Beyond Performance Status: Optimize Cancer Care in Older Adults

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OVERVIEW

Older adults account for approximately 60% of new cancer diagnoses and 70% of cancer-related deaths, yet they remain consistently under-represented in clinical trials and are routinely assessed using performance status (PS) tools developed over seven decades ago. The Karnofsky Performance Status and Eastern Cooperative Oncology Group (ECOG) PS scales, while simple and widely adopted, fail to capture the multidimensional vulnerabilities that define physiologic aging. Studies show that 43%-69% of patients with good PS have geriatric assessment (GA)–identified deficits that independently predict treatment toxicity and survival. Comprehensive GA evaluates functional status, cognition, nutrition, comorbidity burden, polypharmacy, and social support—domains that PS entirely misses. Landmark randomized controlled trials, including GAP70+, GAIN, INTEGERATE, COACH, and PERI-OP, provide level 1 evidence that GA-guided interventions reduce grade 3-5 treatment toxicities by 10%-20% without affecting survival. These trials demonstrate two complementary mechanisms of benefit: treatment modification (dose attenuation and regimen selection) and intensive supportive care. Disease-specific evidence further supports GA integration, including colon, pancreatic, and lung cancers, hematologic malignancies, and surgical oncology. Practical screening tools, including the CARG score, CRASH score, Geriatric 8, and VES-13, can be completed in under 30 minutes and are feasible in routine practice. A proposed clinical algorithm integrates GA findings into treatment decision making alongside standard National Comprehensive Cancer Network, ASCO, and ECOG guidelines. Moving beyond chronologic age and PS toward an understanding of functional reserve is both an evidence-based imperative and an ethical obligation to the fastest growing and most vulnerable segment of the cancer population.

INTRODUCTION

I have a scenario.

- A new therapy is being introduced that reduces the risk of chemotherapy toxicity by 10%-20% in patients with relapsed malignancy. Four randomized trials demonstrated its efficacy.
- It enables more patients to tolerate their therapy and improve.
- It increases quality of life.
- The therapy is cost-effective with no out-of-pocket expense for patients.
- It has no toxicity.

The above scenario represents not a drug or device, but our capacity to improve the quality of life and treatment tolerance in older patients. Were it a drug, it would already be approved and universally adopted. The patients would demand it. So why is uptake of geriatric assessment (GA) so limited? Barriers include time constraints, uncertainty about applying the information, electronic health record integration challenges, reimbursement limitations, and the absence of specific guidelines. Yet in 2026, the clinical imperative demands action. Most assessments take only minutes, and many can be self-administered with family assistance. The remaining barriers are real but surmountable. Experience with these tools will streamline workflow over time.

What are the important issues in older patients with cancer? I polled 35 experts in geriatric oncology. The participants are members of the Alliance for Clinical Trials in Oncology Cancer in the Older Patient committee (Fig 1). The word cloud was a response to the question: "What are the important problems when treating older cancer patients?" It is notable that the words "survival" and "response" were not listed. It demonstrates the focus of decision making and treatment: maximizing benefit without compromising quality of life or function.

Many established guidelines exist from organizations, including ASCO, the European Society for Medical Oncology, and the National Comprehensive Cancer Network (NCCN), which inform decision making in everyday practice.[1,2] The

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PRACTICAL APPLICATIONS

- Clinicians should routinely incorporate brief geriatric assessment (GA) tools such as instrumental activities of daily living (IADL) evaluation, fall history, and polypharmacy review into the initial oncology consultation for patients 70 years and older. They can predict chemotherapy toxicity and survival outcomes beyond what performance status alone captures.
- Treatment decisions for older adults should be guided by functional status rather than chronologic age, using GA-derived frailty classification (fit, unfit, or frail) to determine whether standard full-dose therapy, dose-attenuated regimens, or primarily supportive care is most appropriate for an individual patient.
- GA-identified deficits in IADL should trigger domain-specific supportive care interventions, including pharmacist medication reconciliation, physical or occupational therapy referral, dietitian consultation, and shared decision making before or at the time of initiation of systemic cancer treatment.
- Clinical trialists, cooperative oncology groups, and regulatory bodies should mandate the inclusion of standardized GA measures in trial design and stratification for studies enrolling patients 65 years and older to generate the age-specific evidence base currently lacking for this population.
- Oncology practices can introduce GA gradually by starting with focused, self-administered screening instruments (eg, IADL questionnaire, G8, or VES-13) and building institutional familiarity before progressing to more comprehensive multidisciplinary evaluations as even partial implementation has been shown to improve treatment outcomes.

question then becomes: do we need specific guidelines for older patients? My answer is yes and no. First no. Many such guidelines have been published. We can take the established guidelines and, if necessary, modify them with a GA. Guidelines for dose modification have also been published, but these are not age-specific; instead, they are comorbidity-specific, such as those related to renal dysfunction.[3] Now yes. However, these guidelines are based on data in which older patients are under-represented, and they have not included any form of GA. Therefore, the data are difficult to extrapolate to older patients. So, older patient-specific guidelines and clinical trials will also be needed. Either way, clinicians must familiarize themselves with GA that will most help their patients.

Table 1 summarizes the benefits of following established guidelines. These guidelines offer a structured approach to making decisions. Ultimately, oncology guidelines are tools that connect emerging clinical research with the delivery of consistent, evidence-based oncologic care.

THE DEMOGRAPHIC CHANGES

The demographic changes in the past 25 years have altered the priorities of clinical oncology. As life expectancy has increased globally, cancer has become increasingly recognized as a disease primarily affecting the older population. By 2045, the global incidence of cancer is expected to increase by 63%, rising from 20 million to over 32.6 million cases. The older cancer population is expected to nearly double by 2045, rising 94% to 20.5 million cases. For those 75 years and older, the increase is even sharper at 129%.[4]

Despite these projections, the evidence for treating this population has remained underevaluated. Older adults account for approximately 60% of new cancer diagnoses and 70% of cancer-related deaths annually, yet they have consistently represented less than one third of participants in randomized controlled trials (RCTs) that establish the standard of care. Table 2 shows examples of the representation of older patients. A specific example is the adjuvant treatment of colon cancer. The fluorouracil, leucovorin, and oxaliplatin trial had one third of patients older than 65 years, but the median age at diagnosis was 66-70 years.[5] The folinic acid, fluorouracil, irinotecan, and oxaliplatin trial of metastatic pancreatic cancer had a median age of 61 years and excluded patients older than 76 years.[6] The median age at diagnosis is 71 years. This lack of data creates a critical knowledge gap. Aging brings physiologic and psychosocial changes that can alter how drugs work or increase their toxicity.[7-11]

THE EVOLUTION AND LIMITATIONS OF PERFORMANCE STATUS

The Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) scales have been the standard in oncology for assessing patient status for over seven decades.[12-14] The KPS was first introduced in 1948 by Karnofsky to evaluate the benefit of nitrogen mustard in treating lung cancer. It is a physician-rated scale ranging from 0 (dead) to 100 (well-functioning) in 10-point increments, meant to summarize a patient's ability to perform daily activities and the level of assistance required. The ECOG PS was developed later, in 1960, by Zubrod, simplifying KPS into a six-point scale ranging from 0 (fully active) to 5 (dead).[15]

The use of these measurements began when the therapeutic index of chemotherapy was low. Chemotherapy in the 1940s through 1970s was toxic, with low response rates and very low curative potential. These PS measures persisted for several reasons: simplicity, no required training, and the eyeball test approach. The persistence of these indices is largely historic and sentimental. However, as we have

FIG 1. Word cloud.

learned, this way of assessing a patient is less accurate than a more detailed evaluation.[16] Table 3 summarizes this.

THE REPRESENTATION CRISIS IN CLINICAL TRIALS

The lack of older adults in cancer clinical trials, specifically those older than 70 years and those with comorbid health conditions, complicates the management of malignancy. A US Food and Drug Administration analysis of trial enrollment between 1995 and 2002 found that 36% of participants were at least age 65 years. A subsequent analysis (2015-2019) showed that global participation among those older than 65 years had decreased to 31%.[17,18]

The under-representation is not uniform across cancer types and modalities[19] (Table 2). When older adults are included in

TABLE 1. Benefits of Established Guidelines

Objective	Clinical Impact
Standardization	Reduces medical errors and establishes a universal baseline for best practice
Evidence synthesis	Translates high-volume trial data into clear diagnostic and therapeutic pathways
Equity and access	Mitigates geographic and socioeconomic disparities by defining a minimum standard of care
Safety and efficiency	Optimizes the therapeutic window to reduce toxicity and streamline complex decision making

TABLE 2. Enrollment of Older Adults in Clinical Trials by Cancer Type and Therapeutic Class

Trial Type	Percentage of Older Adults (≥ 65 years)
Prostate cancer trials	49
Pancreatic cancer trials	38
Breast cancer trials	37
Non–small cell lung cancer trials	34
Immunotherapy trials	20
Cytotoxic agent trials	44
Hormonal/targeted therapy trials	54

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TABLE 3. Limitations of Traditional Performance Status Measures

Limitation	Description
Subjectivity	Health care provider-assessed; prone to bias and interobserver variability
Physician-patient discordance	50% interobserver agreement; physicians often overestimate patient function
Unidimensional	Focuses solely on physical function; misses cognitive, nutritional, psychosocial domains
Poor sensitivity	43%-69% of patients with good PS (ECOG 0-1, KPS ≥ 80) have GA-identified deficits
Binary nature	Essentially binary (yes/no to standard care); lacks nuance for modern therapies
Historical context	Developed for low therapeutic index chemotherapy; less relevant in the era of immunotherapy

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GA, geriatric assessment.

trials, systematic reviews indicate that their survival outcomes are generally similar to those of younger patients.[19] This suggests that chronologic age is a poor surrogate for treatment benefit and that physiologic fitness should be the primary determinant of eligibility. Almost all the clinical trials that patients have participated in do not include any GA of age-related analysis.[9,20] It has been a missed opportunity. There is a desperate need to increase the evidence base of older patients. There is developing research on efficacy and effectiveness as a ratio and can inform patients about probabilities of benefit.[21]

GA: A MULTIDIMENSIONAL APPROACH

Definition and Domains of GA

Comprehensive GA is a multidimensional evaluation of older patients that encompasses domains critical for understanding physiologic reserve and vulnerability to treatment-related toxicity.[22] It serves as an important tool because traditional oncology measures, such as PS, are often inadequate for accurately assessing older individuals. A GA identifies vulnerabilities in areas like cognition, nutrition, and social support. Studies show that GA often uncovers hidden problems even in patients with a good performance status (PS 0-1).[23-27] Table 4 shows the core domains, assessment tools, and clinical relevance.

The value of GA over PS lies in its evaluation of multiple domains simultaneously. While PS focuses on physical function, GA identifies clinically relevant deficits across the following areas:

Cognitive and Psychologic Status

Cognitive impairment and depression are potent predictors of treatment toxicity and nonadherence, yet they are rarely detected in a standard oncologic history and physical examination. GA uses validated instruments such as the Mini-Mental State Examination[28] to identify patients whose executive function may be insufficient to manage complex oral regimens or to participate meaningfully in informed consent. Depression screening is similarly predictive of poor treatment tolerance and quality-of-life outcomes.

Functional Status: Activities of Daily Living and IADL

Activities of Daily Living (ADLs) assess basic self-care (bathing, dressing, continence), whereas Instrumental Activities of Daily Living (IADLs) evaluate higher-order tasks such as managing finances, arranging transportation, shopping, and self-administering medications. IADL tasks are more cognitively and physically demanding than ADLs and frequently represent the earliest detectable sign of incipient functional decline.

Dependence on even one IADL task is associated with increased chemotherapy toxicity and unplanned hospitalization, even in patients with an ostensibly good PS. Of clinical importance is the intersection of IADL impairment and social support: a score of IADL <6 combined with the absence of a caregiver produces a nine-fold increase in the risk of

TABLE 4. Core Domains of Comprehensive Geriatric Assessment

Domain	Assessment Tools	Clinical Relevance
Functional status	ADLs, IADLs	Predicts treatment tolerance, hospitalization, and survival
Physical performance	TUG, SPPB, gait speed	Correlated with survival, complications, and functional decline
Comorbidity	Charlson index	Predicts polypharmacy risks and drug interactions
Cognition	Mini-Cog, BOMC	Identifies risk for delirium and treatment-related decline
Nutrition	MNA, weight loss	Predictor of treatment tolerance, survival
Psychologic status	GDS, distress thermometer	Associated with QOL, treatment adherence, and mortality
Social support	Living situation, caregiver availability	Influences treatment feasibility and medication adherence
Polypharmacy	Medication review, PIMs	Risk factor for adverse drug events, falls, and toxicity

Abbreviations: ADLs, activities of daily living; GDS, geriatric depression scale; IADLs, instrumental activities of daily living; MNA, mini nutritional assessment; PIMs, potentially inappropriate medication; QOL, quality of life; SPPB, short physical performance battery; Blessed orientation-Memory-Concentration; TUG, timed get up and go.

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nonadherence to oral cancer therapies.[29] This finding has direct implications for treatment planning. It may necessitate a transition from an oral to an intravenous regimen or mandate formal caregiver supervision as a prerequisite for oral therapy.

Objective Functional Performance Tests

Unlike PS, which is subjective and clinician-assigned, GA incorporates objective performance measures that provide a more accurate characterization of physiologic reserve. The timed up and go (TUG) test, which is a measure of the time required for a patient to rise from a chair, walk 3 m, and return, is a particularly useful surrogate for physical reserve. In a study of home dwellers 65 years and older followed up over a maximum period of 11.8 years, there was robust evidence of an association between poor TUG score and increased all-cause mortality, which was equally strong in men and women. There was also an association with falls and the onset of ADL disability.[30]

Significant unintentional weight loss predicts early mortality independent of a patient's activity level and is a core component of any GA. Malnutrition impairs chemotherapy tolerance and wound healing and is associated with increased treatment-related hospitalizations. Identification of nutritional deficits allows for targeted intervention, including a dietitian referral, nutritional supplementation, or community services such as home meal delivery before or concurrent with treatment initiation.

Social Support and Polypharmacy

Social isolation is strongly associated with treatment nonadherence and poor outcomes, yet it is entirely invisible to PS scores. Polypharmacy, which is the concurrent use of five or more medications, is highly prevalent in older adults. It increases the risk of drug-drug interactions that can exacerbate chemotherapy toxicity or precipitate falls. GA-triggered medication review using structured criteria (eg, Beers Criteria or STOPP/START) can mitigate these risks and, in some cases, enable standard dosing that would otherwise have been contraindicated.[31]

GA Compared With Physician Judgment

Multiple studies have demonstrated that GA adds critical information beyond what oncologists capture through standard evaluation, including PS. Repetto et al found that 43% of patients with good PS had fragile comprehensive geriatric assessment (CGA).[24] Jolly et al[27] demonstrated that 69% of patients with KPS ≥ 80 had at least one GA-identified deficit.

Providers often miss abnormalities that a GA detects. In one study, GA revealed unknown issues in over 50% of patients. This led physicians to change treatment plans for roughly 25%-39% of those patients.[32] Table 5 shows the evidence of the difference between PS (physician judgment) and GA.

TABLE 5. Evidence of Discordance Between Performance Status and Geriatric Assessment

Study	Key Findings
Repetto et al[24]	43% of patients with good PS had fragile CGA
Jolly et al[27]	69% of KPS ≥80 patients had at least one GA-identified deficit
Eriksen et al[33,34]	Oncologists underestimated frailty compared with modified GA
Seedor et al[32]	Providers missed 25.5% of GA-detected abnormalities, surprised by 33%, planned changes for 39%
Kenis et al[35]	GA revealed unknown problems in > 50%; led to interventions in 25%
Hajjar et al[36]	No correlation between CGA and ECOG PS/KPS, 43% danger zone

Abbreviations: CGA, comprehensive geriatric assessment; ECOG PS, Eastern Cooperative Oncology Group performance status; GA, geriatric assessment; KPS, Karnofsky Performance Status.

PREDICTORS OF TREATMENT TOXICITY AND SURVIVAL, INCLUDING GERIATRIC SYNDROMES

Functional Status: IADL

Functional status, particularly IADL, has emerged as one of the most powerful predictors of treatment outcomes in older patients with cancer. IADLs encompass higher-order activities required for independent living, such as managing finances, preparing meals, shopping, using transportation, managing medications, and using the telephone.

IADL in Predicting Treatment Toxicity

Jablonowska-Babij et al[37] found that the IADL scale was a significant predictor of adverse events, with an inverse relationship to nonhematologic adverse events in older patients with lymphoma treated with R-CHOP. The study also showed that IADL predicted treatment response, overall survival (OS), and progression-free survival (PFS).

Cohen et al demonstrated that a deficit accumulation frailty index derived from a self-administered comprehensive GA, which includes IADL assessment, predicted grade 3+ toxicity, dose reduction, dose delay, and treatment discontinuation. It also determines the frailty status.[23] IADL evaluation can be performed in a few minutes.

Falls as a Geriatric Syndrome and Predictor

Falls represent a critical geriatric syndrome that both predicts and results from cancer treatment-related complications. Ji et al[38] found that falls before chemotherapy predicted toxicity-related hospitalization during adjuvant chemotherapy for breast cancer. The GAP70+ trial demonstrated that GA-guided interventions reduced the risk of falls by 42% relative to usual care.[39] Every patient needs to be questioned about their fall history. Table 6 shows the remaining parameters predictive of toxicity and survival.

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TABLE 6. Summary of Predictors of Toxicity and Survival in Older Patients With Cancer

Predictor	Association With Toxicity	Association With Survival
IADL impairment	Increased grade 3+ toxicity, dose reduction, discontinuation	Decreased OS and PFS across cancer types
Physical performance	Treatment complications, functional decline	Gait speed <0.8 m/s associated with increased mortality
Falls (pre-treatment)	Toxicity-related hospitalization; 42% RR reduction with GA	Marker of frailty predicting worse OS
Cognitive impairment	Increased delirium, medication errors, complications	Independent predictor of mortality
Malnutrition/weight loss	Increased treatment toxicity and complications	Higher 90-day and long-term mortality
Polypharmacy	Adverse drug events, drug interactions, falls	Associated with increased mortality
Comorbidity burden	Reduced treatment tolerance, increased complications	Competing mortality risks
Frailty (composite)	Dramatically increased grade 3-5 toxicity	Independent mortality risk

Abbreviations: GA, geriatric assessment; IADLs, instrumental activities of daily living; OS, overall survival; PFS, progression-free survival; RR, response rate.

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Geriatric Syndromes

Geriatric syndromes are multifactorial clinical conditions that do not fit into discrete disease categories and frequently coexist with cancer in older adults.[40-42] They are significant because they represent a state of increased vulnerability to stressors, and they are powerful predictors of adverse outcomes, including increased morbidity, treatment toxicity, functional decline, and mortality. Geriatric syndromes are often hidden and remain invisible to standard oncology PS measures like ECOG PS or KPS. Table 7 lists them with their clinical relevance.

Practical Implementation

Some form of GA is essential in the care of older adults with cancer, but this does not mean that every patient requires a full comprehensive GA. Such an approach would be unrealistic in routine oncology practice. The goal is not to transform oncologists into geriatricians, but to incorporate key geriatric principles into everyday care.

Importantly, clinicians do not need specialized geriatric training to perform meaningful assessments. Research consistently demonstrates that brief, focused evaluations using easily measured geriatric parameters are both feasible in busy practices and highly predictive of important outcomes, including treatment toxicity. Many components can be self-administered by patients or completed with assistance from family members, minimizing disruption to clinic workflow. Tools such as the CARG clinical tool[43] and the CRASH score[44] predict chemotherapy toxicity more accurately than clinical judgment alone. Frailty screening instruments, including Geriatric 8 (G8)[45] and Vulnerable Elders Survey 13 (VES 13),[46-48] offer additional practical options. Studies show that these assessments can often be completed in under 30 minutes, particularly when incorporating self-administered elements.[49,50] ASCO has also published a practical framework for GA[51] (Table 8). The assessment of frailty can be simplified by using the Balducci index and similar criteria.[52-54]

Landmark GA Intervention Trials

The field of geriatric oncology has seen a surge in practice-changing data, particularly from trials evaluating the impact of GA and GA-guided interventions. These landmark trials provide high-level evidence that objective assessment of

TABLE 7. Common Geriatric Syndromes in Older Patients With Cancer

Geriatric Syndrome	Brief Explanation and Clinical Relevance
Frailty	A state of increased vulnerability to stressors resulting from a decline in physiologic reserves across multiple systems. It is a substantial predictor of poor treatment tolerance, chemotherapy toxicity, and shortened survival
Falls and fall risk	Falls are prevalent in older patients with cancer and lead to significant injury, loss of independence, and hospitalization. A history of falls is also a key predictor of chemotherapy toxicity
Malnutrition	Often exacerbated by chemotherapy-induced nausea, malnutrition is a consistent independent predictor of early death and treatment failure
Cognitive impairment	Includes conditions like dementia and delirium. It affects a patient's decision-making capacity and is an independent risk factor for postoperative complications
Depression	One of the most common syndromes, affecting up to 25% of patients with cancer. It is associated with unexpected hospitalizations, functional decline, and poorer survival
Polypharmacy	The concurrent use of multiple medications (often defined as >5) increases the risk of drug-drug interactions, falls, and chemotherapy-related toxicity
Sarcopenia	The loss of muscle mass (sarcopenia) and muscle strength. Both are prognostic factors for poor treatment outcomes and overall survival in older adults
Urinary incontinence	A critical syndrome associated with many adverse outcomes, including depression, anxiety, higher mortality rates, and an increased risk of falls
Sleep disorders	Includes insomnia and excessive daytime sleepiness. These disorders adversely affect a patient's quality of life and can influence treatment outcomes
Delirium	An acute state of mental confusion, particularly problematic in the postoperative period or during intensive care. It is associated with long-term cognitive dysfunction and mortality

TABLE 8. Validated Screening Tools in Geriatric Oncology

Tool	Items	Threshold	Key Domains	Clinical Utility
G8	8	≤14 = abnormal	Appetite, weight loss, mobility, neuropsychologic status	Predicts shortened survival and treatment toxicity; validated trigger for CGA
VES-13	13	Score ≥3 = vulnerable	Functional and physical deficits; self-administered	Identifies risk of health deterioration; may underestimate comorbidities
fTRST	5	≥1 = geriatric risk	Functional status, cognition, social situation	Highly sensitive for predicting functional decline in ADLs
CFS	Pictogram	1-9 scale	Overall frailty level; clinician-assessed	Predicts postoperative complications and treatment utility
CARG	Composite	Low/intermediate/high risk	Falls, hearing, medication use, GA variables	Outperforms KPS in predicting grade 3-5 chemotherapy toxicity
CRASH	Composite	Heme/nonheme risk	Cognition (MMSE), nutrition (MNA), regimen intensity	Provides separate hematologic and nonhematologic toxicity estimates
GFI	15	≥4 = significant frailty	Physical, social, and psychologic frailty domains	Associated with increased mortality in patients receiving chemotherapy

Abbreviations: ADLs, activities of daily living; CGA, comprehensive geriatric assessment; CFS, clinical frailty scale; fTRST, Flemish Triage Risk Screening Tool; GA, geriatric assessment; GFI, Groningen frailty indicator; KPS, Karnofsky performance status; MMSE, mini-mental state examination; MNA, mini nutritional assessment; VES-13, Vulnerable Elders Survey-13.

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frailty can mitigate the harms of aggressive therapy without compromising survival. The trials are summarized in Table 9.

The GAP70+ trial involved 718 older adults (age 70+ years) with advanced solid tumors or lymphoma. The intervention provided oncologists with GA summary and management recommendations. Patients in the intervention arm had significantly lower risk of grade 3-5 toxicities (50% *v* 61%; response rate = 0.74; $P < .01$). While survival at six months was not significantly different, the reduction in severe toxicity underscores the value of GA.

The mechanism of benefit was through treatment modification. There were more patients in the intervention group who received reduced-intensity regimens at cycle one (49% *v* 35%). Secondary benefits included fewer falls (42% relative risk reduction) and greater medication discontinuation.[39]

The GAIN Trial

The GAIN trial enrolled 605 older adults (age 65+ years) randomly assigned 2:1 to GA-driven intervention or standard of care.[55] A multidisciplinary team led the GAIN trial intervention. It resulted in a 10.1% reduction in severe chemotherapy toxicity. It also more than doubled the completion rate of advance directives (24.1% *v* 10.4%). Critically, toxicity reduction was achieved without reducing chemotherapy dosing.

