal events was not significantly reduced with combination therapy compared with either agent alone, a post hoc analysis revealed that the combination notably delayed lower GI disease progression.⁵⁹ Specifically, progression rates were 3.7% with the combination versus 17.0% and 19.6% with sulindac and eflornithine monotherapy, respectively. Moreover, when the excision of large adenomas was excluded, the need for major surgery was nearly eliminated in the combination group, underscoring its superior efficacy in delaying or preventing lower gastrointestinal tract surgery.

Celecoxib, a selective COX-2 inhibitor, effectively reduced gastrointestinal polyp formation and slowed duodenal

polyposis in patients with FAP, with preclinical and clinical studies demonstrating a roughly 30% decrease in polyp burden at high doses. However, concerns over long-term cardiovascular toxicity, similar to those seen with rofecoxib, have limited the use of these agents as ideal chemopreventive options.^{67,68}

Finally, aspirin, a nonselective COX inhibitor, has yielded mixed results in FAP chemoprevention. Early studies using high doses (600 mg daily) in young patients with FAP did not significantly reduce polyp numbers,⁶⁹ although some reduction in polyp size was observed—and a trial using 100 mg once daily was halted because of adverse events.⁷⁰ Despite robust evidence of aspirin's protective effect in sporadic CRC, its impact in FAP remains modest. Notably, a recent Japanese, multicenter, randomized controlled trial demonstrated that low-dose aspirin (100 mg once daily), used in a two-by-two factorial design with mesalazine (an inhibitor of both COX and lipoxygenase pathways), significantly reduced the recurrence of colorectal polyps (≥ 5.0 mm) from 50% to 30% over 8 months (adjusted odds ratio [OR], 0.37 [95% CI, 0.16 to 0.86]).⁷¹ However, limitations of this study—including challenges with end point selection, heterogeneous polyp burdens, and a study population largely comprised of patients with attenuated FAP—may have contributed to an underestimation of aspirin's benefit. Although the observed benefits are modest and the study has certain limitations, aspirin's low cost and broad availability make it an appealing candidate for FAP chemoprevention, warranting further large-scale, long-term studies with refined end point measures. Finally, a small study of eight FAP patients with ileorectal anastomosis found that using indomethacin suppositories (50 mg once or twice daily for 4–8 weeks) reduced rectal polyps from at least 10 to fewer than five in six patients, although the polyps recurred once treatment was stopped.⁷²

mTOR Inhibitors

The mTOR pathway, a key regulator of cell growth, proliferation, and angiogenesis, has emerged as an attractive target for chemoprevention in FAP. Preclinical research has demonstrated that mTOR inhibitors such as rapamycin (sirolimus) can effectively reduce polyp proliferation in APC-mutant models, and early clinical data—including findings from a small case series—indicate improvements in polyp size and dysplasia among patients with FAP. In one pilot study involving four patients with a preserved rectum or ileal pouch, 6 months of sirolimus treatment resulted in an 80% reduction in the size of most polyps and a decrease in overall polyp count, with significant apoptosis induction or proliferation inhibition observed in three of the four patients, although several adverse events were noted.⁷³ Recent efforts have focused on enhancing rapamycin's bioavailability and safety through novel formulations such as eRapa. In a phase II open-label study presented at the 2024 InSIGHT biannual meeting, 30 adult patients with FAP—both with intact colons and postcolectomy ileorectal anastomosis—received eRapa

across three dosing cohorts over a 12-month period. Overall, 75% of patients were classified as nonprogressors at 12 months, with a median 17% reduction in polyp burden; notably, one dosing group (0.5 mg once every other week) achieved a 29% median reduction, with 89% of patients showing no disease progression, marking this regimen as particularly promising.⁷⁴ Importantly, the treatment was generally well tolerated. These encouraging results have paved the way for a planned Phase III trial to further evaluate the efficacy and safety of eRapa in patients with high-risk FAP, reinforcing the potential of optimized rapamycin formulations to delay or even eliminate the need for surgical intervention.

Eicosapentaenoic Acid (Fish Oil)

Fish oil, especially in its eicosapentaenoic acid free fatty acid (EPA-FFA) form, has been studied for its chemopreventive potential in FAP. Its benefits are thought to stem from reducing mucosal arachidonic acid levels and decreasing COX-2 expression. In one study by West et al,⁷⁵ postcolectomy FAP patients with a rectal remnant treated with EPA-FFA for six months experienced a significant decrease in both polyp count (-22.4% , $P = .012$) and polyp size (-29.8% , $P = .027$) compared with placebo, with similar tolerability. Although these results mirror those seen with COX-2 inhibitors, the exact cellular mechanisms remain unclear. The ongoing EPA-POL-04 trial⁷⁶ aims to further evaluate the chemopreventive benefits of fish oil, potentially establishing it as a safe, well-tolerated strategy for reducing CRC risk in this high-risk population.

Challenges in Chemopreventive Study Design

Designing clinical trials for chemoprevention in FAP presents a number of significant challenges. One of the foremost issues is selecting outcomes that are clinically meaningful; a reduction in polyp burden must correlate with tangible benefits such as delaying surgery, preventing advanced neoplasia, or ultimately reducing cancer incidence. Patient heterogeneity further complicates trial design, as patients with FAP range from young, precolectomy individuals to older, postcolectomy patients, making uniform patient selection and end point interpretation difficult. In addition, variability in endoscopic assessments—stemming from inconsistent polyp counting, measurement techniques, and imaging quality—can undermine the reliability of surrogate end points. While advances in imaging technology and the implementation of standardized central review protocols offer potential improvements, establishing robust, universally accepted end points remains a central challenge in FAP chemoprevention trials.

Which Patients With FAP Might Benefit From Chemoprevention?

Currently, no formal guidelines endorse chemoprevention for FAP, so treatment decisions must be individualized.

Chemoprevention may be most beneficial for patients who decline further surgery or for whom surgical intervention carries high morbidity—particularly those with extensive polyposis in the rectum, ileal pouch, or duodenum, who remain at risk of adenoma recurrence despite previous colectomy. Additionally, younger patients with early-stage disease undergoing regular endoscopic surveillance might benefit from tailored chemopreventive strategies that could delay surgery and lessen the need for invasive monitoring. As the field evolves, enrolling patients in clinical trials of promising agents, such as encapsulated rapamycin and the sulindac-eflornithine combination, is critical to establish their efficacy, safety, and optimal patient selection criteria (Table 3).

WHO SHOULD BE OFFERED PC DRUG PREVENTION AND WHEN?

PC is the most common cancer in US men, with a lifetime risk of 12.9%.⁷⁷ While it is ubiquitous, affecting more than 50% of men in their lifetime, 2%–3% of men will die of the disease.⁷⁸ The current disease control focus is early detection with prostate-specific antigen (PSA) screening, which has been found in 1 Phase III trial to reduce PC mortality.⁷⁹ Unfortunately, PSA screening is associated with the risk of overdiagnosis (diagnosing a tumor never destined to cause symptoms or death) and subsequent treatment with potential complications/side effects.

Without screening, PC symptoms usually portend metastatic disease. While newer therapies have improved outcomes with advanced PC, most men with metastatic disease ultimately die of PC. With challenges of PSA testing and poor outcomes with metastatic disease, *prevention* is an attractive option.

Epidemiologic studies provide clues to opportunities for PC prevention. As diet and obesity may be related to PC, a healthy diet may reduce the risk. Unfortunately, to date, no dietary intervention has been proven to reduce PC risk or disease progression.⁸⁰

A possible strategy was signaled by secondary analyses of other Phase III trials. With evidence of PC reduction with vitamin E and selenium in lung cancer⁴⁸ and skin cancer⁸¹ prevention trials, respectively, the Selenium and Vitamin E Prostate Cancer Prevention Trial (SELECT) was initiated by SWOG with National Cancer Institute (NCI) sponsorship. A total of 35,533 men without PC were enrolled and randomly assigned in a 2×2 fashion to selenium, vitamin E, both, or neither and followed with an incident PC primary end point. Surprisingly (as the magnitude of PC reduction in the two studies suggesting benefit was substantial), selenium had no impact on PC risk while vitamin E *increased* the risk of PC by 17%.⁸² These results clearly indicate that before epidemiologic or even secondary analyses prompt clinical prevention recommendations, they must be tested in a randomized clinical trial to ensure that they are truly effective. This is

TABLE 3. Summary of Chemoprevention in FAP

Agent	Mechanism	Design and Dosing	Key Efficacy Findings	Main Limitations
Sulindac (NSAID)	COX-1/COX-2 inhibition → reduces prostaglandins	Multiple observational/RCTs; 150-300 mg once daily Suppositories in some studies	Reduces adenoma size/number; may delay colectomy in attenuated FAP Approximately 90% rectal adenoma reversion in small cohort	Rapid regrowth upon cessation Rectal cancers reported despite treatment One RCT in young FAP found no benefit
Sulindac + erlotinib	COX-2 + EGFR blockade → dual pathway inhibition	Phase II (weekly erlotinib 350 mg for 6 months) RCT (sulindac 300 mg once daily + erlotinib 75 mg once daily for 6 months) in 92 pts with FAP	Erlotinib alone: Approximately 30% reduction in duodenal polyp burden Combo: Approximately 70% decrease in colorectal polyps, mostly mild skin AEs	Frequent grade 2 to 3 side effects (skin rash) Limited data on long-term safety
Sulindac + eflornithine (DFMO)	Inhibits COX-2 + ODC → lowers polyamine levels	48-month RCT in 171 patients with FAP: Sulindac 150 mg once daily + eflornithine 750 mg once daily	No overall composite benefit Post hoc: reduced lower GI progression (3.7% v 17%-19.6%); nearly eliminated major surgery	Primary end point not met Benefit primarily in post hoc analysis
Celecoxib/rofecoxib (COX-2 inhibitors)	Selective COX-2 inhibition → lowers polyp growth	Various trials at high doses (eg, celecoxib 400 mg twice daily) in FAP	Approximately 30% drop in polyp burden Duodenal polyposis also slowed (celecoxib)	Long-term cardiovascular risks Rofecoxib withdrawn from market
Aspirin (nonselective COX inhibitor)	Irreversible COX-1/COX-2 inhibition	Mixed-dose trials (600 mg v 100 mg) Japanese RCT: 100 mg once daily + mesalazine, 8 months	Recent RCT: Polyp recurrence ≥5 mm fell from 50% to 30% (OR, 0.37) Low cost, widely available	Inconsistent results across studies Adverse events at higher doses Effect may be underestimated in attenuated FAP
Indomethacin suppositories (NSAID)	COX-1/COX-2 inhibition via rectal delivery	Small case series (n = 8) for 4-8 weeks in FAP with ileorectal anastomosis	6/8 patients reduced rectal polyps from ≥10 to <5; regrowth after stopping	Transient effect Larger studies needed to confirm long-term benefits
mTOR inhibitors (rapamycin/eRapa)	Blocks mTOR → slows cell proliferation, angiogenesis	Pilot study: 4 FAP patients, 6 months sirolimus Phase II eRapa study: 30 FAP patients, 12 months	Pilot: Approximately 80% reduction in marked polyp size Phase II eRapa: 75% nonprogressors; best cohort approximately 29% burden reduction	Some adverse events (mouth ulcers, etc) Phase III trials underway to confirm efficacy and safety
EPA-FFA (fish oil)	Reduces arachidonic acid, decreases COX-2 activity	6-month placebo-controlled study in postcolectomy FAP (rectal stump) Ongoing EPA-POL-04 trial	Approximately 22% drop in polyp count ($P = .012$) and approximately 30% size reduction ($P = .027$) Good tolerability	Mechanisms not fully elucidated Further trials needed to establish long-term benefit

Abbreviations: AEs, adverse events; COX, cyclooxygenase; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; DFMO, difluoromethylornithine; EGFR, epidermal growth factor receptor; EPA, eicosapentaenoic acid; FFA, free fatty acid; FAP, familial adenomatous polyposis; mTOR, mammalian target of rapamycin; NSAID, nonsteroidal anti-inflammatory drug; ODC, ornithine decarboxylase; OR, odds ratio; RCTs, randomized control trials.

TABLE 4. Chemoprevention Agents Demonstrated to Reduce Prostate Cancer Risk

Agent	Patient Population	Endpoint	Relative Risk Reduction, %	References
Finasteride	Men, age ≥ 55 , PSA ≤ 3.0 ng/mL	Prostate cancer	24.8	⁸⁸
Dutasteride	Men age 40-75, PSA 2.5-10 ng/mL with one prior negative prostate biopsy	Prostate cancer	22.8	⁸⁶
Dutasteride	Patients with prostate cancer on active surveillance age 48-82	Prostate cancer progression	38	⁸⁷

Abbreviation: PSA, prostate-specific antigen.

especially important as, at the time SELECT was recruiting patients, many organizations were recommending vitamin E for PC prevention among older men; thus, it is possible that these recommendations actually caused PC in some men.

As the prostate develops in utero with androgenic stimuli and as it is sensitive to hormonal manipulation, the androgen axis has been considered for chemoprevention. The relationship between androgens and PC is complex, as viewed through randomized trials. In the TRAVERSE trial, in which hypogonadal men were randomly assigned to testosterone or placebo, with 33 months of follow-up, no significant increase in PC or high-grade PC was found.^{83,84} Toremifene is a selective estrogen receptor modulator and was studied in a phase III trial of 1,590 men with high-grade prostatic intraepithelial neoplasia.⁸⁵ With a primary end point of PC, no difference was seen in risk of PC (34.7% in the placebo group and 32.3% in the toremifene group).

By comparison, the most promising opportunities for PC prevention are the five ARIs—dutasteride and finasteride. Both have been found to significantly reduce the risk of PC in Phase III trials, have ancillary urinary symptom improvement benefits, and have an acceptable toxicity profile.

Dutasteride was tested in two trials—REDUCE and REDEEM. REDUCE examined 6,729 men with a PSA of 2.5–10 ng/mL and negative biopsy, randomly assigning to dutasteride or placebo, and performing follow-up biopsies at 2 and 4 years.⁸⁶

TABLE 5. Selected Prostate Cancer Prevention Trial Side Effects

Side Effect	Finasteride, %	Placebo, %
Ejaculate volume reduction	60.4	47.3
Erectile dysfunction	67.4	61.5
Loss of libido	65.4	59.6
Gynecomastia	4.5	2.8
Benign prostatic hyperplasia	5.2	8.7
Urinary urgency or frequency	12.9	15.6
Urinary retention	4.2	6.3
Transurethral resection of the prostate	1.0	1.9
Prostatitis	4.4	6.1

NOTE. Percentage of patients reporting side effect.⁸⁹

Ultimately, dutasteride reduced the risk of PC by 22.8%. In REDEEM, 302 men with low-grade, low-volume PC on active surveillance were randomly assigning to dutasteride or placebo.⁸⁷ With 3 years of follow-up, dutasteride was associated with a 38% reduction of PC progression.

The best studied of the two agents is finasteride, examined in the NCI (US) Prostate Cancer Prevention Trial (PCPT). Men aged 55 years and older with a PSA ≤ 3.0 ng/mL were randomly assigned to finasteride or placebo, followed with PSAs annually and underwent a 7-year end-of-study biopsy.⁸⁸ The primary end point was the 7-year biopsy-proven PC status. The study found a 24.8% reduction in PC risk. The initial concern that there were more high-grade tumors in

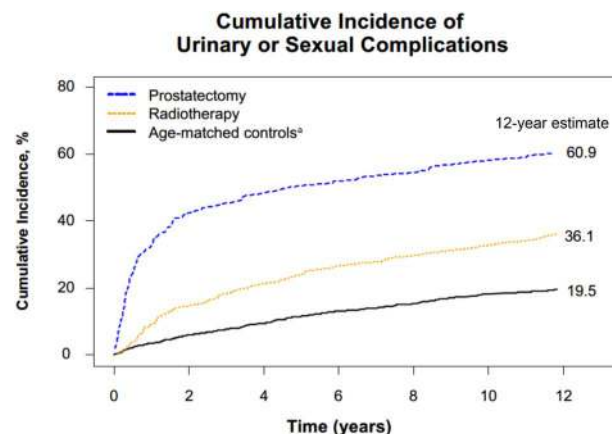


FIG 3. Urinary or sexual complications in men associated with prostate cancer treatment. Cumulative incidence of urinary or sexual complications in men from the Prostate Cancer Prevention Trial and Selenium and Vitamin E Cancer Prevention Trial with prostate cancer treated with radiotherapy or radical prostatectomy compared with the estimated cumulative incidence from a group of age-matched men with no prostate cancer or with untreated prostate cancer. Cumulative incidence was derived from a time-varying covariate design with all men starting as controls. Control group participants were selected such that the age distribution at the beginning of observation time matched the distribution of age at the time of initiation of treatment of patients, using a 2:1 ratio. For age-matched controls, control time for those who ultimately became patient cases was included as well, censored at the time of receipt of prostate cancer treatment (Adapted from ref. 93). ^aEstimated cumulative incidence based on a set of age-matched controls using a 2:1 ratio.

the finasteride-treated group was subsequently alleviated by studies demonstrating multiple biases owing to biopsy, PSA, and rectal examination that increased detection of high-grade tumors in men receiving finasteride that would likely have been missed among men receiving placebo.⁸⁸⁻⁹⁰ Long-term follow-up demonstrated continued PC risk reduction.⁹¹ No differences were seen in the long term in overall survival between study groups.⁹² A summary of key chemoprevention trials evaluating finasteride and dutasteride for PC risk reduction is presented in [Table 4](#).

As these agents are being given to healthy, disease-free men, the side effect profile is important. In general, sexual side effects were greater in men receiving finasteride while urinary symptoms were less common in men receiving finasteride. Selected side effects are displayed in [Table 5](#).

A man undergoing annual PSA testing has more than a 12.9% risk of PC detection in his lifetime and should be informed that a 5ARI will reduce his risk of detection of PC. While survival and PC mortality will be unchanged, a PC diagnosis prevented by the use of a 5ARI would thereby reduce the risk of complications of PC treatment. In a long-term follow-up of SELECT and PCPT, we found risks of urinary or sexual complications to be 7.23-fold and 2.75-fold greater in men treated with surgery or radiation, respectively, for PC ([Fig 3](#)).^{93,94} Radiation was associated with a nearly 3-fold increased risk of bladder cancer and radical cystectomy. If obstructive urinary symptoms are present, they are significantly improved with a 5ARI as is the risk of BPH-related surgery or urinary retention, although 5ARIs do affect sexual function (erections and libido) as well as increase the risk of gynecomastia.

A final opportunity for secondary cancer prevention is the use of a 5ARI in a man with a lower grade PC who is followed

on active surveillance. 5ARIs clearly reduce the risk of subsequent PC detection on follow-up biopsy as well as the risk of disease progression⁸⁶⁻⁸⁸; as both of these outcomes often lead to treatment, with the treatment-related side effects as noted above, some men may prefer the risk of 5ARI side effects to those associated with PC recurrence and progression. For men nervous about the *do nothing* stigma of active surveillance, adding a 5ARI to the surveillance regimen could be attractive.

CONCLUSION

Pharmacologic cancer prevention is underpinned by three unifying principles—dose optimization, drug repurposing, and biomarker-driven personalization—that together offer a roadmap for broad, effective implementation. First, tailoring regimens to the minimal effective dose, as seen with low-dose tamoxifen and intermittent exemestane, maximizes tolerability and adherence without sacrificing efficacy. Second, strategic repurposing of established agents—from GLP-1RAs for obesity-related cancers to NSAIDs, EGFR and mTOR inhibitors in FAP, and 5ARIs in PC—leverages known safety profiles and accelerates clinical translation. Finally, integrating validated biomarkers (eg, changes in mammographic density, Ki-67 suppression, polyp burden metrics, and emerging molecular signatures) enables precise risk stratification, dynamic monitoring of response, and selection of those most likely to benefit. Embedding these pillars into large, well-powered randomized trials—with long-term safety surveillance and harmonized end points—will be critical to refine risk-benefit assessments, inform clinical guidelines, and ultimately establish chemoprevention as a patient-centered pillar of comprehensive cancer control.

EQUAL CONTRIBUTION

M.D.-Á. and A.B. contributed equally to this work. A.D.C., D.R.B., I.M.T., and F.B. shared senior authorship.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Jayasekera J, Zhao A, Schechter C, et al: Reassessing the benefits and harms of risk-reducing medication considering the persistent risk of breast cancer mortality in estrogen receptor–positive breast cancer. *J Clin Oncol* 41:859-870, 2023
- Bychkovsky B, Laws A, Katlin F, et al: Initiation and tolerance of chemoprevention among women with high-risk breast lesions: The potential of low-dose tamoxifen. *Breast Cancer Res Treat* 193:417-427, 2022
- Fourie Zirkelbach J, Shah M, Vallejo J, et al: Improving dose-optimization processes used in oncology drug development to minimize toxicity and maximize benefit to patients. *J Clin Oncol* 40:3489-3500, 2022
- Hershman DL, Shao T, Kushi LH, et al: Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat* 126:529-537, 2011
- Decensi A, Robertson C, Guerrieri-Gonzaga A, et al: Randomized double-blind 2 x 2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in high-risk premenopausal women. *J Clin Oncol* 27:3749-3756, 2009
- Decensi A, Robertson C, Viale G, et al: A randomized trial of low-dose tamoxifen on breast cancer proliferation and blood estrogenic biomarkers. *J Natl Cancer Inst* 95:779-790, 2003
- Guerrieri-Gonzaga A, Sestak I, Lazzeroni M, et al: Benefit of low-dose tamoxifen in a large observational cohort of high risk ER positive breast DCIS. *Int J Cancer* 139:2127-2134, 2016
- DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al: Randomized placebo controlled trial of low-dose tamoxifen to prevent local and contralateral recurrence in breast intraepithelial neoplasia. *J Clin Oncol* 37:1629-1637, 2019
- Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al: Randomized placebo controlled trial of low-dose tamoxifen to prevent recurrence in breast noninvasive neoplasia: A 10-year follow-up of TAM-01 study. *J Clin Oncol* 41:3116-3121, 2023
- Bhatia S, Palomares MR, Hageman L, et al: A randomized phase IIb study of low-dose tamoxifen in chest-irradiated cancer survivors at risk for breast cancer. *Clin Cancer Res* 27:967-974, 2021
- Eriksson M, Eklund M, Borgquist S, et al: Low-dose tamoxifen for mammographic density reduction: A randomized controlled trial. *J Clin Oncol* 39:1899-1908, 2021
- Eriksson M, Czene K, Conant EF, et al: Use of low-dose tamoxifen to increase mammographic screening sensitivity in premenopausal women. *Cancers (Basel)* 13:302, 2021
- Visvanathan K, Fabian CJ, Bantug E, et al: Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. *J Clin Oncol* 37:3152-3165, 2019
- Gradishar WJ, Moran MS, Abraham J, et al: Breast cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 20:691-722, 2022
- Laws A, Punglia RS: Endocrine therapy for primary and secondary prevention after diagnosis of high-risk breast lesions or preinvasive breast cancer. *J Clin Oncol* 41:3092-3099, 2023
- Cornell LF, Klassen CL, Ghosh K, et al: Improved uptake and adherence to risk-reducing medication with the use of low-dose tamoxifen in patients at high risk for breast cancer. *Cancer Prev Res (Phila)* 17:565-570, 2024
- Patel R, Jin C, Jaber D, et al: Low dose tamoxifen for breast cancer prevention: A real-world experience. *Clin Breast Cancer* 25:283-290, 2025
- King TA, DeCensi A: Selecting the right dose to move breast cancer prevention forward. *Cancer Prev Res (Phila)* 17:545-547, 2024
- Serrano D, Gandini S, Thomas P, et al: Efficacy of alternative dose regimens of exemestane in postmenopausal women with stage 0 to II estrogen receptor–positive breast cancer: A randomized clinical trial. *JAMA Oncol* 9:664-672, 2023
- GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al: Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 377:13-27, 2017
- Sung H, Siegel RL, Torre LA, et al: Global patterns in excess body weight and the associated cancer burden. *CA Cancer J Clin* 69:88-112, 2019
- Brenner DR, Poirier AE, Ruan Y, et al: Estimates of the current and future burden of cancer attributable to excess body weight and abdominal adiposity in Canada. *Prev Med* 122:49-64, 2019
- Lauby-Secretan B, Scoccianti C, Loomis D, et al: Body fatness and cancer—viewpoint of the IARC working group. *N Engl J Med* 375:794-798, 2016
- Pati S, Irfan W, Jameel A, et al: Obesity and cancer: A current overview of epidemiology, pathogenesis, outcomes, and management. *Cancers (Basel)* 15:485, 2023
- Fryar CDCM, Carroll MD, Afful J: Products—Health E Stats—Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults Aged 20 and over: United States, 1960–1962 through 2017–2018, 2021. <https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm>
- Government of Canada SC: Overweight and obese adults, 2018, 2019. <https://www150.statcan.gc.ca/n1/pub/82-625-x/2019001/article/00005-eng.htm>
- Government of Canada SC: Measured adult body mass index (BMI) (World Health Organization classification), by age group and sex, Canada and provinces, Canadian Community Health Survey—Nutrition. 2017. <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310079401>
- Bray F, Laversanne M, Sung H, et al: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74:229-263, 2024
- Petrelli F, Cortellini A, Indini A, et al: Association of obesity with survival outcomes in patients with cancer: A systematic review and meta-analysis. *JAMA Netw Open* 4:e213520, 2021
- Carbonell C, Mathew Stephen M, Ruan Y, et al: Next generation weight loss drugs for the prevention of cancer? *Cancer Control* 31:10732748241241158, 2024
- Wang L, Xu R, Kaelber DC, et al: Glucagon-like peptide 1 receptor agonists and 13 obesity-associated cancers in patients with type 2 diabetes. *JAMA Netw Open* 7:e2421305, 2024
- Levy S, Attia A, Elshazli RM, et al: Differential effects of GLP-1 receptor agonists on cancer risk in obesity: A nationwide analysis of 1.1 million patients. *Cancers* 17:78, 2024
- Wang L, Berger NA, Kaelber DC, et al: Association of GLP-1 receptor agonists and hepatocellular carcinoma incidence and hepatic decompensation in patients with type 2 diabetes. *Gastroenterology* 167:689-703, 2024
- Yang CT, Yao WY, Yang CY, et al: Lower risks of cirrhosis and hepatocellular carcinoma with GLP-1RAs in type 2 diabetes: A nationwide cohort study using target trial emulation framework. *J Intern Med* 295:357-368, 2024
- Skriver C, Friis S, Knudsen LB, et al: Potential preventive properties of GLP-1 receptor agonists against prostate cancer: A nationwide cohort study. *Diabetologia* 66:2007-2016, 2023
- Wang L, Wang Q, Li L, et al: Glucagon-like peptide-1 receptor agonists and pancreatic cancer risk: Target trial emulation using real-world data. *J Natl Cancer Inst* 117:476-485, 2025
- Krishnan A, Hadi Y, Hutson WR, et al: Glucagon-like peptide 1-based therapies and risk of pancreatic cancer in patients with diabetes and obesity. *Pancreas* 51:1398-1403, 2022
- American Association for Cancer Research: Abstract 735: The associations between the use of GLP-1 receptor agonists, cancer recurrence and all-cause mortality among cancer survivors | Cancer Research. https://aacrjournals.org/cancerres/article/83/7_Supplement/735/724430/Abstract-735-The-associations-between-the-use-of
- Wilding JPH, Batterham RL, Calanna S, et al: Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 384:989-1002, 2021
- Wadden TA, Bailey TS, Billings LK, et al: Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The STEP 3 randomized clinical trial. *JAMA* 325:1403-1413, 2021
- Jastreboff AM, Aronne LJ, Ahmad NN, et al: Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 387:205-216, 2022
- Sodhi M, Rezaeianzadeh R, Kezouh A, et al: Risk of gastrointestinal adverse events associated with glucagon-like peptide-1 receptor agonists for weight loss. *JAMA* 330:1795-1797, 2023
- Piccoli GF, Mesquita LA, Stein C, et al: Do GLP-1 receptor agonists increase the risk of breast cancer? A systematic review and meta-analysis. *J Clin Endocrinol Metab* 106:912-921, 2021
- Fothergill E, Guo J, Howard L, et al: Persistent metabolic adaptation 6 years after 'The Biggest Loser' competition. *Obesity (Silver Spring)* 24:1612-1619, 2016
- Rubino D, Abrahamsson N, Davies M, et al: Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: The STEP 4 randomized clinical trial. *JAMA* 325:1414-1425, 2021
- Wilding JPH, Batterham RL, Davies M, et al: Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes Obes Metab* 24:1553-1564, 2022
- Manson JE, Chlebowski RT, Stefanick ML, et al: Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 310:1353-1368, 2013
- Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group: The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 330:1029-1035, 1994
- Benamouzig R, Deyra J, Martin A, et al: Daily soluble aspirin and prevention of colorectal adenoma recurrence: One-year results of the APACC trial. *Gastroenterology* 125:328-336, 2003