The mechanism of benefit was through intensive supportive care implementation. In the intervention group, 76.8% of

TABLE 9. Summary of Landmark Geriatric Assessment Intervention Trials

Trial	No.	Population	Primary End Point/Result	Impact
GAP70+[39]	718	70+ years, advanced cancer	11% absolute reduction in grade 3-5 toxicity ($P <$ .01)	GA-guided care reduces toxicity without survival loss via dose modification
GAIN[55]	605	65+ years, chemotherapy	10% reduction in grade ≥3 toxicity ($P = .02$)	MDT improves tolerability through supportive care without dose reduction
INTEGERATE[56]	154	70+ years, systemic therapy	Significant improvement in HRQOL at 18 weeks	Geriatrician comanagement preserves QOL and reduces hospitalization
PERI-OP[57]	137	65+ years, GI surgery	Reduced ICU use and length of stay (per-protocol)	Perioperative GA improves surgical recovery when intervention is completed
COACH[58]	541	Advanced cancer + caregivers	Increased satisfaction and aging-related conversations ($P < .001$)	GA improves communication and patient-centered care
DuMontier et al[59]	160	75+ years, Hematologic malignancies	No survival benefit; 3-fold increase in EOL discussions ($P = .05$)	Enhanced goal-concordant care and advance care planning

Abbreviations: COACH, comprehensive geriatric assessment with extensive patient coaching for improving quality of life in older patients with solid tumors receiving systemic therapy; EOL, end of life; GA, geriatric assessment; GAIN, geriatric assessment-driven intervention; GAP, Geriatric Assessment for Patients 70 years and older; HRQOL, health-related quality of life; ICU, intensive care unit; INTEGRATE, Integrated Geriatric Assessment and Treatment Effectiveness; MDT, geriatrics-trained multidisciplinary team; PERI-OP, perioperative geriatric intervention; QOL, quality of life.

recommended interventions were implemented, compared with only 12.5% in standard care.[56] This highlights that simply identifying problems is insufficient. A structured multidisciplinary implementation is required.

The INTEGERATE Trial

The INTEGERATE trial studied 154 adults 70 years or older who were starting systemic therapy.[56,60] Patients receiving geriatrician-led management had significantly better health-related quality of life at 18 weeks, lower rates of hospital admission, and fewer early treatment discontinuations. The integrated oncogeriatric care group also had significantly fewer unplanned hospital admissions at 24 weeks.

The COACH Trial

The COACH trial enrolled 541 older patients and their caregivers to determine if GA information could improve communication.[61,62] Providing GA summaries to oncologists significantly improved patient and caregiver satisfaction with communication ($P = .04$) and increased the number and quality of aging-related conversations (mean 8.12 *v* 4.43; $P < .001$).

Transplant Trial

DuMontier et al investigated embedding geriatrician consultations for 160 transplant-ineligible patients 75 years and older. While the intervention did not improve 1-year OS ($P = .65$), it significantly increased documented end-of-life goals-of-care discussions by over three-fold (odds ratio 3.12, $P = .05$).[63]

Mechanisms of Benefit

An important distinction emerges from comparing GAP70+ and GAIN: there are multiple pathways through which GA can reduce toxicity. GAP70+ achieved benefit primarily through treatment modification. This included dose reductions and less intensive regimens. GAIN achieved similar toxicity reduction through intensive supportive care without changing chemotherapy dosing.

This suggests that GA can guide two complementary strategies: (1) identifying patients who require dose modification and (2) identifying supportive care interventions that allow patients to receive full-dose therapy with better tolerance. The optimal approach depends on individual patient characteristics, cancer type, treatment goals, and available resources.

The benefits of a geriatric evaluation are now clear. High-level evidence supports its use. What does the clinician do? Interventions will depend on the level of vulnerability and frailty.

GA as a Modifier of Standard Oncologic Therapy

Based on the GA domains described above, clinicians can implement modifications to standard treatment guidelines through several distinct plans. Modifications will depend on the anticipated toxicity and goals of therapy (Table 10).

TREATMENT CONSIDERATIONS FOR OLDER ADULTS WITH CANCER

Physiologic Considerations

Aging is associated with physiologic changes that alter the pharmacokinetics and pharmacodynamics of chemotherapy. For instance, oxaliplatin-induced neurotoxicity affects 15%-20% of older patients and can severely impair daily functioning.[63] These physiologic changes and comorbidities can affect the pharmacokinetics and pharmacodynamics of drug therapy.[64]

De-Escalation Versus Standard Treatment

A critical question in geriatric oncology is when treatment de-escalation is appropriate. Evidence from multiple randomized trials suggests that vulnerable older adults identified through GA can benefit from less intensive regimens without compromising survival. The key is identifying which patients are truly vulnerable versus those who are fit and can tolerate standard therapy. This is particularly important in a noncurative setting to avoid toxicity and maintain function and quality of life.

TABLE 10. GA-Based Modifications to Standard Oncologic Therapy

Strategy	GA Domain–Targeted	Mechanism	Key Evidence/Tools
Pre-emptive dose reduction	Functional status, comorbidity	Proactive dose optimization before toxicity occurs	GAP70+, GAIN trials; 10%-20% reduction in grade 3-5 toxicity
Regimen simplification	Functional status, comorbidity, PS	Shift from polychemotherapy to single-agent, oral, or alternative therapy	Approximately 23% of GA-guided patients transitioned to monotherapy
Toxicity risk quantification	Multiple GA domains	Objective, numeric risk estimates to justify plan modifications	CARG, CRASH calculators
Competing mortality assessment	Comorbidity, life expectancy	Identifies patients unlikely to outlive treatment lag-to-benefit period	Lee index, Schonberg index, ePrognosis platform
Targeted supportive interventions	Functional deficits, nutrition, polypharmacy	Rehabilitate reversible deficits to enable standard dosing	PT referral, nutritional support, medication reconciliation

Abbreviations: GA, geriatric assessment; PS, performance status; PT, physical therapy.

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TABLE 11. Colon Cancer: Treatment Strategy by Setting, Fitness, and Molecular Profile

Setting	Patient Type	Preferred Regimen	Key Evidence/Notes	Median Age, Years
ADJUVANT (stage II-III)				
Stage III, fit	Oxaliplatin-eligible	CAPOX ×3 months	IDEA trial: noninferior to 6 mo; dramatic ↓ grade 3/4 neurotoxicity	61-67
Stage III, fit	Age ≥70 years (oxaliplatin benefit attenuated)	Capecitabine monotherapy	HR 1.02 for oxaliplatin in patients 70 years and older (*v* 0.74 in younger); 31.4% early discontinuation	>70
Stage II-III, vulnerable	Frail/pre-existing neuropathy	Capecitabine 1,000 mg/m^2 twice a day (approximately 80% dose)	SIOG/ESMO endorsed; AVEX trial data; ↓ hand-foot syndrome and diarrhea	76
dMMR, stage III	Any fitness	Adjuvant ICI (eg, atezolizumab)—emerging	dMMR = poor 5-FU response in stage II; predictive of ICI benefit	
METASTATIC (mCRC)				
Fit, any molecular	Standard candidate	Doublet chemotherapy (FOLFOX/FOLFIRI/CAPOX) + bevacizumab	Bev benefits preserved in patients 70 years and older (PFS HR, 0.54; OS HR, 0.79); ↑ATE risk > 65 (1.7%→4.5%+)	
dMMR/MSI-H	First line	Pembrolizumab monotherapy	KEYNOTE-177: PFS 16.5 *v* 8.2 months (HR, 0.60); better QOL *v* cytotoxic doublet	
dMMR/MSI-H	Nonmetastatic, neoadjuvant	Nivolumab + ipilimumab	NICHE-2: 95% MPR, 67%-69% pCR; may avoid surgery in frail elderly	
BRAF V600E	Second line+	Encorafenib + cetuximab	BEACON: mOS 9.3 months; 35% prevalence in elderly makes this highly relevant	
BRAF V600E	1st line (emerging)	Encorafenib + cetuximab + FOLFOX	BREAKWATER: 60.9% ORR *v* 40% chemotherapy alone	
HER2+, RAS/RAF WT	Pretreated	Trastuzumab + tucatinib OR T-DXd	MOUNTAINEER: 38.1% ORR; DESTINY-CRC01: 45.3% ORR (monitor for ILD)	
RAS WT	Any fitness	Cetuximab/panitumumab with or without chemotherapy	Effective as mono or combo; skin/nail toxicity harder to manage in elderly; exclude HER2 amp/BRAF before use	

Abbreviations: CAPOX, capecitabine and oxaliplatin; dMMR, deficient mismatch repair; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; mCRC, metastatic colorectal cancer; mOS, median overall survival; MPR, major pathological response; MSI-H, microsatellite instability-high; OR, odds ratio; ORR, overall response rate; OS, overall survival; QOL, quality of life; pCR, pathologic complete response; PFS, progression-free survival; T-DXd, Trastuzumab Deruxtecan; WT, wild type.

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In colorectal cancer, the AVEX trial demonstrated that capecitabine plus bevacizumab in patients 70 years and older significantly improved the median PFS from 5.5 months to 9.1 months (hazard ratio [HR], 0.53; $P = .0002$), establishing this as standard first-line therapy for older patients ineligible for intensive chemotherapy.[65,66]

The PANDA trial compared mFOLFOX6 plus panitumumab against 5-fluorouracil (FU)/leucovorin plus panitumumab in 183 patients 70 years and older. Median PFS was similar (9.6 *v* 9.0 months), but the doublet regimen had higher rates of grade >2 adverse events (60% *v* 37%), suggesting that the doublet adds toxicity without proportional efficacy gain.[67]

DISEASE-SPECIFIC CONSIDERATIONS

Colon Cancer

Table 11 describes the molecular evaluation of colon cancer and treatment options for older patients. The table separates adjuvant treatment and metastatic disease therapy.

MOLECULAR EPIDEMIOLOGY AND GENETIC EVALUATION

Adjuvant and Metastatic Treatment: A Practical Framework

Treatment decisions must balance absolute benefit against toxicity risk. Treatment completion is the strongest predictor of survival. Patients receiving <50% of the planned oxaliplatin dose eliminate its benefit (ACCENT analysis). Chronologic age necessitates meticulous stratification, not exclusion from therapy, for geriatric oncology patients. Genetic evaluation is a prerequisite because *BRAF V600E* and *dMMR* mutations are increased in older patients.[68] For specific deficient mismatch repair colon cancers, pembrolizumab is the preferred first-line therapy. Neoadjuvant immunotherapy (IO) can also be highly effective. In some cases, it may even allow frail patients to avoid surgery entirely.[69] Oxaliplatin offers no significant survival benefit for patients older than 70 years (HR, 1.02) and should be limited to a 3-month course of capecitabine and oxaliplatin in fit patients; capecitabine (1,000 mg/m^2 twice a day) is the preferred oral fluoropyrimidine for vulnerable individuals.

TABLE 12. Evaluation Framework: The Simplified Geriatric Assessment in LBCL

Category	Criteria (ADLs, IADLs, comorbidities)	Goal of Care
FIT	Independent in ADLs and instrumental ADLs; <3 mild comorbidities	Curative: Full-dose standard therapy
UNFIT	Impairment in IADLs or 3+ mild comorbidities/1 moderate comorbidity	Curative (adapted): dose-attenuated therapy to maintain efficacy while reducing toxicity
FRAIL	Impairment in ADLs, presence of geriatric syndromes (dementia), or severe comorbidities	Palliative: Symptom control and quality of life; often non–chemotherapy-based

NOTE. Patients should be categorized based on fitness rather than chronologic age. This is typically done using the simplified geriatric assessment or the EPI.
Abbreviations: ADLs, activities of daily living; EPI, Elderly Prognostic Index; IADLs, instrumental activities of daily living.

While bevacizumab benefits persist across age groups, rigorous cardiovascular risk assessment is mandatory before using it in patients older than 75 years as the risk of arterial thromboembolic events significantly increases in those older than 65 years (1.7% → ≥4.5%).[60,62,70,71]

GI Malignancies

The Dana Farber Cancer Institute is developing pragmatic ways to evaluate older patients. The Older Adults with Gastrointestinal Cancer (OAGC) Program at Dana-Farber Cancer Institute: OAGC screens all adults 65 years and older for frailty across validated domains of physical and social function, cognition, disability, nutrition, and polypharmacy using an Epic-integrated patient assessment. Thus far, over 3,000 older adults have been assessed with an 80% response rate across seven languages reflecting our diverse patient population (English, Spanish, Portuguese, Russian, Traditional Chinese, Haitian Creole, and Arabic), documenting 30% as frail or prefrail, facilitating genomic testing and clinical trial consideration, and coordinating care inclusive of early geriatrician and pharmacist comanagement, nutrition, social work, palliative care, and supportive oncology consultation alongside their oncologic care. Frailty data are correlated with genomic and disease-related information to inform treatment decisions for older adults.[72] A validated questionnaire is being used.[73]

Pancreatic Cancer

The GIANT trial (EA2186) was designed for vulnerable patients 70 years and older with metastatic pancreatic adenocarcinoma. Vulnerability was defined by screening GA. The trial compared gemcitabine and nab-paclitaxel with 5-FU, leucovorin, and liposomal irinotecan. No significant difference in median OS was observed (4.7 *v* 4.4 months; $P = .72$), but both attenuated combinations proved to be feasible for older, vulnerable patients.[38]

Lung Cancer and IO

The ACHIEVE trial (EA5221) is an active phase III trial targeting older adults (age 70+ years) with stage IIIB-IV non–small cell lung cancer and a PD-L1 tumor proportion score of 1%-49%, comparing pembrolizumab alone with chemotherapy plus pembrolizumab. A key feature is the inclusion of patients with an ECOG PS of 2, a group often ineligible for standard IO trials.[74]

Hematologic Malignancies

Older adults with hematologic malignancies face distinct challenges related to bone marrow reserve and high treatment intensity. Disease-specific frailty indices have been developed, such as the International Myeloma Working Group myeloma frailty score.[70] In diffuse large B-cell lymphoma, the IADL scale has proven to be a significant predictor of adverse events, treatment response, and survival in older patients receiving R-CHOP therapy.[45] Klepin has shown the benefit of GA and physical therapy (PT) in older patients with acute leukemia.[75-78]

Diffuse Large B-Cell Lymphoma

There has been significant progress in the evaluation of older patients with large cell lymphoma. This is an example[79,80] (Table 12 and 13).

TABLE 13. Limitations of Traditional Performance Status Measures

Phase	Fit Patient	Unfit/Very Old Patient	Frail Patient
A: Evaluation	No IADL/ADL limits	1+ IADL limits	ADL limits/dementia
B: Frontline	Full R-CHOP	R-miniCHOP	Palliative/rituximab-only
C: Relapse	CAR-T or ASCT	CAR-T or bispecifics	Best supportive care

Abbreviations: ADL, activities of daily living; ASCT, autologous stem cell transplant; CAR-T, Chimeric Antigen Receptor T-cell; IADL, instrumental activities of daily living; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

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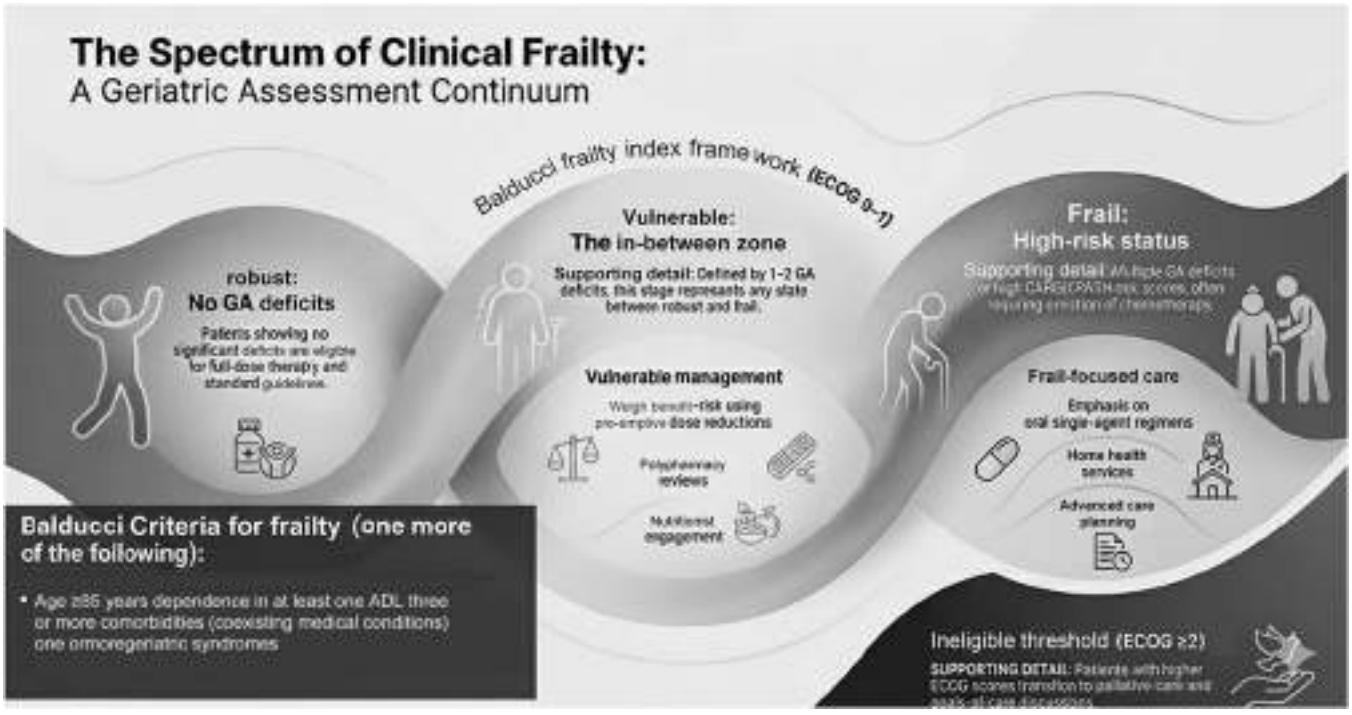

FIG 2. Navigating the spectrum of clinical frailty. ADL, activities of daily living; ECOG, Eastern Cooperative Oncology Group; GA, geriatric assessment.

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Treatment Algorithm: Frontline and Relapsed Settings

The following algorithm outlines the clinical pathway suggested by Lugtenburg and Mutsaers (2023) and Iyengar et al (2024):

Phase A: Pretreatment (the prephase)

- Action: 5-7 days of prednisone (100 mg) ± vincristine.
- Purpose: Improves PS and "cools down" the inflammatory state of the lymphoma before starting intensive chemotherapy.

Phase B: Frontline Therapy Selection

- Standard (Fit): R-CHOP (21-day cycles).
- Very Old (>85 years) or Unfit: R-miniCHOP (dose-reduced cyclophosphamide, doxorubicin, and vincristine).
- Cardiac Contraindications: Replace doxorubicin with etoposide or gemcitabine.
- Supportive Care: MANDATORY use of granulocyte colony-stimulating factor (prophylaxis for neutropenia) and antibiotics (if high risk).

Phase C: Relapsed/Refractory Management

- Early Relapse (<12 months): Chimeric Antigen Receptor T-cell therapy (now standard of care for older adults who can tolerate the process).
- Late Relapse (>12 months): Salvage chemotherapy followed by autologous stem-cell transplant (for fit patients).
- Ineligible for intensive therapy:
  - Bispecific antibodies (eg, epcoritamab, glofitamab).
  - Polatuzumab vedotin + rituximab + bendamustine.

TABLE 14. Immunotherapy Efficacy in Older Patients With TNBC—Key Trial Findings

Trial	Setting	Agent	Overall Population	Older Patients (≥65 years)	Outcome
KEYNOTE-522	Early-stage TNBC	Pembrolizumab	Significant improvement in pCR and EFS	Trends favored pembrolizumab (pCR +22.3%; EFS HR, 0.79); not statistically significant (n = 71)	Promising, underpowered
IMPASSION-031	Early-stage TNBC	Atezolizumab	Significant improvement in pCR	No age-stratified data reported	Data unavailable
KEYNOTE-355	Metastatic TNBC (PD-L1 CPS ≥10)	Pembrolizumab	Improved median OS in the high–PD-L1 subgroup	mOS 28.3 *v* 12.6 months (HR, 0.51)—benefit stronger than the overall population	Significant benefit
IMPASSION-130	Metastatic TNBC	Atezolizumab	No significant OS i mprovement	No significant OS improvement in any age group	No significant benefit

NOTE. Summary of age-stratified outcomes from major randomized trials evaluating checkpoint inhibitors in triple-negative breast cancer.
Abbreviations: CPS, combined positive score; EFS, event-free survival; HR, hazard ratio; mOS, median overall survival; OS, overall survival; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

TABLE 15. Evidence-Based Recommendations for Optimal Treatment of Older Patients With Cancer

No.	Recommendation	Key Action	Evidence/Tool
Assessment recommendations			
1	Implement geriatric assessment for all patients age 70-75+ years before systemic therapy	Assess: ADLs/IADLs, falls risk, cognition, nutrition, polypharmacy, comorbidities	G8, VES-13, CARG (<30 minutes; self-administered)
2	Do not exclude patients based on age or performance status alone	Use physiologic reserve (GA) as the primary predictor of outcomes	Fit older adults benefit equally from standard therapy
3	Prioritize IADL impairment as a key toxicity/mortality predictor	Administer Lawton IADL scale	5 minutes; predicts grade 3+ toxicity, discontinuation, and survival
4	Incorporate objective physical performance testing when feasible	Measure gait speed, TUG, or SPPB; gait speed <0.8 m/s → consider dose modification	Gait speed, TUG, SPPB
5	Screen for cognitive impairment using brief validated tools	Identify deficits to guide caregiver involvement and simplified regimens	Mini-Cog or BOMC (3-5 minutes)
Treatment recommendations			
6	Use GA to guide treatment intensity; avoid reflexive dose reduction by age	Fit patients → standard dose; vulnerable patients → up-front reduction or intensive support	GAP70+, GAIN trial evidence
7	Implement comprehensive medication review and polypharmacy management	Pharmacist-led review; deprescribe benzodiazepines, anticholinergics, NSAIDs	Drug-drug interaction screening
8	Address falls risk proactively before and during treatment	PT referral, home safety evaluation, gait training, medication review	GAP70+: 42% relative risk reduction in falls
9	Optimize nutritional status before and during treatment	Refer to nutritionist; offer dietary counseling and oral supplements for at-risk patients	Malnutrition predicts toxicity and mortality
10	Consider disease-specific de-escalation strategies in vulnerable patients	mCRC: capecitabine + bevacizumab or 5-FU/LV + biologics as alternatives to doublet chemo	Equivalent survival with reduced toxicity
Implementation and systems recommendations			
11	Establish multidisciplinary geriatric oncology teams	MDT: oncologist, NP, social worker, pharmacist, nutritionist, PT/OT	GAIN: 76.8% *v* 12.5% success rate for supportive care interventions
12	Reduce logistical barriers through telehealth and integrated delivery	Telehealth GA consults; self-administered GA at home; integrate into oncology visits	Reduces separate appointment burden
13	Prioritize patient-centered communication and shared decision making	Use GA results to discuss treatment goals, tolerance, and patient priorities	COACH trial: improved patient/caregiver satisfaction
14	Facilitate advance care planning and goals-of-care discussions	Especially for patients with limited life expectancy; document ACP/GOC	GA-guided interventions increase advance directive completion
15	Use patient-reported outcomes to capture symptomatic toxicity	Use PRO-CTCAE and electronic PRO systems for real-time symptom monitoring	PRO captures patient perspective distinct from physician assessment
16	Continue assessment longitudinally after treatment completion	Determine chronic toxicity of treatment	

Abbreviations: ACP, advance care planning; ADLs, activities of daily living; BOMC, Blessed Orientation Memory Concentration; GA, geriatric assessment; GOC, goals of care; IADLs, instrumental activities of daily living; LV, leucovorin; mCRC, metastatic colorectal cancer; MDT, multidisciplinary team; NP, nurse practitioner; PRO-CTCAE, Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events; PT, physical therapy; PT/OT, physical/occupational therapy; SPPB, Short Physical Performance Battery; TUG, timed up and go.

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IO in Triple-Negative Breast Cancer in Older Women

A systematic review examined how well IO works in older patients (65 years and older) with triple-negative breast cancer (TNBC), a population historically under-represented in clinical trials[81,82] (Table 14).

Researchers searched major databases and identified 18 papers from 11 RCTs using the checkpoint inhibitors atezolizumab, durvalumab, and pembrolizumab. Only four of the 11 RCTs reported age-specific results for patients 65 years and older, and older patients represented just 18.1% of the combined enrollment across those trials.

Data on IO efficacy in older patients with TNBC remain sparse and largely underpowered. Pembrolizumab shows the most promise, particularly in the metastatic high–PD-L1 subgroup, but dedicated trials enrolling adequate numbers of older patients are needed before firm conclusions can be drawn.

Surgical Considerations

The PERI-OP trial evaluated a perioperative geriatric intervention for patients 65 years and older undergoing surgery for GI cancer. Per-protocol analysis for those who completed both pre- and postoperative intervention components

TABLE 16. Proposed GA-Guided Treatment Modification Algorithm

PS Classification	GA Category	Treatment Approach	Supportive Interventions
ECOG ≥2	—	Ineligible for standard chemotherapy; consider best supportive care or clinical trial	Palliative care referral; goals-of-care discussion
ECOG 0-1 → robust	No significant GA deficits	Standard guidelines; full-dose therapy	Routine monitoring; standard supportive care
ECOG 0-1 → vulnerable	1-2 GA deficits in key domains	Pre-emptive dose reduction or less intensive regimen; weigh benefit-risk	Polypharmacy review; PT/OT; nutritionist; caregiver engagement
ECOG 0-1 → frail	Multiple GA deficits; CARG/CRASH high risk	Consider omitting chemotherapy; best supportive care or oral/single-agent regimen	Social work; home health services; advanced care planning

Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance Status; GA, geriatric assessment; OT, occupational therapy; PS, performance status; PT, physical therapy.

showed a significant reduction in postoperative length of stay (5.9 *v* 8.2 days; $P = .02$).[57]

Researchers in multiple myeloma and ovarian cancer have developed disease-specific scores for the evaluation of older patients.[83,84]

A Proposed Clinical Algorithm

Integrating the foregoing evidence, the following algorithm provides a practical workflow for GA-guided treatment modification in older patients with cancer (Tables 15, 16). The algorithm is designed to be performed alongside but not replace standard NCCN, ASCO, or ECOG guidelines. The GA functions as a mandatory step when the treating oncologist is considering systemic therapy in an older patient.

A key principle in this algorithm is that an adequate ECOG PS score of 0-1 should be interpreted only as a requirement before proceeding to a GA evaluation. It is not a definitive determination of treatment fitness. This algorithm recommends omitting chemotherapy for any patient classified as frail by a GA. This applies even if they have a good PS, especially if tools like CARG or CRASH predict a high risk of severe toxicity. It needs to be emphasized that the availability of less toxic treatment, such as IO or targeted therapy, changes the therapeutic ratio. It may allow for patients with marginal fitness or vulnerable have drug therapy. While Table 16 seems to indicate that these classifications are stepwise and fixed, Figure 2 is a more accurate representation. It shows that between robust and frail, there are not well-defined demarcations; they are more fluid. There is a continuum between robust, vulnerable, and frail; in addition, anything not robust or frail is vulnerable. The Balducci Frailty criteria are useful in this setting.

IADL-Guided Supportive Care Interventions

When GA identifies IADL dependency, the following domain-specific supportive care interventions should be initiated concurrently with or before the start of treatment:

- Medication management: Pharmacist referral for medication reconciliation, implementation of pill-dispensing aids or medication calendars, simplification of regimens, and consideration of transitioning from oral to intravenous therapy when independent administration cannot be ensured.
- Physical rehabilitation: PT or occupational therapy referral for strength and balance training, home safety evaluation, assessment for assistive devices, and home exercise programs.
- Nutritional support: Dietitian referral, nutritional supplementation, and community-based services (eg, home meal delivery programs) to ensure caloric adequacy during treatment.
- Cognitive and capacity assessment: Formal evaluation of decision-making capacity, early identification of a health care proxy, and family counseling regarding risks of chemotherapy-induced delirium or postoperative cognitive dysfunction.
- Caregiver engagement: Multidisciplinary care planning with identified caregivers and structured monitoring of functional response to treatment to guide escalation or de-escalation of supportive interventions.

CONCLUSION

The convergence of demographic trends, therapeutic advances, and clinical trial evidence demands a fundamental

BOX 1. WHAT TO DO IN A FEW MINUTES

1. Watch the patient walk to the examination room and get on the table
2. While examining the patient can ask for a 3- to 5-minute memory recall and ADL/IADL
3. Evaluate for polypharmacy with routine drug reconciliation
4. History of falls
5. While the patient waits, they can do a self-evaluation, such as some questions of G8 or the CARG toxicity predictor
6. Balducci's frailty criteria

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shift in how we assess and treat older adults with cancer. PS measures, developed over seven decades ago, are inadequate for the complexity of modern geriatric oncology. The evidence is clear: 43%-69% of patients with good PS have GA-identified deficits that independently predict treatment toxicity and survival.

Comprehensive GA provides a multidimensional evaluation that captures functional status, comorbidities, cognition, nutrition, polypharmacy, and psychosocial factors. They are domains that PS entirely misses. Landmark randomized controlled trials are GAP70+, GAIN, INTEGERATE, COACH, and PERI-OP. They provide randomized clinical trials that provide strong evidence that GA-guided interventions reduce treatment toxicity and improve patient-centered outcomes. GA-guided interventions significantly reduce grade 3-5 toxicities by 10%-20% without compromising survival.

Specific GA parameters have emerged as powerful independent predictors of outcomes. IADL impairment predicts both treatment toxicity and survival. Physical performance measures provide objective, reproducible assessments. Falls, cognitive impairment, malnutrition, and polypharmacy are all modifiable risk factors that GA can identify and target.

The clinical trial landscape is evolving but remains inadequate for the geriatric population. Despite older adults accounting for 60% of cancer diagnoses and 70% of cancer deaths, they represent less than one third of trial participants. Trial end points remain focused on tumor response rather than the functional independence and quality of life that older adults prioritize.

Moving forward requires action at multiple levels: regulatory bodies must enforce inclusive enrollment criteria, cooperative groups must integrate GA into trial design, pharmaceutical sponsors must include patient-centered end points, and practicing oncologists must incorporate GA into routine clinical care. The evidence base now supports this transition. What remains is the will to implement it.

Table 15 summarizes the evidence-based recommendations for optimal treatment of older patients with cancer. Table 16 combines the results of PS and GA to give a suggested treatment approach. It is not necessary or likely feasible for a CGA. There are many rapid ways of assessing patients. Just watching a patient walk and ask a few simple questions, that is, IADL, falls, cognition, and will go a very long way to more completely assess the patient. By moving away from chronologic age and toward a nuanced understanding of functional reserve and patient preferences, the oncology community can ensure that older adults receive therapies that are both effective and aligned with their priorities for survival and quality of life. The evidence base for GA is now robust. It has been validated in multiple randomized trials. Assessment does not need to be exhaustive or applied uniformly to every patient. A focused strategy is often sufficient. For example, identifying deficiencies in IADL, documenting falls, or reviewing polypharmacy as part of routine medication reconciliation can yield highly actionable information. Practices can introduce these elements gradually, gaining familiarity with their value and refining workflows over time. GA is not an added burden but an investment in better clinical judgment and improved patient care. A suggestion for an evaluation when very little time is available is given in Box 1.

Implementation requires commitment from clinicians, researchers, regulators, and payers to fundamentally transform how we approach cancer care in the fastest-growing and most vulnerable segment of the cancer population. It is an ethical imperative. They deserve nothing less.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Harnessing Artificial Intelligence for the Management of Patients With GI Cancers

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OVERVIEW

Artificial intelligence (AI) has the potential of reshaping GI oncology by enabling more nuanced interpretation of complex clinical, imaging, and molecular data, while supporting more timely and patient-centered decisions. This article synthesizes perspectives across the GI cancer continuum, beginning with a framework for context-aware AI that emphasizes metadata, multimodal integration, and lifecycle quality and safety as foundations for trustworthy tools that clarify, rather than conceal, uncertainty. Next, AI in endoscopy is highlighted as an example in clinic practice, focusing on computer-aided detection and diagnosis systems that not only increase adenoma detection rates but also raise questions about surveillance burden, real-world effectiveness, and the balance between skill enhancement and potential deskilling of endoscopists. Another section explores how AI can help GI oncologists design, prioritize, and implement highly innovative clinical trials—particularly multi-omic and imaging-driven approaches—while envisioning a future in which far more patients participate in trials that align with their goals and values. The final section reviews emerging AI-enabled clinical trial matching pipelines, including large language model–based retrieval and prescreening tools that operate on real-world electronic health record and protocol data, and discusses challenges related to bias, privacy, explainability, and workflow integration. Together, these contributions argue that the greatest impact of AI in GI oncology will come from deliberately aligning technical capabilities with highly relevant patient-centered clinical questions, ethical governance, and implementation strategies that expand access to trials and improve outcomes for patients with GI malignancies.

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INTRODUCTION

Artificial intelligence (AI) is rapidly integrating into daily life and work, changing the way we consume data and make decisions. In this article, we aim to provide a multifaceted look at the promise and challenges of harnessing AI for the management of patients with GI cancers. We describe key issues in deciding which models to build and understanding and choosing data to include, making sure we stay patient centered and focused on augmenting our work as physicians. Next, we describe the current status of AI in endoscopy, which is already in routine clinical practice, and introduce clinical needs for decision support when managing patients with GI cancers, using an example from prostate cancer. Finally, we review the complexities of using AI in clinical trial matching.

Data and AI: Context Exposes Complexity and Provides Clarity

Medicine has long grappled with uncertainty, and oncology sits at its most complex frontier with the need to reconcile tumor biology with comorbidities, social realities, patient values, and evolving understanding and evidence. The exponential growth of data in the digital era in combination with emerging capabilities of AI and data science tools are not antidotes to uncertainty, but they bring promise to inform clinicians and patients to better understand and navigate it. The critical step is to ensure context is considered in terms of the purpose (ie, intended use), the data, workflows, technology, and even regulations, as they may affect how decisions are made. If designed effectively, these tools have great potential to leverage probability and uncertainty into practical information that allow for decision making that is centered on the person and not just the illness.[1,2]

The transformative promise of AI in cancer research and care emerges when we move beyond single signals and embrace multimodal data. Histopathology, radiology, genomics, clinical trajectories, and patient-reported outcomes each carry complementary aspects to inform the underlying biology for discovery science or to be considered in the clinical decision. However, with each additional data source comes an additional source of uncertainty and cost in the model output. Therefore, a model's complexity needs to be fit for its purpose and suitable for its context.

PRACTICAL APPLICATIONS

- We are at the beginning stages of artificial intelligence (AI) integration into GI oncology.
- Data context is critical to consider in developing robust models which can guide patient-centered, timely management decisions.
- AI is already in routine clinical use for GI endoscopy, reducing interoperator variability and enhancing procedural completeness overall, but potentially increasing false positives and leading to deskilling of endoscopists who rely on this augmentation.
- There are many situations in which AI can enhance standard patient management and clinical trial design. Improved decision support is needed to advise patients on nonoperative management, choice of systemic therapy, and others treatments. AI also will aid in innovative yet feasible clinical trial design to accelerate progress for patients.
- AI is also being used for clinical trial matching and execution, with the goal of drastically increasing overall clinical trial participation, to both potentially improve care for individual patients and test what can become new groundbreaking treatments.

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Effective solutions begin with a clear purpose: defining the decision to be supported, the user of the output, and the decision or outcome to be influenced. Considering the intended purpose will inform the context of use and the acceptable uncertainty. Who must adopt the tool, and how will it change their work? What data are available and with what completeness, timeliness, provenance, and bias? Which operational processes constrain or enable safe use? And which regulatory, privacy, and ethical requirements shape acceptable deployment? This sequence starting from purpose to context to design is increasingly recognized as foundational to trustworthy health AI.[1,3,4]

Consider adjuvant therapy decisions in early-stage colorectal cancer (CRC). A recurrence-risk model might combine pathology features, tumor genomics, clinical variables, tumor changes on imaging, and treatment details. For impact, its predictions must appear when tumor boards convene or when oncologists select regimens; they must be interpretable, documentable, and actionable, with standardized follow-up workflows. Data lineage and quality from across the different data inputs can affect the model outputs and the related uncertainty: coding variation across sites, missingness, differences in assays, or imaging equipment and protocols as well as temporal drift in any of these data sources over time.[3-5]

The context of the data, often captured through metadata (ie, data about the data), plays a key role in understanding why an AI model may perform differently across settings. Metadata describes attributes such as data source, collection method, timestamp, device specifications, preprocessing steps, and even institutional workflows. These details can explain performance variations that might otherwise appear as model failures. For example, an image classifier trained on radiological imaging data from one institution may underperform on images from another site, not because the algorithm is flawed, but because the metadata reveal differences in scanner type, imaging protocol, or image processing. Recognizing and documenting these contextual factors brings clarity and prevents misinterpretation of results.[6]

At the same time, metadata exposes the complexity of healthcare data ecosystems, which are often oversimplified in the pursuit of big data aggregation. Efforts to combine disparate data sets to satisfy the data hunger of AI can inadvertently strip away critical contextual signals—such as variations in clinical coding practices, device calibration, or patient demographics—leading to models that detect patterns in noise rather than signal. When metadata are ignored, subtle but meaningful differences are lost, increasing the risk of spurious correlations and biased predictions. Conversely, leveraging metadata can guide harmonization strategies, inform feature engineering, and support fairness audits, ensuring that AI systems learn from clinically relevant variation rather than artifacts of data collection. In short, metadata are not a peripheral detail; they are a lens that reveal both the why behind model behavior and the how to design robust, context-aware solutions.[7]

Quality and safety extend across the entire lifecycle of AI and are collective responsibilities across the entire ecosystem. Clinicians and multidisciplinary teams articulate the clinical problem and steward interpretation at the point of care. Patients and caregivers contribute preferences and consent expectations. Data and engineering teams maintain reliable pipelines, observability, and rollback paths. Quality and safety leaders run hazard analyses and incident learning. Privacy and compliance teams manage governance and alignment with law. Executives provide resources and accountability, ensuring AI programs align with ethics, regulations, and strategy. Although rapidly evolving, regulators are increasingly emphasizing real-world performance monitoring, transparency (eg, model cards), and predetermined change-control plans—recognizing that health AI is a living system, not a static product.[4,8,9]

AI and data will not simplify cancer care; they will make it more intelligible. When we embrace complexity and uncertainty as something to characterize, not to conceal, and when we anchor innovation in purpose and context, we convert complexity into clarity. Person-centered oncology is advanced when probabilities are communicated honestly, decisions are supported thoughtfully, and quality and safety are treated as life-long disciplines. In that setting, AI

becomes not an end in itself but a catalyst for more precise, compassionate care—where evidence and values meet to serve the person at the center.

AI Applications in Endoscopy: Current Status, Evidence, and Future Perspectives

Endoscopy is one concrete area in which AI is beginning to be integrated into clinical care, to augment the human eye in identifying pathology. Interest in AI endoscopy has arisen partly because of the inherent human error risk in endoscopic observation. Tandem colonoscopy studies reveal adenoma miss rates are around 25%,[10] while the accuracy of optical biopsy remains below 90% for both sensitivity and specificity.[11] Similar diagnostic uncertainty exists for Barrett esophagus and early gastric cancer. These gaps highlight the promise of AI—computer-aided detection (CADe) to reduce missed lesions and computer-aided diagnosis (CADx) to assist optical diagnosis—aiming to complement, not replace, human judgment.

Although AI technology evolves daily, its translation into durable clinical value requires robust, patient-centered evidence. Current enthusiasm often outpaces validated outcomes, but research progress in this field is exceptionally rapid, promising a near-term shift in evidence quality.

Regulatory and Market Landscape

Developing prototype endoscopic AI software is technically straightforward, but clinical deployment requires regulatory clearance as a medical device. As of late 2025, more than 30 CADe/CADx systems for luminal endoscopy have gained clearance across the United States, Europe, and Asia including China, Korea, and Japan. In the United States, there several US Food and Drug Administration (FDA)–cleared CADe systems, which include Medtronic GI Genius, Olympus/Odin CADDIE, MICRO-TECH Endoscreener, ITERATIVE HEAHT SKOUT, and MAGENTIQ-COLO. All systems function as assistive tools, with the endoscopist retaining diagnostic responsibility.

In upper GI endoscopy, investigational AI systems, such as WISENSE and ENDOANGEL, provide blind-spot tracking and procedural quality feedback. Experimental models for early esophageal and gastric neoplasia detection show promise but remain primarily in research phases. In endoscopic ultrasound and endoscopic retrograde cholangiopancreatography, AI for pancreatic lesion differentiation and cannulation guidance is under study, but no major bedside devices are broadly available.

Clinical Evidence and Guideline Divergence

Meta-analyses of randomized trials demonstrate that colonoscopic CADe increases adenoma detection rate (ADR) by approximately 5%-15%, implying fewer missed lesions and potential CRC prevention.[12] Modeling studies suggest that such ADR gains could reduce CRC incidence by roughly 0.1% across large screening populations.[13] However, this modest absolute benefit is accompanied by increased patient burden—more follow-up colonoscopies because of higher polyp detection.[14]

In March 2025, three international guidelines were published simultaneously:

- BMJ recommended *against* routine CADe use.[15]
- American Gastroenterological Association withheld formal recommendation pending further data.[16]
- European Society of GI Endoscopy *endorsed* CADe adoption.[17]

Each organization used identical evidence yet reached different conclusions because the benefit (minor cancer risk reduction) and burden (6% more surveillance procedures) were finely balanced, and the certainty of evidence was low. These discrepancies underscore the need for context-specific evaluation of AI technologies rather than blanket adoption.

Skill Enhancement or Skill Decay?

Whether AI strengthens or weakens clinical skills remains unsettled. A multicenter Polish study reported a 6% drop in adenoma detection once endoscopists switched from AI-assisted to unaided colonoscopy, suggesting potential deskilling.[18] Conversely, prospective Japanese data indicate sustained performance improvement through AI-augmented training.[19]

These contrasting findings mirror broader educational research: AI can accelerate short-term efficiency yet may erode deep learning if overused. Therefore, AI should serve as an adjunct to active observation, not a substitute for it. Periodic AI-off sessions and trainee protocols that require independent assessment before revealing AI output may preserve human expertise.

Future Outlook

Despite differing guideline positions, AI has clearly become part of modern endoscopy. Evidence supports its benefit in detection but is weaker for diagnosis or long-term patient outcomes. The rapid evolution of research, including large multicenter randomized trials promises clarity in coming years.

AI's ultimate success will depend on aligning technological potential with patient-centered value—improving detection and efficiency without overwhelming health care systems or eroding physician skill. Continuous feedback, data transparency, and professional education in digital literacy[20] are essential to cultivate effective human-AI collaboration.

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OPPORTUNITIES AND CAUTIONS

Opportunities

- Improved detection and quality standardization: CADe reduces interoperator variability and enhances procedural completeness.
- Educational value: Real-time feedback helps trainees internalize optimal mucosal exposure techniques.
- Workflow integration: AI systems increasingly incorporate documentation, timing, and quality metrics into endoscopy suites.

Cautions

- Alert fatigue and distraction: False positives can increase cognitive load.
- Generalizability issues: Domain shifts across hardware, preparation quality, or populations may impair accuracy.
- Data governance: Cloud-based systems require strict data protection and update traceability.
- Medicolegal ambiguity: Responsibility for missed or false alerts remains with the physician.
- Resource burden: Increased lesion detection may strain endoscopic capacity and surveillance scheduling.

Safeguards against the Black box issues in AI

Adopting AI safely requires structured steps which may include the following examples:

1. Local validation: Conduct silent trials comparing AI-on and AI-off performance before rollout.
2. Threshold calibration: Adjust confidence levels to balance sensitivity and false alerts (if possible).
3. Governance and version control: Record model version, update logs, and data flow.
4. Dual reasoning: Endoscopists make independent assessments before consulting AI, maintaining cognitive engagement.
5. Continuous monitoring: Track ADR, withdrawal time, and alert-confirmation ratios.
6. Periodic AI-off audits: Possibly ensure skills retention and detect performance drift.
7. Transparent reporting: Document unconfirmed AI alerts neutrally, avoiding false miss language.

Such measures may transform AI from a black box into a transparent, auditable collaborator.

AI for GI Malignancies Will Facilitate Management Decisions and Accelerate Access to Complex Clinical Trials

Many patients with GI malignancies face uphill battles toward the prospects of a cure without morbidity. Current methods of treatment simply do not provide high rates of durable cure for malignancies such as pancreatic adenocarcinoma or metastatic CRC.[21,22] Even when a cure is relatively common, such as with early stage anal cancer, or early-stage rectal adenocarcinoma, such cures are often associated with lifelong morbidity.[23] Patients and their families present to cancer centers with the expectation of a cure from their devastating malignancies, without life-altering side effects. How can we as oncologists meet these expectations more consistently? AI presents a novel and unprecedent method to move us closer to this laudable goal. Such a goal will be achieved by routine enrollment in novel clinical trials.

Clinical trials are by far the most promising strategy to improve outcomes for patients with cancer. Well-designed trials using end points such as quality of life, organ preservation, or overall survival, bring patients closer to improved results following cancer treatment. Indeed, each trial result, positive or negative, moves us toward a durable and morbidity-free cure. Completed clinical trials are essential to achieving this result. Despite this, only a small fraction of patients with cancer are enrolled onto clinical trials, with most estimates indicating a dismal 5%-8% participation rate.[24] The reasons for this seemingly insurmountable truth of our current oncologic landscape are understandable for anyone who has tried to fund or complete a clinical trial. The barrier stems from the clear logistical complexity of clinical trials, administrative burden, cost, and tremendous (often uncompensated) time associated with creating and implementing clinical trials. AI is positioned to considerably affect this reality in a dramatically positive way, as discussed in more detail in the next section.

There is a never-ending stream of promising hypotheses that brilliant oncologists believe, justifiably, will improve outcomes for patients with cancer. Secondary to limited funding and feasibility, many promising trials are never opened. The time is now to radically reimagine what cancer therapy looks like, and AI is positioned to enable this. Oncologist must envision and use AI to realize a future where almost all patients with cancer (who are willing and able) are enrolled into a promising clinical trial. This could enable oncologist to learn from >90% of the patients who are currently not enrolled into clinical trials. With the appropriate focus and commitment, this future is highly feasible using AI.

One cannot help but to speculate, what is the role of human oncologists with the approaching transformation that will be associated with routine integration of AI into cancer

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management? Fortunately for the future of clinical trials, it is unlikely that oncologists will be relied on to provide routine, standard-of-care recommendations. Some AI tools have already demonstrated that the highest degree of evidence can be immediately and rapidly called upon to provide cutting edge and standard-of-care recommendations.[25] It is unclear when, but likely, that such AI tools may reduce the need for oncologists to make routine, standard-of-care recommendations. Tools like the ASCO Guidelines Assistant and OpenEvidence are ready assisting clinicians with treatment decisions. Where instead will oncologists focus their time? Wonderfully, this AI-facilitated change will enable oncologist to shift their time to data review, interpretation, and novel trial integration. Such activities, at the present time, are often a foggy after thought following a busy day of encounter closing and electronic order placement. Our field is ready for AI to enable us to shift our focus.

Making innovative and creative improvements in our existing care paradigms will represent one of the most important functions we can provide as oncologists into the future. Such improvements will likely fall into one the four categories empowered by AI: (1) designing highly innovative yet feasible clinical trials, (2) asking critically important questions that ethically integrate both patient desires and new hypotheses into those trials, (3) clearly explaining these trials to patients and their families, taking into account their personal preferences and life goals, and (4) correctly interpreting trials and applying their results to the next generation of patients with cancer. Note that this is a cyclical future of oncologic care delivery and innovation that will be accelerated by AI tools. Asking the most important questions is one of the fundamental roles for the future of any oncologic discipline extending through medical, surgical, and radiation oncology. Certainly, asking pivotal yet feasible questions is a uniquely human trait that depends on elastic and innovative thinking balancing the unpredictability of the human condition. One day, we may be facing AI tools that can ask questions that meet these criteria, yet as of today we are far from this reality. Moreover, many of the existing AI tools draw only on current management paradigms and publications. Entirely novel approaches using previously unimagined techniques are a current limitation that AI faces.

There are examples of promising results that are using AI to address critically important questions in other malignancies. Such information is actively being incorporated into ongoing clinical trials. For example, in prostate cancer, a critical question to patients is when to apply androgen deprivation therapy (ADT) with definitive radiation therapy (RT). Using a multimodal tool and existing randomized clinical trials, ArteraAI was able to successfully develop and validate a test which is both prognostic for development of metastases and also predictive for benefit of ADT. This test is currently being used in the clinic to help guide men in this often difficult decision of whether to proceed with ADT, a treatment with many side effects.[26] This is the first AI-based test incorporated into the National Comprehensive Cancer Network guidelines, and its underlying technology is the first of its type to receive an FDA de novo authorization. The test is rapid and does not consume tissue because it is based on a simple, standard, scanned hematoxylin and eosin slide. This work illustrates how existing clinical trial data sets can be repurposed in innovative ways to develop clinically actionable AI tools.

What remains essential for oncologists treating GI malignancies is asking the most important questions and pressing AI to help us address these questions in new ways. Some examples of important questions that remain unanswered across GI malignancies include (1) which patients with rectal adenocarcinoma will achieve a durable complete response with nonoperative management and (2) which patients with pancreatic adenocarcinoma will respond to neoadjuvant fluorouracil, leucovirin, irinotecan, and oxaliplatin based chemotherapy as compared with gemcitabine/nab-paclitaxel based chemotherapy. These questions will likely only be answerable through an AI multi-omic approach using sophisticated image processing, simultaneously with genomic, along with circulating minimal residual disease assays.

AI is ideally positioned to help GI oncologists address some of the most complex and important questions in GI oncology by accelerating design, implementation, and participation in highly innovative clinical trials. We are entering into one of the most exciting eras of innovation to date, and accelerating entry into clinical trials testing new and important questions should be one of the prime targets for this exciting new tool. Oncologists must rise to meet the opportunity.

AI and Clinical Trials Matching and Execution: The Clinical Trials Accrual Challenge

Despite decades of effort, rates of participation in cancer treatment trials among adults with cancer remains low. A contemporary US estimate puts overall participation around 7%, with substantial variation by health system context.[24] Low participation slows evidence generation, limits representativeness, and risks widening disparities.[27] if enrollment disproportionately favors better-resourced or digitally connected patients. Beyond awareness and logistics, identifying the right trial at the right moment is a difficult challenge, both for clinicians facing time pressure and for patients navigating complex criteria across multiple institutions and sponsors.