50. Grover S, Kastrinos F, Steyerberg EW, et al: Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. *JAMA* 308:485-492, 2012
51. Bussey HJR: Familial Polyposis Coli: Family Studies, Histopathology, Differential Diagnosis, and Results of Treatment. Baltimore, MA, Johns Hopkins University Press, 1975. p 130. <http://archive.org/details/familialpolyposi0000bussey>
52. Tudyka VN, Clark SK: Surgical treatment in familial adenomatous polyposis. *Ann Gastroenterol* 25:201-206, 2012
53. Cwalinski J, Zasada W, Cholerzynska H, et al: Endoscopic surveillance after (Procto)Colectomy with gastrointestinal reconstruction in patients with familial adenomatous polyposis (FAP)-principles, goals and practical aspects based on 12 years of observation. *Life (Basel)* 14:1000, 2024
54. Matsumoto T, Nakamura S, Esaki M, et al: Effect of the non-steroidal anti-inflammatory drug sulindac on colorectal adenomas of uncolectomized familial adenomatous polyposis. *J Gastroenterol Hepatol* 21:251-257, 2006
55. Cruz-Correa M, Hyland LM, Romans KE, et al: Long-term treatment with sulindac in familial adenomatous polyposis: A prospective cohort study. *Gastroenterology* 122:641-645, 2002
56. Neuhaan TM, Haub K, Steinke-Lange V, et al: Long-term chemoprevention in patients with adenomatous polyposis coli: An observational study. *Fam Cancer* 21:463-472, 2022
57. Kim KY, Jeon SW, Park JG, et al: Regression of colonic adenomas after treatment with sulindac in familial adenomatous polyposis: A case with a 2-year follow-up without a prophylactic colectomy. *Ann Coloproctol* 30:201-204, 2014
58. Burke CA, Dekker E, Lynch P, et al: Eflornithine plus sulindac for prevention of progression in familial adenomatous polyposis. *N Engl J Med* 383:1028-1039, 2020
59. Balaguer F, Stoffel EM, Burke CA, et al: Combination of sulindac and eflornithine delays the need for lower gastrointestinal surgery in patients with familial adenomatous polyposis: Post hoc analysis of a randomized clinical trial. *Dis Colon Rectum* 65:536-545, 2022
60. Nugent KP, Farmer KC, Spigelman AD, et al: Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br J Surg* 80:1618-1619, 1993
61. Giardiello FM, Yang VW, Hyland LM, et al: Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 346:1054-1059, 2002
62. Samadder NJ, Foster N, McMurray RP, et al: Phase II trial of weekly erlotinib dosing to reduce duodenal polyp burden associated with familial adenomatous polyposis. *Gut* 72:256-263, 2023
63. Samadder NJ, Neklason DW, Boucher KM, et al: Effect of sulindac and erlotinib vs placebo on duodenal neoplasia in familial adenomatous polyposis: A randomized clinical trial. *JAMA* 315:1266-1275, 2016
64. Samadder NJ, Kuwada SK, Boucher KM, et al: Association of sulindac and erlotinib vs placebo with colorectal neoplasia in familial adenomatous polyposis: Secondary analysis of a randomized clinical trial. *JAMA Oncol* 4:671-677, 2018
65. Meyskens FL, McLaren CE, Pelot D, et al: Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: A randomized placebo-controlled, double-blind trial. *Cancer Prev Res (Phila)* 1:32-38, 2008
66. Burke CA, Dekker E, Samadder NJ, et al: Efficacy and safety of eflornithine (CPP-1X)/sulindac combination therapy versus each as monotherapy in patients with familial adenomatous polyposis (FAP): Design and rationale of a randomized, double-blind, phase III trial. *BMC Gastroenterol* 16:87, 2016
67. Lynch PM, Burke CA, Phillips R, et al: An international randomised trial of celecoxib versus celecoxib plus difluoromethylornithine in patients with familial adenomatous polyposis. *Gut* 65:286-295, 2016
68. Hallak A, Alon-Baron L, Shamir R, et al: Rofecoxib reduces polyp recurrence in familial polyposis. *Dig Dis Sci* 48:1998-2002, 2003
69. Burn J, Bishop DT, Chapman PD, et al: A randomized placebo-controlled prevention trial of aspirin and/or resistant starch in young people with familial adenomatous polyposis. *Cancer Prev Res (Phila)* 4:655-665, 2011
70. Ishikawa H, Wakabayashi K, Suzuki S, et al: Preventive effects of low-dose aspirin on colorectal adenoma growth in patients with familial adenomatous polyposis: Double-blind, randomized clinical trial. *Cancer Med* 2:50-56, 2013
71. Ishikawa H, Mutoh M, Sato Y, et al: Chemoprevention with low-dose aspirin, mesalazine, or both in patients with familial adenomatous polyposis without previous colectomy (J-FAPP study IV): A multicentre, double-blind, randomised, two-by-two factorial design trial. *Lancet Gastroenterol Hepatol* 6:474-481, 2021
72. Hirota C, Iida M, Aoyagi K, et al: Effect of indomethacin suppositories on rectal polyposis in patients with familial adenomatous polyposis. *Cancer* 78:1660-1665, 1996
73. Roos VH, Meijer BJ, Kallenberg FGJ, et al: Sirolimus for the treatment of polyposis of the rectal remnant and ileal pouch in four patients with familial adenomatous polyposis: A pilot study. *BMJ Open Gastroenterol* 7:e000497, 2020
74. Administrator B. Biodepha Pharmaceuticals: Twelve Month Phase 2 Clinical Trial Results of eRapa™ in Familial Adenomatous Polyposis (FAP) to Be Presented at Prestigious Biennial InSIGHT 2024 Meeting in Barcelona. 2024. <https://biodepharma.com/twelve-month-phase-2-clinical-trial-results-of-erapa-in-familial-adenomatous-polyposis-fap-to-be-presented-at-prestigious-biennial-insight-2024-meeting-in-barcelona/>
75. West NJ, Clark SK, Phillips RKS, et al: Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut* 59:918-925, 2010
76. S.L.A. Pharma AG. Randomised, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of EPA-FFA Gastro-Resistant Capsules, in Patients with Familial Adenomatous Polyposis (FAP). clinicaltrials.gov; 2024. Report No: [NCT03806426](https://clinicaltrials.gov/study/NCT03806426). <https://clinicaltrials.gov/study/NCT03806426>
77. Siegel RL, Giaquinto AN, Jemal A: Cancer statistics, 2024. *CA Cancer J Clin* 74:12-49, 2024
78. Carter HB, Piantadosi S, Isaacs JT: Clinical evidence for and implications of the multistep development of prostate cancer. *J Urol* 143:742-746, 1990
79. Schröder FH, Hugosson J, Roobol MJ, et al: Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 360:1320-1328, 2009
80. Parsons JK, Zahrieh D, Mohler JL, et al: Effect of a behavioral intervention to increase vegetable consumption on cancer progression among men with early-stage prostate cancer: The MEAL randomized clinical trial. *JAMA* 323:140-148, 2020
81. Clark LC, Combs GF, Turnbull BW, et al: Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* 276:1957-1963, 1996
82. Klein EA, Thompson IM, Tangen CM, et al: Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 306:1549-1556, 2011
83. Lincoff AM, Bhasin S, Flevaris P, et al: Cardiovascular safety of testosterone-replacement therapy. *N Engl J Med* 389:107-117, 2023
84. Bhasin S, Travison TG, Pencina KM, et al: Prostate safety events during testosterone replacement therapy in men with hypogonadism: A randomized clinical trial. *JAMA Netw Open* 6:e2348692, 2023
85. Taneja SS, Morton R, Barnette G, et al: Prostate cancer diagnosis among men with isolated high-grade intraepithelial neoplasia enrolled onto a 3-year prospective phase III clinical trial of oral toremifene. *J Clin Oncol* 31:523-529, 2013
86. Andriole GL, Bostwick DG, Brawley OW, et al: Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 362:1192-1202, 2010
87. Fleshner NE, Lucia MS, Egerdie B, et al: Dutasteride in localised prostate cancer management: The REDEEM randomised, double-blind, placebo-controlled trial. *Lancet (London, England)* 379:1103-1111, 2012
88. Thompson IM, Goodman PJ, Tangen CM, et al: The influence of finasteride on the development of prostate cancer. *N Engl J Med* 349:215-224, 2003
89. Thompson IM, Chi C, Ankerst DP, et al: Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* 98:1128-1133, 2006
90. Lucia MS, Epstein JI, Goodman PJ, et al: Finasteride and high-grade prostate cancer in the prostate cancer prevention trial. *J Natl Cancer Inst* 99:1375-1383, 2007
91. Unger JM, Hershman DL, Till C, et al: Using Medicare claims to examine long-term prostate cancer risk of finasteride in the prostate cancer prevention trial. *J Natl Cancer Inst* 110:1208-1215, 2018
92. Thompson IM, Goodman PJ, Tangen CM, et al: Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med* 369:603-610, 2013
93. Unger JM, Till C, Tangen CM, et al: Long-term adverse effects and complications after prostate cancer treatment. *JAMA Oncol* 10:1654-1662, 2024
94. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 1.2024. PA, Plymouth Meeting, NCCN, 2024

Navigating Ongoing Challenges in GI Stromal Tumors

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OVERVIEW

GI stromal tumors (GISTs) are mesenchymal neoplasms with variable natural histories, originating in the GI tract, most commonly in the stomach. They are frequently characterized by *KIT* or *platelet-derived growth factor receptor alpha* (*PDGFRA*) oncogenic mutations. Surgical resection remains the cornerstone treatment for localized GISTs. Clinical trials have demonstrated the benefits of adjuvant imatinib in patients selected on the basis of recurrence risk and gene mutations, although the optimal duration of therapy is yet to be established. Some data suggest that longer durations of adjuvant imatinib (>3 years) may provide additional benefit, which is being investigated in ongoing trials. Management of imatinib-related adverse effects is essential during treatment, and longitudinal abdominal imaging is mandatory both during and after adjuvant therapy. Once GISTs are more advanced and unresectable, *KIT*- and *PDGFRA*-directed tyrosine kinase inhibitors (TKIs) become the key treatment in most patients with *KIT* mutation. Several TKIs have regulatory approval for advanced GISTs, but in most patients, resistance to TKIs eventually emerges, mainly from secondary resistance mutations in *KIT*. Each TKI has different coverage of oncogenic *KIT* mutations, suggested by preclinical and clinical findings, which has given rationale to an ongoing clinical trial that includes molecular selection as eligibility criteria. Furthermore, novel treatment approaches, from TKI combinations to an antibody-drug conjugate, are being investigated. Despite the significant advance in managing GISTs with *KIT* mutations, those without *KIT* or *PDGFRA* mutation, which consists of 10%–15% of patients with GIST, can be a clinical challenge in the advanced setting. These non-*KIT*/*PDGFRA* GISTs could be driven by genomic or epigenomic alterations in *SDHx*, *NF1* mutations, and other genomic alterations. Non-*KIT*/*PDGFRA* GISTs are less responsive to currently available TKIs than GISTs driven by *KIT*/*PDGFRA* mutations, and each subset of non-*KIT*/*PDGFRA* GIST has distinctive biology and clinical features. Therefore, individualized, multidisciplinary, biology-based management and consideration for clinical trial enrollment are critical for non-*KIT*/*PDGFRA* GISTs.

INTRODUCTION

GI stromal tumors (GISTs) are neoplasms with widely variable malignant potential that arise from the GI tract, most frequently in the stomach. Their annual incidence is approximately 10 per million.¹

Approximately 80%–90% of GISTs are localized at the time of initial detection.^{2,3} These tumors can give rise to metastases, most commonly in the abdominal cavity or liver. The majority (70%–80%) of GISTs are driven by an activating mutation in the *KIT* oncogene, about 15% harbor a mutation in the *platelet-derived growth factor receptor alpha* (*PDGFRA*) gene, and approximately 10% lack mutations in these genes. In treatment-naïve GISTs, *KIT* mutations are most frequently found in exon 11 (80%–90%) or exon 9 (5%–10%).^{2,4}

Although surgery remains the cornerstone of treatment for localized GISTs, systemic therapies have advanced substantially. The tyrosine kinase inhibitor (TKI) imatinib, which targets several kinases, including *KIT* and *PDGFRA*,

has been the standard first-line treatment for advanced GIST for over two decades.⁵ In addition, several other TKIs have been approved for the treatment of advanced disease.^{6–9} Adjuvant imatinib is now considered the standard treatment for most patients who have undergone macroscopically complete surgery for GISTs with a high risk of recurrence.^{10–13}

Herein, we focus on three key aspects of multidisciplinary management: (1) prognostication and adjuvant therapy for patients with localized *KIT*-mutant GIST, (2) resistance to systemic therapies, and (3) emerging strategies for managing GIST without *KIT* or *PDGFRA* mutations.

ADJUVANT TREATMENT OF *KIT*-MUTANT GIST

Tumor Mutation Analysis as the Basis for Adjuvant Therapy

Mutation analysis of tumor tissue is essential for all patients being considered for adjuvant imatinib, as the mutation type

PRACTICAL APPLICATIONS

- Although most localized GI stromal tumors (GISTs) are cured by surgical resection, adjuvant imatinib should be considered when the risk of recurrence is high and the tumor harbors an imatinib-sensitive *KIT* or *platelet-derived growth factor receptor alpha* (*PDGFRA*) mutation.
- The optimal duration of adjuvant imatinib has yet to be determined, and clinical trials are ongoing to address this.
- *KIT*-directed tyrosine kinase inhibitors (TKIs) are the key treatment for advanced GISTs, but TKI resistance because of secondary mutations often emerges.
- Novel approaches to overcome TKI resistance, including strict mutation-based patient selections, TKI combinations, novel TKIs, non-*KIT* targeted therapies, and an antibody-drug conjugate, are being investigated.
- Non-*KIT*/*PDGFRA* GISTs are a clinical challenge given their rarity and distinct biology from GISTs with *KIT*/*PDGFRA* mutations, necessitating individualized, multidisciplinary, biology-based management.

and location predict sensitivity to the drug. Patients at high risk of GIST recurrence despite macroscopically complete surgery are candidates for adjuvant imatinib, provided the GIST genotype suggests tumor sensitivity to imatinib, which is the only drug that has been studied in adjuvant trials.^{10–13}

Most *KIT*-mutant GISTs are sensitive to imatinib. Among *KIT* exon 11 variants, deletions and insertion/deletion (indel) mutations are more common than substitutions or insertions/duplications.^{2,4} Generally, *KIT* exon 11 deletions and indels show the highest sensitivity to imatinib, whereas *KIT* exon 9 variants (nearly all are p.Ala502_Tyr503 duplication mutations) exhibit less sensitivity. GISTs with *KIT* exon 11 substitution mutations or insertion/duplication mutations are also generally sensitive to imatinib.^{14–16} The most common mutation in *PDGFRA*, p.(Asp842Val) (D842V) in *PDGFRA* exon 18, is resistant to imatinib, whereas most other *PDGFRA* mutations are sensitive. GISTs that lack both *KIT* and *PDGFRA* mutations are also not sensitive to imatinib.^{16,17}

GIST Risk of Recurrence

Approximately 60% of patients with localized GIST are cured through surgical resection.¹⁸ Estimating the risk of recurrence is therefore essential when considering adjuvant imatinib treatment after surgery. Although numerous single prognostic factors have been identified, risk estimation

schemes that incorporate multiple independent prognostic factors are generally more accurate. Key factors in prognostication include tumor size, cell proliferation rate (usually assessed by mitotic count), tumor site within the GI tract (with gastric tumors having the best prognosis), and the presence of tumor rupture.¹⁹

The most commonly used multifactorial schemes are the Armed Forces Institute of Pathology (AFIP) scheme and the modified National Cancer Institute (National Institutes of Health [NIH]) scheme.^{19–21} The primary difference between these two schemes is that the AFIP classification categorizes patients into eight groups with progressively increasing risk of recurrence from group 1 to group 6B, while the modified NIH classification consolidates patients into a single high-risk group versus those classified as very low risk, low risk, or intermediate risk of recurrence.¹⁸ Prognostic contour maps¹⁸ and nomograms²² are also available for more individualized risk assessment. Combining data from more than one method may be helpful in stratifying prognosis on an individual basis.

Randomized Trials on Adjuvant Imatinib

Several studies have evaluated the safety and efficacy of imatinib as an adjuvant treatment after surgery for GIST, with the most robust evidence coming from four randomized trials (Table 1). In all trials, imatinib was administered orally at 400 mg once daily, although the duration of treatment, control groups, patient eligibility criteria, and median follow-up times varied. Two of the trials demonstrated that adjuvant imatinib significantly prolonged recurrence-free survival (RFS) compared with either placebo^{23,24} or observation.²⁵ Another trial found that 3 years of adjuvant imatinib improved RFS compared with 1 year of treatment,²⁶ while a fourth trial reported longer disease-free survival with 6 years of adjuvant imatinib compared with 3 years.²⁷

The main goal of adjuvant treatment is to extend overall survival. In the Scandinavian Sarcoma Group (SSG) XVIII/AIO trial, patients randomly assigned to the 3-year group had longer survival compared with those in the 1-year group, with 79% and 65%, respectively, being alive 10 years after random assignment (hazard ratio, 0.55 [95% CI, 0.37 to 0.83]; $P = .004$).²⁶ However, statistical significance favoring the adjuvant imatinib was not observed for overall survival in the ACOSOG Z9001 or EORTC 62064 trials, which recruited lower-risk patients and used shorter durations of adjuvant imatinib.^{24,25} In the ACOSOG Z9001 trial, crossover from the placebo group to the imatinib group was allowed in patients of tumor recurrence.²³

Duration of Adjuvant Imatinib

Adjuvant imatinib is more likely to suppress occult metastatic disease rather than eradicate it.²⁸ Therefore, the duration of adjuvant therapy may need to be sufficiently long—several years—to improve overall survival. Current treatment

TABLE 1. Randomized Phase III Trials on Adjuvant Imatinib in GIST

Trial	Patients Randomly Assigned, No.	Experimental Group	Control Group	Selected Risk Group	Median Follow-Up, Years	Recurrence-Free Survival/Disease-Free Survival	Overall Survival
						HR (95% CI), <i>P</i>	HR (95% CI), <i>P</i>
ACOSOG Z9001	713 ^a	Imatinib for 1 year	Placebo for 1 year	Size ≥3 cm	1.6	At 1 year: IM, 98%; PI, 83% HR, 0.35 (0.22 to 0.53); <i>P</i> < .0001	At 1 year: IM, 99%; PI, 100% HR, 0.66 (0.22 to 2.03), <i>P</i> = .47 ^b
EORTC 62064 ^c	908	Imatinib for 2 years	Observation	Intermediate or high risk (NIH)	9.1	At 5 years: IM, 70%; Obs, 63% At 10 years: IM, 63%; Obs, 61% HR, 0.71 (0.57 to 89), <i>P</i> = .002	At 5 years: IM, 93%; Obs, 92% At 10 years: IM, 80%; Obs, 78% HR, 0.88 (0.65 to 1.21), <i>P</i> = .43
SSG XVIII/German	400	Imatinib for 3 years	Imatinib for 1 year	High risk (modified NIH)	9.9	At 5 years: 3-year, 71%; 1-year, 53% At 10 years: 3-year, 53%; 1-year, 42% HR, 0.66 (0.49 to 0.87); <i>P</i> = .003	At 5 years: 3-year, 92%; 1-year, 86% At 10 years: 3-year, 79%; 1-year, 65% HR, 0.55 (0.37 to 0.83); <i>P</i> = .004
IMADGIST	135	Imatinib for 6 years	Imatinib for 3 years	Risk ≥35% (AFIP)	4.6	At 3 years: 6-year, 72%; 3-year, 42% HR, 0.40 (0.19 to 0.80), <i>P</i> = .008	Not available ^d

Abbreviations: 1-year, 1-year group; 3-year, 3-year group; 6-year, 6-year group; ACOSOG, American College of Surgeons Oncology Group; AFIP, Armed Forces Institute of Pathology; EORTC, European Organisation for Research and Treatment of Cancer; GIST, GI stromal tumor; HR, hazard ratio; IM, imatinib; NIH, National Institutes of Health; Obs, observation group; PI, placebo; SSG, Scandinavian Sarcoma Group.

^aAccrual was stopped early on the basis of the results of a planned interim analysis.

^bCrossover from placebo to imatinib was allowed in the event of tumor recurrence.

^cThe primary end point in the trial was imatinib failure-free survival.

^dSeven overall survival events had been observed at the time of the trial analysis resulting in overlapping Kaplan-Meier plots between the groups. The HR is not available.

guidelines from the European Society for Medical Oncology, the British Sarcoma Group, and the Japan Society of Clinical Oncology recommend adjuvant imatinib for 3 years after macroscopically complete surgery for high-risk GIST with an imatinib-sensitive mutation,¹¹⁻¹³ whereas the US National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant imatinib for at least 3 years.¹⁰

Adjuvant imatinib durations longer than 3 years might improve survival further compared with the 3-year duration, as suggested by some analyses on the basis of registry data or other sources,^{28,29} but confirmation of this hypothesis in randomized trials is currently lacking. In addition to the IMADGIST trial,²⁷ (Table 1), the SSG XXII trial may provide further guidance on treatment durations exceeding 3 years. The SSG XXII trial, which compares 5 years with 3 years of adjuvant imatinib for high-risk GIST, has fully recruited 255 patients and is expected to report results in 2026.

Patient Selection for Adjuvant Imatinib

Patients with high-risk GIST (approximately 40% of all patients with GIST^{2,18}) should be considered for adjuvant imatinib, whereas lower-risk patients, most of whom are

likely cured by surgery, should not receive adjuvant imatinib. Most patients tolerate the daily dose of 400 mg of imatinib moderately well, although nearly all experience some adverse effects.^{23,30} The most common side effects include anemia, eyelid edema, mild diarrhea, painful muscle cramps, and hypophosphatemia.

In practice, patients with low-risk or intermediate-risk GIST, as defined by the modified NIH risk classification criteria, who have a ≤10% risk of recurrence,¹⁸ should not be offered adjuvant therapy, regardless of the GIST genotype. Similarly, patients with a low risk according to the AFIP classification or the prognostic contour maps should likely be excluded from adjuvant imatinib.

Although most high-risk patients with a *KIT* exon 11 mutation—particularly those with exon 11 deletion or indel mutations—are likely to benefit from adjuvant imatinib, it remains unclear whether patients with a *KIT* exon 9 mutation experience similar benefits. Exploratory subgroup analyses from two randomized trials suggest no survival benefit for these patients,^{15,24} but these analyses were substantially underpowered. Evidence from the treatment of advanced GIST indicates that an 800-mg daily dose of

imatinib may be more effective than the 400-mg dose evaluated in randomized adjuvant trials.³¹ However, a retrospective study suggests that the 800-mg dose might not provide greater efficacy in the adjuvant setting.³² Since many patients poorly tolerate the 800-mg dose, a reasonable approach might be to administer the highest dose the patient can tolerate well in the long term, although this strategy is not currently supported by evidence.

Imaging During and After Adjuvant Imatinib

Periodic imaging of the abdomen with computed tomography (CT) or magnetic resonance imaging (MRI) during and after adjuvant imatinib therapy is a critical component of patient care. Since nearly all recurrent tumors are found in the liver and abdominal cavity, imaging of the abdomen alone is sufficient. With periodic longitudinal imaging using CT or MRI, the majority of recurrences are detected as asymptomatic, small-volume disease. When GIST recurs after the completion of adjuvant imatinib therapy, most patients are restarted on imatinib. In most patients, the GIST stabilizes or responds to the reintroduced therapy, resulting in overall survival durations comparable with those of patients with imatinib-naïve, newly diagnosed overtly metastatic disease.²⁶ By contrast, failure to perform longitudinal imaging may result in bulky, symptomatic recurrences, with an increased risk of imatinib resistance mutations emerging early, potentially compromising survival.

The risk of recurrence is greatest within the 2–3 years after the discontinuation of adjuvant imatinib.^{23–28} Few studies have investigated the optimal frequency and timing of imaging, but it seems reasonable to image patients frequently, at 3- to 4-month intervals, during this high-risk 2- to 3-year period. Imaging frequency can then be reduced, for example, first to 6-month intervals and later to 12-month intervals. The risk of GIST recurrence after the first 10 years following surgery is low.¹⁸ Although relatively few recurrences occur while patients with *KIT*-mutated GISTs are still receiving adjuvant imatinib,²⁸ abdominal imaging should be performed approximately every 6 months while the patient is on imatinib.

Ruptured GIST

GIST rupture, either before or during surgery, occurs in approximately 5%–10% of patients and is a serious adverse prognostic factor.^{18,33,34} In some series, tumor rupture invariably led to recurrence.³³ The NCCN guidelines consider rupture equivalent to metastatic disease,¹⁰ which is treated with the permanent administration of TKIs. However, it is important to note that tumor rupture into the bowel lumen, without seeding into the peritoneal cavity, does not increase the risk of recurrence. Similarly, minor rupture, such as uncomplicated transabdominal needle biopsy or iatrogenic peritoneal damage during surgery, has little influence on prognosis.^{34,35} In an exploratory analysis of a randomized

trial, approximately 20% of patients with major tumor rupture who were treated with adjuvant imatinib did not experience GIST recurrence during the first 10 years of follow-up. Additionally, most patients with a *KIT* exon 11 deletion/indel mutation survived for 10 years after random assignment despite tumor rupture, with a strategy of rapidly restarting imatinib when recurrence was detected on longitudinal imaging.³⁶

Patients with major tumor rupture should be considered for imatinib therapy if they have an imatinib-sensitive mutation. Given the uncertainty about whether major tumor rupture constitutes metastatic disease, the optimal duration of adjuvant imatinib should be at least 3 years, and possibly even lifelong.¹² Efforts should be made to avoid inadvertent tumor rupture during surgery and to avoid incisional biopsy of the tumor for diagnosis.

Supportive Care During Adjuvant Imatinib

Despite the proven efficacy of imatinib, maintaining adherence to adjuvant treatment can be challenging.³⁷ Patient support and management of imatinib-related adverse effects are essential to reduce the risk of premature discontinuation of adjuvant therapy, a concern noted in some studies. Patients should be informed about the potential benefits and risks of adjuvant therapy, and an early follow-up visit should be scheduled shortly after treatment initiation to address any possible side effects. Imatinib-related diarrhea may be alleviated with antidiarrheal agents such as loperamide, while splitting the 400 mg daily dose into 200 mg in the morning and 200 mg in the evening can help reduce nausea. Edema may be managed with diuretics. Some patients, particularly elderly individuals, may struggle to tolerate the standard 400-mg dose despite supportive measures.³⁸ In such patients, reducing the daily dose to 300 mg may be considered to prevent early discontinuation of adjuvant imatinib. Measurement of imatinib plasma trough levels may help guide individualized dosing,³⁹ but this strategy has not been evaluated in randomized trials.