Complexity of Trial Eligibility Criteria

Modern trial protocols commonly include lengthy, nested inclusion/exclusion criteria with temporal qualifiers (eg, no checkpoint inhibitor within 4 weeks), laboratory thresholds tied to specific windows, disease-burden definitions (eg, RECIST measurability, which may not be readily available in routine practice), and biomarker requirements with nuanced exceptions. These details are rarely stored as first-class,

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structured fields in the electronic health record (EHR), making deterministic, rules-only matching brittle. Consensus efforts from ASCO and Friends of Cancer Research have argued for modernization—eg, relaxing rigid prior-therapy restrictions—to improve generalizability and access while maintaining safety, underscoring how current criteria can impede enrollment and automation alike.[28] AI tools that can extract and interpret relevant information from both patient records and trial protocols may be essential to accrual across care contexts given this complexity.

History of AI Tools for Trial Retrieval and Prescreening

Early systems combined keyword/rule engines with natural language processing to extract features from notes and protocols. IBM Watson for Clinical Trial Matching popularized this concept but struggled with generalizability and real-world integration; MD Anderson ultimately discontinued the collaboration, catalyzing more cautious expectations around AI in oncology operations.[29] However, the advent of large language models (LLMs) has facilitated development of AI tools for trial matching in both academia and industry that can overcome the limitations of structured data. These tools tackle the related challenges of retrieving and ranking reasonable trials for consideration from a large denominator of trials active at any given time and prescreening patients for eligibility for specific trials.

In the academic space, cancer centers as well as the National Institutes of Health have developed trial matching tools. MatchMiner, for example, maps tumor genomics and cancer type to structured protocol criteria, demonstrating reduced time from sequencing to trial consent at a comprehensive cancer center.[30] The MatchMiner-AI pipeline in development seeks to expand beyond genomically matched trials, using LLMs to summarize patient histories and vector embeddings to retrieve trial options.[31] TrialGPT combined components for the retrieval/ranking and prescreening tasks, demonstrating good performance on public benchmarks.[32]

Commercial offerings span several archetypes. EHR-anchored recruitment platforms emphasize workflow integration for site teams, including patient identification, screening, recruitment, and tracking.[33] Molecular testing laboratories offer matched clinical trial information to promote the utility and relevance of their assay results.[34] Specialized companies partner with health systems to mine structured and unstructured EHR data, positioning themselves for both feasibility (prestudy) and ongoing accrual support.[35] Finally, patient-facing products aim to channel community demand toward appropriate trials through guided questionnaires and other engagement strategies.[36]

Delivering Clinical Trial Information at the Right Time

Information about clinical trials is only relevant to patients and their clinicians at moments in time when treatment decisions must be made. One pragmatic approach is to detect clinical inflection points (eg, imminent treatment change, often triggered by disease progression),[37] then push curated, genomically matched options. A pilot deployment of this approach not only demonstrated feasibility but also revealed that downstream factors, including clinical and information workstreams, patient and oncologist preferences, and eligibility criteria beyond genomics and recent progression, still impact accrual.[38] Furthermore, a 2025 randomized study of AI-triggered progression alerts linked to genomic trial suggestions found no overall improvement in enrollment, highlighting the importance of surfacing trial options that might not otherwise be considered, for the right patients, at the right times.[39]

Challenges in AI for Clinical Trial Matching

Several barriers must be overcome for AI tools to have a measurable impact on clinical trial enrollment. For example, one corollary of complex trial eligibility criteria is that some trial protocols include requirements that cannot be assessed until consent is signed and screening has begun. This occurs when their ascertainment is not part of routine clinical care, such as when trials target biomarkers for which no approved therapies yet exist. This can increase the difficulty of the trial matching task because any AI tool needs a way to determine when it can safely ignore eligibility criteria for this reason. Indicating within trial protocols when biomarker testing is performed as part of screening may help address this. A related barrier to AI-based trial matching is the frequent variability in slot availability for a given target population at a given time because most health systems lack a centralized, electronic trial slot tracking system. Other challenging eligibility criteria include requirements that patients have an expected survival of at least some minimum amount of time. Because this can never be ascertained precisely at scale without deploying a separate prediction model trained specifically for this purpose with attention to minimizing biases, it may be appropriate to omit such criteria from protocols entirely. Indeed, mitigating bias is an important component of AI applications in healthcare generally and of clinical trial matching tools specifically. It may be tempting, for example, to train models that predict whether an eligible patient will actually enroll on a trial and complete all study procedures. However, this must be done very carefully and with attention to model interpretability, lest such models learn to reinforce existing undesirable disparities in enrollment patterns.

Other practical challenges arise from the nature of current AI technologies, especially LLMs. Modern LLMs are generally trained by first pretraining them on a large corpus of unlabeled text[40] and then performing instruction fine-tuning to improve their ability to generate output rated highly by human users.[41] This tends to encourage models to provide confident outputs, even when confidence may not be clinically justified, presenting an obvious challenge for LLM-

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based clinical decision support tools. Better uncertainty-aware LLM training strategies are needed to develop models for clinical research use that accurately capture real-world clinical dynamics.

The performance of modern AI models also tends to scale with the size of their training datasets. In this context, patient privacy questions that arise from training models on protected health information (PHI) can raise another barrier to rapid dissemination and adoption of AI for trial matching. When models are trained directly on PHI, there is a risk that they may memorize their training data and later expose it to attacks designed to recover those data or predict whether a given patient's data were included in training.[42] Federated learning, in which data stay at source institutions but model weight updates are shared with an orchestrator, does not solve this problem on its own. Further research is needed to quantify the practical model- and task-specific privacy risks conferred when models are trained on PHI and to measure the reduction in risk conferred by privacy-aware training techniques, such as differential privacy-stochastic gradient descent[43] and Private Aggregation of Teacher Ensembles.[44] Synthetic data may be a useful resource for privacy-preserving AI training as well,[45] but they may never quite capture the richness of real data. Synthetic data must also be developed carefully, because any grounding in real clinical data—even if deidentified by traditional standards—can confer residual privacy risks.[46]

Finally, for widespread adoption of trial matching tools, clinicians need traceable rationales for AI predictions—eg, which criteria were met, which were uncertain, and what data backed each call. This may be especially important for trial prescreening, as opposed to initial retrieval and ranking of possible options. Systems that expose criterion-level evidence alongside rankings[32] may therefore be easier to adopt.

Conclusions and Future Directions for Trial Matching

AI constitutes an important new tool for matching patients to clinical trials, with potential to lower barriers to identifying trial options and accelerating accrual. The critical work for maximizing impact will be in careful design of implementation strategies. Underlying AI pipelines must be reliable, accurate, and unbiased, and software tooling integrated unobtrusively into workflows for clinicians and investigators. Additionally, although a complex undertaking, available patient slots must be included. This work will benefit from targeting toward the greatest current need, including health systems and care settings where trial enrollment rates have historically been lower than those observed in academic centers. Finally, although AI may help match patients to trials for which they may qualify based on eligibility criteria as currently written, efficient accrual of representative populations will require further work to broaden eligibility criteria and minimize the patient burden of trial participation.

CONCLUSION

AI is reshaping the landscape of GI oncology by transforming how data are collected, interpreted, and operationalized across the continuum of cancer care, from screening and diagnosis through therapeutic decision making and clinical trial participation. Against a backdrop of exploding multimodal data—encompassing histopathology, imaging, genomics, clinical trajectories, and patient-reported outcomes—AI offers the promise of tools which should be deployed with careful attention to clinical purpose and context of use. In GI malignancies, these technologies have already arrived in real-time endoscopic CADe and diagnosis. For personalized patient management and clinical trial design, as well as automated matching in increasingly complex clinical trials, there is still much work to be done.

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Evolving Treatment Paradigms in Hormone Receptor–Positive, Human Epidermal Growth Factor 2–Negative Metastatic Breast Cancer

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OVERVIEW

Hormone receptor–positive, human epidermal growth factor 2 (HER2)–negative metastatic breast cancer (MBC) represents the most common subtype of MBC and has undergone substantial therapeutic evolution. Treatment has shifted from sequential endocrine therapy (ET) and chemotherapy toward personalized strategies incorporating molecularly targeted agents and antibody-drug conjugates (ADCs), with increasing emphasis on quality of life and shared decision making. CDK4/6 inhibitors plus ET remain a first-line standard of care in high-resource settings, demonstrating consistently improved progression-free survival (PFS) and, for select agents, overall survival (OS). Management in special populations requires additional consideration of trial and real-world data, toxicity profiles, and patient preferences. Beyond ET, ADCs are reshaping the landscape. Trastuzumab deruxtecan expanded therapeutic utility across HER2-low and HER2-ultralow disease, whereas sacituzumab govitecan and datopotamab deruxtecan provide later-line options. As ADCs emerge as earlier therapies, questions regarding sequencing, cross-resistance, and toxicity remain central to clinical decision making. Metastasis-directed therapy (MDT) in oligometastatic and oligoprogressive breast cancer also requires nuanced decision making. Despite high local control rates with stereotactic body radiotherapy, randomized trials have not demonstrated consistent improvements in PFS or OS in unselected populations. Current evidence supports systemic therapy as the foundation of management, with MDT selectively considered for oligoprogression, symptom prevention, or within clinical trials. Ultimately, management of hormone receptor–positive/HER2-negative MBC requires dynamic integration of tumor biology, systemic therapy advances, and patient-defined goals of care. As therapeutic complexity increases, shared decision making and equitable access to evidence-based and supportive care services remain essential for delivering high-quality, individualized oncology care.

Patients want accessible, effective, and tolerable treatments that align with each unique patient's definition of quality of life (QoL) born from shared discussion with their care team. Patients are living with metastatic breast cancer (MBC), not statistics. The burden of travel, time away from work and family, and physical exhaustion matters. For many patients living with MBC, oral therapies are preferred as they reduce the need for frequent trips to infusion centers and allow maintenance of normalcy.

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) represent important progress in the treatment landscape and are often considered tolerable by many patients and clinicians when used alongside endocrine therapy (ET) among patients diagnosed with the most common biologic subtype of MBC, hormone receptor–positive, estrogen receptor–positive, progesterone receptor–positive, human epidermal growth factor 2 (HER2)–negative (hormone receptor–positive/HER2-negative). Combined with ET, CDK4/6i have consistently demonstrated significant improvements in progression-free survival (PFS) across first- and later-line settings, and select agents have also shown overall survival (OS) benefit. Despite broad efficacy, patient-specific factors including age, comorbidities, disease burden, and molecular profile remain central to optimal treatment selection. Oral anticancer therapies should not be treated as easier simply because they are taken at home. They require the same level of monitoring, education, toxicity management, and adherence support as infusion-based treatments. Furthermore, they are only the first piece in a complex continuum, and now, careful thought to ET partner, timing of initiation, and sequencing of remains paramount.

In clinical practice, patients with hormone receptor–positive/HER2-negative MBC typically receive multiple lines of treatment. However, most patients receive only one line of

PRACTICAL APPLICATIONS

- CDK4/6 inhibitor + endocrine therapy remains a first-line standard for most patients with hormone receptor–positive/ human epidermal growth factor 2 (HER2)–negative metastatic breast cancer; agent selection should reflect overall survival data, toxicity profile, comorbidities, and patient preference.
- Comprehensive molecular testing at metastatic diagnosis is essential, including PIK3CA and germline BRCA1/2; results meaningfully influence the use of PI3K-targeted therapy and poly(ADP-ribose) polymerase inhibitors.
- Antibody-drug conjugates (ADCs) have shifted the postendocrine landscape: trastuzumab deruxtecan is preferred in HER2-low/ultralow hormone receptor–positive metastatic disease, with careful monitoring for interstitial lung disease; TROP2-directed ADCs are appropriate in later lines.
- Systemic therapy remains the foundation in oligometastatic breast cancer; metastasis-directed therapy has not demonstrated survival benefit in unselected patients.
- Stereotactic body radiotherapy is most appropriate for oligoprogression, symptom prevention, or carefully selected favorable biology, ideally within clinical trials or in scenarios where delaying a systemic therapy change is clinically meaningful.

ET before discontinuation or transition to chemotherapy, despite guidelines recommending up to three lines of ET before chemotherapy in the absence of visceral crisis or endocrine resistance. As antibody-drug conjugates (ADCs) move earlier in the treatment continuum, critical questions remain regarding patient selection, optimal sequencing, toxicity management, and mechanisms of resistance. A subgroup of patients (classically individuals with good performance status, few comorbidities, a long disease-free interval, no visceral crisis/rapid progression, with bone-only or limited metastatic disease) will receive multiple sequential lines of therapy. Patients should have access, at the time of prescribing, to information about their treatment and reasonable alternatives. For true informed, shared decision making, they must also receive clear, timely, and understandable information about available clinical trial opportunities. Shared decision making is not optional—it is fundamental to ethical cancer care. From the time of diagnosis, clinicians should ask how patients prefer to receive information and how actively they wish to participate in treatment decisions and reassess these preferences over time.

Clinical decision making in MBC increasingly requires synthesis of trial evidence, guideline recommendations, toxicity profiles, and patient preferences, with careful attention to QoL considerations. Clinicians and patients face challenges in scenarios where multiple treatment options exist; evidence is nuanced, and there is no single right answer. Even in the absence of clear-cut evidence, decisions must be made for patients in front of us—requiring a thoughtful blend of science, patient values, and clinical judgment. This review summarizes current evidence supporting available therapeutic options in hormone receptor–positive/HER2-negative MBC, with a focus on practical considerations that guide treatment selection beyond ET.

CDK4/6 INHIBITORS IN Hormone Receptor–Positive/ HER2-NEGATIVE METASTATIC BREAST CANCER

Three CDK4/6i, palbociclib, ribociclib, and abemaciclib, are approved for hormone receptor–positive/HER2-negative MBC. In first-line trials combined with aromatase inhibitors, all three CDK4/6i improved PFS with hazard ratios (HR) of 0.54-0.57 and median PFS gains of 10-14 months over ET alone.[1-4] However, OS outcomes and toxicities differ. Ribociclib is the only first-line aromatase inhibitor–based trial to show statistically significant OS benefit (63.9 *v* 51.4 mos, HR = 0.76; $P = .008$).[2] Abemaciclib showed a clinically meaningful but not statistically significant OS gain (66.8 *v* 53.7 months, HR = 0.80; $P = .066$).[3] Palbociclib did not demonstrate OS benefit (HR = 0.96; $P = .34$), potentially confounded by higher postprogression CDK4/6i use in the control arm (27% *v* 12%).[4]

Toxicity profiles guide individualized selection. Palbociclib causes frequent grade 3-4 neutropenia (50%-66%) but low infection risk and minimal gastrointestinal toxicity, with low discontinuation rates.[5] Ribociclib has similar hematologic toxicity but carries a risk of QTc prolongation and hepatotoxicity, requiring electrocardiograms and liver monitoring; it is also the only CDK4/6i with robust data in pre-/perimenopausal women.[6] Abemaciclib causes less neutropenia but substantially more gastrointestinal toxicity (diarrhea in approximately 81%, grade 3-4 in approximately 10%), higher venous thromboembolism risk, and higher discontinuation rates.[5-9]

For patients who relapse on or shortly after completing adjuvant ET, fulvestrant is the preferred ET partner.[10] Early-relapsing disease also should be tested for phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha *(PIK3CA)* mutations as the addition of targeted therapy is appropriate in select groups, discussed in greater detail below.

The phase III SONIA trial investigated the clinically relevant question of whether CDK4/6i should be used in the first-line or deferred to the second-line setting, given multiple available lines of treatments and increased toxicity and costs. It compared first-line versus second-line CDK4/6i use in

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TABLE 1. Key Trials Comparing Options Postprogression on First-Line Endocrine Therapy With or Without CDK4/6i

Trial	Drug	Biomarker	Population	Comparator	Median PFS (HR [95% CI], significance)	Median OS (HR [95% CI], significance)	Most Common Adverse Events[a] (%) and Significant Grade ≥3 Events[b] (%)
OlympiAD[26]	Olaparib	Germline *BRCA1/2* mutation	Hormone receptor–positive/HER2-negative MBC or mTNBC ≤2 prior chemotherapy lines	Physician's choice chemotherapy (capecitabine, eribulin, vinorelbine)	7.0 mo *v* 4.2 mo (HR = 0.58 [0.43 to 0.80], *P* < .001)	19.3 mo *v*. 17.3 mo (HR = 0.90 [0.66 to 1.23]; *P* = .513)	Nausea (57), anemia (39), vomiting (32.2), fatigue (29.8), neutropenia (27.3), diarrhea (20.5), headache (20.5) G ≥3: anemia (16.1), neutropenia (9.3), fatigue (3.4), leukopenia (3.4)
EMBRACA[27]	Talazoparib	Germline *BRCA1/2* mutation	Hormone receptor–positive/HER2-negative MBC or mTNBC ≤3 prior chemotherapy lines	Physician's choice chemotherapy (capecitabine, eribulin, gemcitabine, vinorelbine)	8.6 mo *v* 5.6 mo (HR = 0.54 [0.41 to 0.71]; *P* < .001)	19.3 mo *v* 19.5 mo (HR = 0.848 [0.670 to 1.073]; *P* = .17)	Anemia (52.8), fatigue (50.3), nausea (48.6), neutropenia (34.6), headache (32.5), thrombocytopenia (26.9), alopecia (25.2), vomiting (24.8), diarrhea (22), constipation (22), decreased appetite (21.3), back pain (21) G ≥3: anemia (39.2), neutropenia (20.9), thrombocytopenia (14.7), leukopenia (6.6), lymphopenia (3.1)
SOLAR-1[21]	Alpelisib + fulvestrant	*PIK3CA* mutation	Hormone receptor–positive/HER2-negative MBC; post-AI with or without CDK4/6i	Placebo + fulvestrant	11.0 mo *v* 5.7 mo (HR = 0.65; [0.50 to 0.85]; *P* < .001)	39.3 mo *v* 31.4 mo (HR = 0.86 [0.64 to 1.15] *P* = .15)	Diarrhea (57.7), nausea (44.7), decreased appetite (35.6), rash (35.6), vomiting (27.1), weight loss (26.8), stomatitis (24.6), fatigue (24.3), asthenia (20.4) G ≥3: hyperglycemia (36.3), rash (9.9), diarrhea (6.7), fatigue (3.5), weight loss (3.9)
CAPItello-291[22]	Capivasertib + fulvestrant	*PIK3CA*/*AKT1*/*PTEN* alterations	Hormone receptor–positive/HER2-negative MBC; post-AI with or without CDK4/6i	Placebo + fulvestrant	7.3 mo *v* 3.1 mo (HR = 0.50; [0.38 to 0.65] *P* < .001)	Immature	Diarrhea (72.4), rash (37), nausea (34.6), fatigue (20.8), vomiting (20.6) G ≥3: rash (12.1), diarrhea (9.3)
EMERALD[28]	Elacestrant	*ESR1* mutation	Hormone receptor–positive/HER2-negative MBC; post-ET + CDK4/6i	Fulvestrant or AI	3.8 mo *v* 1.9 mo (HR = 0.55; [0.39 to 0.77]; *P* = .0005)	Immature	Nausea (35%) G ≥3: all <3%
EMBER-3[29]	Imlunestrant	*ESR1* mutation	Hormone receptor–positive/HER2-negative MBC; post-AI with or without CDK4/6i	Fulvestrant or exemestane	5.5 mo *v* 3.8 mo[d] (2.6 months; [1.2 to 3.9]; *P* < .001)	Immature	Fatigue (22.6), diarrhea (21.4) G ≥3: all <3%

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TABLE 1. Key Trials Comparing Options Postprogression on First-Line Endocrine Therapy With or Without CDK4/6i (continued)

Trial	Drug	Biomarker	Population	Comparator	Median PFS (HR [95% CI], significance)	Median OS (HR [95% CI], significance)	Most Common Adverse Events[a] (%) and Significant Grade ≥3 Events[b] (%)
EMBER-3[29]	Imlunestrant + abemaciclib	Unselected	Hormone receptor–positive/HER2-negative MBC; post-AI with or without CDK4/6i	Imlunestrant alone	9.4 mo *v* 5.5 mo (HR = 0.57 [0.44 to 0.73]; *P* < .001)	Immature	Diarrhea (86.1), nausea (48.6), fatigue (38.5), anemia (43.8), vomiting (31.2), neutropenia (48.1), leukopenia (26), hypercreatinemia (21.6) G ≥3: fatigue (4.8), ALT increase (4.8), diarrhea (8.2), anemia (7.7), neutropenia (19.7)
VERITAC-2[30]	Vepdegestrant	*ESR1* mutation	Hormone receptor–positive/HER2-negative MBC; post-CDK4/6i + ET with or without 1 additional line of ET	Fulvestrant	5.0 mo *v* 2.1 mo (HR = 0.58 [0.43 to 0.78], *P* < .001)	Immature	Fatigue (26.6) G ≥3: all <3%
evERA[30]	Everolimus + giredestrant	*ESR1* mutation	Hormone receptor–positive/HER2-negative MBC post-AI + CDK4/6i	Exemestane, tamoxifen, fulvestrant	9.99 mo *v* 5.45 mo (HR = 0.38 [0.27 to 0.54] *P* < .0001)	Immature	Stomatitis (47.3), diarrhea (26.9), anemia (23.6)[c] G ≥3: anemia (6%), hypokalemia (3.8%)[c]
VIKTORIA[31]	Gedatolisib + fulvestrant	*PIK3CA* wild-type	Hormone receptor–positive/HER2-negative MBC post-AI + CDK4/6i	Fulvestrant	7.4 mo *v* 2.0 mo (HR = 0.33 [0.24 to 0.48]; *P* < .001)	Immature	Stomatitis (56.9), nausea (43.1), rash (32.3), vomiting (23.1), fatigue (20.8) G ≥3: stomatitis (12.3), rash (5.4)
VIKTORIA[31]	Gedatolisib + palbociclib + fulvestrant	*PIK3CA* wild-type	Hormone receptor–positive/HER2-negative MBC post-AI + CDK4/6i	Fulvestrant	9.3 mo *v* 2.0 mo (HR = 0.24 [0.17 to 0.35] *P* < .001)	Immature	Stomatitis (69.2), neutropenia (65.4), nausea (43.8), rash (27.7), vomiting (27.7), fatigue (22.3) G ≥3: neutropenia (62.3), stomatitis (19.2), leukopenia (7.0), nausea (3.8), rash (4.6)

Abbreviations: AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; ER, estrogen receptor; ET, endocrine therapy; G ≥3, grade ≥3; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROTAC, Proteolysis Targeting Chimera; SERD, selective estrogen receptor degrader.

[a]Common adverse events = those occurring ≥20%.

[b]Significant adverse events = grade ≥3 events are those occurring ≥3%.

[c]May be incompletely reported given abstract form.

[d]EMBER-3 used a restricted mean survival time analysis in lieu of hazard ratios.

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1,050 treatment-naïve patients.[11,12] No significant difference in outcomes was observed, with up-front CDK4/6i therapy resulting in longer drug exposure and higher rates of grade ≥ 3 adverse events, without QoL benefit. Interpretation is limited by predominant use of palbociclib, which, as compared with the other CDK4/6i, lacks OS benefit based on PALOMA-2,[4] and under-representation of premenopausal patients. For prescribers' resource-rich environments, the fulvestrant control arm has been criticized given that newer oral targeted approvals or combinations are commonly used after progression on CDK4/6i. Exploratory circulating tumor DNA (ctDNA) analysis suggested that patients with high baseline ctDNA may benefit more from up-front CDK4/6 inhibition.[13] Without a clear biomarker or clinical predictor, engaging patients in dialogue remains critical.

One special population for consideration includes patients presenting with visceral crisis. ABC7 defines visceral crisis as severe organ dysfunction requiring immediate effective therapy, for which chemotherapy remains standard.[14] While not completely superposable to visceral crisis, in aggressive disease among patients with symptomatic visceral metastasis and/or rapid disease progression, phase II trials (ABIGAIL [abemaciclib], RIGHT Choice [ribociclib]) still support CDK4/6 inhibitors plus ET as first-line therapy, showing comparable or superior PFS and response rates versus chemotherapy, with improved tolerability. Limitations include small sample size, enrichment for de novo disease, and premenopausal-only cohorts.[15,16]

A second special population includes older patients with hormone receptor–positive MBC. A pooled analysis of MONALEESA-2, MONALEESA-3, and MONALEESA-7 (n = 1,229) demonstrated consistent PFS and OS benefit with ribociclib plus ET across age groups (< 65, 65-74, ≥ 75 years) and delayed time to first chemotherapy.[17] The phase IV RibOB study further supported this finding, showing consistent efficacy but higher rates of grade ≥ 3 events, further reinforcing the need for thoughtful dose optimization among older patients with MBC.[18] Pooled analysis data also indicate that dose reductions are common and do not compromise efficacy, supporting careful monitoring and individualized dose adjustment in elderly patients.[19]

BEYOND CDK4/6 INHIBITOR PROGRESSION: BIOMARKER-DIRECTED THERAPY

The median PFS of first-line CDK4/6 inhibitor + aromatase inhibitor in hormone receptor–positive/HER2-negative MBC ranges from approximately 25 to 28 months across the three pivotal phase III trials.[20] After progression, if the patient is not endocrine-refractory, alternate ET with/without additional targeted therapy should be considered, guided by biomarker testing. Comprehensive molecular profiling identifies actionable targets that allow individualized therapy, which has become the foundational component of contemporary oncology care, including oral targeted agents, and may delay or obviate the need for intravenous cytotoxic chemotherapy.

Guidelines recommend a comprehensive multigene panel (via next-generation sequencing [NGS] or the multiplex polymerase chain reaction) to evaluate actionable alterations. Blood-based ctDNA testing is often preferred initially because of its rapid turnaround time and ability to capture tumor heterogeneity across metastatic sites, particularly for subclonal ESR1 mutations. Tissue-based testing remains important in select scenarios, including low tumor fraction on ctDNA or when confirmation of receptor status is required.[21]

Despite its importance, biomarker testing rates remain suboptimal in MBC (< 40% in the United States), reflecting multifactorial barriers at the system, clinician, patient, and technical levels.[22] These barriers are compounded in low- and middle-income countries where resources for testing and targeted therapeutics are limited.

PIK3CA MUTATIONS: BIOLOGY AND CLINICAL IMPACT

Mutations in *PIK3CA* occur in approximately 35%-40% of hormone receptor–positive/HER2-negative MBCs, are enriched at relapse,[23] and are associated with shorter PFS and OS compared with wild-type tumors.[24] In the SOLAR-1 trial, alpelisib plus fulvestrant improved median PFS as compared with placebo plus fulvestrant (11.0 months *v* 5.7 months, HR, 0.65 [95% CI, 0.50 to 0.85], $P < .001$) in patients with *PIK3CA*-mutated, hormone receptor–positive/HER2-negative MBC and although OS showed a numerical improvement of 7.9 months (39.3 *v* 31.4 months), it did not reach statistical significance[25] (Table 1).

Capivasertib improved PFS when combined with fulvestrant in the CAPItello-291 in patients with *PIK3CA*, *AKT1*, or *PTEN* alterations after CDK4/6i progression in the pathway-altered population as compared with fulvestrant alone (7.3 months *v* 3.1 months, HR, 0.50 [95% CI, 0.38 to 0.65], $P < .001$). While OS is immature, the trend favors the addition of capivasertib (HR, 0.69 [95% CI, 0.45 to 1.05]). This broader indication compared with alpelisib makes capivasertib an important option for *AKT1*- and *PTEN*-altered tumors[32] (Table 1).

Despite guideline support and availability of alpelisib and capivasertib, real-world utilization remains suboptimal, with only a minority of patients tested before first-line therapy and many patients with mutations never receiving *PI3K*-targeted treatment.[33] Concerns have included timing of testing, availability of tissue, and implementation of workflow in clinical practice. Our expert opinion is that tissue should be tested at diagnosis and routinely sent from the same biopsy that confirms a metastatic diagnosis, with plasma-based assays sent at diagnosis and disease progression for optimal turnaround time and to capture MBC heterogeneity. Tissue testing shows higher sensitivity and approximately 70%–94% concordance and is preferred when feasible, whereas plasma assays are vulnerable to false negatives at low ctDNA fractions.[10]

The INAVO120 trial evaluated inavolisib, a selective *PI3Kα* inhibitor, added to ET and palbociclib in patients with *PIK3CA*-mutated, endocrine-resistant disease, including those with early relapse as discussed above.[28,29,34] In this high-risk cohort, inavolisib improved both PFS (15.0 *v* 7.3 months; HR = 0.43, 95%CI 0.32-0.59; *P* < .001) and median OS (34.0 *v* 27.0 months; HR = 0.67, 95%CI 0.48-0.94, *P* = .02). Early separation of the survival curves speaks to the very high-risk population selected in INAVO120, and the added toxicity of the triplet therapy is balanced by the more aggressive nature of the disease.[23,35] A criticism of INAVO120 is that few patients crossed over to receive *PIK3CA*-targeting therapy in later lines of treatment, but with many patients not receiving any further therapy, this may not be an argument in favor of sequencing, rather an argument for early action. Whether earlier incorporation in first-line or de novo metastatic disease could further improve outcomes remains unknown.

SECOND-LINE TARGETED THERAPY

After progression on ET in combination with a CDK4/6i, second-line treatment selection is increasingly guided by identification of actionable genomic alterations. *ESR1* mutations arise under the selective pressure of ET, particularly aromatase inhibitors, and are typically absent in primary tumors; therefore, routine testing at recurrence or progression, preferably using blood-based circulating tumor DNA, is recommended. Oral selective estrogen receptor degraders (SERDs) have been shown to have specific activity targeting the mutations. In the EMERALD trial, elacestrant improved PFS compared with ET in patients with *ESR1*-mutated disease (mPFS, 3.8 *v* 1.9 months; HR = 0.55[95% CI 0.39-0.77] *P* = .0005), with benefit confined to the *ESR1*-mutant subgroup[26] (Table 1).

Imlunestrant, a next-generation, brain-penetrant SERD, received US regulatory approval in September 2025 for *ESR1*-mutated, hormone receptor–positive/HER2-negative MBC after at least one line of ET. In the EMBER-3 trial, imlunestrant improved PFS compared with standard therapy (fulvestrant or exemestane) in patients with *ESR1*-mutant disease, 5.8 months *v*. 3.8 months (estimated restricted mean survival time = 2.6 months [95%CI 1.2-3.9 months]; *P* < .001). Updated data demonstrated a median OS of 34.5 months with imlunestrant versus 23.1 months with standard therapy (HR = 0.60; *P* = .0043)[27] (Table 1).

Whether continuing CDK4/6i in the second line remains appropriate is unresolved. Both post-Monarch (abemaciclib) and MAINTAIN (ribociclib) have all suggested that some patients benefit from the continued utilization of CDK4/6i in combination with fulvestrant.[30,36] In EMBER-3, imlunestrant in combination with abemaciclib improved PFS regardless of *ESR1* mutation status compared with oral SERD alone (HR = 0.57 [95%CI 0.44- 0.73]; *P* < .001;[27] Table 1). CDK4/6i combinations remain a consideration for shared decision making with patients, which should incorporate a patient's prior CDK4/6i experience and tumor biology.

For patients with germline *BRCA1/2* mutations who are no longer benefiting from ET, poly(ADP-ribose) polymerase (PARP) inhibitors (olaparib or talazoparib) are a consideration (Table 1). The OlympiAD trial, which included a patient population with approximately half triple-negative breast cancer (TNBC) and half hormone receptor–positive/HER2-negative disease, showed that olaparib improved the mPFS to 7.0 months versus 4.2 months with TPC chemotherapy (HR, 0.58 [95% CI, 0.43 to 0.80]; *P* < .001), with notable response rates (59.9% *v* 28.8%) and long-term follow-up showing improved OS (19.3 months *v*. 17.3 months, HR, 0.90 [95% CI, 0.66 to 1.23]; *P* = .513).[31] The EMBRACA trial demonstrated that talazoparib improved the mPFS to 8.6 months versus 5.6 months (HR, 0.54 [95% CI, 0.41 to 0.71]; *P* < .001).[37]

New therapies and combinations are emerging in the treatment of hormone receptor–positive/HER2-negative MBC. Vepdegestrant (VERITAC-2), the first Proteolysis Targeting Chimera (PROTACs) ER degrader, improved PFS only in patients with *ESR1* mutant (5.0 *v* 2.1 months with fulvestrant, HR, 0.58 [95% CI, 0.43 to 0.78], *P* < .001) but not in the overall population.[38] In addition to CDK4/6i combinations discussed above, new mechanistic target of rapamycin inhibitors (mTORi) combinations are emerging. Giredestrant plus everolimus (evERA trial) combined an oral SERD with mTORi post-CDK4/6i therapy, demonstrating a 26.7% objective response rate predominantly in patients with *ESR1* mutations.[39] Finally, gedatolisib (VIKTORIA-1), a pan-*PI3K/mTOR* inhibitor, demonstrated improved PFS when added to fulvestrant (doublet, PFS 7.4 months, HR, 0.33 [95% CI, 0.24 to 0.48]; *P* < .001) and to fulvestrant and palbociclib (triplet, PFS 9.3 months, HR, 0.24 [95% CI, 0.17 to 0.35]; *P* < .001), each as compared with fulvestrant alone (PFS 2.0 months) in *PIK3CA* wild-type tumors.[40] These trials highlight the continued shifting landscape of mutation testing and novel therapeutics in overcoming endocrine resistance (Table 1).

Determining when a patient with hormone receptor–positive/HER2-negative MBC remains a candidate for ET is challenging as endocrine resistance exists along a biological continuum that remains incompletely understood. In practice, secondary resistance does not preclude further ET options, whereas primary endocrine resistance (relapse while during the first 2 years of adjuvant ET or rapid progression within 6 months of first-line ET for MBC) is a strong consideration for ADC or chemotherapy.[41] Conversely, patients with limited disease burden, indolent disease, and sustained benefit to prior lines of ET may all benefit from continued ET, particularly given a more favorable toxicity profile. As indolent hormone receptor–positive/HER2-negative MBC can complicate progression assessments, rigorous radiographic-clinical correlation is essential, and emerging data support utilization of ctDNA dynamics in this paradigm. Uniform research definitions of

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endocrine resistance and response are needed to standardize both research advances and clinical care.

Shared decision making including toxicity profiles, clinical factors, and comorbidities guides individualized therapy. Reflecting on combination versus sequenced targeted therapy and special populations including the elderly, it is important that we recognize that individual patient goals are not fixed; rather, they evolve as the disease progresses as treatments change and as life circumstances shift.[42] Younger patients may be balancing treatment while raising children and caring for aging parents. Older adults—who are too often undertreated and subject to age-related bias—might have additional comorbidities that influence therapeutic decisions, yet maintain priorities related to independence, work, retirement, and family. The shortage of geriatric oncology expertise further highlights the need for individualized, age-inclusive care. For example, while *PIK3CA* mutations identify patients at higher risk of resistance, they do not preclude benefit from CDK4/6i but identify some for early administration of *PIK3CA*-targeting triplet therapy. Taking time to assess what is clinically meaningful to each individual patient is the much-needed *art of oncology* that clinicians are asked to practice.

METASTASIS-DIRECTED THERAPY FOR OLIGOMETASTATIC AND OLIGOPROGRESSIVE BREAST CANCER: WHEN AND WHY?

Oligometastatic breast cancer (OMBC) represents a state of limited metastatic burden between localized and widely disseminated disease.[43] The working hypothesis is that ablating all visible metastases alongside first-line systemic therapy may delay new metastatic events and improve PFS and possibly OS—although randomized trials have not confirmed this in unselected patients. For selected patients, metastasis-directed therapy (MDT), typically with stereotactic body radiotherapy (SBRT)/stereotactic ablative body radiotherapy (SABR), can provide durable local control, defer systemic therapy escalation, and occasionally yield long-term remission. However, unlike prostate cancer or non–small cell lung cancer (NSCLC), randomized MDT trials in breast cancer have not demonstrated PFS or OS benefits despite excellent local control. Contemporary definitions remain imaging-based: the ESTRO/EORTC framework classifies oligometastatic disease as 1-5 lesions and distinguishes de novo, induced, and repeat/recurrent states. Clinically, differentiating oligoprogression, oligorecurrence, and oligopersistence is essential as these subtypes reflect distinct biology, risks of occult systemic disease, and appropriate therapeutic goals and trial designs.

BIOLOGY AND SUBTYPE: BREAST CANCER'S DEVIATION

Multiple population-based and translational studies suggest that de novo MBC can have more favorable outcomes than metachronous recurrence,[43] in part because metachronous disease may reflect selection of clones capable of early dissemination and systemic escape (Fig 1). For example, studies of clonal evolution across cancer subtypes (including breast) show that parallel dissemination patterns are more common in metachronous disease than in synchronous presentations, consistent with a higher likelihood of early systemic escape.[44]

Molecular subtypes strongly influence metastatic rate, patterns of failure, and the plausibility that ablating visible lesions will meaningfully change the natural history. While this review focuses on hormone receptor–positive/HER-negative MBC, trials in MDT are rarely limited to distinct cancer types, much less cancer subtypes. In general, hormone receptor–positive/HER2+ disease has the most favorable prognosis, followed by hormone receptor–positive/HER2-negative, hormone receptor-negative/HER2+, and TNBC.[5] Importantly, within oligometastatic cohorts, TNBC often fails to benefit from classic favorable features (solitary metastasis, long disease-free interval), suggesting a higher probability of subclinical dissemination even when well-defined by axial imaging.[45] It is also possible that as systemic therapies continue to improve, the incremental benefit of MDT may become smaller, more dependent on the subtype, and more sensitive to the accuracy of staging.

SYSTEMIC THERAPY REMAINS THE FOUNDATION

Before considering MDT, it is worth emphasizing that the best evidence for improving outcomes in limited-volume breast cancer recurrence comes from systemic therapy. CALOR established that chemotherapy improves disease-free survival after isolated locoregional recurrence, underscoring that micrometastatic disease control remains essential even when disease appears limited. The trial also reinforces the importance of the tumor subtype in both trial design and decisions regarding MDT.[46] In OMBC, MDT should be framed as an *adjunct* to effective systemic therapy in most circumstances (Fig 1). In rare and highly selected scenarios (eg, long disease-free interval, solitary metastasis, favorable subtype, and strong patient preference), forgoing systemic therapy in favor of MDT may be appropriate.

MDT USING SBRT: EVIDENCE IN BREAST CANCER

SBRT delivers highly conformal, image-guided radiation in 1-5 fractions (sometimes 8-10 for select sites) to achieve ablative biological doses while respecting organ-at-risk constraints.[47] Across prospective series, meta-analyses, and the NRG BR001 phase I trial in oligometastatic cancer, ablative SBRT is generally safe and achieves high local control.[48] In OMBC specifically, the most consistent benefit of SBRT is reliable lesion control with short treatment courses, which can prevent symptoms, avoid complications (eg, fracture, cord compression), and reduce the need for repeated palliative RT.

In the mixed-histology phase II SABR-COMET trial (breast subgroup n = 18), an OS signal was observed overall, but this was hypothesis-generating only and not specific to breast

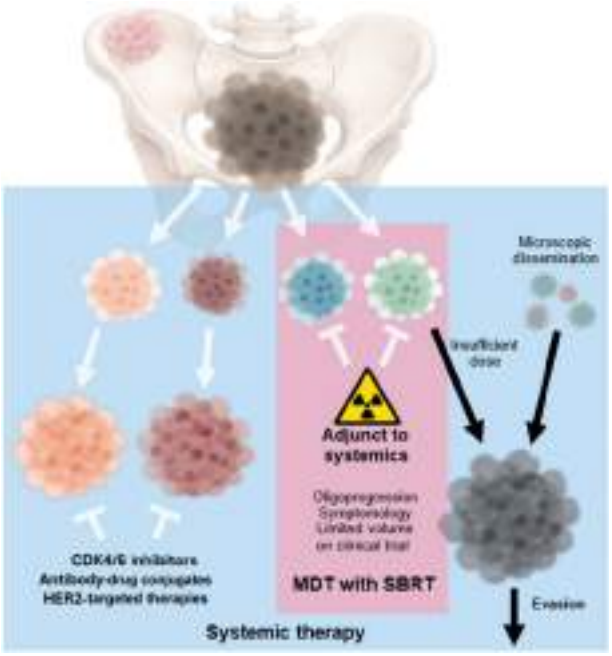

FIG 1. Metastasis-directed therapy within the systemic framework: oligometastasis represents subclonal variants of the primary cancer with the ability to shed further metastatic disease. Systemic therapy acts as an overarching mechanism of treatment targeting shared mechanisms across these subclonal variants (blue). SBRT may benefit in targeting anatomic populations (pink). The current data showing no PFS or OS benefit to the addition of MDT are thought to be driven by inadequate dosing and microscopic dissemination leading to evasion. (*Portions of this figure were generated using OpenAI and edited by the authors for accuracy and content.*) CDK4/6, cyclin-dependent kinase 4 and 6; HER2, human epidermal growth factor 2; MDT, metastasis-directed therapy; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiotherapy.

cancer. Notably, MDT did not reduce the rate of new metastases, undermining the central biological rationale.[47] In breast cancer–specific randomized data, the signal has been consistently neutral (Table 2).

The NRG-BR002 phase II/III trial presented at ASCO 2022 randomly assigned patients with newly oligometastatic breast cancer (≤4 metastases) who had not progressed after initial systemic therapy to standard systemic therapy alone versus systemic therapy plus MDT (SBRT and/or surgery). The initial results showed no improvement in PFS or OS with MDT and, importantly, no reduction in the rate of new metastases (approximately 40% in both arms;[49] Table 2). Despite excellent local control, MDT did not change progression patterns. The phase III portion was therefore not pursued.

Similar to NRG BR002, the MD Anderson–led EXTEND (External Beam Radiation to Eliminate Nominal Metastatic Disease) trial provides randomized data, adding MDT to standard systemic therapy in oligometastatic breast cancer. In the breast cancer subcohort, MDT did not improve PFS or OS. While local control of treated lesions in the MDT arm was 100%, all progression events in the MDT arm occurred at new, untreated distant sites—again at rates similar to the control arm. This suggests that in unselected OMBC, occult disease outside treated targets are the dominant driver of disease progression[50] (Table 2).

In the oligoprogressive setting, the CURB trial randomly assigned patients with oligoprogressive NSCLC or breast cancer to SOC systemic therapy with or without SBRT. The overall PFS benefit reported was driven by NSCLC; in the breast cancer subgroup, PFS was not improved.[51] By contrast, AVATAR (TROG 20.03), a single-arm phase II trial in hormone receptor–positive/HER2-negative oligoprogressive disease on CDK4/6i, met its short-term event-free survival end point, supporting SBRT as a strategy to prolong the utility of an effective systemic regimen in carefully selected patients[52] (Table 2).

The data discussed to this point have shaped ongoing investigations that address patient selection and SBRT technique. The developing NRG phase II CLARITY looks to circulating tumor cells (CTC) as a means of selecting patients with OMBC who will benefit from MDT. This trial expands on ad hoc analysis of BR002 which found that patients in the lowest quartile of CTC counts experienced significant PFS benefit from MDT.[53]

WHO SHOULD BE CONSIDERED FOR SBRT?

Given the presented randomized trials, SBRT in OMBC has not shown benefit in unselected patients and systemic therapy should remain the cornerstone of management in this setting. While ongoing trials seek to define the patient phenotype and SBRT technique that MDT may benefit, current implementation should be targeted to scenarios where its benefits are most plausible:

1. Oligoprogression on an otherwise effective systemic regimen: especially hormone receptor–positive/HER2-negative on CDK4/6i and HER2+ on HER2 therapy where SBRT can ablate resistant clones and delay systemic therapy change.
2. Symptom prevention or risk mitigation: high-risk bone lesions, spinal metastases threatening cord compression, weight-bearing sites,[53] or lesions likely to ulcerate/bleed.
3. Limited-volume, favorable biology recurrence: long disease-free interval, solitary metastasis, low-grade hormone receptor–positive disease, and low overall tumor burden.
4. Eligible for a clinical trial: Many are in development including CLARITY (patient selection based on circulating tumor markers).[54]

BEYOND ORAL, TARGETED THERAPY

Despite the advances of oral therapy and molecularly targeted agents including CDK4/6i, oral SERDs, and PIK3CA agents, MBC inevitably becomes endocrine-refractory.[41] Historically, treatment options beyond ET were limited to single-agent chemotherapy, associated with modest PFS

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TABLE 2. Evidence Summary of MDT/SBRT in OM and OP Breast Cancer

Trial	Setting	Phase/No. (breast)	Intervention	Key Finding
SABR-COMET[46]	OM (mixed histologies)	Phase II; breast subset (n = 18)	SOC systemic with or without SABR to all lesions	Improved PFS/OS overall; breast subgroup small—hypothesis-generating only
NRG-BR002[48]	OM	Phase II/III (n = 125)	SOC systemic *v* SOC + MDT (SBRT and/or surgery)	No improvement in PFS or OS reported; supports caution in unselected OMBC
EXTEND[49]	OM	Phase II basket; n = 43 randomly assigned	SOC systemic *v* SOC + MDT to all sites	No PFS benefit (15.6 *v* 24.9 months; HR = 0.91; *P* = .86); 100% LC; failures at new sites
CURB[50]	OP	Phase II; breast subgroup	SOC systemic with or without SBRT to progressing sites	Overall PFS benefit driven by NSCLC; no PFS benefit in the breast subgroup
AVATAR (TROG 20.03)[51]	OP	Phase II single-arm; ER+/HER2−	SABR to progressing lesions while maintaining CDK4/6 inhibitors	Met short-term EFS end point; supports SBRT to delay line the change in selected patients

NOTE. This table summarizes key studies that have explored MDT/SBRT in OM/OP breast cancer, showing consistent neutral results and small subgroups.[42,44-46]

Abbreviations: CDK4/6, cyclin-dependent kinase 4 and 6; EFS, event-free survival; ER+, estrogen receptor–positive; HR, hazard ratio; HER2, human epidermal growth factor 2; LC, local control; MDT, metastasis-directed therapy; NSCLC, non–small cell lung cancer; OM, oligometastatic; OP, oligoprogressive; OMBC, oligometastatic breast cancer; OS, overall survival; PFS, progression-free survival; SOC, standard of care; SABR, stereotactic ablative body radiotherapy; SBRT, stereotactic body radiotherapy.

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benefit and cumulative toxicities that negatively affect QoL. The introduction of ADCs fundamentally altered this paradigm, with improved efficacy and a shift toward more favorable tolerability profiles for many patients.

EXPANDING THE HER2 SPECTRUM

Fam-trastuzumab deruxtecan (T-DXd) has emerged as a key therapeutic option in hormone receptor–positive MBC with low levels of HER2 expression. In the DESTINY-Breast04 trial, T-DXd demonstrated superiority over treatment of physician's choice (TPC) chemotherapy in patients with HER2-low MBC (immunohistochemistry [IHC] 1+ or IHC 2+ and ISH nonamplified) who had received one to two prior chemotherapy regimens. Among patients with hormone receptor–positive/HER2-low MBC, the median PFS was 10.1 months with T-DXd compared with 5.4 months with TPC (HR, 0.51 [95% CI, 0.40 to 0.64]; *P* < .001), leading to improved OS (T-DXd 23.9 months *v* 17.5 months TPC; HR, 0.64 [95% CI, 0.48 to 0.86]; *P* = .003). Benefit was consistent regardless of prior exposure to CDK4/6i[55,56] (Table 3).

The DESTINY-Breast06 trial extended these findings to first-line infusion therapy and broadened the HER2 spectrum to include patients with HER2-ultralow disease, defined as IHC-0 with detectable membrane staining. In patients who had progressed on ET but had not received prior chemotherapy for hormone receptor–positive/HER2-low/HER2-ultralow MBC, T-DXd significantly improved median PFS compared with chemotherapy in all patients (13.2 months *v* 8.1 months, HR, 0.62 [95% CI, 0.52 to 0.75]; *P* < .001).[57] These results support the use of T-DXd as a preferred option in the post-ET, pre-chemotherapy setting for patients with hormone receptor–positive/HER2-low or hormone receptor–positive/HER2-ultralow MBC (Table 3).