TREATMENT OF METASTATIC GIST—A SUMMARY OF DRUG DEVELOPMENT IN ADVANCED GIST

TKIs for Advanced GIST

Imatinib has been the worldwide standard-of-care first-line therapy for metastatic GIST for over 20 years. The initial clinical trials compared imatinib 400 mg versus 600 mg per day with an overall response rate of 53.7%.⁵ Subsequent studies compared imatinib 400 mg versus 800 mg per day with similar outcomes and no clear benefit to higher doses with the exception of patients with tumors that harbor *KIT* exon 9 mutations.^{40,41} Long-term follow-up of the 695 patients with advanced GIST who were assigned to either 400 mg once or twice daily in a randomized trial (SWOG study S0033) demonstrated a median overall survival of 52 months, with a 10-year estimate of overall survival of 23%

(95% CI, 20% to 26%), demonstrating deep and durable disease control.⁴²

Despite the dramatic successes of imatinib, resistance develops in nearly all patients with advanced GIST. Sunitinib, regorafenib, and ripretinib have achieved regulatory approval in second-, third-, and fourth-line settings, respectively, each demonstrating improved progression-free survival (PFS) versus placebo in a series of pivotal phase III randomized trials.^{6,7} Ripretinib demonstrated an improvement in overall survival in the fourth-line setting versus placebo, despite a study design that allowed crossover from placebo to ripretinib (INVICTUS trial).⁸

Resistance Mechanism to TKIs

As clinical successes of imatinib were observed in the early 2000s, the first patients treated with imatinib began to develop resistance. Interestingly, understanding of the mechanisms of imatinib resistance emerged in parallel to the development of other *KIT*-directed TKIs.

Sunitinib, a broad-spectrum kinase inhibitor, was initially developed for advanced renal cell carcinoma because of potent vascular endothelial growth factor receptor (VEGFR) inhibition. Because sunitinib was a potent *KIT* inhibitor in addition to VEGFR, the drug was explored in GIST. The earliest phase Ib trials of sunitinib in advanced GIST after progression on imatinib demonstrated clinical activity in this setting, and the drug then went on to be evaluated in a pivotal phase III trial. Only after sunitinib development was well underway was it learned that not all primary mutations in *KIT* responded similarly to imatinib. Patients whose tumors harbored primary exon 11 mutations had longer PFS compared with those with primary exon 9 mutations. Around this same time, imatinib-resistant tumor samples were also being sequenced for the first time, and it was found that the primary resistance mechanism was indeed the emergence of secondary resistance mutations in *KIT*. Structural changes in *KIT* are rendered by the secondary *KIT* mutations, leading to failure of imatinib to bind to *KIT*, and subsequent disease progression. Imatinib resistance mutations occur in a nonrandom pattern and are clustered in the ATP-binding pocket (exons 13/14) or the activation loop (exons 17/18).⁴³ It also became clear that the emerging resistance mutations were spatially heterogeneous; within a single patient, multiple different mutations could be present in different tumors. This finding further complicated the approach to overcoming imatinib resistance. As these findings emerged, it allowed investigations to understand the relative benefit of TKIs across different primary and secondary mutations in *KIT*.

Somewhat fortuitously, it became clear that sunitinib was very active against primary *KIT* exon 11 and even more active against primary *KIT* exon 9—a now known relative vulnerability with imatinib. In addition, sunitinib has significant activity against the secondary imatinib resistance mutation, V645A, in *KIT* exon 13. Retrospectively, this

mutation was found to be present in about 50% of the patients enrolled on the pivotal phase III trial.

Regorafenib was studied in a molecularly unselected population of patients with advanced GIST after both imatinib and sunitinib in a phase II trial and then in a randomized phase III trial compared with placebo. Regorafenib demonstrated a significant PFS benefit in the pivotal phase III trial, which subsequently led to US Food and Drug Administration (FDA) approval. Follow-up exploratory mutational analysis suggested broad activity across primary and secondary *KIT* mutations.⁴⁴

Distinctive Response to TKIs From Variable Oncogenic *KIT*/*PDGFRA* Mutations

From this point forward, collection and understanding of *KIT* mutations in patients with GIST enrolled on clinical trials became a standard part of study design, and most *KIT*-directed clinical trials of novel agents modified eligibility requirements to ensure *KIT* mutation was present, excluding tumors without oncogenic *KIT* mutations and excluding the subset of GIST cases that are driven by non-*KIT* drivers. In addition, a phase II trial of ponatinib had a preplanned primary analysis population of GIST with primary *KIT* exon 11 mutation, the first trial which developed a study design powered on a specific mutation thought to be of unique sensitivity to the investigational agent.⁴⁵ As expected, patients with *KIT* exon 11 mutation demonstrated a numerically higher clinical benefit rate at 16 weeks (36% v 20% in patients without *KIT* exon 11 mutation).

This more selective approach has continued with compounds specifically developed to be highly selective and potent against specific mutations. Avapritinib, a highly selective inhibitor of *PDGFRA* mutation D842V, a previously undruggable primary mutation in GIST, received global regulatory approval from the expansion phase of a phase I trial of avapritinib in this unique molecular subset, with an overall response rate of 88%.⁹

By contrast, when avapritinib was studied in a randomized phase III trial compared with regorafenib in patients with GIST after failure of at least imatinib and sunitinib, there was no significant difference in PFS, likely because of a highly selective kinase inhibitor, avapritinib, being evaluated in a molecularly heterogeneous population.⁴⁶ Interestingly, patients on study with baseline circulating tumor DNA (ctDNA) positive for *KIT* exon 13/14 mutations treated with avapritinib did quite poorly when compared with regorafenib, again, likely because of the inactivity of avapritinib in this molecular context.⁴⁷

Additional trials have continued to shed light on the complexities and heterogeneity of *KIT* resistance mutations beyond imatinib. The INVICTUS trial compared ripretinib with placebo in metastatic GIST in the fourth line and beyond. Ripretinib led to a significantly longer mPFS and OS

compared with placebo. This benefit was across multiple *KIT* primary and secondary mutations.⁸

The INTRIGUE trial then evaluated the efficacy of ripretinib against an active control, sunitinib, in the second-line setting, after the failure of imatinib. Patients with advanced GIST with primary *KIT* exon 11 mutations, who were previously treated with imatinib, were randomly assigned to ripretinib versus sunitinib. The two arms demonstrated a similar median PFS of ripretinib versus sunitinib, 8.3 months versus 7.0 months.⁴⁸ However, a preplanned analysis demonstrated significant differences in outcomes on the basis of baseline ctDNA. Specifically, patients with ctDNA positive for *KIT* exon 11 + *KIT* exon 17/18 mutations had significantly longer median PFS with ripretinib (median, 14.2 v 1.5 months), while patients with baseline *KIT* exon 11 + exon 13/14 mutations had significantly longer median PFS when treated with sunitinib (median, 15.0 v 4.0 months). These results highlight the strong inhibitory effect of ripretinib on *KIT* exon 11 and exon 17/18, and by contrast, the strong inhibitory effect of sunitinib on *KIT* exon 11 and exon 13/14.⁴⁹ On the basis of these findings, a phase III INSIGHT trial to compare ripretinib versus sunitinib as a second-line therapy for advanced GIST with a specific *KIT* mutation (comutations of exon 11 and 17/18 and absence of exon 9/13/14 mutation) is ongoing (ClinicalTrials.gov identifier: [NCT05734105](#)).

Newer Approaches to Overcome TKI Resistance

Secondary *KIT* mutations in GIST tend to be heterogeneous, therefore, disease progression remains a challenge. Newer approaches aim to target the broad spectrum of primary (exon 11 and exon 9) and secondary *KIT* mutations (exon 13/14 and exon 17/18). This has been approached with the combination of sunitinib (exon 11/9 and 13/14) and the novel compound bezuglastinib (exon 17), which demonstrated promising results in a phase II trial⁵⁰ and is currently being evaluated in a phase III randomized trial as a second-line treatment after imatinib failure (ClinicalTrials.gov identifier: [NCT05208047](#)), and in a phase II trial as a third-line treatment after progression on imatinib and sunitinib (ClinicalTrials.gov identifier: [NCT06208748](#)). Similarly, newer agents, such as DCC-3009 (ClinicalTrials.gov identifier: [NCT06630234](#)), IDRX-42 (ClinicalTrials.gov identifier: [NCT05489237](#)), and NB003 (ClinicalTrials.gov identifier: [NCT04936178](#)), have demonstrated promising activity as single agents across a wide spectrum of primary and second *KIT* mutations. Beyond *KIT* inhibition, an antibody-drug conjugate that targets c-Kit combined with cytotoxic monomethyl auristatin E payload is being investigated in a phase I trial (ClinicalTrials.gov identifier: [NCT06805825](#)).

Despite improvements in the understanding of the emergence of secondary *KIT* mutations and novel therapies with broad activity against these mutations, metastatic GIST remains incurable. Recently, it was reported that resistant *KIT* mutations in the activation loop (exon13/14) and the ATP binding pocket (exon 17/18) may occur on the same allele

(ie, in *cis*), resulting in a highly resistant clone resistant to all currently available TKIs.⁵¹ The exact frequency of these mutations and their impact remain understudied and may inform future drug development in GIST.

In addition to targeting *KIT*, future and ongoing studies are exploring combinations of *KIT* inhibitors while exploiting non-*KIT* pathways (eg, a menin inhibitor, ziftomenib, ClinicalTrials.gov identifier: [NCT06655246](#)). It is likely that drug development in advanced *KIT*-mutant GIST will continue to see creative approaches such as these, particularly as TKIs become more selective and more effective at targeting the range of *KIT* primary and secondary mutations. Additional future approaches will also likely begin to explore these new TKIs earlier in lines of therapy with the aim to reduce the emergence of clinically significant *KIT* mutations to the currently available via use of more narrow spectrum agents.

There has been tremendous progress in management of metastatic *KIT*-mutant GIST; however, despite this progress, it remains a disease without a cure and more work to explore novel combinational approaches with or without TKIs, newer TKIs with broader mutation coverage and brand new modalities to target oncogenic proteins, must be done (Table 2).

EMERGING STRATEGIES FOR MANAGING NON-*KIT*/ *PDGFRA*-MUTANT GIST SUBTYPES

GIST are driven most often by oncogenic mutations in the *KIT* or *PDGFRA* genes. However, about 10%–15% of tumors do not possess genomic alterations in these genes.⁵² These non-*KIT*/*PDGFRA*-mutant GISTs represent a subset of tumors that often require distinct strategies for diagnosis and multidisciplinary management. This section will explore emerging treatment strategies and controversies for these subtypes, including GIST associated with (1) genomic or epigenomic alterations in *SDHx* subunits; (2) germline or somatic *NF1* mutations; (3) *BRAF* mutations or fusions; (4) *ETV6*-*NTRK6* fusions; and (5) other rarer molecular subsets.

Succinate Dehydrogenase-Deficient GIST

SDHx-related GISTs are defined by mutations in the succinate dehydrogenase (SDH) complex genes, which lead to a loss of SDH complex function in the mitochondria of tumor cells. These tumors lack SDHB expression by immunohistochemistry and are therefore considered SDH-deficient. They can be categorized into two main subgroups, namely those associated with germline *SDHx* mutations (ie, in descending order of GIST incidence: *SDHA* > *SDHB* > *SDHC* > *SDHD*) and those associated with sporadic SDH deficiency, commonly linked to *SDHC* promoter hypermethylation (ie, so-called SDH epimutants^{53,54}).

TKIs, such as sunitinib and regorafenib, are both FDA-approved for treating GIST and are frequently used for

TABLE 2. Summary of Currently Active Clinical Trials Targeting Advanced GIST

Trial Name	NCT Number	Phase	Population	Intervention	Key Points
INSIGHT	NCT05734105	III	With progression on imatinib and co-occurring <i>KIT</i> exon 11+17/18 mut and absence of <i>KIT</i> exon 9/13/14 mut	Ripretinib v sunitinib	Strict molecular selection of patients
Peak	NCT05208047	III	With progression/intolerance with imatinib and absence of <i>PDGFRA</i> mut	Bezuclastinib + sunitinib v sunitinib	Combination of two TKIs with distinct <i>KIT</i> mutation coverage
SARC044	NCT06208748	II	With progression on sunitinib and with progression/intolerance with imatinib and <i>KIT</i> exon 9/11 mut	Bezuclastinib + sunitinib	A subset of patients (N = 20) undergoes PET-CT at baseline and tumor biopsies at cycle 2 for correlative studies
DCC-3009-01-001	NCT06630234	I/II	With progression/intolerance with TKI and <i>KIT</i> or <i>PDGFRA</i> mut	DCC-3009	A newer TKI active against multiple resistance mutations
NB003-01	NCT04936178	I	<i>KIT</i> or <i>PDGFRA</i> mut	NB003	A newer TKI active against multiple resistance mutations
StrateGIST 1	NCT05489237	I	<i>KIT</i> or <i>PDGFRA</i> mut except for <i>PDGFRA</i> exon 18 mut	IDRX-42	A newer TKI active against multiple resistance mutations
KO-MEN-015	NCT06655246	I	With progression/intolerance with imatinib and <i>KIT</i> mut except for T670X	Ziftomenib + imatinib	A novel combination of TKI with non- <i>KIT</i> -directed therapy
NN3201-ST100	NCT06805825	I	With progression/intolerance with imatinib	NN3201	A novel c-Kit targeting antibody-drug conjugate

Abbreviations: CT, computed tomography; GIST, GI stromal tumor; mut, mutation; NCT, National Clinical Trial; *PDGFRA*, platelet-derived growth factor receptor alpha; PET, positron emission tomography; TKI, tyrosine kinase inhibitor.

managing patients with advanced or metastatic SDH-deficient GIST. However, their effectiveness in SDH-deficient GISTs is modest (Fig 1). It is postulated that these objective responses^{55,58} may be due to sunitinib's and regorafenib's ability to better target the VEGF/HIF1a pathway, which is stabilized in the setting of SDH-deficiency.⁷¹ But, in all patients with SDH-deficient GIST, the lack of a targetable oncogenic driver mutation (eg, *KIT* or *PDGFRA*) has limited the efficacy of these TKIs. This has spurred research in the field to discover better treatment strategies.

Recent preclinical studies suggested that SDH-deficient GISTs may exhibit upregulation of fibroblast growth factor ligands FGF3 and FGF4 with signaling through Fibroblast Growth Factor Receptor 1 (FGFR1).^{72,73} In light of these findings, the FGFR 1-4 inhibitor, rogaratinib, was studied in a phase II trial (ClinicalTrials.gov identifier: [NCT04595747](#)) with promising results. The preliminary results reported that partial responses (PRs) were observed in 42% (10/24) of patients with SDH-deficient GIST with a median PFS of >31 months (upper limit of confidence interval not yet reached) with nine patients who remain on treatment.⁶⁷ Unfortunately, Bayer, the manufacturer, has sunset the development of this drug. More recently, another drug with *KIT*, VEGF, and FGFR inhibition, olverembatinib has been investigated. In a trial in China (ClinicalTrials.gov identifier: [NCT03594422](#)), preliminary results reported 23% (6/26) of patients with PRs by RECIST.⁶⁶ In addition to targeting FGFR signaling, recent preclinical work has suggested DNA damage/repair as another target in these tumors. Given the

defect in mitochondrial function associated with SDH loss,⁷¹ the use of temozolomide, a DNA-damaging agent, was effective in vitro. A clinical trial (ClinicalTrials.gov identifier: [NCT03556384](#)) exploring this agent has been completed. The preliminary results demonstrated that 22% (5/23) of patients achieved PR by RECIST.⁶⁴ Additional reports have described single-case PRs (Fig 1).^{69,70} What remains to be determined is which patient or which *SDHx* genomic alteration may be best served by administering a given drug. Further research will be needed to determine the optimal patient selection or sequencing for each of these drugs.

In addition, the role of cytoreductive surgery in SDH-deficient GISTs remains another area of debate. Some surgeons advocate for resection only in the setting of symptom control or palliation,⁷⁴ while others have advocated for more aggressive surgical intervention to cytoreduce disease,^{75,76} especially when these tumors are responsive to systemic therapy. At present, the decision to pursue resection should be individualized, considering disease biology, indications for surgery, tumor burden, technical factors, the patient's overall health, and the risk-to-benefit ratio of an operation.

NF1-Associated GISTs

Neurofibromatosis type 1 (NF-1) is a genetic disorder caused by germline mutations in the *NF1* gene, which encodes neurofibromin, a negative regulator of the RAS pathway. In GISTs, *NF1* mutations are most often germline, but can also be somatic, leading to abnormal activation of the MAPK (ie,

	Drug	KIT	PDGFR	BCR-ABL	VEGFR	RET	FLT3	FGFR	BRAF	DNMT	EGFR	IGF-1R	MEK1/2	DNA Alkylation	SRC	DNA Topo1	PARP1/2	N	CR	PR	Best ORR
SOC Lines	Imatinib (1L)																	61	0	2	3%
	Sunitinib (2L)																	49	1	4	10%
	Regorafenib (3L)																	16	0	3	19%
	Ripretinib (4L)																	2	0	0	0%
	Guadecitabine																	7	0	0	0%
Prospective trials	Vandetanib																	9	0	0	0%
	Linsitinib																	15	0	0	0%
	Imatinib + Binimetinib																	5	0	1	20%
	Temozolomide ^a																	23	0	5	22%
	Olverembatinib																	26	0	6	23%
	DS-6157a																	3	0	1	33%
	Rogaratinib ^a																	24	0	10	42%
Series	Temozolomide																	5	0	2	40%
Report	Temozolomide + Olaparib																	1	0	1	100%

FIG 1. Best ORR in SDH-deficient GIST from different systemic treatments: imatinib,^{42,55} sunitinib,⁵⁵⁻⁵⁷ regorafenib,^{58,59} ripretinib,⁶⁰ guadecitabine,⁶¹ vandetanib,⁶² linsitinib,⁶³ temozolomide (prospective trial),⁶⁴ imatinib + binimetinib,⁶⁵ olverembatinib,⁶⁶ rogaratinib,⁶⁷ DS-6157a,⁶⁸ temozolomide (case series),⁶⁹ and temozolomide + olaparib.⁷⁰ ^aReported in abstract form only. 1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; CR, complete response; GIST, GI stromal tumor; ORR, objective response rate; PR, partial response; SDH, succinate dehydrogenase; SOC, standard of care.

RAS/RAF/MEK/ERK) pathway.⁷⁷ These patients may present with multifocal small bowel GIST when associated with NF-1 or as a solitary tumor at the duodenal-jejunal flexure (ie, ligament of Treitz) when caused by somatic mutations. In general, most NF1-associated GISTs are slow-growing with indolent biology,⁷⁸ but a subset may exhibit more aggressive features. However, we do not have an approach for distinguishing these subtypes. Finally, there is no established standard of care for advanced NF1-associated GIST. Although MEK inhibitors, such as selumetinib, have been approved for benign NF1-related tumors,^{79,80} there is currently insufficient evidence to recommend their routine use in the context of GIST or any other NF1-associated malignancy for that matter. Given the rarity of the disease, little is known about the role of cytoreductive surgery in patients with advanced NF-1-associated GIST. But, the general approach for deciding on surgical intervention is the same as that for SDH-deficient GIST. This includes palliating symptoms, while considering patient factors, anatomic factors, disease biology, and risk-to-benefit ratio (ie, morbidity) of resection.

BRAF-Mutant GIST

Mutations in the *BRAF* gene, particularly the V600E substitution most often associated with melanoma, are found in a small subset of GISTs. *BRAF* V600E-mutant GISTs may behave similarly to *KIT*-mutant tumors in terms of aggressiveness and metastasis, but they offer a unique treatment opportunity. Histology-agnostic clinical trials have demonstrated that combination therapy with dabrafenib (a *BRAF* inhibitor) and trametinib (a MEK inhibitor) can be highly effective in treating many *BRAF* V600E-mutant

tumors, including GIST.^{81,82} This combination has been shown to induce significant tumor regression and is now FDA-approved in a histology-agnostic fashion for patients possessing tumors with this mutation. Although the management of *BRAF* V600E-mutant GISTs is generally straightforward, the treatment of GISTs with other less common alterations, such as *BRAF* fusions^{83,84} or non-V600E mutations, remains more uncertain. These fusion cases must be treated on a case-by-case basis, with the potential use of targeted therapies under clinical trial protocols.

ETV6-NTRK3 Fusion GIST

GISTs harboring *ETV6-NTRK3* fusions are a rare (< 1%) but a notable subset of non-*KIT*/*PDGFR*A-mutant tumors.⁸⁵ These tumors are characterized by the fusion of the *ETV6* gene to the *NTRK3* receptor tyrosine kinase gene, leading to constitutive activation of the TRK signaling pathway. After the discovery of this fusion in GIST, some pathologists questioned whether these tumors were actually GIST. This debate is now settled, and there is clearly a subset of GISTs harboring *ETV6-NTRK3* fusions.⁸⁶⁻⁸⁸ Importantly, these GISTs are imatinib-resistant. Thus, the discovery of this fusion along with the development of three FDA-approved TRK inhibitors (ie, larotrectinib, entrectinib, and repotrectinib) has revolutionized the treatment of tumors with *NTRK* fusions. These drugs are highly effective in patients with *ETV6-NTRK3*-positive GISTs, leading to durable responses and excellent clinical outcomes.⁸⁹ *NTRK* inhibitors are currently the treatment of choice for patients with confirmed *ETV6-NTRK3* fusions independent of histology. Thus, molecular testing of GIST should include investigations for this fusion.

FGFR Fusion GIST

FGFR fusions are rare but can also drive GIST oncogenesis.⁸⁵ These tumors often show overexpression of FGFRs, leading to aberrant cell signaling and tumor growth. Although various FGFR inhibitors (eg, infigratinib and pemigatinib) are FDA-approved, there is currently no consensus on the best FGFR inhibitor for treating GISTs with FGFR fusions.

Unclassified GIST

Some GISTs lack identifiable driver alterations, some of which might be due to the limitation of the sequencing technology. Sanger sequencing generally requires a higher variant allele frequency to detect gene alterations, compared with next-generation sequencing, which can cause false-negative results. Nevertheless, even the most extensive molecular testing sometimes fails to identify driver alterations. Confirmed unclassified GISTs are rare and represent a significant challenge in terms of management.⁹⁰ In these patients, treatment decisions are often based on clinical factors such as tumor size, location, and metastasis rather

than molecular alterations. Given the lack of molecularly matched targeted therapies, treatment options are usually limited to traditional TKIs, with clinical trial enrollment being an important consideration for these patients when they fail standard-of-care options. With further investigations, we will likely continue to classify and subset tumors within this group.

Challenges in Managing Non-*KIT*/*PDGFRA*-Mutant GIST

One of the overarching challenges to all of these tumors is their variable clinical behavior, even within GISTs harboring the same gene alterations. For instance, although SDH-deficient GISTs are generally associated with more indolent clinical courses, recent evidence suggests that mutations in *SDHB* may correlate with a more aggressive biology.⁹¹ Similarly, most of *NF1*-associated GISTs have indolent biology but a subset can behave more aggressively. Further studies are warranted to define reliable biomarkers to stratify these subsets of patients with non-*KIT*/*PDGFRA*-mutant GIST.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Ducimetière F, Lurkin A, Ranchère-Vince D, et al: Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. *PLoS One* 6:e20294, 2011
2. Emile JF, Brahimi S, Coindre JM, et al: Frequencies of KIT and PDGFRA mutations in the MolecGIST prospective population-based study differ from those of advanced GISTs. *Med Oncol* 29: 1765-1772, 2012
3. Woodall CE, Brock GN, Fan J, et al: An evaluation of 2537 gastrointestinal stromal tumors for a proposed clinical staging system. *Arch Surg* 144:670-678, 2009
4. Joensuu H, Rutkowski P, Nishida T, et al: KIT and PDGFRA mutations and the risk of GI stromal tumor recurrence. *J Clin Oncol* 33:634-642, 2015
5. Demetri GD, von Mehren M, Blanke CD, et al: Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 347:472-480, 2002
6. Demetri GD, van Oosterom AT, Garrett CR, et al: Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: A randomised controlled trial. *Lancet* (London, England) 368:1329-1338, 2006
7. Demetri GD, Reichardt P, Kang YK, et al: Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* (London, England) 381:295-302, 2013

8. Blay JY, Serrano C, Heinrich MC, et al: Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 21:923-934, 2020
9. Heinrich MC, Jones RL, von Mehren M, et al: Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): A multicentre, open-label, phase 1 trial. *Lancet Oncol* 21:935-946, 2020
10. Anne Bergman Lisa Hang ME, Armstrong SA, Balach T, et al: NCCN guidelines version 2.2024 gastrointestinal stromal tumors. 2024
11. Casali PG, Blay JY, Abecassis N, et al: Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 33:20-33, 2022
12. Judson I, Jones RL, Wong NACS, et al: Gastrointestinal stromal tumour (GIST): British sarcoma group clinical practice guidelines. *Br J Cancer* 132:1-10, 2025
13. Hirota S, Tateishi U, Nakamoto Y, et al: English version of Japanese clinical practice guidelines 2022 for gastrointestinal stromal tumor (GIST) issued by the Japan Society of Clinical Oncology. *Int J Clin Oncol* 29:647-680, 2024
14. Heinrich MC, Corless CL, Demetri GD, et al: Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 21:4342-4349, 2003
15. Joensuu H, Wardelmann E, Eriksson M, et al: KIT and PDGFRA mutations and survival of gastrointestinal stromal tumor patients treated with adjuvant imatinib in a randomized trial. *Clin Cancer Res* 29:3313-3319, 2023
16. Wong NACS, Garcia-Petit C, Dangoor A, et al: A literature review and database of how the primary KIT/PDGFRA variant of a gastrointestinal stromal tumour predicts for sensitivity to imatinib. *Cancer Genet* 268:269-46-54, 2022
17. Cassier PA, Fumagalli E, Rutkowski P, et al: Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. *Clin Cancer Res* 18:4458-4464, 2012
18. Joensuu H, Vehtari A, Riihimäki J, et al: Risk of recurrence of gastrointestinal stromal tumour after surgery: An analysis of pooled population-based cohorts. *Lancet Oncol* 13:265-274, 2012
19. Zhang H, Liu Q: Prognostic indicators for gastrointestinal stromal tumors: A review. *Transl Oncol* 13:100812, 2020
20. Miettinen M, Lasota J: Gastrointestinal stromal tumors: Pathology and prognosis at different sites. *Semin Diagn Pathol* 23:70-83, 2006
21. Joensuu H: Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol* 39:1411-1419, 2008
22. Gold JS, Gönen M, Gutiérrez A, et al: Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: A retrospective analysis. *Lancet Oncol* 10:1045-1052, 2009
23. DeMatteo RP, Ballman KV, Antonescu CR, et al: Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: A randomised, double-blind, placebo-controlled trial. *Lancet* 373:1097-1104, 2009
24. Corless CL, Ballman KV, Antonescu CR, et al: Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: The ACOSOG Z9001 trial. *J Clin Oncol* 32:1563-1570, 2014
25. Casali PG, Le Cesne A, Velasco AP, et al: Final analysis of the randomized trial on imatinib as an adjuvant in localized gastrointestinal stromal tumors (GIST) from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), the Australasian Gastro-Intestinal Trials Group (AGITG), UNICANCER, French Sarcoma Group (FSG), Italian Sarcoma Group (ISG), and Spanish Group for Research on Sarcomas (GEIS). *Ann Oncol* 32:533-541, 2021
26. Joensuu H, Eriksson M, Sundby Hall K, et al: Survival outcomes associated with 3 years vs 1 year of adjuvant imatinib for patients with high-risk gastrointestinal stromal tumors: An analysis of a randomized clinical trial after 10-year follow-up. *JAMA Oncol* 6:1241-1246, 2020
27. Blay J-Y, Schiffer C, Bouché O, et al: A randomized study of 6 versus 3 years of adjuvant imatinib in patients with localized GIST at high risk of relapse. *Ann Oncol* 35:1157-1168, 2024
28. Nishida T, Sato S, Ozaka M, et al: Long-term adjuvant therapy for high-risk gastrointestinal stromal tumors in the real world. *Gastric Cancer* 25:956-965, 2022
29. Bertsimas D, Margonis GA, Sujichantararat S, et al: Interpretative artificial intelligence to optimise use of imatinib after resection in patients with localised gastrointestinal stromal tumours: An observational cohort study. *Lancet Oncol* 25:1025-1037, 2024
30. Joensuu H, Eriksson M, Sundby Hall K, et al: One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: A randomized trial. *JAMA* 307:1265-1272, 2012
31. Debiec-Rychter M, Sciort R, Le Cesne A, et al: KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer* 42:1093-1103, 2006
32. Vincenzi B, Napolitano A, Fiocco M, et al: Adjuvant imatinib in patients with GIST harboring exon 9 KIT mutations: Results from a multi-institutional European retrospective study. *Clin Cancer Res* 28:1672-1679, 2022
33. Hohenberger P, Ronellenfisch U, Oladeji O, et al: Pattern of recurrence in patients with ruptured primary gastrointestinal stromal tumour. *Br J Surg* 97:1854-1859, 2010
34. Holmehakk T, Hompland I, Bjerkhagen B, et al: Recurrence-free survival after resection of gastric gastrointestinal stromal tumors classified according to a strict definition of tumor rupture: A population-based study. *Ann Surg Oncol* 25:1133-1139, 2018
35. Nishida T, Holmehakk T, Raut CP, et al: Defining tumor rupture in gastrointestinal stromal tumor. *Ann Surg Oncol* 26:1669-1675, 2019
36. Joensuu H, Reichardt A, Eriksson M, et al: Survival of patients with ruptured gastrointestinal stromal tumour treated with adjuvant imatinib in a randomised trial. *Br J Cancer* 131:299-304, 2024
37. Blay JY, Rutkowski P: Adherence to imatinib therapy in patients with gastrointestinal stromal tumors. *Cancer Treat Rev* 40:242-247, 2014
38. Rutkowski P, Bylina E, Lugowska I, et al: Treatment outcomes in older patients with advanced gastrointestinal stromal tumor (GIST). *J Geriatr Oncol* 9:520-525, 2018
39. Wu X, Ge Y, He X, et al: Changes in imatinib plasma trough level during long-term treatment in patients with intermediate- or high-risk gastrointestinal stromal tumors: Relationship between covariates and imatinib plasma trough level. *Front Surg* 10:1115141, 2023
40. Blanke CD, Rankin C, Demetri GD, et al: Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol* 26:626-632, 2008
41. Verweij J, Casali PG, Zalcberg J, et al: Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: Randomised trial. *Lancet* 364:1127-1134, 2004
42. Heinrich MC, Rankin C, Blanke CD, et al: Correlation of long-term results of imatinib in advanced gastrointestinal stromal tumors with next-generation sequencing results: Analysis of phase 3 SWOG intergroup trial S0033. *JAMA Oncol* 3:944-952, 2017
43. Heinrich MC, Maki RG, Corless CL, et al: Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol* 26:5352-5359, 2008
44. Jeffers M, Kappeler C, Kuss I, et al: Broad spectrum of regorafenib activity on mutant KIT and absence of clonal selection in gastrointestinal stromal tumor (GIST): Correlative analysis from the GRID trial. *Gastric Cancer* 25:598-608, 2022
45. George S, von Mehren M, Fletcher JA, et al: Phase II study of ponatinib in advanced gastrointestinal stromal tumors: Efficacy, safety, and impact of liquid biopsy and other biomarkers. *Clin Cancer Res* 28:1268-1276, 2022
46. Kang YK, George S, Jones RL, et al: Avapritinib versus regorafenib in locally advanced unresectable or metastatic GI stromal tumor: A randomized, open-label phase III study. *J Clin Oncol* 39:3128-3139, 2021
47. Serrano C, Bauer S, Gómez-Peregrina D, et al: Circulating tumor DNA analysis of the phase III VOYAGER trial: KIT mutational landscape and outcomes in patients with advanced gastrointestinal stromal tumor treated with avapritinib or regorafenib. *Ann Oncol* 34:615-625, 2023
48. Bauer S, Jones RL, Blay JY, et al: Ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumor after treatment with imatinib (INTRIGUE): A randomized, open-label, phase III trial. *J Clin Oncol* 40:3918-3928, 2022
49. Heinrich MC, Jones RL, George S, et al: Ripretinib versus sunitinib in gastrointestinal stromal tumor: ctDNA biomarker analysis of the phase 3 INTRIGUE trial. *Nat Med* 30:498-506, 2024
50. Wagner AJ, Severson PL, Shields AF, et al: Association of combination of conformation-specific KIT inhibitors with clinical benefit in patients with refractory gastrointestinal stromal tumors: A phase 1b/2a nonrandomized clinical trial. *JAMA Oncol* 7:1343-1350, 2021
51. Mühlenberg T, Falkenhörst J, Schulz T, et al: KIT ATP-binding pocket/activation loop mutations in GI stromal tumor: Emerging mechanisms of kinase inhibitor escape. *J Clin Oncol* 42:1439-1449, 2024
52. Xie F, Luo S, Liu D, et al: Genomic and transcriptomic landscape of human gastrointestinal stromal tumors. *Nat Commun* 15:9495, 2024
53. Neppala P, Banerjee S, Fanta PT, et al: Current management of succinate dehydrogenase-deficient gastrointestinal stromal tumors. *Cancer Metastasis Rev* 38:525-535, 2019
54. Killian JK, Miettinen M, Walker RL, et al: Recurrent epimutation of SDHC in gastrointestinal stromal tumors. *Sci Transl Med* 6:268ra177, 2014
55. Boikos SA, Pappo AS, Killian JK, et al: Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors: A report from the National Institutes of health gastrointestinal stromal tumor clinic. *JAMA Oncol* 2:922-928, 2016
56. Janeway KA, Albritton KH, Van Den Abbeele AD, et al: Sunitinib treatment in pediatric patients with advanced GIST following failure of imatinib. *Pediatr Blood Cancer* 52:767-771, 2009
57. Liu W, Zeng X, Wu X, et al: Clinicopathologic study of succinate-dehydrogenase-deficient gastrointestinal stromal tumors: A single-institutional experience in China. *Medicine (Baltimore)* 96:e7668, 2017
58. Ben-Ami E, Barysauks CM, von Mehren M, et al: Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. *Ann Oncol* 27:1794-1799, 2016

59. Martin-Broto J, Valverde C, Hindi N, et al: REGISTRI: Regorafenib in first-line of KIT/PDGFRA wild type metastatic GIST: A collaborative Spanish (GEIS), Italian (ISG) and French Sarcoma Group (FSG) phase II trial. *Mol Cancer* 22:127, 2023
60. Bauer S, Heinrich MC, George S, et al: Clinical activity of ripretinib in patients with advanced gastrointestinal stromal tumor harboring heterogeneous KIT/PDGFRA mutations in the phase III INVICTUS study. *Clin Cancer Res* 27:6333-6342, 2021
61. Ligon JA, Sundby RT, Wedekind MF, et al: A phase II trial of guadecitabine in children and adults with SDH-deficient GIST, pheochromocytoma, paraganglioma, and HLRCC-associated renal cell carcinoma. *Clin Cancer Res* 29:341-348, 2023
62. Glod J, Arnaldez FI, Wiener L, et al: A phase II trial of vandetanib in children and adults with succinate dehydrogenase-deficient gastrointestinal stromal tumor. *Clin Cancer Res* 25:6302-6308, 2019
63. Von Mehren M, George S, Heinrich MC, et al: Linsitinib (OSI-906) for the treatment of adult and pediatric wild-type gastrointestinal stromal tumors, a SARC phase II study. *Clin Cancer Res* 26:1837-1845, 2020
64. Burgoyne AM, Heinrich MC, Von Mehren M, et al: An Open-Label, Phase II Efficacy Study of Temozolomide in Advanced Succinate Dehydrogenase-Mutant/Deficient Gastrointestinal Stromal Tumor. *Dublin, CTOS*, 2023
65. Chi P, Qin LX, Camacho N, et al: Phase Ib trial of the combination of imatinib and binimetinib in patients with advanced gastrointestinal stromal tumors. *Clin Cancer Res* 28:1507-1517, 2022
66. Qiu H, Zhou Z, Zhou Y, et al: Updated efficacy results of olverembatinib (HQP1351) in patients with tyrosine kinase inhibitor (TKI)-resistant succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors (GIST) and paraganglioma. *J Clin Oncol* 42:11502, 2024 (suppl 16; abstr 11502)
67. Merriam P, Mazzola E, Chi P, et al: A Phase 2 Study of Rogaratinib (Bay 1163877) in Soft Tissue Sarcomas: Initial Results in Cohort of Patients With Succinate Dehydrogenase (SDH)-Deficient Gastrointestinal Stromal Tumor (GIST). *Dublin, CTOS*, 2023
68. George S, Heinrich MC, Somaiah N, et al: A phase I, multicenter, open-label, first-in-human study of DS-6157a in patients with advanced gastrointestinal stromal tumor. *Clin Cancer Res* 29:3659-3667, 2023
69. Yebra M, Bhargava S, Kumar A, et al: Establishment of patient-derived succinate dehydrogenase-deficient gastrointestinal stromal tumor models for predicting therapeutic response. *Clin Cancer Res* 28:187-200, 2022
70. Singh C, Bindra RS, Glazer PM, et al: Metastatic and multiply relapsed SDH-deficient GIST and paraganglioma displays clinical response to combined poly ADP-ribose polymerase inhibition and temozolomide. *Pediatr Blood Cancer* 70:e30020, 2023
71. Selak MA, Armour SM, MacKenzie ED, et al: Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF- α prolyl hydroxylase. *Cancer Cell* 7:77-85, 2005
72. Flavahan WA, Drier Y, Johnstone SE, et al: Altered chromosomal topology drives oncogenic programs in SDH-deficient GISTs. *Nature* 575:229-233, 2019
73. Astolfi A, Pantaleo MA, Indio V, et al: The emerging role of the FGF/FGFR pathway in gastrointestinal stromal tumor. *Int J Mol Sci* 21:3313, 2020
74. Weldon CB, Madenci AL, Boikos SA, et al: Surgical management of wild-type gastrointestinal stromal tumors: A report from the National Institutes of health pediatric and wildtype GIST clinic. *J Clin Oncol* 35:523-528, 2017
75. Fero KE, Coe TM, Fanta PT, et al: Surgical management of adolescents and young adults with gastrointestinal stromal tumors: A US population-based analysis. *JAMA Surg* 152:443-451, 2017
76. Chen KY, Antkowiak M, Mallory R, et al: Complete Peritoneal Cyto-reductive Surgery in Highly Selected Patients with Aggressive Metastatic SDH-Deficient Gist Can Prolong Event-Free Survival. *Dublin, CTOS*, 2024
77. Burgoyne AM, De Siena M, Alkhuziem M, et al: Duodenal-jejunal flexure GI stromal tumor frequently heralds somatic NF1 and notch pathway mutations. *JCO Precis Oncol* 10.1200/PO.17.00014
78. Nishida T, Naito Y, Takahashi T, et al: Molecular and clinicopathological features of KIT/PDGFRA wild-type gastrointestinal stromal tumors. *Cancer Sci* 115:894-904, 2024
79. Wisinski KB, Flamm Y, Wilson MA, et al: Trametinib in patients with NF1-GNAQ-or GNA11-mutant tumors: Results from the NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocols S1 and S2. *JCO Precis Oncol* 10.1200/PO.22.00421
80. Fukuda M, Mukohara T, Kuwata T, et al: Efficacy of trametinib in neurofibromatosis type 1-associated gastrointestinal stromal tumors: A case report. *JCO Precis Oncol* 10.1200/PO.23.00649
81. Subbiah V, Kreitman RJ, Wainberg ZA, et al: Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: The phase 2 ROAR trial. *Nat Med* 29:1103-1112, 2023
82. Gowda S, Sandow L, Heinrich MC: Treatment of BRAF V600E mutant gastrointestinal stromal tumor with dabrafenib: A case report. *J Gastrointest Oncol* 15:788-793, 2024
83. Charo LM, Burgoyne AM, Fanta PT, et al: A novel PRKAR1B-BRAF fusion in gastrointestinal stromal tumor guides adjuvant treatment decision-making during pregnancy. *J Natl Compr Canc Netw* 16:238-242, 2018
84. Torrence D, Xie Z, Zhang L, et al: Gastrointestinal stromal tumors with BRAF gene fusions. A report of two cases showing low or absent KIT expression resulting in diagnostic pitfalls. *Genes Chromosomes Cancer* 60:789-795, 2021
85. Denu RA, Joseph CP, Urquiola ES, et al: Utility of clinical next generation sequencing tests in KIT/PDGFRA/SDH wild-type gastrointestinal stromal tumors. *Cancers (Basel)* 16:1707, 2024
86. Ranjbarian T, Antkowiak M, Mallory RJ, et al: A systematic review with a demonstrative case of KIT and DOG-1 expressing gastrointestinal stromal tumors harboring ETV6-NTRK3 fusions. *Clin Cancer Res* 10.1158/1078-0432.CCR-24-3203 [epub ahead of print on February 24, 2025]
87. Shi E, Chmielecki J, Tang CM, et al: FGFR1 and NTRK3 actionable alterations in "wild-type" gastrointestinal stromal tumors. *J Transl Med* 14:339, 2016
88. Brenca M, Rossi S, Polano M, et al: Transcriptome sequencing identifies ETV6-NTRK3 as a gene fusion involved in GIST. *J Pathol* 238:543-549, 2016
89. Drilon A, Laetsch TW, Kummar S, et al: Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 378:731-739, 2018
90. Alkhuziem M, Burgoyne AM, Fanta PT, et al: The call of "the wild"-type GIST: It's time for domestication. *J Natl Compr Canc Netw* 15:551-554, 2017
91. Dermawan JK, Kelly C, Gao Z, et al: Novel genomic risk stratification model for primary gastrointestinal stromal tumors (GIST) in the adjuvant therapy era. *Clin Cancer Res* 29:3974-3985, 2023

Connecting the Dots: Practical Strategies for Academic and Community Oncology Synergy to Advance Multidisciplinary Management in Immunotherapy Toxicity Care

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OVERVIEW

Immunotherapy has significantly affected cancer treatment and survival rates, accompanied by an increase in immune-related adverse events (irAEs) requiring new management strategies. irAEs can affect various organ systems and have varying severity levels, with higher rates observed when combining immune checkpoint inhibitors. National organizations such as ASCO, the National Comprehensive Cancer Network, the Society for Immunotherapy of Cancer, and the European Society for Medical Oncology have created guidelines for managing irAEs. This chapter expands on these guidelines by discussing practical strategies to improve the multidisciplinary management in irAE care, focusing on the who, what, and how to bridge gaps in care and enhance collaboration between academic and community oncology practices. Effective irAE management involves early recognition and guideline-adherent approaches using a multidisciplinary team, including oncologists, other subspecialists, primary care clinicians, and all care team members. Institutions are developing methods to integrate irAE care into clinical workflows, such as incorporating urgent care clinics and e-consults for efficient irAE management and developing hub-and-spoke models to extend specialized care from academic centers to community hospitals for equitable care delivery. Additionally, effective patient education is critical for improving irAE recognition and health literacy. The new ASCO Community of Practice called the Alliance for Support and Prevention of Immune-Related Adverse Events consortium and patient advocacy group Standing Together to Optimize Research, Interventions, and Education in irAEs initiatives aim to advance irAE clinical care, research, and education through global collaboration, standardized data collection, and improved outreach to patients and caregivers.

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INTRODUCTION

Expanded immunotherapy use over the past decade has improved patient outcomes in various cancer subtypes.¹⁻⁴ This growth has prompted the oncology community to develop strategies to address treatment-related toxicities.⁵ With increased US Food and Drug Administration (FDA) approvals for immunotherapy, the proportion of people living with cancer who are eligible for FDA-approved immune checkpoint inhibitor (ICI) therapy (Table 1) has significantly increased from 1.5% in 2011 to 56.5% in 2023.⁶ By activating the immune system to fight cancer, a systemic inflammatory response is generated that can broadly affect any organ system, commonly presenting as endocrinopathies, skin reactions, musculoskeletal complications, pneumonitis, and gastroenterocolitis.^{7,8} Any grade immune-related adverse events (irAEs) affect 74%-90% of patients receiving ICI.^{9,10} Although most cases are self-limited, some patients experience severe (14%-55%) or even fatal (0.6%-1.3%) toxicities.^{11,12}

Hospital systems are developing specialized multidisciplinary teams to advance care and to address this growing patient population experiencing acute and chronic irAEs. These models streamline care delivery, guide therapeutic management, and foster interdepartmental clinical and research collaborations.¹³⁻¹⁶ Furthermore, to enhance access for patients affected by irAEs, specialized multidisciplinary teams at academic medical centers have created collaborative networks connecting community practices to expert-level care using a hub-and-spoke model. This article explores best practices for developing multidisciplinary immunotherapy toxicity services across various care settings.

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IDENTIFYING irAEs

Although immunotherapy has revolutionized cancer treatment, it can lead to significant irAEs, which can vary widely

PRACTICAL APPLICATIONS

- Effective immune-related adverse event (irAE) management involves early recognition and guideline-adherent approaches using a multidisciplinary team, including oncologists, subspecialists, primary care clinicians, and all healthcare team members. Institutions are developing methods to integrate irAE recognition and management into clinical workflows, such as incorporating urgent care clinics and e-consults for efficient irAE management.
- Specialized multidisciplinary teams at academic medical centers have created collaborative networks connecting community practices, who have the potential to identify and manage irAEs earlier than academic medical centers. Academic medical centers can also provide expert-level care using a hub-and-spoke model to extend specialized care from academic centers to community hospitals for equitable care delivery.
- Effective patient education is critical for improving irAE recognition and patient and caregiver health literacy. Initiatives like the ASPIRE consortium and STORIES aim to advance irAE clinical care, research, and education through global collaboration, standardized data collection, and improved outreach to patients and caregivers.
- Multidisciplinary tumor boards and case conferences can enhance engagement with subspecialists in complex management of irAE. Structured training programs should also be developed to integrate trainees into all aspects of irAE management, including patient care and research activities.
- Institutions can develop user-friendly standardized protocols and algorithms, resource libraries, and tailored guidelines per organ to streamline clinical decision-making.

depending on cancer type, patient characteristics, the specific ICI used, and treatment regimen. As this chapter provides only a brief overview of irAEs, clinicians are encouraged to consult the medical literature on specific cancer-directed therapeutic regimens to better anticipate the presentation and course of irAEs in diverse clinical contexts. Patients are at risk of irAEs from the first dose of immunotherapy and remain at risk for months to years after stopping therapy (range 6 to >11 months).^{17,18} The unique spectrum of irAEs can affect nearly any organ system, ranging in severity from mild (grade 1) to life-threatening (grade 3–4) complications. Toxicity rates are higher with combination immunotherapy than monotherapy with any agent.¹⁹ Cytotoxic T-lymphocyte-associated protein 4 (CTLA-

4) inhibitors often lead to gastroenterocolitis and dermatitis (Fig 1),²⁰ and PD-1/PD-L1 inhibitors commonly cause dermatitis, thyroid dysfunction, and pneumonitis.²¹ Colitis is the leading cause of death from irAEs after CTLA-4 inhibition, and pneumonitis is most common with PD-1 or PD-L1 inhibition (Fig 1).¹² irAE grading and general management are listed in Table 2. irAEs persisting beyond 12 weeks after discontinuation are defined as chronic; they are most commonly hypothyroidism, arthritis, dermatitis, and adrenal insufficiency. The mortality rate of irAEs ranges from 0.3% to 1.3%, with the highest rates observed in myocarditis, pneumonitis, and neurologic toxicities.¹² To date, there is no clear evidence for predicting which individuals will have a tendency toward irAEs, although some experts have postulated that a predisposition to autoimmunity or triggers from the microbiome may be contributing.^{22,23} Although irAEs can adversely affect quality of life, research shows that irAEs are associated with better clinical outcomes, such as higher response rates and survival.^{8,24–29}

The key to rapid identification is for clinicians to consistently and promptly consider irAEs as a potential cause for any complications in patients receiving ICI therapy. Our practical experience has shown that time and resource constraints, missed communication opportunities, and knowledge gaps about irAE and guideline-based management are the primary barriers to timely intervention—examples include hospital subspecialists abruptly discontinuing steroids prescribed for an irAE without consulting the treating oncologist, or oncologists missing the signs of an irAE during a patient's evaluation. These scenarios illustrate common gaps resulting from insufficient clinician awareness of irAEs, as well as time constraints in busy, understaffed clinical environments. Therefore, it is essential to develop low-cost and practical solutions that can be applied across both academic and community settings. Examples of ongoing efforts to automate the diagnosis of irAEs include the Scripps Clinic Medical Group implementing best practice advisory prompts to remind clinicians to consider irAE on the differential diagnosis and direct them to irAE management guidelines and an order set. Similarly, the University of Massachusetts medical group is developing separate inpatient and outpatient order sets to empower nononcology teams to initiate timely evaluation of irAEs. The data for these initiatives are currently being collected for final analysis and dissemination. However, preliminary analysis reveals that electronic alerts alone are insufficient, underscoring the need for direct clinician education and improved interprofessional communication. The use of artificial intelligence, such as that used at the Mayo Clinic, is an emerging tool that can help alleviate administrative burdens and address time constraints in the clinic, allowing for a focus on irAE management, which is time-intensive compared with standard oncologic care.

MOVING TOWARD MULTIDISCIPLINARY irAE MANAGEMENT

Delayed recognition and treatment of irAEs can be life-threatening or even fatal.¹² With the rapid rise in ICI

TABLE 1. Currently Available Immune Checkpoint Inhibitors

PD-1 Inhibitors	PD-L1 Inhibitors	CTLA-4 Inhibitors	Anti-LAG-3 and PD-1
Nivolumab	Atezolizumab	Ipilimumab	Relatimab + nivolumab
Pembrolizumab	Avelumab	Tremelimumab	
Cemiplimab	Durvalumab		
Dostarlimab			
Retifanlimab			
Toripalimab			
Tislelizumab			

Abbreviations: CTLA-4, cytotoxic T-lymphocyte–associated protein 4; LAG-3, lymphocyte-activation gene 3.

indications and utilization, irAEs are increasingly more widespread. It is unclear how well oncology and nononcology clinicians are equipped to recognize and manage irAEs in both inpatient and outpatient settings.³⁰ Despite the growing use of ICIs, retrospective data indicate that approximately half of the irAEs are not managed per established clinical guidelines, highlighting a gap between recommended practices and clinical implementation.^{31,32} However, retrospective studies are limited by inconsistent documentation and partial data capture, which make it challenging to identify the reasons for this discrepancy.³¹ Possible reasons that irAEs are not consistently managed according to guidelines include atypical or variable irAE presentations, knowledge gaps, fragmented care, hesitation to use corticosteroids, limited access to specialists, or systemic barriers in busy and underresourced settings. Resource constraints further complicate irAE management, particularly in community settings where it may be challenging to hire clinicians because of regional market competition. Financial sustainability is also a concern, especially in relative value units (RVU) based clinics where managing irAEs demands longer patient visits, potentially conflicting with productivity-driven compensation models.

There is also wide variation in settings where emergent or urgent oncology care is delivered: emergency departments, urgent care centers, primary care offices, and specialist clinics. Clinicians in these settings commonly encounter irAEs, sometimes even before the oncology team is aware of them, but they may have a limited understanding of irAEs and their unique clinical management. The presenting symptoms and signs of several life-threatening irAEs, such as adrenal insufficiency or myocarditis, often mimic other conditions such as sepsis and congestive heart failure. The workup of irAEs in a community setting is usually managed by emergency department, hospital medicine, or intensive care unit teams that may not be familiar with ICI therapy. Furthermore, knowledge gaps among health care providers may add to the delay in workup for a timely diagnosis. Although one review found only 5% of oncology-related admissions were for confirmed irAEs, most (65%) were for high-grade or uncommon events.³³ Therefore, a critical gap exists in the education and multidisciplinary management of immunotherapy toxicity for all health care team members. Here, we describe a practical approach toward the who, what,

and how of building a multidisciplinary care model on the basis of multiple existing institutional models to expeditiously identify and effectively manage irAEs.

WHO: Identifying Key Team Members

The inspiration to develop multidisciplinary teams specializing in immunotherapy toxicity draws from the challenge of rapidly engaging medical subspecialty experts to establish a diagnosis and initiate appropriate treatment.³⁴ Core teams are composed of oncologists and subspecialists with expertise in irAEs, spanning key disciplines such as cardiology, gastroenterology, rheumatology, dermatology, neurology, pulmonology, endocrinology, and nephrology. A designated subspecialty stakeholder or lead often leads the team, developing protocols and orchestrating a centralized communication system to coordinate clinical efforts. Effective implementation relies on a diverse group of clinicians in various clinical roles, including registered nurses, advanced practice providers (APPs), and pharmacists.

Furthermore, clinical and translational research is critical in advancing the field of irAEs. The collaboration between clinicians and researchers is crucial to advancing our understanding of the biological mechanisms underlying irAEs, establishing biomarkers that identify at-risk patients, and informing next-generation treatment approaches.³⁵ Integrating translational research into clinical workflows requires a structured approach, including standardized sample

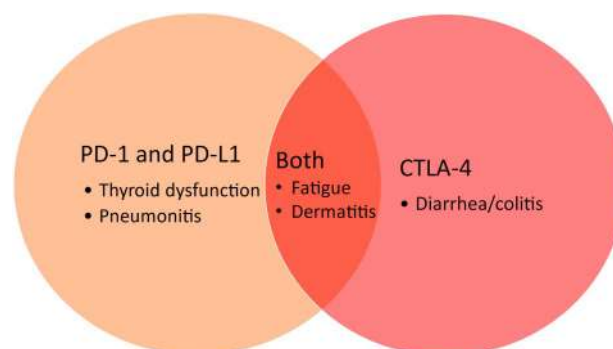


FIG 1. Side effects of PD-1/PD-L1 and CTLA-4 inhibitors. CTLA-4, cytotoxic T-lymphocyte–associated protein 4.

TABLE 2. irAE Grading and General Management

irAE Grade	Presentation	Management
Grade 1	Mild symptoms	Continue immunotherapy unless cardiac, neurologic, hematologic Supportive measures
Grade 2	Moderate symptoms	Hold immunotherapy until grade 1 or less Supportive measures Consider prednisone 0.5 mg/kg/day if symptoms > 1 week
Grade 3-4	Severe symptoms	Hold immunotherapy until grade 1 or less Supportive measures Prednisone 1-2 mg/kg

Abbreviations: G, grade; irAE, immune-related adverse event.

collection from eligible patients at relevant time points to facilitate meaningful investigation.³⁶ Additionally, national biorepositories are under development through multisite collaborations to address future research questions.³⁷

Finally, to prepare the next generation to recognize and manage irAEs, key team members should develop structured training programs to integrate trainees into all aspects of irAE management, including patient care and research activities. For example, at Massachusetts General Hospital, postdoctoral fellows serve as liaisons between clinical and translational research efforts on the severe immunotherapy complications team to gain critical insights and experience to champion immunotherapy toxicity services at other institutions.³⁶

For effective multidisciplinary irAE management, a clear commitment to interdisciplinary collaboration is essential. An example of how stakeholders collaborate to advance patient care is through scheduled multidisciplinary tumor boards or case conferences. These sessions allow for complex decision making, strengthen professional connections, and foster a critical sense of community across clinical and research silos. For instance, at the Cleveland Clinic, physicians who participated in an immunotherapy toxicity tumor board reported enhanced engagement with subspecialists in the care of patients with complex cases.³⁸ Similarly, a group in France demonstrated that implementing multidisciplinary care meetings improved clinical decision making in complex patients and fostered interdepartmental collaborations.³⁹ However, we recognize this may not be feasible—integrating irAE management into existing tumor board meetings can be challenging because of tight schedules and increasing specialist compartmentalization, which limits effective multidisciplinary dialogue. When possible to schedule, these meetings inform clinical care, identify knowledge gaps, and inspire new research questions, which push the field forward.