Although T-DXd offers substantial clinical benefit, its use requires careful attention to safety, particularly the risk of pneumonitis or interstitial lung disease (ILD). Across DESTINY-Breast04 and DESTINY-Breast06, ILD was reported in approximately 11%-12% of patients, with fatal events occurring in 0.7%. The time to onset was as early as 5 weeks and persisted up to 28 months in DESTINY-Breast06, underscoring the need for ongoing vigilance.[55,57]

Patients with active ILD or significant pulmonary comorbidities were excluded from trial enrollment, raising concern that real-world incidence may be higher. Retrospective data suggest increased ILD risk in heavily pretreated patients and those with prior ADC exposure. Early recognition, prompt treatment interruption, and corticosteroid initiation are critical components of ILD management and should be emphasized in routine clinical practice and discussion of ILD as a risk component of shared decision making in ADC selection (Table 4).[61,62]

The evolving definition and utilization of HER2 in treatment decisions make accurate HER2 assessment central to treatment selection. Emerging data suggest that HER2 assessment from metastatic biopsy specimens may better predict benefit from T-DXd than primary tumor testing, and tissue collected at the closest time point to the current clinical decision or obtained from a new biopsy is likely to yield best response information.[63] Identification of HER2-ultralow disease requires meticulous IHC interpretation and experienced pathology review, given known interobserver variability.[64] At this time, the efficacy of T-DXd in patients

TABLE 3. Key Clinical Trials: ADC Therapies in Hormone Receptor -Positive/HER2-Low/HER2-Negative Metastatic Breast Cancer

Trial	Drug	Target	Population	Comparator	Median PFS (HR [95% CI] significance)	Median OS (HR [95% CI] significance)	Grade ≥ 3 Toxicities[a] (%)
DESTINY-Breast04[55]	Trastuzumab deruxtecan (T-DXd)	HER2	HER2-low MBC; 1-2 prior chemotherapy lines	Physician's choice chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel)	10.1 mo *v* 5.4 mo (HR = 0.51 [0.40 to 0.64; *P* < .001)	23.9 mo *v* 17.5 mo (HR = 0.64 [0.48 to 0.86]; *P* = .003)	Any-grade ILD (12.1), neutropenia (13.7), anemia (8.1), fatigue (7.5), leukopenia, (6.5), thrombocytopenia (5.1), nausea (4.6), LFT elevation (3.2)
DESTINY-Breast06[57]	Trastuzumab deruxtecan (T-DXd)	HER2	Hormone receptor–positive/HER2-low or HER2-ultralow MBC; post-ET, no prior chemotherapy for MBC	Physician's choice chemotherapy (paclitaxel, nab-paclitaxel, capecitabine)	13.2 mo *v* 8.1 mo (HR = 0.62 [0.52 to 0.75], *P* < .001)	Immature	Any-grade ILD (11.3) neutropenia (20.7), leukopenia (6.9), anemia (5.8), fatigue (3.7)
TROPiCS-02[58]	Sacituzumab govitecan (SG)	Trop-2	Hormone receptor–positive/HER2-negative MBC; 2-4 prior chemotherapy lines; prior CDK4/6 inhibitor and taxane required	Physician's choice chemotherapy (eribulin, vinorelbine, capecitabine, gemcitabine)	5.5 mo *v* 4.0 mo (HR = 0.66 [0.53 to 0.83]; *P* = .0003)	14.4 mo *v* 11.2 mo (HR = 0.79 [0.65 to 0.96]; *P* = 0 · 020)	Any-grade ILD: no events reported neutropenia (50), diarrhea (9), leukopenia (9), fatigue (6), anemia (6), febrile neutropenia (5), lymphopenia (4)
ASCENT-07[59]	Sacituzumab govitecan (SG)	Trop-2	Hormone receptor–positive/HER2-negative MBC eligible for first-line chemotherapy after progression on ET	Physician's choice chemotherapy (eribulin, vinorelbine, capecitabine, gemcitabine)	8.3 mo *v* 8.3 mo (HR = 0.85, 95%CI 0.69 to 1.05)	Immature	Any-grade ILD: no events reported[b] neutropenia (55), leukopenia (14), anemia (10), diarrhea (7), anemia (5)
TROPION-Breast01[60]	Datopotamab deruxtecan (Dato-DXd)	Trop-2	Hormone receptor–positive/HER2-negative MBC; 1-2 prior chemotherapy lines; post-ET	Investigator's choice chemotherapy (eribulin, capecitabine, vinorelbine, gemcitabine)	6.9 mo *v* 4.9 mo (HR = 0.63 [0.52 to 0.76], *P* < .0001)	18.6 mo *v* 18.3 mo (HR = 1.01 [0.83 to 1.22]; *P* = .94)	Any-grade ILD (3.3), stomatitis (6.4)

NOTE. Including DESTINY-Breast04 and DESTINY-Breast06 evaluating T-DXd, TROPiCS-02 evaluating SG, and TROPION-Breast01 evaluating Dato-DXd. ADCs demonstrated improved progression-free survival compared with physician's choice chemotherapy, with varying overall survival outcomes and distinct toxicity profiles, compared with physician's choice chemotherapy. Image formatting was adjusted using Claude for presentation purposes only.

Abbreviations: ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; ET, endocrine therapy; G ≥3, grade ≥3; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ILD, interstitial lung disease/pneumonitis; LFT, liver function testing; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.

[a]Significant adverse events = grade ≥3 events those occurring ≥3%.

[b]May be incompletely reported given abstract form.

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with HER2-null MBC is unknown; although DESTINY-Breast15 (ClinicalTrials.gov identifier: NCT05950945) is exploring that question, the temptation to expand use should be curtailed.

TARGETING TROP2

Sacituzumab govitecan (SG), a trophoblast cell surface antigen 2 (TROP2) ADC, demonstrated significant survival benefits in the phase III TROPiCS-02 trial. Eligible patients had received two to four prior chemotherapy regimens or experienced early relapse after (neo)adjuvant therapy. SG improved the mPFS to 5.5 months compared with 4.0 months with TPC chemotherapy (HR, 0.66 [95% CI, 0.53 to 0.83]; *P* = .0003). Improvement in mOS was also reported (SG 14.4 months *v* TPC 11.2 months, HR, 0.79 [95% CI, 0.65 to 0.96], *P* = .020), establishing SG's role in heavily pretreated hormone receptor–positive/HER2-negative MBC[58] (Table 3).

The ASCENT-07 trial evaluated SG among patients with hormone receptor–positive/HER2-negative MBC eligible for first-line chemotherapy after disease progression on ET, and both treatment arms demonstrated a median PFS of 8.3 months (HR, 0.85 [95% CI, 0.69 to 1.05]; *P* = .130), showing no superior advantage for SG. While OS data remain immature, these results do not support routine use of SG in chemotherapy-naïve patients with hormone receptor–positive/HER2-negative MBC[59] (Table 3). In this setting, chemotherapy remains an appropriate option, particularly for patients with HER2-null disease who are not candidates for T-DXd.

TABLE 4. Shared Decision-Making Algorithm for Endocrine-Resistant or Endocrine-Ineligible Hormone Receptor–Positive/HER2-Negative Metastatic Breast Cancer

Step-Wise Considerations	Key Variables
STEP 1 Assess HER2 expression	Rebiopsy the metastatic site if feasible, use tissue from the most recent sample if feasible Assess prior chemotherapy and/or ADC exposure HER2-low/HER2-ultralow: Consider trastuzumab deruxtecan (T-DXd) if no contraindication (eg, prior ILD). HER2-null (IHC 0): Consider standard chemotherapy ADC after chemotherapy (sacituzumab govitecan or datopotamab deruxtecan)
STEP 2 Safety considerations	Trastuzumab deruxtecan Nausea Fatigue ILD risk Sacituzumab govitecan Neutropenia (consider growth factor support) Diarrhea Datopotamab deruxtecan Stomatitis/mucositis Ocular toxicity Lower ILD risk than T-DXd Chemotherapy In some settings including prior chemotherapy or first-line HER2-null, chemotherapy may be preferred
STEP 3 Shared decision making	Reassess current goals of care, value system; include caregivers as patient desires To represent shared decision making, two or more reasonable treatment options need to be discussed, or one preferred with an alternative approach Treatment schedule and visit frequency Side effect profile compared with prior therapy experiences Quality-of-life priorities Disease burden (rapidity, extent) Limited efficacy data for ADC after ADC, particularly with the same payloads or same antibodies
Final therapy selection; continued assessments for appropriate therapeutic adjustments based on changing patient goals, toxicity, and/or disease response	

NOTE. Highlighting key considerations when selecting chemotherapy versus ADCs. Major decision factors include assessment of HER2 status, anticipated toxicity profiles in the context of patient comorbidities, and incorporation of patient values and preferences. Image formatting was adjusted using ClaudeAI for presentation purposes only.
Abbreviations: ADC, antibody-drug conjugates; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease/pneumonitis.

Datopotamab deruxtecan (Dato-DXd), another TROP2 ADC, was evaluated in the TROPION-Breast01 trial among patients with ET-refractory disease who had received one to two prior chemotherapy lines. Dato-DXd improved the mPFS to 6.9 months compared with 4.9 months with TPC chemotherapy (HR, 0.63 [95% CI, 0.52 to 0.76]; $P < .0001$) although OS did not reach statistical significance (18.6 months Dato-DXd *v.* 18.3 months TPC; HR, 1.01 [95% CI, 0.83 to 1.22]; $P = .94$). An imbalance in subsequent ADC use might have influenced OS outcomes. Dato-DXd demonstrated fewer grade ≥3 adverse events than TPC chemotherapy and a lower incidence of ILD (3.3%) compared with T-DXd, supporting its potential role in later lines of therapy[60] (Table 3).

SEQUENCING AND RESISTANCE: DECIDING AMID THE UNKNOWNS

The optimal sequencing of ADCs remains unknown. Retrospective, real-world studies suggest diminishing benefit with sequential ADC use, with shorter PFS observed with the second ADC independent of the drug.[65] Primary resistance occurs in approximately half of patients, and intervening chemotherapy does not appear to restore sensitivity.[66] Cross-resistance among ADCs sharing topoisomerase inhibitor payloads has been described, with emerging evidence linking TOP1 mutations to clinical resistance.[67] ADCs with alternative payloads are in development, and reason calls for introduction into the clinical trial landscape to allow for implementation and understanding of rational sequencing strategies.[68]

ADCs have transformed the management of hormone receptor–positive/HER2-negative MBC. At this time, given the significant improvement seen in PFS and OS with T-DXd among patients with HER2-low or HER2-ultralow expression, the authors favor T-DXd as the initial ADC. Critically, we encourage exhausting all ET and targeted oral agents first. Among those ineligible for T-DXd based on comorbidities or HER2 expression, the improvement in OS gained with SG creates a slight therapeutic advantage over Dato-DXd, with careful consideration at the time of shared decision making with patients of differing toxicity profiles and infusion schedules, which, for any individual patient, may alter the decision. For those patients eligible for sequencing ADC, we rely heavily on shared decision making, with emphasis on little evidence supporting efficacy for any therapeutic after ADC exposure. Therefore, we reassess patients' individual goals of care and include available information on the treatment schedule, toxicity profile including cost, and median PFS in a longer discussion about what treatment would be most appropriate. This conversation can develop slowly over therapeutic exposure to first ADC to facilitate optimal clinician workflow (Table 3).

Supportive and integrative services such as palliative care, massage, acupuncture, and meditation can meaningfully improve symptom management and QoL. While these offerings are often presented as standard components of care, many patients cannot access or afford them. Financial toxicity is not theoretical; it is a daily reality for people living with MBC. The cost of treatment, supportive care, transportation, and lost income continues to place an unsustainable burden on patients and families. Both financial support resources and supportive care resources should be offered at every opportunity for best care.[69]

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CONCLUSION

Hormone receptor–positive/HER2-negative MBC has seen rapid advances in treatment, with a shift toward personalized, targeted therapies and ADCs that improve outcomes while emphasizing QoL. CDK4/6i combined with ET remains the foundation of first-line treatment, whereas subsequent therapy is increasingly guided by molecular profiling (eg, *ESR1*, *PIK3CA*, *BRCA*) and patient-specific factors, both of which we are still learning to optimally use in clinic for best care.

As treatment options expand, clinical decision making has become more complex, requiring careful consideration of matching disease mutation with targeted therapy and patient goal, incorporating benefits, toxicity, and sequencing considerations into clinical conversation. ADCs are reshaping later-line treatments although optimal sequencing and long-term strategies remain uncertain. Metastasis-directed therapies such as SBRT may benefit select patients but have not demonstrated consistent survival advantages in broader populations, reinforcing systemic therapy as the cornerstone of care.

From a patient perspective, shared decision making is essential. Treatment choices must align with individual goals, QoL priorities, and practical realities such as treatment burden, access, and financial toxicity. Despite therapeutic progress, many patients face significant barriers to supportive care and financial resources.

Ultimately, optimal care requires integrating evolving scientific evidence with individualized, patient-centered approaches—ensuring equitable access, clear communication, and alignment with what matters most to each person living with metastatic breast cancer.

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Optimizing Breast Cancer Survivorship: Addressing Lifestyle, Weight Management, and Psychological Health

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OVERVIEW

With more than 4 million breast cancer (BC) survivors in the United States, oncologic care has expanded to encompass the long-term health, physical function, and quality of life of this growing population. Cancer survivorship is an active, longitudinal phase demanding ongoing adaptation to persistent physical symptoms, metabolic sequelae, and the psychological burden of uncertainty. This chapter examines three critical pillars of BC survivorship care: lifestyle interventions, weight management, and psychological well-being. Lifestyle medicine is an evidence-based field grounded in six core pillars: nutrition, physical activity, stress management, sleep, avoidance of risky behaviors, and positive social connection. Higher physical activity levels are associated with reductions in BC-specific and all-cause mortality, while adherence to a plant-forward, minimally processed dietary pattern is associated with lower overall mortality. Despite this evidence, implementation remains inconsistent, with key barriers including insufficient time, training, and referral resources. Elevated BMI at diagnosis and weight gain after treatment are associated with poorer BC outcomes and increased all-cause mortality. Although lifestyle modifications produce modest weight loss with mixed effects on survival outcomes, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a promising alternative, with emerging retrospective data suggesting improvements in overall survival and cardiovascular outcomes. Fear of cancer recurrence (FCR) is an unmet need among cancer survivors, affecting up to 59%, and does not decrease over time without intervention. Routine screening, honest information delivery, and a stepped-care referral model are recommended. Addressing these pillars will empower BC survivors to flourish during treatment and beyond.

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INTRODUCTION

There are over 4 million breast cancer (BC) survivors living in the United States. BC survivors have unique needs that should be addressed during survivorship. Key elements of survivorship care include monitoring for recurrence, addressing medical and psychosocial consequences of treatment, and providing education about lifestyle interventions that decrease risk of recurrence, enhance quality of life, and improve outcomes.[1] After completion of treatment for BC, many survivors experience concerns related to physical functioning, fatigue, weight gain and cardiometabolic changes, and fear of recurrence (FCR). To optimize BC survivorship care, it is imperative that these issues are addressed. In this chapter, we will address three critical components of BC survivorship care, namely the importance of lifestyle interventions, weight management, and psychological well-being.

THE LIVED EXPERIENCE IN SURVIVORSHIP CARE

People are increasingly living many years, and often decades, with or beyond a BC diagnosis, reflecting rising survival rates and a growing population of survivors in the United States and globally.[2] As survival improves, attention has appropriately shifted from short-term treatment outcomes to long-term health, physical function, and quality of life across the survivorship continuum.[3]

Cancer survivorship is not passive recovery and nor simply the absence of disease. It is a longitudinal phase of active navigation—requiring ongoing adaptation to physical symptoms, metabolic shifts, and the psychological realities of uncertainty. Persistent treatment-related symptoms, changes in body composition, and excess weight gain are common and contribute to reduced physical function and long-term cardiovascular and metabolic risk among BC survivors.

PRACTICAL APPLICATIONS

- Oncology clinicians should routinely incorporate evidence-based lifestyle counseling and address physical activity, nutrition, sleep, and stress management into cancer survivorship care, including multidisciplinary care teams including nurses, dietitians, and social workers.
- Breast cancer survivors should be screened for weight gain and elevated BMI at diagnosis and throughout survivorship, with structured referrals to lifestyle modification programs and, when appropriate, consideration of pharmacologic interventions such as glucagon-like peptide-1 receptor agonists as emerging data on their safety and efficacy in this population continue to evolve.
- Fear of cancer recurrence (FCR) should be assessed routinely at the end of treatment and at all subsequent follow-up appointments using validated screening tools, as FCR does not diminish over time without intervention and is the most unmet psychological need among cancer survivors.
- A stepped-care model for FCR management, ranging from clinician-led normalization and provision of honest prognostic information, to referral for evidence-based cognitive-behavioral or mind-body interventions for those with persistent or severe FCR, supports efficient allocation of psychosocial resources.
- Digital tools such as wearables, mobile applications, telehealth platforms, and patient-reported outcome measures offer scalable strategies to extend lifestyle medicine support beyond clinic visits, enabling more equitable and sustained delivery of survivorship care across diverse patient populations.

This chapter examines three interconnected domains central to optimizing BC survivorship: the clinical foundations and implementation of lifestyle medicine (LM); the identification and management of fear of recurrence; and contemporary approaches to obesity management, including behavioral and pharmacologic interventions. Together, these perspectives underscore that survivorship care must extend beyond surveillance for disease recurrence, or progression, to encompass function, metabolic health, and psychological well-being across the lifespan.

Laura Carfang, EdD, CEO, SurvivingBreastCancer.org

LM: A KEY COMPONENT OF BC SURVIVORSHP CARE

Introduction: Definition of LM

Advances in early detection and treatment have improved cancer outcomes, with the combined 5-year overall survival (OS) for all cancers in the United States approaching 70%.[4] At the same time, an estimated 40% of newly diagnosed cancers and approximately half of cancer-related deaths are attributable to modifiable lifestyle factors.[5] As survival improves, a growing population of individuals live with treatment-related and cancer-associated sequelae, including impaired quality of life, social isolation, psychological stress, and sleep disturbances, often at higher rates than the general population.[6]

LM is an evidence-based specialty that applies therapeutic lifestyle interventions to prevent, manage, and, in some cases, reverse chronic disease. LM is grounded in six pillars: nutrition, physical activity, stress management, sleep, avoidance of risky substances, and social connectedness (Fig 1). When integrated with standard treatment, LM plays an important role in cancer care, by optimizing function, enhancing treatment tolerance, and improving quality of life. LM is a key component of supportive care for BC survivors, who experience a high prevalence of unmet needs that are often insufficiently addressed by traditional models.

The American Cancer Society (ACS)/ASCO BC Survivorship Guideline highlights the role of lifestyle factors in BC

FIG 1. The six pillars of lifestyle medicine. Figure used with permission from the American College of Lifestyle Medicine.

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survivorship by emphasizing that health promotion, as well as assessment and management of physical and psychological long-term and late effects of BC treatment, should be addressed.[1] Persistent symptoms such as fatigue, sleep disturbance, pain, neuropathy, and cognitive complaints are common after completion of primary treatment and frequently coexist with physical deconditioning, sarcopenia, and reduced functional reserve.[7,8] Psychological sequelae, including anxiety, FCR, depression, sexual dysfunction, relationship strain, and body image concerns, are also prevalent among BC survivors, with younger patients reporting high levels of emotional distress related to fertility, menopause, weight gain, and identity.[9,10] Studies have shown that a substantial proportion of survivors report at least one unmet need, indicating limited use of systematic needs assessment tools and insufficient integration of multidisciplinary survivorship care.[10]

These ongoing symptoms and functional limitations have consequences for quality of life, return to work, social participation, treatment adherence, and financial well-being. Lymphedema and chronic pain syndromes, including aromatase inhibitor–associated arthralgias and chemotherapy-induced peripheral neuropathy, can worsen over time and further impair function. In parallel, cardiovascular disease and metabolic dysfunction represent leading competing risks for morbidity and mortality in BC survivors. Increasing evidence links lifestyle behaviors, particularly physical activity, nutrition, and weight management, to improved symptom control, better treatment tolerance, and preservation of functional independence.[9,11] Introducing evidence-based LM early and reinforcing LM longitudinally is essential to meeting the complex needs of BC survivors and supporting long-term health beyond cancer.

Core Lifestyle Domains: Survivorship-Specific Priorities

Physical Activity

Physical inactivity and obesity are associated with higher risks of BC-specific and all-cause mortality.[12–14] By contrast, women who participate in regular moderate-to-vigorous physical activity several days per week experience an estimated 20%–40% lower risk of BC compared with sedentary individuals.[15] Evidence from survivorship cohorts further supports the prognostic relevance of physical activity after diagnosis. In a meta-analysis of 16 prospective observational studies of BC survivors, researchers reported that higher physical activity levels were associated with a 28% reduction in BC-specific mortality (risk ratio [RR], 0.72 [95% CI, 0.60 to 0.85]) and a 48% reduction in all-cause mortality (RR, 0.52 [95% CI, 0.42 to 0.64]) when comparing the most active with the least active survivor.[16]

Beyond survival outcomes, exercise has been shown reduce cancer-related fatigue and is associated with improvements in cardiorespiratory fitness, muscle strength, physical function, sleep, cognitive symptoms, quality of life, and psychological distress.[9,17–21] Despite this evidence, exercise counseling remains inconsistent in oncology practice. An ASCO patient survey found that 43% of patients reported that exercise was not discussed during oncology visits, although those who received counseling were more likely to adopt lifestyle changes and engage in regular physical activity.[22]

ASCO, the ACS, and the American College of Sports Medicine recommend routine physical activity for cancer survivors.[9,17,18] Current guidelines recommend 150-300 minutes per week of moderate-intensity activity or 75-150 minutes per week of vigorous-intensity activity, along with muscle-strengthening activities at least 2 days per week. Of note, variability in exercise modality, intensity, and duration across studies limits the ability to define a single optimal prescription, emphasizing the need for individualized, feasible approaches tailored to the patient.

Nutrition

Nutrition is a key component for both survivorship and for reducing the risk of chronic health conditions, including metabolic syndrome, cardiovascular disease, and obesity. Currently, the ACS, American Institute of Cancer Research, and National Comprehensive Cancer Network (NCCN) recommend a diet consisting of fruits, vegetables, whole grains, and low in red and processed meats. There is insufficient evidence to support special diets, such as a ketogenic or a vegan diet.[23–27] In a large meta-analysis of 117 studies, adherence to a high-quality diet (consisting of higher intake of fruits, vegetables, and whole grains, and low in red and processed meats, refined grains, and high-fat foods) was associated with lower overall mortality, while Western dietary patterns were associated with increased mortality.[28] Alcohol intake was associated with higher risk of BC recurrence but not overall mortality.[26] Additional analyses of Mediterranean dietary patterns further demonstrate an inverse association with BC mortality, with observed benefits largely attributable to higher intake of fruits, vegetables, and whole grains, and no consistent association with recurrence.[29]

Evidence supports a low-fat, minimally processed, plant-forward dietary pattern, rich in vegetables, fruits, whole grains, legumes, nuts, and seeds for BC survivors, with limitation of red and processed meats, sugar-sweetened beverages, and alcohol.[6,30] Effective nutritional counseling should also consider socioeconomic, cultural, and structural factors that influence access to and adherence to dietary recommendations.

Sleep

It has been reported that up to 70% of BC survivors experience sleep disturbance.[31] The causes of sleep disturbance are multifactorial, often secondary to vasomotor symptoms, pain, decreased energy, anxiety, depression, and FCR.[32]

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Impaired sleep can impair immune function, increase chronic inflammation, impair DNA repair, and disrupt metabolic and hormonal regulation.[32-34] In the Women's Health Initiative study, BC survivors who slept <5 hours per night compared with those who slept 7-8 hours a night were noted to have reduced BC survival.[35] By contrast, in the Women's Healthy Eating and Living Study, increases in sleep duration to ≥9 hours per night among women previously sleeping 7-8 hours were associated with higher risks of recurrence (48%, hazard ratio [HR], 1.48 [95% CI, 1.01 to 2.00]), BC-specific mortality (52%, HR, 1.52 [95% CI, 1.09 to 2.13]), and all-cause mortality (43%, HR, 1.43 [95% CI, 1.07 to 1.92]), independent of changes in lifestyle, comorbidities, or physical and mental health.[36] Oncology clinicians should assess patients' sleep patterns, identify the causes of sleep disturbance, and offer evidence-based treatment recommendations, such as cognitive-behavioral therapy for insomnia.

Stress Management and Social Connections

Psychosocial stress plays an important role in patients with BC and has been associated with increased risk of cardiovascular, metabolic, and psychiatric disease.[37] Therefore, ASCO also recommends routine screening for all patients for symptoms of depression and anxiety.

In addition, strong social support has been associated with improved emotional adjustment, reduced symptom burden, and overall well-being across the cancer continuum and demographic factors.[38] A systematic review suggests that among BC survivors, social support is strongly linked disease outcomes, with both structural and perceived support associated with improved disease-free survival (DFS) and lower mortality.[39] Furthermore, there is a growing recognition of loneliness as a public health concern, underscoring the importance of routinely assessing social support and incorporating strategies to reduce isolation and strengthen social connections as part of comprehensive BC survivorship care.

How to Implement LM Without a Dedicated Clinic

As outlined above, the six pillars of LM are essential components of oncology for patients with BC. Research suggests that when oncology clinicians address the role of LM with their patients, cancer survivors are more likely to improve their health behaviors.[40] However, in a clinic setting, there are numerous barriers to addressing these concerns.

To gain a better understanding of practice patterns regarding addressing lifestyle factors in oncology follow-up care, the Obesity and Energy Balance Subcommittee of ASCO's Cancer Prevention Committee surveyed oncology clinicians in 2019.[41] Most survey respondents (75.9%) were medical oncologists. Most respondents (79%) agreed that oncology clinicians should address lifestyle factors, specifically the role of physical activity, weight management, and nutrition, with their patients with cancer. However, 83% of respondents reported that oncology clinicians did not have adequate training to address these issues in patients with cancer.[41] Most respondents (84%) reported that counseling regarding lifestyle interventions should be conducted by other staff with relevant expertise.[41]

The results of this survey identified barriers to the incorporation of lifestyle interventions into oncology care.[41] Survey respondents indicated that significant challenges included lack of time for counseling patients and setting up referrals (66%), perceived patient resistance to behavior interventions (73%), lack of resources for referrals for lifestyle interventions (63%), concern for limited reimbursement (45%), and lack of training or experience in discussing weight management and behavior change with patients (49.1%).[41]

Continued progress in incorporating LM into oncology care will require further education on LM, as well as strategies to ease oncology clinicians' workload by developing standardized screening protocols that assess each patient's needs and readiness to change. There is a need to facilitate referrals to appropriate supportive services. Oncology programs can extend LM support beyond clinic visits by leveraging the existing care team, including nurses, advanced practice practitioners, physical therapists, dietitians, and social workers, and by considering shared medical visits and digital tools such as wearables, mobile apps, telehealth, and patient-reported outcome platforms.

Integrating the six pillars of LM into routine oncologic care provides an evidence-based framework for enhancing treatment tolerance, mitigating therapy-related toxicities, and optimizing long-term health-related quality of life in BC survivors. These lifestyle pillars also constitute the fundamental building blocks for achieving and sustaining healthy weight and metabolic health among BC survivors. However, a comprehensive weight-management strategy often requires additional modalities, and pharmacologic tools such as glucagon-like peptide-1 receptor agonists (GLP-1 RA) can be incorporated to facilitate clinically meaningful reductions in BMI and improve cardiometabolic profiles, and complement the benefits conferred by LM. In the section that follows, we will explore how GLP-1 RAs can be thoughtfully integrated into breast oncology care.

TACKLING OBESITY AFTER A BC DIAGNOSIS: FROM BEHAVIOR CHANGE TO UNDERSTANDING THE POTENTIAL FOR GLP-1 THERAPIES

Introduction: Obesity and Weight Gain in BC

The prevalence of obesity in Americans is increasing, with 49% of adults predicted to have obesity by 2030.[42] Obesity is associated with increased risk of BC in postmenopausal women.[43] After early-stage diagnosis, 50%-90% of patients with BC gain weight during and after treatment, especially

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those receiving adjuvant chemotherapy.[44,45] Weight gain in these patients often involves gain of adipose but not lean tissue, and worsening of other metabolic syndrome parameters, such as fasting glucose and blood pressure.[44,46]

Elevated BMI at the time of BC diagnosis and significant weight gain afterward are associated with poorer outcomes. Studies in early-stage BC have found that obesity at diagnosis is associated with a 21%-41% increased risk of all-cause mortality,[14,47,48] 17-38% increased BC-specific mortality (BCSM),[14,47,49] and 12-46% increased risk of distant recurrence.[47,49] Although studies on weight gain after diagnosis are more limited, weight gain of 10% or more appears to be associated with increased all-cause and BCSM.[47,50]

Lifestyle Modifications in BC Survivors

Several RCTs testing the impact of lifestyle modifications (LSM) on weight in BC survivors have been conducted (Table 1). Through various modalities, these trials reported significantly more weight loss in the intervention groups[51,54,55,57-60,62,63] aside from the WHEL study.[56] Notably, in some studies such as ENERGY and BWEL, younger, premenopausal patients or those identifying as Black or Hispanic/Latina experienced less weight loss.[58,62] Meta-analyses show that LSM resulted in loss of approximately 3%-12.5% of baseline weight or 1.3-3.8 kg and improved quality of life without adverse events.[64,65]

Findings regarding impacts on BC and survival outcomes are mixed. The WINS trial found a 24% lower risk of relapse and 22% lower risk of all-cause mortality with a low-fat dietary intervention.[51,52] However, the WHEL trial reported no difference in event-free survival (EFS) or OS after 7.3 years, although notably, no significant difference in weight loss between groups was achieved with the dietary intervention.[56] The LISA trial also did not find a significant difference in DFS at 8 years; however, the study sample size was limited by early closure to accrual.[61] The DIANA-5 trial did not show improvement in BC recurrence in the intention-to-treat (ITT) analysis, but reported a 41% lower recurrence risk among women in the upper tertile of dietary adherence.[59] Finally, in the SUCCESS C trial, there was no difference in DFS in ITT analyses, but among those who completed the 2-year LSM program, patients in the intervention arm had better DFS.[54] Overall, these results indicate that long-term adherence to LSM and weight loss may be necessary to observe improvements in BC recurrence and survival.

Overview of GLP-1 RAs

GLP-1 RAs mimic the natural function of GLP-1, an intestinal hormone that promotes insulin secretion, suppresses glucagon, and inhibits gastric emptying, leading to decreased food intake.[66] GLP-1 RAs were first developed and approved for treatment of type 2 diabetes mellitus (T2DM) based on multiple phase III clinical trials demonstrating greater glycemic control and improved cardiovascular outcomes compared with placebo and alternative medications.[67-72] GLP-1 RAs were subsequently studied for weight management in people without T2DM based on clinically relevant weight loss seen in people with T2DM. Three GLP-1 RAs have been US Food and Drug Administration–approved for a weight management indication in adults with obesity or with BMI ≥ 27 and at least one weight-related comorbidity (hypertension, dyslipidemia, or T2DM). These include liraglutide, semaglutide, and tirzepatide, the latter a dual agonist of receptors for GLP-1 and glucose-dependent insulinotropic polypeptide, a hormone that also increases insulin secretion, working synergistically with GLP-1.[73] As an adjunct to LSM, liraglutide was shown to induce an 8% decrease in baseline weight or 8.4 kg mean weight loss at 56 weeks,[74] semaglutide a 15% or 15.3 kg mean weight loss at 68 weeks,[75] and tirzepatide a 15%-21% or 16.1-23.6 kg mean weight loss at 72 weeks.[76] A greater reduction in fat mass than lean body mass was found in these studies.[75,76]

GLP-1 RAs After a BC Diagnosis

None of the major phase 3 trials on GLP-1 RAs for weight loss included patients with BC, so the safety and efficacy of these medications among BC survivors remain unclear. Preliminary analyses based on small retrospective studies in the neoadjuvant setting have reported mixed effects of GLP-1 RA use on pathologic complete response (pCR). One study of patients with early-stage triple negative BC (TNBC; N = 343) found that concurrent use with the KEYNOTE-522 chemo-immunotherapy regimen was associated with a lower pCR rate (30.8% in users *v* 64.4% in nonusers, $P = .001$),[77,78] although another study (N = 77, notably 61.5% Hispanic) found no significant difference (46.2% *v* 51.6%, $P = .77$).[79] Among 42 patients with human epidermal growth factor receptor 2–posotive (HER2+) BC receiving chemotherapy and anti-HER2 therapy, those using GLP-1 RA had a numerically lower pCR rate, although this was not statistically significant (33% *v* 58%, $P = .21$).[80] These small studies raise the question of whether GLP-1 RA may reduce the efficacy of chemotherapy or immunotherapy, but larger confirmatory studies are needed.

More studies have focused on the use of GLP-1 RAs in the adjuvant setting (Table 2). These studies included primarily patients with early-stage BC receiving adjuvant endocrine therapy (ET) and have reported that GLP-1 RAs were associated with a 2.3%-11% weight loss. Notably, in these studies, GLP-1 RAs were prescribed mainly in the context of diabetes, with 71%-100% of participants diagnosed with T2DM.[81-84,87,89] Several studies have found no difference in weight loss by ET use.[82,83,87] Finally, a recent study reported worse ET side effects particularly in patients age 50 years and younger, including increased incidence of arthralgias (risk ratio [RR], 1.4 [95% CI, 1.2 to 1.5]), hot flashes (RR, 1.5 [95% CI, 1.2 to 1.8]), venous thromboembolism (VTE; RR, 1.4 [95% CI, 1.09 to 1.9]), depression (RR 1.6 [95% CI, 1.4 to 1.9]), and gastrointestinal side effects (RR ranging from 1.3 to 1.4) with

TABLE 1. Major Randomized Clinical Trials Testing Lifestyle Modifications After a Breast Cancer Diagnosis

Trial Name	Sample Size	Cohort	BMI (kg/m^2)	Intervention	Primary End Point	Weight Loss Achieved	Additional Outcomes
Women's Intervention Nutrition Study (WINS)[51-53]	2,437	Early-stage BC (stage I or II) after surgery on adjuvant therapy	All	Intensive, individualized low-fat dietary counseling	RFS	Significantly lower weight in intervention group (71.3 kg *v* 73.1 kg at 3 years; $P = .005$)	24% lower risk of relapse in intervention group at 60 months (HR, 0.76 [95% CI, 0.60 to 0.98]); 22% lower risk of all-cause mortality (HR, 0.78 [95% CI, 0.65 to 0.94])
SUCCESS C[54] (interim analysis)	2,292	HER2-negative early BC treated with FEC-D or DC	24-40	Telephone-based individualized lifestyle intervention counseling (diet, exercise, psychosocial)	DFS	1.0 kg average weight loss *v* 0.95 kg average weight gain in control at 2 years ($P < .001$)	ITT analysis: No difference in DFS (HR, 0.91 [95% CI, 0.70 to 1.18] in cox MVA); in patients who completed the 2-year program: 49% lower risk of relapse/mortality (HR, 0.51 [95% CI, 0.33 to 0.78] Cox MVA) in intervention group
Daughters and Mothers Against Breast Cancer (DAMES)[55]	136	Stage 0 to III postmenopausal BC after primary treatment and biological daughter	25+	Individually or team tailored instructions via mailed materials on exercise and diet	BMI change	Mothers in individual arm lost 3.77 kg *v* 0.87 kg in control arm at 12 months ($P = .04$)	Mothers in individual arm lost 6.5 cm in waist circumference *v* 1 cm in control arm ($P = .004$), daughters in individual arm lost 5.3 cm in waist circumference *v* 1 cm in control at 12 months ($P = .03$)
Women's Healthy Eating and Living (WHEL)[56]	3,088	Early-stage BC after primary treatment	All	Telephone dietary counseling and cooking classes	EFS, OS	No significant difference in average weight between groups at 12 months	No difference in EFS (aHR, 0.96 [95% CI, 0.80 to 1.14]) or OS (aHR, 0.91 [95% CI, 0.72 to 1.15]) at 7.3 years
Lifestyle, Exercise, and Nutrition (LEAN)[57]	100	Stage 0 to III BC after primary treatment	25+	In-person *v* telephone counseling on diet, exercise, and behavior	Weight change	6.4% weight loss for in-person ($P = .004$) *v* 5.4% for telephone ($P = .009$) *v* 2% for control groups at 6 months	30% decrease in C-reactive protein levels among women in the combined intervention groups *v* 1% decrease in control group ($P = .05$)
Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY)[58]	692	Early-stage BC after primary treatment	25-45	Group-based dietary and exercise counseling + newsletters and calls/emails	Weight change	6.0% mean weight loss *v* 1.5% in control group ($P < .001$) at 12 months and 3.7% *v* 1.3% ($P < .001$) at 24 months	Lower systolic and diastolic blood pressure ($P \leq .05$) at follow-ups and greater physical activity ($P < .001$) in intervention group at 6 and 12 months but not afterward
Diet and Androgen (DIANA-5)[59]	1,542	Stage I to III BC after surgery ± chemotherapy at high risk of recurrence (ER−, high testosterone, insulin, metabolic syndrome, and history of T2DM or HLD)	All	Macro-Mediterranean dietary intervention via cooking courses + community meals and encouraged physical activity	Recurrence	1.5 kg more weight loss at 12 months *v* control ($P < .001$)	ITT analysis: no difference in recurrence (HR, 0.99 [95% CI, 0.69 to 1.40]); by compliance to dietary recommendations: Upper tertile of dietary change 41% lower risk of recurrence (HR, 0.59 [95% CI, 0.36 to 0.92])

(continued on following page)

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TABLE 1. Major Randomized Clinical Trials Testing Lifestyle Modifications After a Breast Cancer Diagnosis (continued)

Trial Name	Sample Size	Cohort	BMI (kg/m^2)	Intervention	Primary End Point	Weight Loss Achieved	Additional Outcomes
Lifestyle Intervention in Adjuvant Treatment of Early Breast Cancer (LISA)[60,61]	338	Stage I to III BC after surgery on letrozole	24+	Telephone-based dietary and exercise counseling	DFS	3.9 kg more mean weight loss at 12 months and 2.8 kg more at 24 months *v* control ($P < .001$)	No difference in DFS at 8 years (HR, 0.71 [95% CI, 0.41 to 1.24]), although limited by small sample size due to early closure to accrual
Breast Cancer Weight loss (BWEL; interim analysis)[62]	3,180	Stage II to III HER2− BC after primary therapy	27+	Telephone-based dietary and exercise counseling	IDFS	4.3 kg or 4.7% mean weight loss *v* 0.9 kg or 1% mean weight gain at 1 year in controls ($P < .001$)	Not yet reported

Abbreviations: aHR, adjusted hazard ratio; BC, breast cancer; DC, docetaxel, cyclophosphamide; DFS, disease-free survival; EFS, event-free survival; FEC-D, fluorouracil, epirubicin, cyclophosphamide, docetaxel; HER2, human epidermal growth factor receptor 2; HLD, hyperlipidemia; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intention-to-treat; MVA, multivariable analysis; OS, overall survival; RFS, recurrence-free survival; T2DM, type 2 diabetes mellitus.

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concurrent GLP-1 RA use. Patients older than 50 years also had increased risk of osteoporosis (RR, 1.1 [95% CI, 1.03 to 1.2]), but no increased VTE risk.[88]

GLP-1 RAs appear to improve OS and reduce major adverse cardiovascular events (MACE, a composite of heart failure, myocardial infarction, and atrial fibrillation/flutter) in patients with BC; however, they have not been shown to affect DFS in preliminary studies. One single-center retrospective study (N = 1,022) in patients with nonmetastatic BC found no significant difference in DFS but improved OS in those who used GLP-1 RAs (HR, 0.37 [95% CI, 0.27 to 0.53]). GLP-1 RA users had a 2.6% median weight loss at 12 months.[82] Another study (N = 5,430) in nonmetastatic BC also preliminarily did not find a significant impact on BC recurrence despite a mean weight loss of 3 kg in GLP-1 RA users.[81] Several others have also reported improved OS in GLP-1 RA users, even in those with metastatic BC. In one study including all stages of BC (N = 15,586), the RR for all-cause mortality was 0.4-0.6 (95% CI, 0.27 to 0.6 and 0.5 to 0.7, respectively) depending on age group.[88] Another study in patients with T2DM and BC (N = 954) found a HR of 0.34 (95% CI, 0.19 to 0.6) for all-cause mortality.[85] A study in hormone receptor–positive metastatic BC (N = 3,586) found improved 2-year OS with a HR of 0.6 (95% CI, 0.48 to 0.77).[86] Weight loss was not reported in the above studies. Finally, several studies have found lower risk of MACE in patients with BC and obesity/T2DM using GLP-1 RA, with a HR of 0.63 ($P = .001$) for tirzepatide and 0.78 ($P = .032$) for semaglutide reported in one study, and a HR of 0.59 (95% CI, 0.41 to 0.86) reported in another that included patients treated with an anthracycline or anti-HER2 therapy.[89,90]

Conclusions and Ongoing Trials

Elevated BMI and weight gain after a BC diagnosis are associated with worse BC-related outcomes and increased all-cause mortality. Although LSM can have modest impacts on weight after a BC diagnosis, this can be difficult to sustain with mixed effects on BC and survival outcomes. GLP-1 RAs are a promising weight loss alternative, with emerging data in the BC population. Retrospective studies show that GLP-1 RA use among patients with BC is associated with weight loss; however, the degree of weight loss appears to be less than in patients without cancer, although this has been studied primarily in patients using GLP-1 RA for a T2DM indication. GLP-1 RA use in the adjuvant setting may improve OS and MACE. Notably, their safety in the neoadjuvant setting with concurrent chemoimmunotherapy remains unclear. Three prospective trials are underway to investigate these questions further. The FITWISE trial is a single-arm, phase 2 non-randomized trial on the effect of tirzepatide on weight change during adjuvant treatment of early-stage hormone receptor–positive BC.[91] TRIM-EBC is a trial in HR+ high-risk early BC with positive circulating tumor DNA (ctDNA) to determine the impact of tirzepatide-induced weight loss on ctDNA clearance and DFS.[92] Finally, a recently initiated study aims to determine the feasibility and effect of tirzepatide use on weight loss and other metabolic parameters in postmenopausal hormone receptor–positive BC survivors.[93] Additional prospective studies and long-term data are needed to further clarify the role of GLP-1 RAs in weight management after a BC diagnosis.

We have reviewed how the pillars of LM provide the foundation for BC survivorship care and how pharmacologic tools, such as GLP-1 RAs, can augment weight management. These strategies are important for improving metabolic health and reducing recurrence risk. However, truly comprehensive survivorship care must extend beyond physical health to address the psychological sequelae of a BC diagnosis. The following section therefore focuses on evidence-based approaches for assessing and addressing the psychosocial dimensions of survivorship, with

TABLE 2. Studies Reporting on GLP-1 RA Use in the Adjuvant Setting Among Patients With Breast Cancer

Study	Sample Size N (No. of GLP-1 RA users)	Cohort	GLP-1 RAs Studied	Mean Weight Loss	Concurrent Endocrine Therapy (% of patients)	Overall Survival	BC-Specific Outcomes
Fischbach et al[81]	5,430 (70)	BC type: Stage I to III, 80.2% HR+ % of patients with diabetes: NR Mean BMI: 35.9 kg/m^2	Semaglutide Tirzepatide	3.03 kg	74	NR	No significant difference in local, locoregional, distant recurrence
Sukumar et al[82]	1,022 (442)	BC type: 91.4% Stage I to III, 8.6% DCIS % of patients with diabetes: 79% Median BMI: 33.5 kg/m^2	Semaglutide Tirzepatide	2.6% at 12 months	65.9	Improved OS in GLP-1 RA group: HR, 0.37 (95% CI, 0.27 to 0.53)	No significant impact on DFS
Shen et al[83]	75 (75)	BC type: 91% Stage 0 to III, 84% ER+ % of patients with diabetes: 79% Median BMI: 34 kg/m^2	Semaglutide (60%) Liraglutide (49%) Exenatide (17%) Tirzepatide (11%) Dulaglutide (8%)	5% or 4.2 kg at 12 months	57	NR	NR
Portillo et al[84]	NR	BC type: HR+ % of patients with diabetes: NR BMI: NR	Semaglutide Liraglutide Dulaglutide Tirzepatide	2.31%-4.34% at 12mos	100	NR	NR
Nelson et al[85]	954 (232)	BC Type: Invasive BC % of patients with diabetes: 100% Median BMI: 33 (cases) *v* 29 (controls)	NR	NR	NR	Improved OS in GLP-1 RA group: HR, 0.34 (95% CI, 0.19 to 0.60)	NR
Khan et al[86]	3,586 (1,793)	BC type: ER+ stage IV % of patients with diabetes: NR BMI: NR	NR	NR	100	Improved 2-year OS in GLP-1 RA group: HR, 0.612 (95% CI, 0.484 to 0.773)	NR
Song et al[87]	1,753 (1,753)	BC type: 19.6% DCIS, 83% stage I/II, 83.1% ER+ % of patients with diabetes: 71% Mean BMI: approximately 36-37 kg/m^2	Semaglutide	Mean maximum weight loss: 11.2% (no diabetes), 8.6% (diabetes)	39.1	NR	NR
Jones et al[88]	15,586 (7,793)	BC type: HR+ % of patients with diabetes: NR Mean BMI: 37 kg/m^2	NR	NR	100	Improved OS in GLP-1 RA group: RR, 0.414 (95% CI, 0.271 to 0.633; age 50 years and younger), RR, 0.6 (0.513 to 0.701; age 51+ years)	NR

Abbreviations: BC, breast cancer; DCIS, ductal carcinoma in situ; DFS, disease-free survival; ER+, estrogen receptor–positive; GLP-1, glucagon-like peptide-1; HR, hazard ratio; NR, not reported; OS, overall survival; RA, receptor agonists; RR, risk ratio.

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particular attention to mitigating fear of cancer recurrence (FCR), an often pervasive and impactful component of life after treatment.

WHEN THE CANCER IS GONE, BUT FEAR REMAINS

Introduction: Addressing Fear of Recurrence

As the number of cancer survivors continues to rise, many face persistent psychological concerns, including FCR.[94-96] FCR is defined as the fear, worry, or concern relating to the possibility that cancer may return or progress[95] and is the top unmet need among survivors of cancer.[96] Notably, FCR may be experienced by both disease-free survivors (ie, fear of recurrence) and those with active disease (ie, fear of progression), as patients do not clearly distinguish between these experiences.[97] To date, studies have revealed few differences between FCR and fear of progression in terms of their correlates and consequences, but research is ongoing. Until further evidence is gathered, the recommendations below apply to disease-free survivors, and those with active disease.

FCR reflects a continuum, ranging from normative worry that may serve an adaptive function (eg, adherence to screening recommendations) to clinical significance, characterized by persistent, intense worry, preoccupation, and constant hypervigilance to somatic symptoms.[98] Clinically significant FCR is associated with reduced quality of life, mental health challenges, and a lack of planning for the future.[95,99-102] Although FCR frequently co-occurs with symptoms of anxiety and depression, instrument validation research, structured clinical interviews, and network analyses demonstrate that it is a distinct construct with limited covariation.[103-105] Beyond patient level outcomes, higher FCR is also associated with greater health care utilization, including increased contacts with primary and oncology care providers and ER visits.[106,107]

Up to 59% of cancer survivors report at least moderate FCR, and 19% report clinically significant FCR requiring specialized intervention.[108] Without intervention, FCR remains stable over time—it does not decrease with time from diagnosis or treatment into longer-term survivorship.[96,108] In addition to survivors themselves, approximately 48% of caregivers report clinically significant FCR, emphasizing the scope of this concern.[109]

FCR is not associated with objective prognostic indicators such as tumor size or disease stage; however, younger age, female sex, and more physical symptoms are consistently associated with higher FCR.[96,108,110] Weak associations with receiving radiation and chemotherapy have been reported in meta-analyses.[111,112] Emerging evidence suggests that FCR may also be higher among underrepresented groups, including Latinx patients, although empirical findings remain limited and these populations continue to be substantially underrepresented in research on FCR.[113]

Assessment of FCR

Patients may be hesitant to raise concerns about FCR with their health care providers, fearing that this is inappropriate or will make them seem ungrateful for survival.[114] Clinicians, on the other hand, may hesitate to raise the topic themselves because of concerns that asking about FCR could introduce or exacerbate distress; however, empirical evidence indicates that asking about FCR does not increase distress.[115] Instead, when providers proactively initiate these discussions, they may help reduce stigma and alleviate patient anxiety (see intervention section below for recommendations).

Although FCR can be assessed using various approaches, general distress measures (eg, distress thermometer) are often insufficient for identifying clinically significant FCR due to their broad focus.[116] Instead, brief, well-validated one-item screening tools are available, including the FCR-1[117] and the FCR-1r.[118] They require patients to score their perceived levels of FCR on a scale of 1-100 or 1-10, respectively. These can be given to patients as they sit in the waiting room.[119] Open-ended verbal questions may also be helpful during appointments. For example, "Many people worry about the cancer coming back, even when everything looks good. Has that been coming up for you?" Questions like this help to normalize FCR and communicate to the patient that these fears are normative and can be discussed.[120] In a cluster-randomized controlled trial in the United Kingdom, the addition of FCR screening did not add extra time to appointments and allowed patients to talk about this issue.[121]

When a health care provider has sufficient capacity, more comprehensive measures can be used to assess severity (see recent systematic review of FCR measures for specific recommendations[122]). Importantly, there is some indication that FCR may be expressed differently across cultural groups.[113] Physicians should therefore approach FCR with cultural humility and accommodate for diverse expressions of distress, including somatic manifestations, spiritual, or behavioral presentations. Overall, screening is recommended at the end of treatment and at all subsequent follow-up appointments as FCR may increase as contact with the health care system decreases.[119] Notably, FCR naturally fluctuates and often peaks around tests and appointments (eg, scanxiety).[119,123,124] Thus, assessment is most accurate when conducted frequently and on nonscan days. Ongoing reassessment also allows for systematic monitoring of FCR and escalation of care when needed.

Interventions to Address FCR

Starting early in survivorship, physicians should discuss with patients which symptoms warrant monitoring and immediate attention. Discussion on what follow-up care will entail should happen early, as survivors with high FCR often experience distress and reluctance to leave the cancer center since they feel safest there. For patients with repeated questions about signs of recurrence or requests for

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additional tests, reassurance may come naturally in conversations, though it is rarely enough. Although occasional reassurance may provide temporary relief, repeated reassurance can be counterproductive, unintentionally reinforcing reassurance-seeking behaviors and increasing symptom monitoring over time.[114] In a systematic review of 16 FCR intervention studies delivered by non–mental health specialists, Liu et al[114] found that consultation duration, empathy, and clear information delivery helped decrease FCR and concluded that the provision of honest information about prognosis and recurrence risk was helpful to address FCR. For example, clear information delivery may include explaining surveillance recommendations using established guidelines (eg, NCCN) and outlining when additional testing would be indicated. When patients request additional testing, clinicians can acknowledge and normalize their concerns, while communicating that additional testing has not been shown to improve outcomes and may paradoxically increase fear over time. For newer surveillance tests, such as ctDNA, clinicians may wish to discuss the risks and benefits of testing, while acknowledging that evidence is still emerging to guide routine use of these tests. Additionally, physicians should provide brief advice on healthy coping (eg, stress reduction, exercise, and mindfulness) and referral to appropriate services, when warranted. A brief (7-minute), clinician-delivered intervention called Clinician Intervention to Reduce Fear of Recurrence (CIFeR), which includes these recommendations, has shown promise to reduce FCR in BC survivors and improve clinician confidence in addressing this issue. CIFeR training can be accessed online at cifer.thinkific.com.[125]

When it comes to referral, a stepped-care approach may be especially beneficial as it allows psychosocial support to be allocated based on severity and impact of FCR, and supports efficient use of limited resources.[123,126] For instance, mild FCR may respond well to the above-mentioned oncologist-led strategies such as normalization and provision of information, along with referrals to exercise programs[119] and guided self-management resources.[127] Moderate levels of fear often benefit from referral to clinician-led interventions, including group programs or Internet-based self-help modules on survivorship, or professionally led support groups.[119] When FCR is persistent or severe, a referral to a mental health specialist for evidence-based intervention is warranted.[119] Meta-analyses support brief cognitive-behavioral therapies and mind-body interventions, whether delivered individually or in a group format, in person, online, or in a blended format.[128,129] As the patient's FCR changes over time, intervention intensity can be adjusted.