WHAT: Communication and Protocols

Once members of the immunotherapy toxicity teams are established, they can be integrated into clinical workflows.

Institutions worldwide are adopting innovative approaches to meet the diverse needs of patients across various settings. At the onset of symptoms, patients may first contact outpatient oncologists or primary care clinicians.⁴⁰ To reduce emergency department visits, some tertiary care centers have established oncology urgent care clinics.^{41,42} A single-institution study at the Sidney Kimmel Cancer Center demonstrated that most patients with irAE could be effectively managed in this setting, thereby avoiding the need for inpatient admission.⁴³ Another pilot program at the Dana-Farber Cancer Institute used a similar approach, where oncology APPs in the ambulatory setting reviewed and managed patients with suspected irAEs—this reduced admission rates and hospital length of stay.⁴⁴

The next step is often a timely referral to outpatient subspecialists with expertise in the affected organ system. To mitigate long wait times, referral pathways with virtual or e-consults enable subspecialists to review patients via electronic health records and communicate recommendations with the primary team. For example, the Duke Cancer Institute used an endocrinology e-consult platform, which reduced wait times for subspecialty appointments and decreased hospitalization rates from endocrine irAEs from 11% to 2%.⁴⁵ Another unique challenge with irAEs is the potential need to engage multiple subspecialists promptly if multiple organ systems are affected. A working group at Stanford is addressing this issue by establishing a subspecialty clinic that combines rheumatology and nephrology in the care of patients with irAEs.⁴⁶

If patients present to the hospital, triage protocols help to identify irAE diagnoses and direct patients to specialty toxicity services. For example, at the Dana-Farber Cancer Institute and Brigham and Women's Hospital, patients hospitalized with a cancer diagnosis who receive ICIs are reviewed by APPs, who then refer potential patients with irAE to an immunotherapy-toxicity service supported by medical oncologists and subspecialists.⁴⁷ In inpatient toxicity services, oncologists with expertise in irAEs serve as consultants to the primary team and have streamlined communication with subspecialist team members. Massachusetts General Hospital pioneered this model by developing the Severe Immunotherapy Complications service, which comprises more than 60 team members and is staffed 24/7 by medical oncologists. This service expedited the diagnosis and management of irAEs and reduced inpatient readmission rates.³⁶ Similarly, Johns Hopkins University uses an inpatient consult service activated by an electronic referral system, which improved the management of complex patients and expedited the follow-up with subspecialty clinicians.^{13,14}

Prompt management is initiated once patients are directed to the appropriate team and irAEs are diagnosed and graded. To streamline the delivery of evidence-based care, care teams follow the recommendations outlined by professional society guidelines, including ASCO, the National Comprehensive

TABLE 3. Common irAEs^a

irAE	Presentation	Median Time From Treatment Initiation	Workup	Initial Management	Refractory Disease Management
Colitis/diarrhea	Watery diarrhea, cramping, urgency	6-7 weeks	Clostridium difficile, stool pathogen studies, fecal calprotectin	Systemic steroids, loperamide	Vedolizumab
Dermatitis	Maculopapular rash and pruritus	4 weeks	Consider punch biopsy	Systemic steroids, topical emollients, topical corticosteroids, oral antihistamines	Cyclosporine or TNF-alpha inhibitors
Hepatitis	Elevated AST and ALT	3-12 weeks	Liver function tests, liver biopsy if > 5× upper limit of normal	Systemic steroids	First line: mycophenolate mofetil Second line: tacrolimus Third line: tofacitinib
Pneumonitis	Cough, shortness of breath, hypoxia, dyspnea, fever	34 weeks	Chest imaging, oxygen saturation, ± bronchoscopy	Systemic steroids	IVIg, infliximab, mycophenolate mofetil, cyclophosphamide, azathioprine, and tocilizumab
Endocrine	Thyroid (fatigue)	14.5 weeks	TSH, ± free T3, ± free T4	Levothyroxine	
	Adrenal (fatigue, hypotension)		8:00 AM ACTH, 6-8:00 AM cortisol	Hydrocortisone 10 mg every morning, 5 mg every evening	Hydrocortisone 50 mg once every 6 hours
	Hypophysitis (fatigue, headache, vision changes)		Renin, aldosterone, LH, FSH, testosterone (males), estrogen (females), ± MRI brain	Hydrocortisone 20 mg every morning, 10 mg every evening	
	Diabetes (polyuria, polydipsia)		Glucose each visit and at least 6 months after completion of therapy, urine/serum ketones, anion gap, anti-GAD or anti-islet cell antibodies, C-peptide level	Insulin	

Abbreviations: ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GAD, glutamic acid decarboxylase; irAE, immune-related adverse event; IVIg, intravenous immunoglobulin; LH, luteinizing hormone; MRI, magnetic resonance imaging; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone.

^aThis table provides a broad overview of management for all irAE grades. The authors recommend referring to society guidelines for in-depth management recommendations based on specific irAE grading.

TABLE 4. Rare but Serious irAEs^a

irAE	Presentation	Median Time From Treatment Initiation	Workup	Initial Management	Refractory Disease Management
Cardiac	Myocarditis, pericarditis, arrhythmias, cardiomyopathy, acute heart failure	6 weeks	ECG, troponin, CK, BNP, ± TTE	Systemic steroids	Mycophenolate, infliximab, or antithymocyte globulin
Musculoskeletal	Muscle or joint pain or weakness	38 weeks	CK, aldolase, ESR, CRP	Acetaminophen, NSAIDs, systemic steroids	Tocilizumab, apremilast
Neurologic	Headache, encephalitis, aseptic meningitis, peripheral neuropathy, cranial nerve deficit, myasthenia gravis, Guillain-Barre syndrome	4 weeks	ESR, CRP, ± AChR and antistriated muscle antibodies, ± MRI brain, ± LP	Systemic steroids	High dose IVIG or plasmapheresis ×5 days
Ocular	Ocular inflammation, usually concurrent with colitis	5 weeks	Vision testing, color vision testing, pupil shape/size/reactivity, fundoscopic examination, slit-lamp examination, eye pressure	Ophthalmology referral, artificial tears, topical corticosteroids	Systemic steroids
Renal	Elevated creatinine, electrolyte imbalances, decreased urinary output	14-15 weeks	Kidney biopsy	Systemic steroids	Infliximab, azathioprine, cyclophosphamide, cyclosporine, mycophenolate
Hematologic	Cytopenias, MDS, aplastic anemia, autoimmune hemolytic anemia, ITP	5-7 weeks	CBC, DIC panel, PT/INR, PTT, PNH screening, bilirubin, LDH, haptoglobin, direct agglutinin test, ± bone marrow biopsy, ± G6PD level, ± ADAMTS13	Discontinue drug, transfusion support, systemic steroids	IVIG, rituximab, plasma exchange
Infusion-related reactions	Fever, chills, headache, nausea, hypotension	During infusion	Vital signs, pulse oximetry, ± ECG	Acetaminophen, antihistamines, IV fluids	IV dexamethasone or methylprednisolone

Abbreviations: AChR, acetylcholine receptors; BNP, B-type natriuretic peptide; CK, creatine kinase; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; irAE, immune-related adverse event; ITP, immune thrombocytopenia; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; LP, lumbar puncture; MDS, myelodysplastic syndromes; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PNH, paroxysmal nocturnal hemoglobinuria; PT, prothrombin; PTT, partial thromboplastin time; TTE, transthoracic echocardiogram.

^aThis table provides a broad overview of management for all irAE grades. The authors recommend referring to society guidelines for in-depth management recommendations based on specific irAE grading.

Cancer Network, the Society for Immunotherapy of Cancer, and the European Society for Medical Oncology.^{18,48–50} Tables 3 and 4 summarize the presentation, diagnosis, and overall management approach of common and rare irAEs. The specific management of irAEs depends on their grading, so we recommend referencing society guidelines for the specific treatment and dosing of medications. In general, irAEs are managed by suppressing the immune system with corticosteroids. In some cases, immune-modulating agents are relevant to the affected organ system.⁴⁹ For specific low-grade toxicities, ICIs may be continued with close monitoring. For more severe cases of irAEs, ICIs should be held or even permanently discontinued.¹⁸ To reduce variability in care delivery and promote standardization across all sites, institutions may establish user-friendly algorithms that outline hospital-specific protocols and implement shared order sets to streamline clinical decision making.⁵¹ Resource libraries are also helpful to promote continued education. For example, at MD Anderson Cancer Center, an Immuno-Oncology Toxicity initiative, available through their intranet, led to the development of tailored guidelines for each organ system in patients with high medical complexity.⁵² Together, these examples demonstrate how clinicians across various disciplines have developed innovative team structures to address complex clinical needs in both outpatient and inpatient settings.

HOW: Integration With Community Hospitals

Although specialized, multidisciplinary teams have largely been established at academic medical centers, most Americans receive oncologic care in community settings. Community oncology practices have the potential to identify and manage irAEs earlier than academic medical centers. As demonstrated in an Australian retrospective study, regional and rural centers were able to establish robust programs for irAEs, resulting in a shorter median time to corticosteroids compared with tertiary care centers (1 day v 5 days, respectively).⁵³ Although no specifics about their workflow processes were provided, this Australian study is an example that care delivery models can be scaled to enhance access broadly. For more complex patients with irAE that require nononcology specialists, however, tertiary referral centers with dedicated immunotherapy toxicity programs should prioritize collaboration with community hospitals via hub-and-spoke communication models to connect the dots in patient care, education, and research opportunities.

Community partners may designate a point person at each site who interacts directly with programs within the larger health care system. Alternatively, a centralized communication system, such as a dedicated phone line or pager service at the academic center, could be established to provide real-time support. This communication and connection can be fostered by inviting community partners to regular immunotherapy toxicity tumor board meetings, virtual case conferences, and continuing education sessions. Tailored education content should be developed to train local

clinicians and delivered through grand rounds, workshops, or online modules.⁵⁴ Institution-specific protocols and referral pathways must be adapted and scaled to reach the community settings. This expanded reach can be achieved through prepopulated order sets tailored to smaller hospitals or decision support in an electronic medical record, designed to optimize clinical decision making in alignment with irAE guidelines and facilitate referrals for more complex patients. Additionally, telemedicine structures can streamline documentation and follow-up between centers, ideally through a shared electronic health record. Telemedicine also enables greater access to care in rural and underserved regions. The caveat is that it is difficult to address certain irAEs, such as cutaneous and musculoskeletal irAEs, over telemedicine. Additionally, obtaining the appropriate testing locally for patients can be challenging in smaller urgent care or emergency department settings. Virtual or on-call pager systems can connect community members to specialist care for urgent cases. One example of these locoregional referral pathways is the Cancer Immunotherapy Toxicity Evaluation Program at the University of California San Francisco. Patients with complex or treatment-resistant irAEs are referred to a team of specialists for a formal second opinion with opportunities to enroll in clinical trials.⁵⁵

Once these systems are established, intentional strategies should be implemented to sustain relationships at the local and national levels. Feedback loops are being developed to enable patients and clinicians in the community to communicate real-world challenges to academic partners, thereby uniting stakeholders. These efforts include the ASCO Community of Practice's Alliance for Support and Prevention of Immune-Related Events (ASPIRE), and the patient advocacy group, Standing Together to Optimize Research, Interventions, and Education in irAEs (STORIES).^{56,57} Through annual meetings, networking sessions, newsletters, and shared registries, these groups aim to develop novel therapeutic approaches and care delivery models to improve care of patients with irAEs. Although grassroots efforts are limited by funding, increasing visibility to challenges in this space promotes recognition from institutional leadership and enhances the potential for increased resource allocation. A suggested algorithm for establishing irAE management teams at community hospitals is depicted in Figure 2.

ASPIRE AND STORIES: ADVANCING CLINICAL CARE, RESEARCH, AND ADVOCACY IN IMMUNOTHERAPY-RELATED ADVERSE EVENTS

The ASPIRE consortium was launched in 2024 to address critical gaps in the recognition, prevention, management, and education about irAEs. ASPIRE is an international initiative to unite the global medical and scientific community to advance clinical care, research, education, and advocacy for patients with cancer at risk of or living with adverse events from immunotherapy. By fostering collaborations with clinicians from all subspecialties, patients, caregivers, industry partners, and researchers, the consortium aims to

Establishing irAE Management Teams



FIG 2. Establishing irAE management teams in the community. EMR, electronic medical record; ESMO, European Society for Medical Oncology; irAE, immune-related adverse event; NCCN, National Comprehensive Cancer Network; SITC, Society for Immunotherapy of Cancer.

advance collective knowledge on diagnosing, preventing, and managing irAEs.⁵⁶ In parallel, STORIES was conceived as a sister organization to develop patient education, advocacy, and caregiver support for irAEs. STORIES will be an international resource for the patient community, helping the medical community understand patient-centered perspectives on irAEs. STORIES aims to enhance the quality of life for patients experiencing irAEs by fostering a community of connection, empowerment, advocacy, education, and research.

With representatives from 28 organizations, a shared framework was developed at the inaugural meeting of ASPIRE and STORIES in 2024 to identify four high-priority areas: patient education and advocacy, reconsideration of irAE definitions, interventional clinical trials, and biomarker research. A critical initiative spearheaded by ASPIRE leaders resulted in the approval of specific ICD codes for irAEs, which went live in October 2024. Using irAE-specific ICD-10 codes will facilitate the recognition of the real-world incidence of irAEs and foster population health science research, while increasing awareness of irAEs among health care clinicians outside of oncology. These ICD-10-CM codes are the following:

- T45.AX: This code is used to specifically document poisoning, adverse effects, or underdosing related to ICIs and immunostimulant drugs.
- T45.AX5: This code specifically refers to the adverse effects of ICIs and immunostimulant drugs.
- T45.AX5A: Initial encounter.
- T45.AX5D: Subsequent encounter.
- T45.AX5S: Sequela.
- Z92.26: This code is used to indicate a personal history of ICI therapy.

Another goal of the consortium is to develop a standardized platform for data collection to foster multi-institutional, cross-collaborative irAE research and harmonization of higher-quality data collection and dissemination. Additionally, ASPIRE leads training programs, empowering clinicians worldwide with the skills and knowledge needed to

deliver the highest standard of care across various health care settings. Members of the consortium have developed the Checkpoint NOW podcast, which has been well received by clinicians and patients/caregivers. Efforts are underway to develop educational resources in newer formats across various platforms. Working with major national and global professional organizations, ASPIRE and STORIES will enhance patient outcomes, optimize treatment protocols, and drive evidence-based care for patients.

irAE EDUCATION: IDENTIFYING AND CLOSING KNOWLEDGE GAPS

Clinician Education

To empower clinicians worldwide to manage irAEs effectively, it is imperative to recognize medical education needs, format preferences for educational consumption, and provide structured support for high-quality care delivery within both academic and community cancer centers. Recent studies have reported substantial knowledge gaps among health care clinicians regarding irAE recognition and management. These gaps span multiple specialties and practice locations, reflecting the multidisciplinary nature of irAE care and widespread implementation.^{58–60} Previous surveys of internal medicine, emergency medicine, and family medicine clinicians revealed diverse educational preferences, with approximately one third of respondents each preferring printed materials, online teaching modules, and in-person lectures.⁵⁸ The most common resources used by clinicians for irAE management included informally consulting colleagues and searching UpToDate (77% and 75%, respectively).⁵⁸ Although APPs were more open to online educational resources specific to irAEs, oncology physicians were more likely to use online resources than to participate in irAE-specific continuing medical education (CME) sessions.³⁰ Online CME has been demonstrated to be an effective way to improve oncologists' knowledge, competence, and confidence in managing irAE.^{61,62} These data underscore the need for tailored educational interventions that accommodate varied learning styles.

Innovative educational approaches, such as simulation-based training, multidisciplinary case conferences, and virtual patient scenarios, can enhance the engagement and retention of key concepts related to recognizing and managing irAEs. Furthermore, integrating irAE-focused curricula into graduate medical education and continuing professional development programs can help standardize knowledge acquisition and ensure consistency in practice. This approach will develop a medical community skilled in the multidisciplinary management of irAEs across various health care delivery models. The education committee of the ASPIRE consortium is conducting a needs assessment survey to evaluate educational styles and preferences for irAE education among all clinicians, including subspecialists, nurses, and pharmacists, within and outside of hematology oncology, to identify perceived barriers to effective irAE management across diverse health care settings. These and other ongoing efforts will culminate in the development of a framework for targeted educational resources that reflect real-world practice variability and effectively address existing knowledge and competency gaps.

Patient Education

Existing evidence highlights significant gaps in the educational needs of oncology patients, particularly in their understanding of diagnosis, treatment, and side-effect management. These are often compounded by challenges such as low health literacy, emotional distress, and inadequate resources.⁶³⁻⁶⁷ For many patients, a cancer diagnosis represents a traumatic event with a heightened emotional state and challenges to thinking clearly.⁶⁸ Anywhere from 40% to 80% of medical information provided by health care practitioners is immediately forgotten.⁶⁸ Patients often report difficulty finding information about their therapy, and much of the available information is written at reading levels that exceed average literacy skills (average, 12.9; range, 11.2-16.5).⁶⁹⁻⁷¹ For example, printed materials about lung cancer are written at an average of a 10th-grade reading level and do not address common problems such as dyspnea.⁷² Studies focusing on immunotherapy also found that patients living with cancer had difficulty recalling information verbally provided by their oncologist.⁷³⁻⁷⁵

Patient education aims to increase knowledge, change attitudes, and provide necessary tools to manage illness for patients and their caregivers.⁷⁶ Previous research has demonstrated that simplifying materials enhances comprehension.⁷⁷ Patient-centered care and shared decision making are increasingly prioritized in health care. Recently, a pilot trial of a novel immunotherapy toxicity educational video and question prompt list intervention (known as UPLIFT) showed promise in improving knowledge of ICI risks and benefits in participants using UPLIFT compared with the standard of care at 72 hours. However, there was no difference in retained immunotherapy toxicity knowledge at 6 weeks across groups, suggesting that ongoing longitudinal education may be necessary.⁷⁸ Effective education can help patients have more control over their cancer journey.⁷⁹

Meeting informational needs can decrease fear and anxiety,^{80,81} correct erroneous beliefs,⁸² increase adherence to medical care,^{83,84} improve health-related quality of life,^{69,80,85} and enhance pain management.⁸⁶

For patient populations that have varying levels of health literacy and access to resources, some approaches to improve patient education include the use of a counseling video and checklist, which has been shown to significantly improve the frequency of discussion on key topics.⁸⁷ Adjunctive educational aids such as presentations, checklist, and pre-testing and post-testing have also been effective in improving patient knowledge and comprehension.^{87,88} Visual aids can significantly enhance patient satisfaction and comprehension of medical information, particularly among individuals with lower health literacy. A recent systematic review of oncology education strategies in patients with low health literacy found that 74% of studies used multimodal educational methods, although only 55% included a validated tool.⁸⁹

The Internet is commonly used by individuals seeking cancer-related information, which can increase access to patient education resources and enhance health literacy. Anywhere between 63% and 75% of patients with cancer search online for cancer-related or general health-related information.⁹⁰ However, the inconsistency in the quality and accuracy of online resources can affect patient education and care. For instance, in a recent review of 51 online resources about the side effects of immunotherapy, information lacked illustrations and other features to enhance understanding about the risks of treatment and the impact on quality of life.⁹¹ Decreased electronic health literacy also correlates with difficulty managing chronic diseases and adherence to disease prevention such as cancer screenings.^{92,93} A meta-analysis found that interventions focused on improving digital health literacy improved the health status and health management of older adults.⁹⁴ Unfortunately, the promotion of online health-related materials carries the risk of misinformation because of variable source accuracy. Therefore, clinicians play a crucial role in guiding patients to accurate, evidence-based online resources, thereby supporting improvements in digital health literacy and educational content.

We propose that an ideal educational model on irAEs requires a multifaceted approach:⁹⁵

1. Empowering patient knowledge to identify the cancer treatment they are receiving, potential toxicities, and how to report symptoms.
2. Prompting clinicians reliably identify patients receiving immunotherapy and recognize rare and subtle symptoms of toxicity.
3. Enhancing access across institutions to established guidelines and order sets to standardize the workup and treatment of irAEs, including the management of corticosteroid-refractory irAEs and identifying local immunotherapy toxicity experts. Institutional leaders

should also prioritize regular lectures or departmental grand rounds to educate staff on irAEs.

Recommended content of immunotherapy educational materials includes

1. Differences between chemotherapy, immunotherapy, and targeted therapy;
2. Immunotherapy mechanisms of action;
3. Immunotherapy adverse effects; and
4. Management of irAEs.^{96,97}

Using wallet cards has also been an important intervention that empowers patients about immunotherapy. Wallet cards are recommended in the ASCO guidelines and are available from the Oncology Nursing Society, pharmaceutical companies, and various institutions.¹⁸ Ideally, wallet cards should include the drug name, most common and serious adverse events, initial management, and how to access an irAE clinician expert. Health care systems can also use the electronic health record to alert clinicians to patients receiving immunotherapy who may be at risk for irAEs. However, caution must be exercised to avoid alert fatigue and workflow disruption.^{98,99} In a recent interventional experiment, patients starting immunotherapy received an oral presentation on irAE guidelines, watched a video on immunotherapy mechanisms of action, reviewed written materials, and received alert cards.¹⁰⁰ Before the intervention, patients had limited understanding of autoimmune conditions, immunotherapy side effects, and how to manage toxicities; the largest benefit was seen in patients with the least baseline knowledge about immunotherapy. Research studies to elucidate educational preferences for multidisciplinary care teams and the identification of institutional barriers to irAE management are urgently needed at regional and national levels.

PALLIATIVE CARE FOR PATIENTS ON ICI THERAPY

Palliative care is an integral component of multidisciplinary ICI management, providing symptom management, navigating complex decision making, enhancing patient communication and education, and assisting with conversations about goals of care, especially in instances of prognostic uncertainty. A qualitative study of 42 participants with advanced lung cancer or melanoma showed that people initiating ICI felt overwhelmed, afraid, and had difficulty absorbing information; caregivers were very helpful in navigating care, information, and uncertainty related to ICIs.¹⁰¹ The participants identified that having specific case examples about ICI risks, a multipronged approach to communication through different formats (eg, handouts, websites, and one-on-one communication with clinicians), and providing a list of frequently asked questions could improve irAE education and experience.¹⁰¹ This underscores the critical contribution of palliative care clinicians to multidisciplinary irAE management through a comprehensive approach that encompasses symptom management,

psychosocial support, and patient values and goals. To ensure an optimal partnership, it is essential that palliative care clinicians have opportunities to deepen their knowledge through updated guidelines, training sessions, and consultations with oncologists.¹⁰² In a survey study of 492 palliative care physicians in Japan, respondents with more experience treating patients who receive ICI therapy reported greater knowledge of ICI treatments and were more likely to consider irAEs; only 15% of palliative care physicians had no experience managing patients on ICI therapy.¹⁰² Strengthening collaboration and education across oncology and palliative care teams will be crucial to meeting the evolving needs of patients receiving ICI therapy and ensuring high-quality, person-centered care.

LIMITATIONS AND OPPORTUNITIES FOR GROWTH

Although we present practical strategies to improve irAE multidisciplinary management in both academic and community settings, there are several limitations to implementation, particularly in lower-resource environments. Each institution has its unique organizational culture and workflow process, which means that what is effective for one institution may not be feasible for another. We acknowledge that potential systemic barriers, such as organizational culture, resource constraints, financial sustainability, and gaps in patient health literacy, among other factors, may pose challenges that are difficult to surmount. Future studies and implementation initiatives should explicitly address these challenges by developing adaptable, multidisciplinary approaches that are feasible, sustainable, and effective in diverse, resource-constrained clinical environments.

CONCLUSION

We discussed practical strategies for enhancing the multidisciplinary management of irAEs. As immunotherapy has transformed the therapeutic landscape, the rise in irAEs necessitates improved management approaches on the basis of international guidelines for irAEs to ensure patient safety and treatment efficacy. Connecting the dots for early and effective irAE management requires multidisciplinary teams, standardized protocols, research integration, and enhanced educational initiatives. We highlighted several methods for integrating irAE care into training opportunities, multidisciplinary tumor boards, clinical workflows across various clinical settings, and hub-and-spoke models that extend specialized expertise to community settings. We also emphasize the importance of collaboration between academic and community oncology practices, as well as among health care clinicians, to establish a comprehensive support system for patients. The ASPIRE and STORIES initiatives are pivotal in driving these efforts forward, aiming to create a more comprehensive and effective model of care for patients experiencing irAEs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Wolchok JD, Chiarion-Sileni V, Rutkowski P, et al: Final, 10-year outcomes with nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 392:11-22, 2025
2. Wang Y, Kondrat K, Adhikari J, et al: Survival trends among patients with metastatic non-small cell lung cancer before and after the approval of immunotherapy in the United States: A surveillance, Epidemiology, and End Results database-based study. *Cancer* 131:e35476, 2025
3. Andre T, Elez E, Van Cutsem E, et al: Nivolumab plus ipilimumab in microsatellite-instability-high metastatic colorectal cancer. *N Engl J Med* 391:2014-2026, 2024
4. Cohen EEW, Soulières D, Le Tourneau C, et al: Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): A randomised, open-label, phase 3 study. *Lancet* 393:156-167, 2019
5. Nahm SH, Heywood R, Callaghan S, et al: Patient and treatment characteristics of emergency presentations due to immune-mediated toxicities. *Eur J Cancer* 164:62-69, 2022
6. Haslam A, Olivier T, Prasad V: How many people in the US are eligible for and respond to checkpoint inhibitors: An empirical analysis. *Int J Cancer* 156:2352-2359, 2025
7. Gougis P, Jochum F, Abbar B, et al: Clinical spectrum and evolution of immune-checkpoint inhibitors toxicities over a decade-a worldwide perspective. *EClinicalMedicine* 70:102536, 2024
8. Wan G, Chen W, Khattab S, et al: Multi-organ immune-related adverse events from immune checkpoint inhibitors and their downstream implications: A retrospective multicohort study. *Lancet Oncol* 25:1053-1069, 2024
9. Shen X, Yang J, Qian G, et al: Treatment-related adverse events of immune checkpoint inhibitors in clinical trials: A systematic review and meta-analysis. *Front Oncol* 14:1391724, 2024
10. Feng Y, Guo K, Jin H, et al: Adverse events of neoadjuvant combination immunotherapy for resectable cancer patients: A systematic review and meta-analysis. *Front Immunol* 14:1269067, 2023
11. Arnaud-Coffin P, Maillet D, Gan HK, et al: A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. *Int J Cancer* 145:639-648, 2019
12. Wang DY, Salem JE, Cohen JV, et al: Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. *JAMA Oncol* 4:1721-1728, 2018
13. Naidoo J, Zhang J, Lipson EJ, et al: A multidisciplinary toxicity team for cancer immunotherapy-related adverse events. *J Natl Compr Canc Netw* 17:712-720, 2019
14. Balaji A, Zhang J, Suresh K, et al: A multidisciplinary immune-related toxicity (IR-Tox) program for immune-related adverse events: A two-year experience. *J Clin Oncol* 38, 2020 (suppl 15; abstr e15074)
15. Molina GE, Zubiri L, Cohen JV, et al: Temporal trends and outcomes among patients admitted for immune-related adverse events: A single-center retrospective cohort study from 2011 to 2018. *Oncologist* 26:514-522, 2021
16. Chen ST, Molina GE, Lo JA, et al: Dermatology consultation reduces interruption of oncologic management among hospitalized patients with immune-related adverse events: A retrospective cohort study. *J Am Acad Dermatol* 82:994-996, 2020
17. Ryder M, Callahan M, Postow MA, et al: Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: A comprehensive retrospective review from a single institution. *Endocr Relat Cancer* 21:371-381, 2014
18. Schneider BJ, Naidoo J, Santomaso BD, et al: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol* 39:4073-4126, 2021
19. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al: Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 377:1345-1356, 2017
20. Bertrand A, Kostine M, Barneche T, et al: Immune related adverse events associated with anti-CTLA-4 antibodies: Systematic review and meta-analysis. *BMC Med* 13:211, 2015
21. Weber JS, Yang JC, Atkins MB, et al: Toxicities of immunotherapy for the practitioner. *J Clin Oncol* 33:2092-2099, 2015
22. Ramos-Casals M, Brahmer JR, Callahan MK, et al: Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers* 6:38, 2020
23. Postow MA, Sidlow R, Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 378:158-168, 2018
24. Eggermont AMM, Kicinski M, Blank CU, et al: Association between immune-related adverse events and recurrence-free survival among patients with stage III melanoma randomized to receive pembrolizumab or placebo: A secondary analysis of a randomized clinical trial. *JAMA Oncol* 6:519-527, 2020
25. Topalian SL, Hodi FS, Brahmer JR, et al: Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non-small cell lung cancer treated with nivolumab. *JAMA Oncol* 5:1411-1420, 2019
26. Akamatsu H, Murakami E, Oyanagi J, et al: Immune-related adverse events by immune checkpoint inhibitors significantly predict durable efficacy even in responders with advanced non-small cell lung cancer. *Oncologist* 25:e679-e683, 2020
27. Suo A, Chan Y, Beaulieu C, et al: Anti-PD1-induced immune-related adverse events and survival outcomes in advanced melanoma. *Oncologist* 25:438-446, 2020
28. Socinski MA, Jotte RM, Cappuzzo F, et al: Association of immune-related adverse events with efficacy of atezolizumab in patients with non-small cell lung cancer: Pooled analyses of the phase 3 IMpower130, IMpower132, and IMpower150 randomized clinical trials. *JAMA Oncol* 9:527-535, 2023
29. Foster CC, Couey MA, Kochanny SE, et al: Immune-related adverse events are associated with improved response, progression-free survival, and overall survival for patients with head and neck cancer receiving immune checkpoint inhibitors. *Cancer* 127:4565-4573, 2021
30. Wesevich A, He G, Tomczyk G, et al: Role-specific curricular needs for identification and management of immune-related adverse events. *J Cancer Educ* 38:1486-1492, 2023

31. Teimouri A, Minard LV, Scott SN, et al: Real-world adherence to toxicity management guidelines for immune-related adverse events. *Curr Oncol* 29:3104-3117, 2022
32. Shen M, Chen D, Zhao R, et al: Real-world adherence to toxicity management guidelines for immune checkpoint inhibitor-induced diabetes mellitus. *Front Endocrinol (Lausanne)* 14:1213225, 2023
33. Balaji A, Zhang J, Wills B, et al: Immune-related adverse events requiring hospitalization: Spectrum of toxicity, treatment, and outcomes. *J Oncol Pract* 15:e825-e834, 2019
34. Reynolds KL, Sullivan RJ, Fintelman FJ, et al: Case 9-2020: A 64-year-old man with shortness of breath, cough, and hypoxemia. *N Engl J Med* 382:1150-1159, 2020
35. Bayless NL, Bluestone JA, Bucktrout S, et al: Development of preclinical and clinical models for immune-related adverse events following checkpoint immunotherapy: A perspective from SITC and AACR. *J Immunother Cancer* 9:e002627, 2021
36. Zubiri L, Molina GE, Mooradian MJ, et al: Effect of a multidisciplinary Severe Immunotherapy Complications Service on outcomes for patients receiving immune checkpoint inhibitor therapy for cancer. *J Immunother Cancer* 9:e002886, 2021
37. Kozono DE, Sharon E, Le-Rademacher J, et al: Alliance A151804: Establishment of a national biorepository to advance studies of immune-related adverse events. *J Clin Oncol* 38, 2020 (suppl 15; abstr TPS3154)
38. Boruah AP, Demski K, Patil PD, et al: Implementation and impact of a novel multidisciplinary immune-related adverse events tumor board for patients receiving immune checkpoint inhibitor therapy. *J Clin Oncol* 39, 2021 (suppl 15; abstr e13541)
39. Varner R, Fontaine-Delaruelle C, Freymond N, et al: Evolving practices in immune-related adverse event management: Insights from the IMMUCARE multidisciplinary board. *JCO Oncol Pract* 21:342-350, 2025
40. Hoimes CJ, McGettigan S, Schwartzberg L: Onco-primary care of patients receiving immune checkpoint inhibitors. *Am J Med* 137:1200-1209, 2024
41. Hoffner B, Rubin KM: Meeting the challenge of immune-related adverse events with optimized telephone triage and dedicated oncology acute care. *J Adv Pract Oncol* 10:9-20, 2019 (suppl 1)
42. D'Avella C, Whoolley P, Milano E, et al: The impact of an oncology urgent care center on health-care utilization. *JNCI Cancer Spectr* 8:pkae009, 2024
43. Liang KL, Tackett S, Myers S, et al: An oncology urgent care clinic for the management of immune-related adverse events: A descriptive analysis. *Curr Oncol* 29:4342-4353, 2022
44. Chaudhuri A, Pimkina JS: Impact of a pilot advanced provider-based comprehensive management program to support patients with immunotoxicity-related adverse events in a cancer care setting. *JCO Oncol Pract* 20, 2024 (suppl 10; abstr 31)
45. Diamond C, Patolia H, Phinney D, et al: e-consults for immune-related toxicities improve patient access and reduce costs. *Oncol Issues* 39:30-35, 2024
46. Immunology and Rheumatology Faculty Reach across Divisions to Fight Disease. Stanford Department of Medicine. <https://medicine.stanford.edu/2020-report/immunology-and-rheumatology.html>
47. Abu-Shawar O, Singh P, Yenulevich E, et al: Novel platform leveraging electronic medical record (EMR) to triage patients admitted with high-grade immune-related adverse events (irAEs) to the immune-toxicity (ITOX) service. *J Immunother Cancer* 8:e000992, 2020
48. Brahmer JR, Abu-Sbeih H, Ascierto PA, et al: Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer* 9:e002435, 2021
49. Thompson JA, Schneider BJ, Brahmer J, et al: NCCN Guidelines® Insights: Management of immunotherapy-related toxicities, version 2.2024. *J Natl Compr Canc Netw* 22:582-592, 2024
50. Haanen J, Obeid M, Spain L, et al: Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol* 33:1217-1238, 2022
51. The University of Texas MD Anderson Cancer Center: Clinical Management Algorithms. <https://www.mdanderson.org/for-physicians/clinical-tools-resources/clinical-practice-algorithms/clinical-management-algorithms.html>
52. Fayle SE, Palaskas NL, Siddiqui BA, et al: Development of a strategic initiative at MD Anderson Cancer Center to improve outcomes in immune-related adverse events. *J Natl Compr Canc Netw* 22:e237119, 2024
53. Hamilton B, Xu K, Honeyball F, et al: Patterns of immunotherapy use and management of toxicities in regional and tertiary settings. *Intern Med J* 49:1010-1015, 2019
54. Zibelman M, Wong V, Reilly J, et al: Multidisciplinary educational program to standardize education and management of immune-related adverse events: Review and outcomes of a single-institution initiative. *Am J Clin Oncol* 47:419-424, 2024
55. UCSF Health: Cancer Immunotherapy Toxicity Evaluation (CITE) Program. <https://www.ucsfhealth.org/clinics/cancer-immunotherapy-toxicity-evaluation-program-cite>
56. Mittal K, Reynolds KL, Funchain P: Introducing ASPIRE and STORIES: A New International Initiative for Faculty Collaboration and Patient Advocacy in Immune-Related Adverse Events. *The ASCO Post*. 2024. <https://ascopost.com/issues/june-10-2024/a-new-international-initiative-for-faculty-collaboration-and-patient-advocacy-in-immune-related-adverse-events/>
57. von Itzstein MS, Gerber DE, Bermas BL, et al: Acknowledging and addressing real-world challenges to treating immune-related adverse events. *J Immunother Cancer* 12:e009540, 2024
58. Khalid AB, Calderon G, Jalal SI, et al: Physician awareness of immune-related adverse events of immune checkpoint inhibitors. *J Natl Compr Canc Netw* 20:1316-1320, 2022
59. Araújo F, Fonseca JE: AB1386 Physician awareness of rheumatic immune-related adverse events in cancer patients treated with immune checkpoint inhibitors. *Ann Rheum Dis* 77:1777-1778, 2018
60. Osarogiagbon RU, Sineshaw HM, Unger JM, et al: Immune-based cancer treatment: Addressing disparities in access and outcomes. *Am Soc Clin Oncol Educ Book* 41:1-13, 2021
61. Pender LK, Kadkhoda H, Lucero KS, et al: Online education about lung cancer immunotherapy: Outcomes over time. *J Clin Oncol* 37, 2019 (suppl 15; abstr e18249)
62. Pender LK, Kadkhoda H, Lucero KS, et al: Effects of online education on the identification and management of immune-related adverse events over time. *J Clin Oncol* 37, 2019 (suppl 15; abstr e18224)
63. McCaughan E, McKenna H: Never-ending making sense: Towards a substantive theory of the information-seeking behaviour of newly diagnosed cancer patients. *J Clin Nurs* 16:2096-2104, 2007
64. Döhler N, Krolow L, Ringsdorf S, et al: Task allocation in cancer medication management—Integrating the pharmacist. *Patient Educ Couns* 83:367-374, 2011
65. Husson O, Thong MS, Mols F, et al: Illness perceptions in cancer survivors: What is the role of information provision? *Psychooncology* 22:490-498, 2013
66. Lambourne T, Minard LV, Deal H, et al: Optimizing patient education of oncology medications: A patient perspective. *J Cancer Educ* 34:1024-1030, 2019
67. van der Molen B: Relating information-needs to the cancer experience. 1. Jenny's story: A cancer narrative. *Eur J Cancer Care (Engl)* 9:41-47, 2000
68. Kessels RP: Patients' memory for medical information. *J R Soc Med* 96:219-222, 2003
69. Thomas R, Daly M, Perryman B, et al: Forewarned is forearmed—benefits of preparatory information on video cassette for patients receiving chemotherapy or radiotherapy—A randomised controlled trial. *Eur J Cancer* 36:1536-1543, 2000
70. Vargas CR, Chuang DJ, Ganor O, et al: Readability of online patient resources for the operative treatment of breast cancer. *Surgery* 156:311-318, 2014
71. Davis TC, Crouch MA, Wills G, et al: The gap between patient reading comprehension and the readability of patient education materials. *J Fam Pract* 31:533-538, 1990
72. Sarna L, Ganley BJ: A survey of lung cancer patient-education materials. *Oncol Nurs Forum* 22:1545-1550, 1995
73. Ihrig A, Richter J, Gröllich C, et al: Patient expectations are better for immunotherapy than traditional chemotherapy for cancer. *J Cancer Res Clin Oncol* 146:3189-3198, 2020
74. Wong A, Billett A, Milne D: Balancing the hype with reality: What do patients with advanced melanoma consider when making the decision to have immunotherapy? *Oncologist* 24:e1190-e1196, 2019
75. Jansen J, Butow PN, van Weert JC, et al: Does age really matter? Recall of information presented to newly referred patients with cancer. *J Clin Oncol* 26:5450-5457, 2008
76. Chiu CJ, Hu YH, Lin DC, et al: The attitudes, impact, and learning needs of older adults using apps on touchscreen mobile devices: Results from a pilot study. *Comput Hum Behav* 63:189-197, 2016
77. Health literacy: Report of the Council on Scientific Affairs. Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs, American Medical Association. *JAMA* 281:552-557, 1999
78. Petrillo LA, Hsu K, Pintro K, et al: Pilot randomized trial of an educational intervention about immunotherapy for patients with advanced cancer and their caregivers. *J Natl Compr Canc Netw* 23:12-20, 2025
79. Treacy JT, Mayer DK: Perspectives on cancer patient education. *Semin Oncol Nurs* 16:47-56, 2000
80. D'haese S, Vinh-Hung V, Bijdekerke P, et al: The effect of timing of the provision of information on anxiety and satisfaction of cancer patients receiving radiotherapy. *J Cancer Educ* 15:223-227, 2000
81. Mills ME, Sullivan K: The importance of information giving for patients newly diagnosed with cancer: A review of the literature. *J Clin Nurs* 8:631-642, 1999
82. Jenkins V, Fallowfield L, Saul J: Information needs of patients with cancer: Results from a large study in UK cancer centres. *Br J Cancer* 84:48-51, 2001
83. Butow PN, Kazemi JN, Beeny LJ, et al: When the diagnosis is cancer: Patient communication experiences and preferences. *Cancer* 77:2630-2637, 1996
84. Hinds C, Streater A, Mood D: Functions and preferred methods of receiving information related to radiotherapy. Perceptions of patients with cancer. *Cancer Nurs* 18:374-384, 1995
85. Fallowfield LJ, Hall A, Maguire GP, et al: Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. *BMJ* 301:575-580, 1990
86. Stewart MA: Effective physician-patient communication and health outcomes: A review. *CMAJ* 152:1423-1433, 1995
87. Mack DP, Foster GA, Bouwers LM, et al: A counseling video with pre- and posttesting and checklist for oral immunotherapy consent improves participant knowledge. *Ann Allergy Asthma Immunol* 125:468-474.e4, 2020
88. Nehme J, El-Khani U, Chow A, et al: The use of multimedia consent programs for surgical procedures: A systematic review. *Surg Innov* 20:13-23, 2013
89. Christiansen K, Buswell L, Fadelu T: A systematic review of patient education strategies for oncology patients in low- and middle-income countries. *Oncologist* 28:2-11, 2023

90. Lange-Drenth L, Schulz H, Endsins G, et al: Patients with cancer searching for cancer- or health-specific web-based information: Performance test analysis. *J Med Internet Res* 23:e23367, 2021
 91. Nicolas-Joseph M, Ould Brahim L, Boureanu MI, et al: An evaluation of the suitability, readability, quality, and usefulness of online resources for patients with cancer receiving immunotherapy. *Patient Educ Couns* 110:107640, 2023
 92. Scott TL, Gazmararian JA, Williams MV, et al: Health literacy and preventive health care use among Medicare enrollees in a managed care organization. *Med Care* 40:395-404, 2002
 93. Davis TC, Gazmararian J, Kneen EM: Approaches to improving health literacy: Lessons from the field. *J Health Commun* 11:551-554, 2006
 94. Dong Q, Liu T, Liu R, et al: Effectiveness of digital health literacy interventions in older adults: Single-arm meta-analysis. *J Med Internet Res* 25:e48166, 2023
 95. Cole S, Zibelman M, Bertino E, et al: Managing immuno-oncology toxicity: Top 10 innovative institutional solutions. *Am Soc Clin Oncol Educ Book* 39:96-104, 2019
 96. Lasa-Blandon M, Stasi K, Hehir A, et al: Patient education issues and strategies associated with immunotherapy. *Semin Oncol Nurs* 35:150933, 2019
 97. Dine J, Gordon R, Shames Y, et al: Immune checkpoint inhibitors: An innovation in immunotherapy for the treatment and management of patients with cancer. *Asia Pac J Oncol Nurs* 4:127-135, 2017
 98. Phansalkar S, van der Sijs H, Tucker AD, et al: Drug-drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records. *J Am Med Inform Assoc* 20:489-493, 2013
 99. Wright A, Aaron S, Seger DL, et al: Reduced effectiveness of interruptive drug-drug interaction alerts after conversion to a commercial electronic health record. *J Gen Intern Med* 33:1868-1876, 2018
 100. Teixeira-Poit SM, Sawicki K, O'Kelley W, et al: Efficacy of a patient education session for cancer patients receiving immunotherapy. *Semin Oncol Nurs* 39:151445, 2023
 101. Falade AS, Boulanger MC, Hsu K, et al: Learning about and living with toxicity: A qualitative study of patients receiving immune checkpoint inhibitors for melanoma or lung cancer and their caregivers. *Support Care Cancer* 32:684, 2024
 102. Usui Y, Miura T, Kawaguchi T, et al: Palliative care physicians' recognition of patients after immune checkpoint inhibitors and immune-related adverse events. *Support Care Cancer* 30:775-784, 2022
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Addressing Barriers in Palliative Care for Rural and Underserved Communities

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OVERVIEW

Thirty-two million Americans live in rural counties and have no access to multidisciplinary cancer care, and patients with cancer describe a greater number of unfavorable social determinants of health (SDoH), experience more serious financial hardship as well as greater symptom burden, and are more likely to die of cancer. Delivering effective symptom management may be achieved through adoption of a *hub and spoke model*, which connects rural community care sites with a cancer center. Modern technologies (electronic medical record and virtual telehealth), advanced practice provider care models, and engagement in symptom management clinical trials can extend more optimal care to connected rural sites. Pragmatic examples of addressing these care barriers include systematic and proactive assessment of SDoH, supported by navigation and social services, and telehealth-enabled palliative care (PC). In low- and middle-income countries, access to supportive cancer care services is very limited, especially in rural areas. Digital health interventions, primarily limited to apps, and community health workers (trained volunteer care providers) have successfully enabled vital symptom management services. Access to PC, considered a basic human right, is unfortunately not available in many parts of the world, especially in rural areas of not only low- and middle-income but also high-income countries. Multiple approaches to deliver effective symptom management have been described but need to be tailored to the respective local health care infrastructure, resources, culture, and social, economic, and political environment.

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INTRODUCTION

The authors will address the following objectives as they relate to rural cancer care in the United States as well as to rural cancer care in low- and middle-income countries: to describe the existing literature in symptom science and palliative care and existing limitations in how well the data can be generalized to some historically underrepresented communities, to recognize the biological influence of social determinants of health and begin to understand how these factors influence response to cancer treatments and treatment outcomes, and to identify concrete strategies and interventions to improve supportive and palliative care quality for patients in rural and underserved settings.

RURAL FOR REAL: SYMPTOM MANAGEMENT IN RURAL POPULATIONS

The United States defines rural areas on the basis of population size and density, with different criteria used by the Office of Management and Budget (OMB) and Census Bureau.¹ On the basis of the 2020 Census criteria, 66 of 332 million US citizens reside in rural areas, and on the basis of the 2023 OMB criteria, 46 of 332 million US citizens reside in nonmetro areas. Of these 46 million residents, 29 million

reside in rural areas as defined by the Census criteria. Furthermore, of the 46 million nonmetro residents as defined by OMB, approximately 10.5 million live in counties with <20,000 residents and that are not adjacent to metro areas. The OMB “nonmetro” and Census “rural” definitions provide different but equally useful perspectives on rural populations. Most counties, metro or nonmetro, contain a combination of urban and rural populations. So, what is then rural for real? Whereas the Census’ rural criteria apply to approximately 20% of the US population, the OMB’s nonmetro criteria apply to approximately 15%. Infrastructure in rural communities can vary widely but is generally assumed to be less developed than in urban areas. From the perspective of access to health care, especially multidisciplinary subspecialty cancer care, the most stringent definition would be the OMB “nonmetro” and “not adjacent” definition that applies to approximately 3% of the US population or to residents living in 836 of 3,144 continental US counties.

The 2020 State of Oncology Workforce in America assessment by ASCO described that 66% of rural counties or 32 million Americans living in rural counties have no access to oncology care.¹ Four in 10 patients with a history of cancer state that there are no oncologists practicing within their rural county.² Geographic access to National Cancer Institute

PRACTICAL APPLICATIONS

- Hub and spoke care delivery models can extend subspecialty care services, including palliative care (PC), from a cancer center to connected rural sites.
- Systematic assessment of social determinants of health combined with comprehensive navigation services can facilitate improved care delivery.
- Advanced practice providers with specialized training can deliver symptom management to patients living in communities where cancer care services are otherwise not available.
- Telehealth-enabled PC can provide essential support to patients living in rural communities.
- App-based symptom management advice as well as trained health care volunteers can provide vital symptom management care in low- and middle-income countries.

(NCI)-designated cancer centers is the lowest in rural areas,³ as is access to cancer treatment service availability in critical access hospitals and prospective payment system hospitals.⁴ Patients facing cancer and survivors who live in rural communities are more likely to die of cancer than patients living in urban communities; they also experience serious financial hardship given that they are more likely to have lower incomes.⁵

In 2018, ASCO undertook an initiative to understand and address factors contributing to rural cancer disparities, which was comprehensively updated in 2022 by Bhatia,⁶ identifying opportunities for future research. Factors described to contribute to rural-urban disparities included oncology and medical care infrastructure (less access to subspecialty medical and surgical care, primary care, behavioral, palliative, and hospice services), health insurance coverage (lower rates of commercial insurance and higher rates of Medicare, Medicaid, and noninsurance), geographic access to care and challenges with transportation (greater travel distance, lack of public transportation, greater cost of transportation, both as it relates to money and time), health behaviors (higher cigarette smoking prevalence, less physical activity, and lower intake of fiber and fruits), access to clinical trials (rural patients less likely to be invited and to participate, given underfunded research infrastructure and limited local experience) and information needs and health literacy (less communication time with experienced provider, lower health literacy associated with limited educational opportunities, less navigation and social services, and greater digital divide).

Social determinants of health (SDoH) are defined as the conditions in which people are born, grow, live, work, and

age. These include underlying social, economic, and environmental conditions faced by individuals and their communities. Described reasons for rural disparities in cancer care such as access to health care; social isolation and cohesion; food, housing, utility and transportation insecurities; education; and socioeconomic status are the main components that determine these SDoH. A greater number of unfavorable SDoH parameters are significantly associated with increased risks of cancer mortality from all causes and cancer. The ASCO Policy Statement on SDoH and Cancer Care provides a summary of the current science of SDoH research along with the importance in measuring these in routine oncology care as well as addressing social needs in the cancer care continuum.⁷

Whereas there is a paucity of symptom science specifically as it relates to rural communities, many NCI-sponsored symptom management trials reach rural communities through NCI Community Oncology Research Program-associated institutions, which enroll the majority of patients in the United States to such trials. Chih et al⁸ provided a narrative review of “The Landscape of Connected Cancer Symptom Management” describing high acceptance, usage, and satisfaction of connected health technologies reported both by rural patients and health care providers. Gilbertson-White provided an insight into how rural residents with advanced cancer experience and manage their symptoms, providing a somber summary: “Just Living with Them.”⁹ The Rural Health Information Hub¹⁰ summarizes current evidence for poor access to palliative care (PC) and hospice services in rural communities and highlights potential solutions including PC training of primary care providers.

In 2012, the National Academies of Sciences, Engineering and Medicine assessed the current state of cancer care and provided recommendations how to improve cancer care delivery from the time of diagnosis through end of life. In “Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis: One Decade Later,”¹¹ 10 specific goals previously described in the original report were updated as those relate to progress achieved. The complexity of applying these recommendations in the community-based cancer care setting along with providing access to coordinated multidisciplinary and supportive care, providing access to a comprehensive portfolio of cancer control and prevention, therapeutic and cancer care delivery research trials, complexity of providing up-to-date precision medicine testing and result management support, complexity of incorporating an exponentially increasing evidence base that informs best cancer care along with the complexity of navigating regulatory, and financial and administrative tasks are truly daunting and have long ago much exceeded the ability of an individual provider, the typical cancer care giver in a rural setting, to provide such high-quality cancer care. From the perspective of this author, a community oncologist practicing at ThedaCare in Wisconsin, a pragmatic solution represents the *hub and spoke model*, where comprehensive cancer services are extended from a

community-based or academic cancer center that encompasses all critically important components of modern cancer care to rural communities, relying on fully integrated electronic medical record (EMR) software, telehealth, physician extenders, and subspecialty services, all facilitated by supportive health systems. Fortunately, modern technologies are increasingly enabling this model of care. At The-daCare, a community-based health system providing care in both urban and rural communities, we have aimed to accomplish this through the following initiatives:

1. **Cancer care delivery:** Structured collaboration between health system programs, employed staff, and private practice groups facilitate comprehensive, multidisciplinary cancer services encompassing a regional cancer center, inpatient care at two urban hospitals and outreach to six regional, primarily rural hospitals. All sites and programs are supported by a single EMR system (Epic). Multidisciplinary disease committees (centers of excellence) support four weekly virtual tumor boards (lung, breast, hematologic malignancy, and GI/general) with integrated precision medicine; clinical trial matching; and palliative, rehabilitation, and nutrition support service recommendations. PC services are provided at rural community hospitals through telehealth and to one outreach site in person, both by Medical Doctor and Advanced Practice Clinician providers. Collaboration with the University of Wisconsin Precision Medicine Molecular Tumor Board along with fully EMR-integrated genomic testing and result reporting (Tempus) informs best practices and clinical trial opportunities.
2. **Comprehensive support services:** Routine SDoH collection along with comprehensive initial and longitudinal navigation services identifies health-related social needs and symptoms, which trigger appropriate referral to social, financial, behavioral, nutrition, rehabilitation, and PC services.
3. **Clinical research:** The regional cancer center research program offers access to a comprehensive portfolio of therapeutic, cancer control and prevention, and observational trials (64 open trials as of February 2025), supported by the NCI Community Oncology Research Program (as a partner site of the Wisconsin NCI Community Oncology Research Program), by community foundations, as well as by industry sponsors and collaboration with the University of Wisconsin. In 2024, 500+ patients have participated in available research trials, many of them living in adjacent rural communities served by the regional cancer center program. Participation in clinical trials engages community-based providers and informs best practices leading to earlier adoption of evidence-based interventions including symptom management and PC as well as cancer care delivery.

We continuously aim to optimize our high-quality cancer care delivery, with a special focus on improving access to clinical trial opportunities and enrollment within the rural communities we serve.¹²

PRAGMATIC INSIGHTS FROM COMMUNITY ONCOLOGY: DESIGNING CARE PLANS TO ADDRESS SOCIAL NEEDS

Community oncology practices and providers, generally situated in key access areas, have a distinct opportunity to affect patients struggling with access to care because of their SDoH and understanding the impact SDoH has on a person's ability to receive adequate care and have positive treatment outcomes. Furthermore, Nelson et al¹³ found that these disparities can adversely affect a person's ability to adequately access and benefit from palliative and hospice care services for chronic illnesses. Therefore, it is critical to establish care plans to address this patient population to ensure ideal outcomes for patients and caregivers.

To fully appreciate the gaps in access to care a patient faces and will face along the continuum of the cancer care journey, proactively assessing SDoH factors with a validated screening tool such as the National Comprehensive Cancer Network Distress Thermometer or Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences can identify unmet needs early in the care process. These tools will reveal areas such as economic stability, education, access to health care, social support, and neighborhood environment¹⁴ that play a significant role in cancer care. For oncology patients, barriers such as transportation, food insecurity, and financial toxicity can lead to delays in treatment or nonadherence.

Practices can substantially benefit from leveraging local resources, especially when it comes to PC. Rural communities often face challenges in accessing specialized care because of distance and limited health care infrastructure. By partnering with local organizations, oncology practices can ensure that patients receive the support they need for both their medical and social needs. For instance, collaborating with transportation services allows patients to attend treatment appointments, while partnerships with food banks or meal delivery services help address food insecurity, common in underserved areas. These partnerships not only enhance the quality of life for patients but also improve their overall care experience by addressing the complex needs of serious illness, especially in rural settings where health care resources may be scarce.

Another opportunity for reaching patients in rural settings for PC opportunities is to leverage technology. Telehealth has emerged as a comparable service to traditional health care as the quality of care has shown to be equivalent and is an opportunity for complex health services.¹⁵ One such pilot study has highlighted the opportunity for PC to be conducted through telehealth for patients at practices within the American Oncology Network. ASCO guidelines include PC as integral to comprehensive, high-quality oncology care. However, access to specialty-level PC can vary significantly from one oncology patient to another. At present, more than 90% of PC physicians and nurse practitioners live in

metropolitan areas, indicating significant disparities in PC access for rural patients.¹⁶ Additionally, it is estimated the US shortage of PC physicians is growing and could be as large as 5,000 by 2040, signaling reduced access to PC for all.¹⁷

To address the challenges many patients face in accessing PC, Thyme Care has created an Enhanced Supportive Care (ESC) program to provide patients virtual access to specialty-level PC. The ESC program, embedded within Thyme Care's comprehensive oncology navigation and support services, is part of a broader suite of interventions to improve care for patients with serious illnesses. By eliminating the geographic barriers to access through their virtual telehealth platform, Thyme Care can deliver vital PC services to a population of patients who could not otherwise gain access.

The team at Hematology Oncology of Indiana (HOI) can refer patients to ESC services through an interface in their EMR, ensuring workflows remain within the oncology team's standard systems. PC providers conduct virtual visits through a secure platform and upload their visit notes and any recommended next steps within the HOI EMR. This keeps PC information visible to the oncology team and allows providers to communicate.

The ESC program aims to support the oncology team in addition to patients. Virtual PC providers follow patients longitudinally and collaborate with the HOI team to share progress on advanced care planning and discussions on goals of care. The ESC provider team also provides symptom management recommendations to the patient's oncologist, reducing the cognitive burden of complex symptom management and fielding the responsibility of patient education and outreach to the pharmacy.

By providing an added layer of support to both patients and clinicians, the PC provider can anticipate and address patient needs as they near the end of life, mitigating the risk of unnecessary utilization and improving patients' quality of life.

In any case, program implementation should be evaluated on the basis of measurable outcomes. Metrics such as treatment adherence, pain management, adverse treatment effects, and quality-of-life surveys can be helpful tools for assessing newer processes.¹⁸ Additionally, measuring emergency department and inpatient stays for pain or other unmanaged symptoms is critical to understanding the success of these programs.

Designing care plans that address social needs is not just a compassionate approach but a pragmatic one that enhances the effectiveness of oncology care. By embedding social support into the fabric of care delivery, community oncology practices can achieve better patient outcomes while reducing systemic burdens. PC is a specialty that, despite its growth, is still inaccessible to many of those patients to whom it would

benefit.¹⁹ The gap may be lessened with a multipronged approach, potentially including telehealth as an option.

PC IN RURAL AREAS IN LOW- AND MIDDLE-INCOME COUNTRIES

The WHO defines PC as an approach that improves the quality of life of patients—adults and children—and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, detailed assessment and treatment of pain, and other problems—whether physical, psychosocial, or spiritual.²⁰ The key for delivering PC is to identify peoples' priorities and customize the care to their preferences in a holistic manner. PC is not just limited to end-of-life care but involves caring for anyone with serious health-related suffering due to any severe illness including those receiving treatment with curative intent. With improved life expectancy, the burden of diseases with serious health-related suffering is expected to rise with approximately 87% increase between 2019 and 2026. This number is growing disproportionately in low- and middle-income countries (LMICs) with almost 155% increase expected by 2026 amounting to 40 million individuals.²¹ Most of the world's population does not have access to high-quality PC with only 14% of the eligible population receiving it—most being in high-income countries.²² To ensure that PC is delivered as part of Universal Health Care, the World Health Assembly resolution 67.19 specifically addressed this shortcoming and recommended measures to be taken. However, despite being recognized as a basic human right, progress in improving access and quality of PC services has been slow, more so in LMICs where 80% of the people who require it live in.

The situation is even more dismal in rural areas. A multitude of factors limit the effective delivery of PC in rural areas.²³ The geographical isolation and lack of infrastructure affects the availability of health care facilities and ability to recruit and retain health care workers, and often, patients need to travel long distances to access health care. Distance from health care facilities and the lack of transportation require considerable efforts from health care workers to visit patients. Often, health care workers are not equipped with the requisite knowledge to manage the symptoms and are overburdened with demands of care delivery for other diseases with very limited resources causing burnout. In addition, geopolitical instabilities often raise concern about the safety of the health care workers in many parts of the world. Complete lack or stockouts of much needed opioid analgesics because of regulatory compliances or limited budgets cause significant disruption in effective pain management and PC delivery causing despair among the patients and health care workers.²⁴ Poverty, socioeconomic position, health literacy, and education levels in rural areas add to disparities in access to PC. Societal misconceptions such as the addictive potential of opioids, belief that PC is only meant for those with cancer or in their last days, and cultural beliefs around death

further impede the integration of PC in the management of serious health-related suffering. The lack of awareness among policymakers prevents the implementation of frameworks to address several of these challenges. Often, these PC programs rely on external funding for drug supply and staffing, which is uncertain and not sustainable.²⁵

Several initiatives have been taken to address these issues for optimizing PC. As per the WHO model, the integration of PC with primary care or community care would reduce the need of traveling long distances to access PC and will allow for efficient use of the existing health system. The decentralization models improved the patient and provider relationship, led to reduction in cost of care and travel, and ensured privacy and confidentiality, but a major limitation was inconsistent drug supplies and lack of access to social support systems that are available in referral hospitals.²⁶

The use of digital health interventions is another method to address the lack of health care facilities and expertise close to patients' homes. In high-income countries, the use of digital health interventions such as video consulting, mobile health, and e-health solutions have shown higher patient satisfaction.²⁷ In low- and middle-income setting, the use of these interventions is largely limited to mobile health solutions using apps, which can provide an important tool for symptom management for patients and caregivers without the need for physical visits. However, widespread application is limited due to the need for smartphones, access to a stable internet connection, language barriers, risk of miscommunication, lack of privacy and confidentiality. These constraints and low digital literacy further limit the use of digital health interventions in rural areas in their current form.²⁸ Nevertheless, digital health solutions are promising tools to bridge disparities in access to PC in rural areas.

To address the shortage of health care professionals to deliver PC, training of alternative care providers has been suggested. Task shifting is especially helpful when health care professionals are either difficult to recruit and retain or have significant workloads. One such model has been the use of community health workers (CHWs). The CHWs work with patients, caregivers, and the community. Their role involves physical and pain assessment, pain management, assessment of adherence, psychosocial support for patients and the family, raising awareness, and record keeping. However, to ensure that the system works efficiently, special attention needs to be paid to training them beyond pain management to address complex psychosocial issues, beliefs around death and dying, and bereavement. Financial incentives and motivations need to be built in for the success of these programs.²⁹ A successful example of using volunteer CHWs is Neighborhood Network in PC in Kerala, India. This model uses the existing community health networks and receives financial support from the community and state government, which is key to sustaining the program.³⁰

Affordability of care often remains a challenge for those residing in rural areas, and this is a by-product of both the need to travel long distances and availing acute care facilities for symptom management or pursuing treatment without any meaningful benefit through loans and debt. This initiates a poverty cycle for generations to come. Inclusion of PC in universal health care to ensure supply of essential medicines for pain and symptom control can help prevent catastrophic health care expenditure. The essential package to alleviate most serious health suffering has been proposed by the Lancet Commission on PC and pain relief.³¹ The essential health benefits package contains the components of safe and effective provision of PC and pain relief interventions including medicines and equipment usable even in primary care settings. The cost is \$0.78 US dollars in low- and middle-income countries, a fraction of the cost of the universal health coverage package. Investing in PC can address health disparities by enhancing the health care systems. The investment would reduce the cost of illness and can be cost-effective by avoiding unnecessary hospitalization and resource utilization.²²

On the basis of existing knowledge, it is evident that there is no one model that will be applicable across all the rural population in LMICs. It will require understanding of the context, resources, culture, social determinants, willingness, and commitment from policymakers. A framework can be considered on the basis of the WHO's six elements for PC model development, which can be contextualized and adapted in different settings across LMICs to enhance services in rural areas. This is imperative to achieve the dream of dignity and comfort for all who have serious health-related suffering.³² This will require close cooperation between the community, health care professionals, policymakers, regulators, and nongovernmental organizations.

Each LMIC would need to develop or adapt resource-stratified guidelines for PC on the basis of the distribution pattern and cause of serious health-related suffering. The guidelines should clearly indicate the essential packages that should be deliverable in the remotest location. The delivery of essential package should be integrated with primary care or delivered through community workers or volunteers as per the resources available. This would improve the quality of life, likelihood of dying at home, quality of overall primary care, and thus, health equity. The development of guidelines should have strong community participation to ensure ownership, inclusivity of cultural beliefs, and social structure. This will ensure active community engagement in delivery and would facilitate adherence to treatment. Public awareness about PC, dying, and death would be an important step to address misconceptions and would be needed to pursue treatments that do not offer any improvement in underlying disease states.

Translation of guidelines to practice would need mechanisms for sustainable funding. This can be achieved through public-private partnership if the government funding

mechanism is unable to support the program. However, all measures should be taken to avoid gaps in funding. The essential medicines needed for PC are inexpensive and should be made available through health benefit packages. Innovative mechanisms for forecasting, amendments in regulations, and licensing would be needed to minimize stockouts and supply chain issues. Well-structured training programs with different competency levels catering to health care providers including specialists, general physicians, students, nurses, primary health care workers, and nonmedical personnel will play an important role in bringing awareness and enhancing the delivery of PC across primary, secondary, and tertiary care levels. This approach will ensure integration of PC at all levels, reduce the burden on PC specialists, and rationalize the use of clinically meaningful treatment with focus on quality of life and holistic care. There is a need to build strong monitoring and evaluation systems to identify areas that are inefficient and help improve the system on the basis of these learnings. A digital

framework for delivery that is mindful of available resources and ease of use by the end-users (patients, caregivers, health care workers, and policymakers) can help streamline delivery, documentation, and monitoring of the entire program.

Access to PC, considered a basic human right, is unfortunately not available in many parts of the world, especially in rural areas. Several challenges exist with lack of integration into routine medical care provision, inadequate trained human resources, societal misconceptions, and supply chains challenges for even basic medicines and pain relief. There is an urgent need to accelerate the pace of expansion of PC services, more so where they are needed the most, which needs strong commitment from governments, policymakers, health care providers, and the community. It is time that the relief of serious health-related suffering and the value of dying and death is respected and addressed appropriately.³³

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Sanders A, Cromartie J: Rural-urban continuum codes. <https://www.ers.usda.gov/data-products/rural-urban-continuum-codes>
- 2020 Snapshot: State of the Oncology Workforce in America. JCO Oncol Pract 17:30, 2021
- Xu Y, Fu C, Onega T, et al: Disparities in geographic accessibility of National Cancer Institute cancer centers in the United States. J Med Syst 4112:203, 2017
- Hung P, Shi K, Probst JC, et al: Trends in cancer treatment service availability across critical access hospitals and prospective payment system hospitals. Med Care 60:196-205, 2022
- Graves S: The costs of cancer in rural communities. American Cancer Society Cancer Action Network
- Bhatia S, Landier W, Paskett E, et al: Rural-urban disparities in cancer outcomes: Opportunities for future research. J Natl Cancer Inst 114:940-952, 2022
- Tucker-Seeley R, Abu-Khalaf M, Bona K, et al: Social determinants of health and cancer care: An ASCO policy statement. JCO Oncol Pract 20:621-630, 2024
- Chih MY, McCowan A, Whittaker S, et al: The landscape of connected cancer symptom management in rural America. J Appalach Health 24:64-81, 2020
- Gilbertson-White S, Chi Y, Wickersham S, et al: "Just living with them": Symptom management experiences of rural residents with advanced cancer. Oncol Nurs Forum 5:531-542
- Rural Health Information Hub: Cancer prevention and treatment in rural areas. <https://www.ruralhealthinfo.org/topics/cancer>
- Nekhlyudov L, Levit L, Ganz P: Delivering high-quality cancer care: Charting a new course for a system in crisis: One decade later. J Clin Oncol 42:4342-4351, 2024
- Stout N, Nikcevic D, Henderson T, et al: Improving rural clinical trial enrollment: Recommendations from the Rural Health Working Group of the Alliance Clinical Trials Network. J Clin Oncol 42:1722-1725, 2024
- Nelson KE, Wright R, Peeler A, et al: Sociodemographic disparities in access to hospice and palliative care: An integrative review. Am J Hosp Palliat Care 38:1378-1390, 2021
- Social determinants of health—Healthy people 2030. <https://odphp.health.gov/healthypeople/priority-areas/social-determinants-health>
- Doolittle GC, Spaulding AO: Providing access to oncology care for rural patients via telemedicine. JCO Oncol Pract 2:228-230, 2006
- Frydman JL, McKendrick K, Chen Y, et al: Disparities in the geographic distribution of palliative care specialists in 2022. J Gen Intern Med 39:1528-1530, 2024
- Lupu D, Quigley L, Mehfood N, et al: The growing demand for hospice and palliative medicine physicians: Will the supply keep up? J Pain Symptom Manage 55:1216-1223, 2018
- Dy SM, Kiley KB, Ast K, et al: Measuring what matters: Top-ranked quality indicators for hospice and palliative care from the American academy of hospice and palliative medicine and hospice and palliative nurses association. J Pain Symptom Manage 49:773-781, 2015
- Cai Y, Lalani N: Examining barriers and facilitators to palliative care access in rural areas: A scoping review. Am J Hosp Palliat Med 39:123-130, 2022
- <https://www.who.int/europe/news-room/fact-sheets/item/palliative-care>

21. Sleeman KE, de Brito M, Etkind S, et al: The escalating global burden of serious health-related suffering: Projections to 2060 by world regions, age groups, and health conditions. *Lancet Glob Health* 7:e883-e892, 2019
 22. ConnorS (ed): *Global Atlas of Palliative Care* (ed 2). London, United Kingdom, Worldwide Hospice Palliative Care Alliance, 2020
 23. Aregay A, O'Connor M, Stow J, et al: Strategies used to establish palliative care in rural low- and middle-income countries: An integrative review. *Health Policy Plan* 358:1110-1129, 2020
 24. Hartwig K, Dean M, Hartwig K, et al: Where there is no morphine: The challenge and hope of palliative care delivery in Tanzania. *Afr J Prim Health Care Fam Med* 6:e1-e8, 2014
 25. Bond MJ, Knopp A: Palliative care in northern Tanzania: Doing a lot with a little. *Int J Palliat Nurs* 24:296-303, 2018
 26. Phiri AS, Mulwafu M, Robbins ZH, et al: Toward enhanced decentralized palliative care services in Neno District, Malawi: A qualitative study. *BMC Palliat Care* 231:132, 2024
 27. Widberg C, Wiklund B, Klarare A: Patients' experiences of eHealth in palliative care: An integrative review. *BMC Palliat Care* 19:158, 2020
 28. Dilhani WNS, Mitchell S, Dale J, et al: A mixed-methods systematic review investigating the use of digital health interventions to provide palliative and end-of-life care for patients in low- and middle-income countries. *Palliat Care Social Pract* 18:26323524241236965, 2024
 29. MacRae MC, Fazal O, O'Donovan J: Community health workers in palliative care provision in low-income and middle-income countries: A systematic scoping review of the literature. *BMJ Glob Health* 55:e002368, 2020
 30. Chacko A: Palliative care movement in Kerala: A historic overview. *IDEAS Working Paper Series from RePEc*, 2017
 31. Knaul FM, Farmer PE, Krakauer EL, et al: Alleviating the access abyss in palliative care and pain relief-an imperative of universal health coverage: The Lancet Commission report. *Lancet* 391: 1391-1454, 2018
 32. Harding R, Hammerich A, Peeler A, et al: Palliative care: How can we respond to 10 years of limited progress. 2025. https://thewhpca.org/resource_category/wish-pc-report-2024/
 33. Sallnow L, Smith R, Ahmedzai SH, et al: Lancet Commission on the Value of Death. Report of the Lancet Commission on the Value of Death: Bringing death back into life. *Lancet* 399:837-884, 2022
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Enhancing Sexual Health for Cancer Survivors

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OVERVIEW

Changes to sexual function after cancer treatment are extremely prevalent, affecting up to 90% of female patients with cancer and 40%–85% of male patients with cancer. Sexual health concerns include low libido, genitourinary syndrome of menopause, dyspareunia, erectile dysfunction (ED), hypogonadism, body image concerns, and impacts on intimate relationships. Given the significant impact of sexual dysfunction on quality of life, oncology professionals should integrate sexual health discussions into routine patient care, regardless of the patient’s age, sex, or cancer type. Sexuality is best understood in a biopsychosocial framework and cancer treatments including chemotherapy, surgery, radiation, and endocrine therapy can affect all of these domains. Management of genitourinary syndrome of menopause includes nonhormonal and low-dose local hormonal options. Pelvic floor dysfunction and vaginal stenosis can be treated with pelvic floor physical therapy and use of vaginal dilator therapy. ED can be treated with phosphodiesterase type 5 inhibitors and if needed, interventions such as intracavernosal injection of vasoactive agents, urethral suppositories, vacuum erection devices, and surgical implants are available. Cancer treatments such as chemotherapy, radiation, and androgen-deprivation therapy can lead to hypogonadism in men, which can be treated with testosterone therapy, unless contraindicated. Psychosocial counseling, sex therapy, and couples counseling are options for impact to sexual response, body image, and relationship concerns. A comprehensive, patient-centered approach to sexual health can help improve outcomes and overall well-being for cancer survivors.

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A PATIENT PERSPECTIVE

As a breast surgeon who has had breast cancer three times, the treatments have challenged me in ways I never anticipated—especially in my intimate life. I thought I knew what to expect. A few menopausal symptoms that would settle in a couple of months. I could not have been more wrong. As a 40-year-old going through chemotherapy, tamoxifen and goserelin, followed by an oophorectomy and letrozole, and then fulvestrant, I was seriously underprepared. And what pains me is that as a breast surgeon, my own patients were never prepared for it either.

Dealing with a complete loss of libido is hard. It is harder still when you have to explain it to your partner without them feeling that you no longer love them. And there is the “bit of vaginal dryness” I told my patients about. The reality was that it now felt like a tube of sandpaper. The dryness meant I got labial skin tears after a long bike ride. Spontaneous penetrative sex was now impossible. Add to that the physical toll of surgery. My mastectomy left me struggling with body image issues; the mirror reflected scars and changes I was not prepared to accept. I felt a profound disconnect from the sexuality I once enjoyed, and I was left questioning my desirability.

What made these challenges even more isolating was the lack of information and support. I do not blame my team for not telling me, as I was just as guilty. But I did not know where to go for guidance and support. How do you bring up sex with your medical team? Will they really know how to help? The silence around these side effects made the journey even more painful. I was lucky. I got help from other patients with cancer who shared what worked for them. I met incredible oncologists online who are pushing the boundaries of sexual health in cancer care, and I share what they taught me with everyone I know.

A good sex life is a basic human need. It is not good enough to tell our patients that sex is off the table, thanks to the side effects of the drugs we give them. We need to tell them what to do to get back on track.

Liz O’Riordan, MD, PhD, FRCS

SEXUAL DYSFUNCTION AFTER CANCER

Female Sexual Dysfunction

Female cancer survivors experience changes in sexual health at high rates across tumor types. Sexual health concerns are reported in up to 90% of gynecologic cancer survivors, 75%–

PRACTICAL APPLICATIONS

- Sexual dysfunction is highly prevalent and distressing to individuals diagnosed with cancer, and oncology professionals should integrate sexual health discussions into routine patient care, regardless of the patient's age, sex, or cancer type.
- A comprehensive biopsychosocial approach to sexual health can address sexual health concerns in cancer survivors.
- Treatments for female patients include vulvovaginal nonhormonal and low-dose local hormonal options, pelvic floor physical therapy and vaginal dilator therapy, and psychosocial interventions.
- Treatments for male patients include management of erectile dysfunction with phosphodiesterase type 5 inhibitors, intracavernosal injection of vasoactive agents, urethral suppositories, vacuum erection devices, and surgical implants as well as treatment of hypogonadism and psychosocial interventions.

90% of breast cancer survivors,^{1,2} 77% of female lung cancer survivors.³ Seventy-five percent of colorectal cancer survivors report sexual health symptoms⁴ and 29%-49% of female stem cell transplant recipients develop sexual concerns, including graft-versus-host disease for vulvovaginal tissue.⁵

Male Sexual Dysfunction

Male sexual dysfunction is the complaint or impedance of proper sexual function and encompasses a variety of categories, including erectile dysfunction (ED), hypogonadism, low libido, orgasmic complaints, and ejaculatory complaints.⁶ The incidence of sexual dysfunction in the male population increases with age and is associated with psychosocial factors, physiologic factors, and intersectionality between these.⁷

A systemic review and meta-analysis of a population of men with cancer reported rates of ED of 40% across different tumor types.⁸ These rates are even higher after pelvic surgery, for example, radical prostatectomy, radical cystectomy, and low anterior or abdominoperineal resection, where <25% fully retain erection quality.⁸ Men with prostate cancer have higher rates of ED regardless of treatment with radical prostatectomy (84%) or watchful waiting (80%) compared with the control group (46%).⁹ Cancer treatments including chemotherapy, radiation, or androgen-deprivation therapy contribute to hypogonadism, and psychologic distress can also affect sexual function.⁸ Other conditions, such as anejaculation

and penile length loss, are not as well studied in the general population but may be more common in specific populations, such as those receiving surgical management for prostate cancer.¹⁰

Barriers to Addressing Sexual Concern

Although the high prevalence of sexual dysfunction after cancer is well known, patients report that their concerns about sexuality are not addressed. In a survey of young breast cancer survivors, 86% reported their health care provider was unable to address sexual health concerns.¹¹ There is a gender disparity as well, with 1 study of patients with cancer reporting that 53% of male patients versus 22% of female patients were asked about sexual changes.¹² Barriers to this discussion include discomfort about the topic, time constraints, and lack of resources and training.^{13,14} The lack of medical education in training programs continues currently as less than half of oncology fellowship program directors offered formal instruction on patient sexual health.¹⁵

Sexual and Gender Minority Inclusion Statement

Sexual and gender minority patients face additional disparities in cancer care and barriers in the medical system.¹⁶ For the purposes of this chapter, we use the terms female/woman and male/man and intend the information provided regarding specific anatomic areas to be applicable across gender identities.

ASSESSMENT OF SEXUAL HEALTH

Biopsychosocial Model of Sexual Health

Sexual health is best understood in a biopsychosocial model. This means that physical or biological factors, psychologic factors, and social—societal and interpersonal—factors all play a role in an individual's experience of sexuality.¹ Disturbances in any and all of these domains can lead to sexual dysfunction. This may be especially true for cancer survivors, who may experience profound physical, psychologic, and interpersonal changes through the course of cancer treatment and survivorship.^{3,14} When considering assessment of and treatment of sexual dysfunction in female cancer survivors, each of these domains must be considered. The physical factors may differ with different types and cancer and treatment. Many cancer treatments result in hormonal changes or induce iatrogenic menopause in women, including chemotherapy, surgery to remove functioning ovaries, pelvic radiation, and endocrine therapy such as aromatase inhibitors, tamoxifen, and gonadotropin-releasing hormone agonists for ovarian suppression. Cancer survivors may experience distress related to body image, fear of recurrence, depression, anxiety, and other psychologic changes that also affect sexuality.^{17,18} The impact of a cancer diagnosis extends to the patient's partner(s) shifting roles of intimate relationship to a caregiver/patient relationship and often creates financial and household burdens,

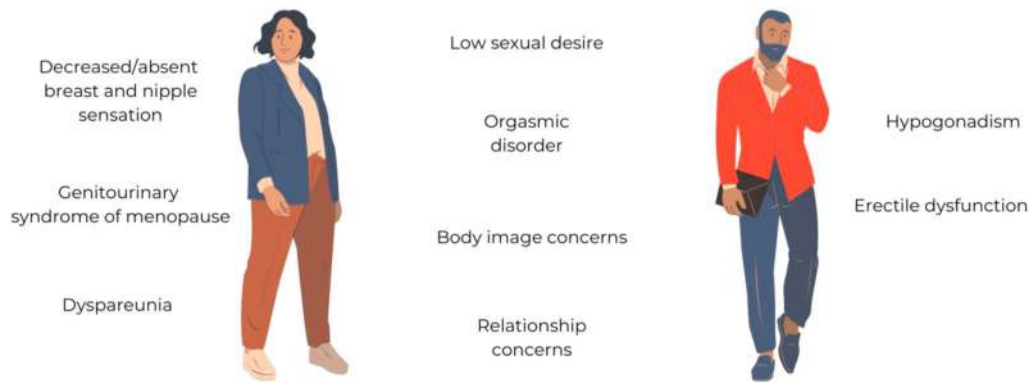


FIG 1. Sexual concerns after cancer.

affecting childcare, careers, and dating—all of which can affect the experience with sexuality.¹⁹

Methods of Female Sexual Function Assessment

Given the lack of inclusion in medical training,¹⁵ it is not surprising that discussion of sexual health is often omitted in medical assessment.¹¹ It is important to note that it is the medical professional's responsibility to raise the topic of sexual health, and there are many methods that can be used to address sexual health within the context of a routine clinic visit.²⁰ A checklist has been published and can be used for assessment of sexual and vulvovaginal symptoms.¹⁴ There are standardized questionnaires available that patients can complete, including the PROMIS sexual health short form and the Female Sexual Function Index. More simply, sexual health can be incorporated into routine assessment of symptoms or review of symptoms. It is key that this is not a one-time conversation but a discussion that is revisited over the course of cancer survivorship.²⁰

Methods of Male Sexual Function Assessment

The Patient-Reported Outcomes Measurement Information System Sexual Function and Satisfaction (PROMIS SexFS) tool is a screening questionnaire that can be administered in clinic settings to evaluate for general sexual dysfunction. Detailed medical and sexual histories of patients and their partners can elucidate general sexual dysfunction as well as one or more specific conditions for targeted treatment.²¹

Various domains of sexual dysfunction can be explored and function quantified by using validated questionnaires. The International Index of Erectile Function investigates sexual function through domains such as erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall sexual satisfaction.²² The Sexual Health Inventory for Men is a shortened version validated questionnaire to guide structured interviews.¹⁰

Diagnosis of hypogonadism should be performed through the use of accurate and precise measurements of serum testosterone compared with appropriate reference intervals in conjunction with symptomatology consistent with hypogonadism (ie, fatigue, cognitive dysfunction, loss of body hair, decreased libido, and depressed mood).²³

FEMALE SEXUAL HEALTH

Genitourinary Syndrome of Menopause

Genitourinary syndrome of menopause includes symptoms of vulvovaginal dryness, decreased lubrication, pain with penetrative intercourse, urinary frequency/urgency or dysuria, and other caused by a decrease in hormones associated with menopause²⁴ (Fig 1). This can occur in cancer survivors after treatments induce menopause or from the side effects of endocrine therapy. Low-dose vaginal hormones are the most effective treatment of these symptoms²⁴ (Table 1).

Vaginal moisturizers can be used on a regular basis three to five times per week to restore moisture to vulvovaginal tissue.²⁵ The addition of hyaluronic acid in a nonhormonal moisturizer can provide additional benefit.²⁶ Vaginal lubricants are intended to reduce discomfort from friction. While there are multitudes of products available, it is important that the medical professionals are able to advise patients on safe products, avoiding excessing additives that can be irritating and considering the pH and osmolality of the products²⁷ (Table 1).

Special consideration is given to the use of vaginal hormones in breast cancer survivors with hormone-sensitive tumors. ASCO guidelines have addressed the use of vaginal hormones in hormone receptor-positive breast cancer and stated that these can be used after discussion of risks and benefits.²⁰ Since the publication of these guidelines, several additional studies have been published. In 2022, a Danish observational cohort study of 8,461 women with breast cancer showed

TABLE 1. Treatment of Sexual Symptoms in Cancer Survivors

Symptom	Treatment	Notes
Genitourinary syndrome of menopause	Vulvovaginal moisturizers	Use 3-5×/week
	Hyaluronic acid-containing vulvovaginal moisturizers	More effective than plain moisturizer
	Vitamin E or D vaginal suppositories	
	Water-based lubricants	pH and osmolality matched, avoid irritants
	Silicone-based lubricants	May stain
	Vaginal estradiol cream	
	Vaginal estradiol insert/suppository	Low-dose products are available in 4 µg and 10 µg dosing
	Vaginal estradiol ring	
Pelvic floor dysfunction	Pelvic floor physical therapy	
Vaginal stenosis	Vaginal dilator therapy	
Sexual response	Psychosocial counseling	
	Sex therapy	
	Couples counseling	
	Mindfulness, hypnosis	
	Flibanserin	FDA approved for female hypoactive sexual desire disorder. Preliminary data available for women with breast or gynecologic cancer
	Bremelanotide	FDA approved for female hypoactive sexual desire disorder. No data available in individuals with cancer
	Testosterone	Limited data in female patients with cancer; lack of safety data in female survivors of hormonally mediated cancer
Body image	Psychosocial counseling	
Erectile dysfunction	Phosphodiesterase type 5 inhibitors	Sildenafil, tadalafil, vardenafil, avanafil
	Intracavernosal injection	Prostaglandin E1, papaverine, phentolamine
	Urethral suppositories	
	Vacuum erection devices	
	Penile prostheses	
Hypogonadism	Testosterone therapy	Contraindications include elevated hematocrit ≥54%, poorly controlled congestive heart failure, recent cardiovascular events, desired fertility, and ongoing treatment with androgen-deprivation therapy

Abbreviation: FDA, US Food and Drug Administration.

overall no increased risk of breast cancer recurrence with an adjusted relative risk of recurrence of 1.08 (95% CI, 0.89 to 1.32). In this study, overall mortality was reported to be lower with VET at 0.78 (95% CI 0.71 to 0.87). In the subgroup receiving aromatase inhibitors, there was a higher risk of recurrence at 1.39 (95% CI, 1.04 to 1.85), but no difference in mortality (hazard ratio [HR], 0.94 [95% CI, 0.70 to 1.26).²⁸ Limitations in interpretation of these data include that with this predated human epidermal growth factor receptor 2 testing and treatment, the vaginal estrogen doses used at that time were higher than the low-dose formulations currently available, and lower risk breast cancer was typically not treated with endocrine therapy.²⁹ A second study reported on breast cancer-specific mortality in two large cohorts from Scotland and Wales. There were 49,237 women included with 5% on vaginal estrogen therapy. There was a reduced risk of breast cancer-specific mortality in VET users overall with a HR of 0.77 (95% CI, 0.63 to 0.94) in the fully

adjusted model.³⁰ In addition, there was no increased risk of mortality for hormone receptor-positive breast cancer with HR 0.88 (95% CI, 0.62 to 1.25) or with aromatase inhibitors with HR 0.72 (95% CI, 0.58 to 0.91).³¹ A third study drawing data from a US Claims Network included 42,113 women with a diagnosis of genitourinary syndrome of menopause after diagnosis of breast cancer and showed that vaginal estrogen users had a similar overall recurrence to nonusers (risk ratio, 1.03 [95% CI, 0.91 to 1.18]), even among those with a positive estrogen receptor (risk ratio, 0.94 [95% CI, 0.77 to 1.15]). In this study, among the 91 patients identified receiving concurrent aromatase inhibitors and vaginal estrogen, there was a higher risk of recurrence reported (77.8% v 15.6%; RR, 5 [95% CI, 3.05 to 8.19]).³² Of note, the study did not control for the stage of the cancer, adherence to endocrine therapy, and had incomplete data on hormone receptor status, which limit the interpretation of this small subgroup on aromatase inhibitors.

Another option for vaginal hormone therapy is dihydroepiandrosterone (DHEA)/prasterone, a hormone that is converted to estrogen by intracellular aromatization. This was evaluated in an Alliance trial of two doses of DHEA (3.24 mg and 6.5 mg once daily) compared with plain moisturizers in patients with breast or gynecologic cancer. Serum estrogen levels were not elevated in aromatase inhibitor users.³³

Pelvic Floor Dysfunction/Vaginal Stenosis

Another source of dyspareunia is pelvic floor dysfunction. Symptoms of pelvic floor dysfunction include pain or impossibility of vaginal penetration, urinary retention or incontinence, and fecal incontinence (Fig 1). Referral to a skilled pelvic floor physical therapist and working with progressive vaginal dilators can improve this symptom²⁰ (Table 1).

Patients who receive pelvic radiation are at risk of vaginal stenosis, loss of elasticity of vaginal tissue, narrowing, and shortening. This can result in pain or inability to have vaginal penetration and medical pelvic examinations or vaginal agglutination—complete adherence of vaginal tissue. Although there are no standardized guidelines on the prophylactic care and management, some experts suggest advising patients to use vaginal dilator therapy as a preventative strategy.^{34–36}

Sexual Response

Sexual response encompasses desire, arousal, and orgasm. It is important to address physical symptoms first as if the patient is experiencing dyspareunia, it will obviously affect the desire to have sex. Interventions include referrals for psychosocial counseling, sex therapy, and couples counseling. There is ongoing research into other modalities including mindfulness³⁷ and hypnosis.³⁸ There are two US Food and Drug Administration–approved medications for hypoactive sexual desire disorder in premenopausal women.^{39,40} Flibanserin, a dual serotonin 1A receptor agonist/2A antagonist that has been evaluated in a single-arm pilot study of breast cancer survivors who may be on endocrine therapy, reported improvements in libido, satisfying sexual events, and decreased distress.⁴¹ Bremelanotide, a melanocortin agonist that is self-injected, has not been specifically studied in cancer survivors.³⁹ Data regarding testosterone for sexual response in female cancer survivors are limited, and there is a lack of robust safety data in female survivors of hormonally mediated cancer (Table 1).

Body Image and Relationships

Body image can be negatively affected through the course of cancer treatment as treatment modalities can result in loss or alteration of body parts, hair loss, weight gain, and other physical changes⁴⁸ (Fig 1). Female cancer survivors may experience body image changes including feeling that their

body has betrayed them or that they feel less whole or feminine. In addition, loss of sensation over the breast after mastectomies or receipt of a breast implant can result in feeling of disconnection or alienation from one's body.⁴² Body image should be assessed throughout cancer treatment and referrals for psychosocial counseling offered.²⁰ A cancer diagnosis affects not only the individual with cancer but also their partner(s). Couples-based psychosocial interventions can be offered to support relationship concerns²⁰ (Table 1).

Importance Across Age and Relationship Status

Cancer treatment can result in concerns about sexuality throughout the lifespan. Clinicians should be mindful of avoiding assumptions about the importance of sexuality to a patient on the basis of their age or marital/relationship status. For cancer survivors who are single, it can be challenging to navigate dating with a cancer diagnosis in terms of when to share their diagnosis as well as any challenges related to sexuality.

MALE SEXUAL HEALTH

Sexual dysfunction is a frequent issue among male patients with cancer of all ages, often manifesting as ED, reduced libido and/or testosterone deficiency (TD), and penile length changes or Peyronie disease. These concerns can arise because of cancer itself, the side effects of treatment, and the psychologic impact of a cancer diagnosis. Sexual health challenges after cancer therapy may lead to diminished quality of life; decreased self-esteem; changes in perceived masculinity; and increased rates of depression, anxiety, and relationship strain. A multidisciplinary approach with psychosocial support is recommended to address these issues effectively.

ERECTILE DYSFUNCTION

ED is defined as the persistent or recurrent inability to achieve or maintain an erection sufficient for satisfactory sexual performance. This condition can significantly affect quality of life, self-esteem, and overall well-being, particularly in male patients with cancer. While ED can occur because of various physiologic and psychologic causes, cancer-related ED is often linked to treatment-induced damage to vascular, neurologic, and hormonal pathways³⁰ (Fig 1).

Pathophysiology

The physiologic process of an erection involves a complex interaction of vascular, neurologic, hormonal, and psychologic factors. Sexual arousal triggers the release of nitric oxide from cavernous nerves, which induces smooth muscle relaxation and vasodilation within the corpora cavernosa. This increases arterial inflow and decreases venous outflow, leading to penile rigidity and glans engorgement.⁴³

Cancer-related ED can have multiple pathophysiologic origins, often categorized as organic, psychogenic, or mixed. Identifiable physiologic changes cause organic ED and tend to have a chronic and progressive onset, independent of situational factors. It includes vascular causes such as arterial insufficiency and venous leakage, neurogenic causes such as spinal cord injuries, brain injuries, multiple sclerosis, Parkinson disease, or iatrogenic damage from pelvic or spinal surgeries, as well as endocrinologic causes such as hypogonadism and diabetes-induced hormonal dysregulation.^{30,44}

Psychogenic ED, on the other hand, results from psychologic factors such as anxiety, stress, or depression.⁴⁵ It is often situational, characterized by a sudden onset of symptoms and often well-preserved nocturnal erections. This form of ED is caused by adrenergic overactivity, which inhibits the parasympathetic pathways necessary for nitric oxide release and smooth muscle relaxation. Many patients experience a combination of both organic and psychogenic factors, particularly those with chronic illnesses such as cancer, making the condition more complex to diagnose and treat.⁴⁴

Risk Factors of ED

Several risk factors contribute to the development and progression of ED in patients with cancer. Lifestyle factors such as obesity, smoking, excessive alcohol use, and a sedentary lifestyle are strongly linked to ED. In addition, metabolic conditions, including diabetes, hypertension, chronic kidney disease, and dyslipidemia, are associated with endothelial dysfunction and vascular impairment, leading to ED. Medications used for hypertension, depression, or chemotherapy can also interfere with erectile function, while sleep disorders, such as obstructive sleep apnea, may impair nitric oxide production and contribute to ED.⁴⁴

Cancer treatments play a significant role in the development of ED. Radical prostatectomy, radiation therapy, androgen-deprivation therapy (ADT), and chemotherapy can cause damage to nerves, blood vessels, or hormonal pathways, significantly affecting erectile function. Psychologic factors such as anxiety, depression, and cancer-related distress further exacerbate the condition. Given the strong association between ED and cardiovascular health, clinicians should consider screening for cardiovascular disease in patients presenting with ED without an obvious cause.^{44,46}

Treatments

Appropriate treatment can be tailored to the patient. Specialized testing, a comprehensive history, and a focused physical examination may be necessary to guide treatment for some patients. First-line treatment of any etiology of ED can be conservative or behavioral in nature. Patients suspected of psychogenic etiologies of ED especially can be referred to a mental health professional for treatment of

underlying contributing conditions as well as to promote treatment adherence. Many patients may also benefit from sexual counseling with or without their sexual partner(s) to promote open communication and healthy sex practices.⁴⁷ Men with certain risk factors or comorbid conditions can be counseled to engage in lifestyle modifications such as smoking or alcohol cessation, changes in diet, and increased physical activity to bolster erectile function.^{44,45} Multiple studies have demonstrated superior results in combined therapy with counseling (cognitive behavioral couples therapy or sex therapy) and medical therapy (oral therapy or intracavernosal injection [ICI]) compared with a single treatment alone³⁰ (Table 1).

Pharmacologic therapies remain a cornerstone of ED treatment. All men diagnosed with ED should be informed about oral treatment options with phosphodiesterase type 5 inhibitors (PDE5is), except where contraindicated. Medications within this class include sildenafil, tadalafil, vardenafil, and avanafil. PDE5i works by competitive inhibition of PDE5 receptors and thus a buildup of cyclic guanosine monophosphate promoting smooth muscle relaxation.⁴⁸ Patients should be educated to take the drug in an appropriate time frame before intercourse based on the half-life. Sildenafil and vardenafil should be taken on an empty stomach to avoid reduced or delayed absorption.⁴⁹ Side effects associated with PDE5is include headache, heartburn, facial flushing, nasal congestion, visual disturbances, and muscle pain. These medications should not be administered concomitantly with nitrate-containing medications.

Alternative medical therapies include medications applied by ICI or urethral suppositories. When oral medications are unsuccessful, ICI therapy offers an effective alternative. Vasoactive agents administered by ICI include prostaglandin E₁, papaverine, and phentolamine. Proper administration requires patient education and appropriate titration of dosing. These agents are effective in inducing erections in more than 90% of patients in the case of combination therapies.⁵⁰ Risks include priapism, pain, intracavernosal fibrosis, bleeding and bruising. Prostaglandin E₁ urethral suppositories can be placed before intercourse, which should be followed by penile massage. The efficacy of intraurethral suppositories has been reported between 46% and 65% in various studies.⁴⁴ Side effects include penile pain, urethral pain, dizziness, blood per urethra, and priapism. A noninvasive option is the use of vacuum erection devices, which use negative pressure to draw blood into the penis, with a constriction ring placed at the base of the penis to maintain the erection. Although these devices are effective, some patients experience adverse effects such as bruising, numbness, and penile coldness.⁵¹

Surgical intervention, in the form of penile prostheses, is an option for patients with refractory ED to first-line or second-line therapies or who are unwilling or unable to use these treatments for ED.³⁰ Surgical implants can be malleable

or inflatable, with high patient satisfaction rates exceeding 90%. The benefit of malleable devices is ease of use and low mechanical failure rate. They are particularly useful for patients with poor manual dexterity. Inflatable penile prostheses allow for the most similar experience to the flaccid and erect states of the penis.⁵² Risks include infection, device malfunction, pain, and the need for additional procedures.

HYPOGONADISM/TD AND LOW LIBIDO

Hypogonadism/TD is a condition characterized by insufficient testosterone production, leading to a range of physical and psychologic symptoms. It can be classified as primary hypogonadism, which results from testicular failure and inadequate testosterone production despite elevated gonadotropin levels, or secondary hypogonadism, which occurs because of dysfunction at the hypothalamic or pituitary level, resulting in decreased gonadotropin stimulation of the testes.²³ Testosterone plays a crucial role in regulating sexual desire, energy levels, mood, and metabolic health. Cancer-related TD can result from direct damage to the testes, as seen with radiation or chemotherapy, or from disruption of the hypothalamic-pituitary-gonadal axis, as seen in ADT for prostate cancer (Fig 1).

The symptoms of hypogonadism can be categorized into sexual, physical, and psychologic domains. Sexual symptoms include low libido, ED, and decreased morning erections. Physical symptoms manifest as fatigue, muscle loss, increased body fat, and reduced bone density. Psychologic symptoms may include depression, irritability, and cognitive decline. Diagnosis requires at least two separate early-morning serum testosterone measurements. Additional tests, including luteinizing hormone and follicle-stimulating hormone, can help differentiate primary from secondary hypogonadism.

Risk Factors

Testosterone levels naturally decline with age, but cancer treatments such as chemotherapy, radiation, and ADT can accelerate this process, leading to TD.⁵³ Obesity and metabolic syndrome further contribute to TD by increasing the conversion of testosterone to estrogen. Chronic illnesses,

including diabetes, chronic kidney disease, and liver disease, have also been linked to TD.⁵³

Treatment

Patients with hypogonadism for which treatment is not otherwise contraindicated can be offered treatment with testosterone therapy (TT). The goal of TT is to restore testosterone levels to the normal physiologic range, thereby improving libido, energy, and overall sexual function. Patients receiving TT require regular monitoring of testosterone levels and hematocrit.⁵⁴

TT modalities include injectable formulations, gels, patches, implanted pellets, and oral capsules. Alternative off-label options for hypogonadal men wishing to preserve fertility include hCG, selective estrogen receptor modulators, aromatase inhibitors, or a combination of these.²³ Contraindications to TT include elevated hematocrit $\geq 54\%$, poorly controlled congestive heart failure, recent cardiovascular events, desired fertility, and ongoing treatment with ADT^{23,55} (Table 1).

CONCLUSION

Given the significant impact of sexual dysfunction on quality of life, oncology providers should integrate sexual health discussions into routine patient care, regardless of the patient's age, sex, or cancer type. A biopsychosocial assessment is needed for a comprehensive sexual health evaluation. For women with cancer, this includes identification and management of physical symptoms including genitourinary syndrome of menopause, vaginal stenosis, and pelvic floor dysfunction as well as addressing psychosocial factors such as sexual response, body image, and relationship concerns. Early-morning testosterone levels can be assessed in male patients experiencing symptoms of low libido or fatigue. First-line ED treatments, including PDE5i, should be offered when appropriate, with further management options or referral considered if initial therapies are ineffective. Referral to a sexual health specialist can provide additional support for patients requiring more advanced interventions. A comprehensive, patient-centered approach to sexual health can help improve outcomes and overall well-being for cancer survivors.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

- Florez N, Kiel L, Meza K, et al: Sexual health assessment in women with lung cancer study: Sexual health assessment in women with lung cancer. *Cancer* 130:375-384, 2024
- Franzoi MA, Aupomerol M, Havas J, et al: Investigating sexual health after breast cancer by longitudinal assessment of patient-reported outcomes. *ESMO Open* 9:102236, 2024
- Kaufman R, Agrawal L, Teplinsky E, et al: From diagnosis to survivorship addressing the sexuality of women during cancer. *Oncologist* 29:1014-1023, 2024
- Canty J, Stabile C, Milli L, et al: Sexual function in women with colorectal/anal cancer. *Sex Med Rev* 7:202-222, 2019
- Li Z, Mewawalla P, Stratton P, et al: Sexual health in hematopoietic stem cell transplant recipients. *Cancer* 121:4124-4131, 2015
- Ospina-Serrano AV: Overview of sexual dysfunction in patients with cancer. *Clin Transl Oncol* 25:3369-3377, 2023
- Irfan M, Hussain NHN, Noor NM, et al: Epidemiology of male sexual dysfunction in asian and European regions: A systematic review. *Am J Mens Health* 14:1557988320937200, 2020
- Pizzol D, Xiao T, Smith L, et al: Prevalence of erectile dysfunction in male survivors of cancer: A systematic review and meta-analysis of cross-sectional studies. *Br J Gen Pract* 71:e372-e380, 2021
- Johansson E, Steineck G, Holmberg L, et al: Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: The Scandinavian Prostate Cancer Group-4 randomised trial. *Lancet Oncol* 12:891-899, 2011
- Arthur EK, Worly B, Carpenter KM, et al: Let's get it on: Addressing sex and intimacy in older cancer survivors. *J Geriatr Oncol* 12:312-315, 2021
- Hanson A, Guglielmino J, Ormerod C, et al: The changing informational needs of young women affected by breast cancer: A national needs assessment. *Cancer Research* 83, 2023 (abstr PD8-07)
- Taylor J, Ruggiero M, Maity A, et al: Sexual health toxicity in cancer survivors: Is there a gender disparity in physician evaluation and intervention? *Int J Radiat Oncol Biol Phys* 108:S136, 2020
- Reese JB, Soric K, Beach MC, et al: Patient-provider communication about sexual concerns in cancer: A systematic review. *J Cancer Surviv* 11:175-188, 2017
- Bober SL, Reese JB, Barbera L, et al: How to ask and what to do: A guide for clinical inquiry and intervention regarding female sexual health after cancer. *Curr Opin Support Palliat Care* 10:44-54, 2016
- Reese JB, Bauman JR, Soric KA, et al: Hematology and oncology fellow education about sexual and reproductive health: A survey of program directors in the United States. *J Clin Oncol* 41, 2023 (suppl 16; abstr 11029)
- Katz A, Agrawal LS, Sirohi B: Sexuality after cancer as an unmet need: Addressing disparities, achieving equality. *Am Soc Clin Oncol Educ Book* 42:11-17, 2022
- Sebri V, Durosini I, Triberti S, et al: The efficacy of psychological intervention on body image in breast cancer patients and survivors: A systematic-review and meta-analysis. *Front Psychol* 12:611954, 2021
- Morales-Sánchez L, Luque-Ribelles V, Gil-Olarte P, et al: Enhancing self-esteem and body image of breast cancer women through interventions: A systematic review. *Int J Environ Res Public Health* 18:1640, 2021
- Galbraith ME, Arechiga A, Ramirez J, et al: Prostate cancer survivors' and partners' self-reports of health-related quality of life, treatment symptoms, and marital satisfaction 2.5-5.5 years after treatment. *Oncol Nurs Forum* 32:E30-E41, 2005
- Carter J, Lacchetti C, Andersen BL, et al: Interventions to address sexual problems in people with cancer: American Society of Clinical Oncology clinical Practice guideline adaptation of Cancer Care Ontario guideline. *J Clin Oncol* 36:492-511, 2018
- Flynn KE, Lindau ST, Lin L, et al: Development and validation of a single-item screener for self-reporting sexual problems in U.S. adults. *J Gen Intern Med* 30:1468-1475, 2015
- Rosen RC, Cappelleri JC, Gendrano N: The International Index of Erectile Function (IIEF): A state-of-the-science review. *Int J Impot Res* 14:226-244, 2002
- Mulhall JP, Trost LW, Brannigan RE, et al: Evaluation and management of testosterone deficiency: AUA guideline. *J Urol* 200:423-432, 2018
- Faubion SS, Larkin LC, Stuenkel CA, et al: Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: Consensus recommendations from the North American Menopause Society and The International Society for the Study of Women's Sexual Health. *Menopause* 25:596-608, 2018
- Edwards D, Panay N: Treating vulvovaginal atrophy/genitourinary syndrome of menopause: How important is vaginal lubricant and moisturizer composition? *Climacteric* 19:151-161, 2016
- Carter J, Baser RE, Goldfrank DJ, et al: A single-arm, prospective trial investigating the effectiveness of a non-hormonal vaginal moisturizer containing hyaluronic acid in postmenopausal cancer survivors. *Support Care Cancer* 29:311-322, 2021
- WHO: Use and Procurement of Additional Lubricants for Male and Female Condoms: WHO/UNFPA/FHI360: Advisory Note. WHO, 2012. <https://apps.who.int/iris/handle/10665/76580>
- Cold S, Cold F, Jensen MB, et al: Systemic or vaginal hormone therapy after early breast cancer: A Danish observational cohort study. *J Natl Cancer Inst* 114:1347-1354, 2022
- Chlebowski RT, Aragaki AK, Pan K: RE: Systemic or vaginal hormone therapy after early breast cancer: A Danish observational cohort study. *J Natl Cancer Inst* 115:222-223, 2023
- Burnett AL, Nehra A, Breaux RH, et al: Erectile dysfunction: AUA guideline. *J Urol* 200:633-641, 2018
- McVicker L, Labeit AM, Coupland CAC, et al: Vaginal estrogen therapy use and survival in females with breast cancer. *JAMA Oncol* 10:103-108, 2024
- Agrawal P, Singh SM, Able C, et al: Safety of vaginal estrogen therapy for genitourinary syndrome of menopause in women with a history of breast cancer. *Obstet Gynecol* 142:660-668, 2023
- Mension E, Alonso I, Cebrecos I, et al: Safety of prasterone in breast cancer survivors treated with aromatase inhibitors: The VIBRA pilot study. *Climacteric* 25:476-482, 2022
- Damast S, Jeffery DD, Son CH, et al: Literature review of vaginal stenosis and dilator use in radiation oncology. *Pract Radiat Oncol* 9:479-491, 2019
- Charatsi D, Vanakara P, Evangelopoulou E, et al: Vaginal dilator use to promote sexual wellbeing after radiotherapy in gynecological cancer survivors. *Medicine (Baltimore)* 101:e28705, 2022
- Martins J, Vaz AF, Grion RC, et al: Topical estrogen, testosterone, and vaginal dilator in the prevention of vaginal stenosis after radiotherapy in women with cervical cancer: A randomized clinical trial. *BMC Cancer* 21:682, 2021
- Sears C, Millman R, Brotto LA, et al: Feasibility and acceptability of a group-based mindfulness intervention for sexual interest/arousal disorder following breast cancer treatment. *J Sex Marital Ther* 49:533-549, 2023
- Barton DL, Brooks TM, Cieslak A, et al: Phase II randomized controlled trial of hypnosis versus progressive muscle relaxation for body image after breast or gynecologic cancer. *Breast Cancer Res Treat* 178:357-365, 2019
- Kingsberg SA, Clayton AH, Portman D, et al: Bremelanotide for the treatment of hypoactive sexual desire disorder: Two randomized phase 3 trials. *Obstet Gynecol* 134:899-908, 2019
- Joffe HV, Chang C, Sewell C, et al: FDA approval of flibanserin—Treating hypoactive sexual desire disorder. *N Engl J Med* 374:101-104, 2016
- Goldfarb SB, Carter J, Arkema A, et al: Effect of flibanserin on libido in women with breast cancer on adjuvant endocrine therapy. *J Clin Oncol* 41, 2023 (suppl 16; abstr 12015)
- Lindau ST, Bensmaia SJ: Using bionics to restore sensation to reconstructed breasts. *Front Neurobot* 14:24, 2020
- MacDonald SM, Burnett AL: Physiology of erection and pathophysiology of erectile dysfunction. *Urol Clin North Am* 48:513-525, 2021
- Yafi FA, Jenkins L, Albersen M, et al: Erectile dysfunction. *Nat Rev Dis Primers* 2:16003, 2016
- Pozzi E, Fallara G, Capogrosso P, et al: Primary organic versus primary psychogenic erectile dysfunction: Findings from a real-life cross-sectional study. *Andrology* 10:1302-1309, 2022
- Gandaglia G, Briganti A, Jackson G, et al: A systematic review of the association between erectile dysfunction and cardiovascular disease. *Eur Urol* 65:968-978, 2014
- Althof SE: Role of psychosexual counseling as an adjuvant to pharmacotherapy in the treatment of erectile dysfunction. *J Sex Med* 20:236-239, 2023
- Lue TF, Tanagho EA: Physiology of erection and pharmacological management of impotence. *J Urol* 137:829-836, 1987
- Nichols DJ, Muirhead GJ, Harness JA: Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: Absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol* 53:5S-12S, 2002 (suppl 1)
- Elena BW, Zachary M, Haritha P, et al: Current status of intracavernosal injection therapy in erectile dysfunction. *Expert Opin Pharmacother* 24:925-933, 2023
- Brisson D, Seftel A, Sadeghi-Nejad H: The resurgence of the vacuum erection device (VED) for treatment of erectile dysfunction. *J Sex Med* 10:1124-1135, 2013

52. Chung E, Bettocchi C, Egydio P, et al: The International Penile Prosthesis Implant Consensus Forum: Clinical recommendations and surgical principles on the inflatable 3-piece penile prosthesis implant. *Nat Rev Urol* 19:534-546, 2022
 53. De Silva NL, Papanikolaou N, Grossmann M, et al: Male hypogonadism: Pathogenesis, diagnosis, and management. *Lancet Diabetes Endocrinol* 12:761-774, 2024
 54. Pencina KM, Travison TG, Cunningham GR, et al: Effect of testosterone replacement therapy on sexual function and hypogonadal symptoms in men with hypogonadism. *J Clin Endocrinol Metab* 109:569-580, 2024
 55. Salonia A, Bettocchi C, Boeri L, et al: European Association of Urology guidelines on sexual and reproductive health-2021 update: Male sexual dysfunction. *Eur Urol* 80:333-357, 2021
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Erratum: Updates on Treatments and Management of Nasopharyngeal Carcinoma

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The Editors of the *ASCO Educational Book* have authorized correction of the following error that published in the paper by Chua et al, entitled “Updates on Treatments and Management of Nasopharyngeal Carcinoma,” on April 10, 2025 (DOI <https://doi.org/10.1200/EDBK-25-472460>).

An author’s name, “Marret Grégoire, MD, PhD,” has been updated to “**Grégoire Marret, MD, PhD.**”

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