Overall, the physician's role in FCR care includes skillful communication, clinical framing to scaffold feelings of uncertainty, the identification of FCR, and referrals to appropriate supports. Physicians do not need to assume the role of a mental health specialist; rather, they can integrate these high-yield practices into their usual care to reduce clinically significant levels of FCR in their patients and limit unnecessary health care utilization.[126]

CONCLUSION

Throughout this chapter, we have emphasized that caring for the *whole* patient with BC begins with a solid behavioral foundation, with a focus on the six pillars of LM, namely nutrition, physical activity, sleep, stress management, social connection, and avoidance of risky substances. When lifestyle interventions alone are not enough to address desired improvements in metabolic health or weight management, pharmacologic tools, such as GLP-1 RAs, can be introduced to complement and reinforce metabolic gains. Furthermore, comprehensive BC survivorship care must also address psychosocial concerns, particularly FCR, which can diminish quality of life long after active therapy ends. Thus, a survivorship model that integrates LM as the cornerstone, evidence-based pharmacologic therapies as tailored reinforcements, and robust psychosocial support to address FCR empowers every person with BC to flourish during treatment and beyond.

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Right-Sizing Locoregional Management in the Era of Neoadjuvant Therapy for Breast Cancer

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OVERVIEW

The increasing use of neoadjuvant systemic therapy (NAC) has led to a significant paradigm shift in the locoregional treatment of breast cancer, with increasing emphasis on response-guided de-escalation. In current practice, both clinical and pathologic responses to treatment are being leveraged to minimize the extent and morbidity of local therapy while maintaining oncologic safety. In patients presenting with clinically node-negative (cN0) disease and high-risk biologic subtypes, sentinel lymph node biopsy (SLNB) omission after NAC is an area of evolving interest. For those presenting with clinically node-positive disease (cN+) yet who attain a pathologic complete response (pCR) in the lymph nodes after NAC, emerging evidence suggests that SLNB alone with omission of regional nodal irradiation (RNI) may be considered. Ongoing trials are evaluating whether cN+ patients with residual micrometastases or macrometastases after NAC may also be treated with SLNB alone, using RNI in lieu of axillary lymph node dissection to achieve adequate locoregional control. Parallel advances in radiation therapy (RT) are reshaping treatment decisions and sequencing, including when to deliver agents concurrently with radiation and when to hold them. Exceptional responders who attain a breast pCR and undergo breast conservation may have little or no residual tumor bed to justify tumor bed boost, and several trials are assessing the safety of radiation omission in these subgroups. Finally, premastectomy RT is being explored as a strategy to facilitate immediate breast reconstruction while avoiding radiation-related complications. Together, these developments highlight a shift toward individualized, response-adapted locoregional management in early-stage breast cancer.

INTRODUCTION

After neoadjuvant systemic therapy (NAC), adapting surgery and radiation therapy (RT) to systemic therapy response has led to a paradigm shift in the locoregional treatment of breast cancer. Historically, locoregional treatment decisions were determined almost entirely by pretreatment anatomy—tumor size, nodal status, and surgical findings. Increasingly, however, the most informative prognostic signal is not where the disease started, but how it responds to therapy. Tumors demonstrating pathologic complete response (pCR) represent treatment-sensitive disease with favorable outcomes, while residual disease identifies patients with intrinsic resistance and elevated locoregional and systemic risk.[1,2] Surgery and RT now sit at the center of this response-adapted framework, serving not simply as a uniform postoperative treatment, but as a modality that must be right-sized—de-escalated when systemic therapy has already achieved maximal disease control and optimized or intensified when residual risk persists.

Determining who derives meaningful incremental benefit from locoregional therapy after contemporary systemic therapy remains a key area of future research; some patients are likely overtreated with traditional locoregional strategies, particularly when therapy has already sterilized disease. Others remain undertreated if residual resistant disease is not appropriately addressed.[2–4] The challenge is to distinguish these groups using response as a clinical biomarker and to tailor treatment to individual patients to avoid excess morbidity while optimizing oncologic outcomes. This response-indexed lens aligns naturally with contemporary multidisciplinary care: how the axilla is staged and treated after NAC shapes nodal radiation decisions; reconstructive planning is influenced by whether chest wall and nodal basins are treated; and the intensity of breast irradiation (including boost decisions) increasingly depends on the quality of response and confidence in response assessment.

APPROACH TO THE AXILLA AFTER NEOADJUVANT THERAPY

De-escalating Axillary Surgery in Clinically Node-Negative Disease: Can We Omit SLNB After NAC in Certain Subtypes?

In patients presenting with clinically node-negative (cN0) disease who receive NAC for biologically aggressive subtypes

PRACTICAL APPLICATIONS

- In clinically node-negative patients undergoing neoadjuvant systemic therapy (NAC) for triple-negative or human epidermal growth factor receptor 2–positive breast cancer, ongoing trials are evaluating omission of sentinel lymph node biopsy (SLNB) or whole-breast radiotherapy after pathologic complete response (pCR).
- For select patients presenting with clinically node-positive disease (cN1) who achieve a nodal pCR after NAC, evidence suggests that SLNB alone with omission of regional nodal irradiation may be considered.
- The use of completion axillary lymph node dissection versus axillary radiation is an area of active investigation for cN1 patients with residual micrometastases or macrometastases on SLNB after NAC.
- Response-assessed dose-adaptive radiation and adaptive response radiation therapy (ART^2) are emerging concepts that use neoadjuvant radiation therapy (RT) for in vivo response assessment, similar to NAC.
- Neoadjuvant RT is being explored as a strategy to facilitate immediate microsurgical breast reconstruction while avoiding radiation-related complications in patients planned for mastectomy.

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such as triple-negative breast cancer (TNBC) or human epidermal growth factor receptor 2–positive (HER2+) disease, axillary surgery recommendations remain similar to those in the upfront surgery population. In this setting, single- or dual-tracer sentinel lymph node biopsy (SLNB) is favored for axillary staging due to the high likelihood of pathologically node-negative (ypN0) disease, which is seen in over 90% of cases. Index tumor response can further predict ypN0 status; among cN0 patients who achieve complete radiologic response or pCR in the breast, 95.8%-98.4% of TNBC and 97.2%-100% HER2+ cancers will be ypN0, respectively.[5-7] These exceptionally high rates of ypN0 disease support ongoing clinical trials evaluating the safety of omission of SLNB in TNBC and HER2+ patients receiving NAC (Table 1). Notably, these trials exclude patients with estrogen receptor–positive (ER+)HER2– breast cancer, for whom ypN0 status is less predictable, as well as T4/inflammatory cases and those suspicious lymph nodes on axillary imaging unless fine-needle aspiration or negative pretreatment biopsies are performed.[8,9]

For cN0 patients who undergo NAC yet are found to have nodal disease on SLNB, guidelines recommend multidisciplinary tumor board discussion with consideration of completion axillary dissection (axillary lymph node dissection [ALND]) and/or regional nodal irradiation (RNI), as is seen in patients presenting with node-positive (cN+) disease.[10] An assessment of tumor biology and nodal burden, including the number of lymph nodes involved, the size of the largest nodal metastases, and the number of lymph nodes removed, should be undertaken to tailor additional locoregional therapy.

Approach to the Axilla in Biopsy-Proven Node-Positive Breast Cancer That Responds to NAC

SLNB in Patients Who Convert to Clinically Node-Negative

The results of four prospective multicentered trials performed in North America[11,12] and Europe[13,14] support the feasibility of SLNB in patients who present as cN+ but respond favorably to NAC, provided certain technical parameters are met. In the setting of biopsy-proven positive nodal disease that converts to cN0 by axillary palpation post-treatment, dual-tracer SLNB with retrieval of a minimum of three lymph nodes provides accurate assessment of nodal response.[11-14] Approaches that selectively retrieve the biopsy-proven positive lymph node after NAC, including targeted axillary dissection (TAD) or the marking axillary lymph node with radioactive iodine seed (MARI) procedure, may be used as procedural adjuncts to optimally lower the false-negative rate.[15,16] In one large multicentered cohort, the mean number of sentinel lymph nodes (SLN) and total lymph nodes removed was lower with TAD versus SLNB (3 *v* 4, $P < .001$, and 3.95 *v* 4.44, $P < .001$, respectively). Ongoing registry studies are evaluating whether this small difference in the number of lymph nodes removed translates to clinically meaningful differences in quality of life, lymphedema, and arm and shoulder function.[17,18]

Management of Patients With Nodal pCR After SLNB

For initially cN+ patients who attain an axillary pCR, performing SLNB alone in lieu of ALND avoids significant morbidity without compromising oncologic outcomes. Over the past decade, several large multi-institutional series have confirmed the safety of SLNB alone in cN1-2/ypN0 patients, demonstrating low 3-year rates of axillary recurrence, between 0.3% and 0.8%, with ALND omission.[19-21] In one large cohort study of 1,144 patients with biopsy-proven N1-N3 breast cancer who achieved a nodal pCR, there was no difference in 3-year axillary recurrence between patients undergoing SLNB versus TAD (0.8% *v* 0.5%, $P = .55$).[20] These data suggest that both of these approaches are reliable for staging the axilla and providing effective local control for nodal pCR patients after NAC.

TABLE 1. Studies Evaluating Omission of Sentinel Lymph Node Staging in Clinically Node-Negative (cN0) HER2+ and TNBC Patients After Neoadjuvant Systemic Therapy

Clinical Trial	Study Design and Location	Inclusion Criteria	Planned Enrollment	Primary End Point
ASICS (NCT04225858)	Prospective, single-arm trial (the Netherlands)	HER2+ or TNBC with cT1-T3 cN0 breast cancer treated with NAC; cN0 confirmed on ultrasound and FDG-PET-CT[a]	N = 340	5-year axillary recurrence rate
EUBREAST-01[8] (NCT04101851)	Prospective, multicentered, single-arm trial (Germany, Austria, Italy, Spain)	HER2+ or TNBC with cT1-T3 cN0 breast cancer treated with NAC; cN0 by examination and confirmed on ultrasound[a]	N = 350	3-year axillary recurrence-free survival
ASLAN[9] (NCT04993625)	Prospective, multicentered, single-arm trial (South Korea)	HER2+ or TNBC with cT1-T3 cN0 breast cancer treated with NACwith complete remission on physical examination and documented radiologic response	N = 178	5-year recurrence-free survival

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; HER2, human epidermal growth factor receptor 2; NAC, neoadjuvant systemic therapy; PET, positron emission tomography; TNBC, triple-negative breast cancer.
[a]In the case of suspicious lymph nodes on imaging, negative cytology/histopathology required for enrollment;

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Level I evidence from the NSABP B-51/RTOG 1304 further supports a de-escalated axillary approach for cN1/ypN0 patients, with 909 patients on trial undergoing SLNB only (Table 2).[22] In these patients, SLNB followed by omission of RNI was associated with similar outcomes to SLNB followed by RNI (hazard ratio [HR], 0.75 [95% CI 0.44 to 1.26]), with very few axillary recurrences at 5 years of median follow-up. Taken together, these data suggest that providers can leverage pathologic response in the axillary nodes to safely de-escalate both axillary surgery and radiation.

Residual Low-Volume Nodal Disease: Isolated Tumor Cells and Micrometastases

Residual low-volume nodal metastases, including isolated tumor cells (<0.2 mm) or micrometastases (0.2-2.0 mm), are identified in 1.5% and 3.2% of patients undergoing NAC, respectively.[27] Historically, concern existed that these patients were similar to those macrometastases, representing a subgroup with chemoresistant disease for whom completion ALND was necessary to optimize locoregional control. However, several recent retrospective series support the oncologic safety of ALND omission in these patients. In the OPBC-05/ICARO study that assessed outcomes in 583 women with residual isolated tumor cells after NAC (ypN0i+), axillary recurrences were rare (2.0% at 3 years) after SLNB, TAD, or MARI alone, although the majority of patients also received RNI.[28] In one third of patients who underwent ALND, only 5% had macrometastases identified on ALND pathology, and oncologic outcomes were no different from those who omitted ALND. For individuals with residual micrometastases (ypN1mi), findings have been remarkably similar; in the OPBC-07/microNAC study of 1,585 patients with ypN1mi disease on SLNB, ALND omission was associated with a 2.0% axillary recurrence rate at 3 years.[29] In adjusted analyses, TNBC and omission of nodal radiotherapy, but not omission of ALND, were independently associated with an increased risk of axillary recurrence. Taken together, these data suggest that ALND can be safely omitted in the majority of ypN0(i+) or ypN1mi patients regardless of nodal status at presentation, provided RNI is considered after axillary surgical staging. The inclusion of patients with low-volume nodal disease into clinical trials—including ypN0(i+) patients in NSABP B-51/RTOG 1304 and ypN1mi patients into the ALLIANCE A011202 trial—will strengthen the available evidence for optimal axillary management in this rare subgroup of patients after NAC.

Residual Macrometastases Identified on SLNB

Guidelines currently favor the use of ALND followed by RNI when axillary macrometastases are identified on SLNB after NAC.[10] However, prospective registry studies and ongoing clinical trials are actively evaluating whether completion ALND is truly required for all patients with residual macrometastases on SLNB (Table 2). The phase III ALLIANCE A011202 trial (ClinicalTrials.gov identifier: NCT01901094) has successfully randomly assigned 1,736 eligible cT1-3cN1 patients with residual micrometastases (16%) or macrometastases (84%) on SLNB, and will evaluate whether axillary radiation can be used in lieu of ALND in this setting.[24] Notably, randomly assigned patients were predominantly ER+HER2− (70%), with the majority having only one (55%) or two (25%) SLN positive on staging, suggesting the trial population largely represents those with biologically low-risk disease. While the trial matures, preliminary results are available for 841 patients randomly assigned to the ALND arm, of whom 46% had additional positive non-SLNs with significant differences based on nodal burden. In patients with macrometastatic SLNs, 48% demonstrated additional positive nodes on ALND, compared with 37% of patients with micrometastases. Furthermore, in those with 1, 2, or ≥3

TABLE 2. Studies Evaluating Omission of ALND in Clinically Node-Positive (cN+) Patients Who Convert to Clinically Node-Negative (cN0) After Neoadjuvant Systemic Therapy

Clinical Trial	Study Design and Location	Inclusion Criteria	Interventions	Target Enrollment	Primary End Point(s)
Clinical trials					
NSABP B-51/RTOG 1304[22] (NCT01872975)	Prospective, multicentered RCT (North America)	cT1-T3 cN1 (stage II to IIIA) Biopsy-proven node-positive ypN0 after NAC on SLNB/ALND	Arm 1: RNI Arm 2: No RNI	N = 1,641	IBRFI
ATNEC[23] (NCT04109079)	Prospective, multicentered RCT (United Kingdom)	cT1-T3 cN1 (stage II to IIIA) Biopsy-proven node-positive ypN0 after NAC on SLNB	Arm 1: No additional axillary treatment Arm 2: ALND or axillary RT	N = 1,900	DFS, lymphedema
ALLIANCE A011202[24] (NCT01901094)	Prospective, multicentered RCT (North America)	cT1-T3 cN1 (stage II-IIIA) Biopsy-proven node-positive cN0 after NAC ypN1mi/ypN1 on SLNB/TAD	Arm 1: ALND + RNI (without RT to the dissected axilla) Arm 2: Axillary RT + RNI	N = 2,012	IBRFI
TAXIS trial[25] (NCT03513614)	Prospective, multicentered RCT (Europe, North America, South America, Asia)	cT1-T3 cN1-N3 (stage II-III) Biopsy-proven node-positive NAC or upfront surgery (y)pN+ on TAS	Arm 1: ALND + RNI (without RT to the dissected axilla) Arm 2: Axillary RT + RNI	N = 1,500	DFS
Prospective cohort studies					
AXSANA[26] (NCT04373655)	Prospective multicentered cohort study (Europe, South America, Asia)	cT1-T4c cN1-N3 (stage II-III) Planned for NAC cN0 after NAC ypN0 or ypN+	ALND *v* less invasive axillary staging (SLNB/TAD/TLNB)[a]	N = 2,632	IDFS, axillary recurrence-free survival, QOL, and arm morbidity
MINIMAX[18] (NCT04486495)	Prospective, multicentered registry study (the Netherlands)	cN1-N3 (stage II to III) Biopsy-proven node-positive Planned for NAC	ALND *v* less invasive axillary staging[a]	N = 4,000	DFS, breast cancer–specific survival, overall survival, axillary recurrence rate, QOL

ALND, axillary lymph node dissection; DFS, disease-free survival; IBRFI, invasive breast cancer recurrence–free interval; IDFS, invasive DFS; NAC, neoadjuvant systemic therapy; QOL, quality of life; RCT, randomized controlled trial; RNI, regional nodal irradiation; RT, radiation therapy; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; TAS, tailored axillary surgery.
[a]With adjuvant systemic/locoregional treatments performed according to institutional or national guidelines.

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positive SLNs on SLNB, 33%, 53%, and 76% had the additional positive nodes on ALND, respectively. Whether local control of this additional nodal disease, which upstaged ypN category in one fourth of patients, can be achieved with axillary radiation alone will be assessed with the primary end point analysis. Reassuringly, large prospective cohort studies have suggested that despite documenting substantial additional nodal involvement, completion ALND does not appear to provide clinically meaningful information that results in significant systemic therapy modifications.[26]

Additional studies, including the European phase III TAXIS Trial (ClinicalTrials.gov identifier: NCT03513614), have completed enrollment of 1,500 patients with cN+ breast cancer, including patients undergoing upfront surgery or NAC.[25] TAXIS is evaluating whether tailored axillary surgery (TAS), a procedure that includes dual-tracer SLNB, confirmation of retrieval of the biopsy-proven positive clipped node(s), and selective removal of all palpable nodal disease, can effectively debulk the axilla and reduce tumor load to an extent where axillary radiation is sufficient for local control. In an effort similar to the ALLIANCE A011202 trial, TAXIS is randomly assigning patients after TAS with ypN+ disease to axillary radiation with RNI versus completion ALND with RNI, sparing the dissected axilla (Table 2).

RESPONSE-GUIDED ADJUVANT RADIATION IN EARLY-STAGE DISEASE

De-escalation for Excellent Responders: Lessons From NSABP B-51

The clearest contemporary example of response-guided de-escalation of locoregional radiation comes from the aforementioned NRG/NSABP B-51/RTOG 1304, which evaluated cN+ patients who converted to ypN0 after NAC (Table 2).[22] In this study, 1,641 patients were enrolled and 1,556 were included in the primary-event analysis (772 assigned to RNI

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and 784 to no RNI), with a median follow-up of 59.5 months. The primary end point—invasive breast cancer recurrence–free interval—showed no significant benefit with RNI (HR, 0.88 [95% CI, 0.60 to 1.28]; $P = .51$), with 5-year point estimates of 92.7% with RNI versus 91.8% without. Secondary end points were similarly neutral: locoregional recurrence–free interval, distant recurrence–free interval, disease-free survival, and overall survival were not improved by adding RNI, and absolute locoregional event rates were low in both arms at 5 years. No treatment-related deaths were observed, and grade 4 adverse events were uncommon (0.5% with RNI *v* 0.1% without), reinforcing that the clinical signal of B-51 is primarily about diminishing incremental benefit rather than unexpected toxicity. The implication of this study is profound: nodal pathologic response may supersede initial clinical stage when determining the need for comprehensive nodal radiation. This trial also validates a principle that has long been hypothesized—eradication of nodal disease by systemic therapy identifies a population in whom additional regional treatment may provide diminishing returns relative to toxicity. Importantly, B-51 does not diminish the value of radiation as a modality; it refines where and when nodal radiation is most likely to change outcomes.

Several limitations and persistent controversies deserve emphasis before B-51 is applied routinely. First, it represents a time-driven analysis with 109 primary events—approximately two thirds of the planned events for the definitive analysis—so longer follow-up remains important, particularly for ER-positive disease where late events accrue. Second, event rates were low, which is reassuring clinically but also means the trial is best interpreted as showing that the average absolute benefit of RNI is small in this population; it does not exclude the possibility that select higher-risk subgroups (eg, heavier baseline nodal burden, biologically aggressive disease, or suboptimal response ascertainment) might still derive benefit. Third, translation to practice hinges on the quality of response assessment: variability in axillary surgery approach, adequacy of nodal evaluation, and confidence that ypN0 truly reflects nodal sterilization (rather than undersampling) remain the most common practical fault lines. Finally, there is ongoing debate about what exactly is being omitted when clinicians omit RNI—particularly internal mammary coverage and the degree of incidental nodal dose from modern tangents—as well as how to harmonize B-51 with evolving systemic therapy (HER2-directed therapy and immunotherapy) and reconstruction goals. In other words, B-51 defines a powerful de-escalation boundary, but its safest application is still within a disciplined, response-confirmed workflow rather than as an anatomy-agnostic default.

In practice, B-51 should be interpreted as a boundary condition for de-escalation. When a patient's baseline nodal positivity is well documented (biopsy-proven disease, ideally with clip placement in the biopsied node) and post-NAC nodal evaluation is high-confidence (eg, targeted axillary approaches that retrieve the clipped node and confirm ypN0), the incremental absolute benefit of RNI may be small for many patients. In that setting, the decision becomes an explicit tradeoff: a small or uncertain gain in regional control versus a tangible risk of lymphedema and other late effects. However, the most clinically useful insight from B-51 may be its inverse question. If excellent responders may safely receive less nodal radiation, what should be done for patients who do not achieve nodal clearance?

The Flip Side of B-51: Residual Disease After NAC (and why A011202 matters)

Residual nodal disease after NAC represents one of the highest-risk locoregional scenarios in modern breast oncology. Persistent nodal involvement reflects therapy-resistant biology and correlates strongly with recurrence risk across molecular subtypes. In many patients, it also implies a higher probability of additional non-SLN disease, which historically justified completion ALND. This clinical space is being directly addressed by ALLIANCE A011202, a randomized phase III trial comparing completion ALND versus axillary RT in patients with positive SLNs after NAC (Table 2). A011202 does not simply test surgery versus radiation. Rather, it evaluates whether regional radiation can function as biologic escalation while simultaneously reducing surgical morbidity. The trial acknowledges an emerging reality: escalation in the modern era is less about adding treatment indiscriminately and more about selecting the optimal modality for risk control.

Pending mature results, current practice often favors aggressive locoregional management for residual nodal disease, frequently including RNI or postmastectomy RT (PMRT), and many clinicians still default to ALND for ypN+ disease. Yet, practice variability is wide, and observational data suggest increasing omission of ALND in carefully selected, low-burden residual disease scenarios—often motivated by lymphedema risk and reconstruction considerations. In this environment, A011202 serves as the critical risk-resolution trial. It is poised to define whether axillary radiation can replace, rather than merely supplement, morbid surgical interventions in the ypN+ population.

Breast RT Intensity and the Lumpectomy Boost Question in the Era of pCR (HERO and ROSALIE)

Although nodal management has received substantial attention, a parallel—and increasingly relevant—question concerns boost radiation to the lumpectomy cavity after NAC. Historically, the boost was driven by age, margin status, and high-risk pathology rather than treatment response. The widespread adoption of NAC introduces a distinct clinical scenario: patients who achieve breast pCR may have little or no residual tumor bed to justify additional focal dose escalation.

This is not merely an academic question. The boost is a meaningful contributor to local dose heterogeneity, fibrosis risk, cosmesis, and patient-reported outcomes (PROs),

particularly in younger patients and in the setting of oncoplastic techniques. If systemic therapy has sterilized the tumor bed (true pCR), the incremental local control benefit of a boost may be diminished for many patients—yet the toxicity and cosmetic penalty can persist.

Ongoing trials are now addressing adjacent and complementary questions that will shape how we conceptualize breast RT intensity in exceptional responders.

NRG-BR008 (HERO) is testing whether carefully selected patients with favorable biology—particularly HER2-positive disease treated with contemporary HER2-directed therapy—may safely omit breast radiation after breast-conserving surgery.[30] Although HERO is not limited exclusively to post-NAC pCR populations, it is fundamentally a response- and biology-driven concept: when systemic therapy efficacy dominates prognosis, the marginal value of breast irradiation may be small enough to test omission.

ROSALIE (ClinicalTrials.gov identifier: NCT05866458) extends this logic further by directly evaluating omission of whole-breast irradiation in clinically node-negative patients who achieve pCR after neoadjuvant chemotherapy and undergo lumpectomy. ROSALIE therefore sits closer to the pragmatic pCR question many clinicians face: if the breast is sterilized and the axilla is negative, does every component of local therapy still add value? The key shift is conceptual: the boost is no longer a default add-on (Table 3). It becomes a risk-modifying tool that should be justified by expected absolute benefit in the context of response, baseline risk, and competing priorities such as reconstruction and cosmesis.

Escalation Beyond Dose: What Optimization Really Means

Modern escalation rarely requires higher total radiation dose. Instead, optimization occurs through (1) regional target selection, (2) integration with systemic escalation strategies, (3) precision treatment planning, and (4) avoidance of unnecessary morbidity.

Residual disease after NAC often reflects systemic resistance rather than inadequate local therapy. Radiation therefore functions as a complement to biologic risk—improving local control while systemic therapy addresses micrometastatic disease. For ypN+ patients, this frequently means comprehensive regional management, careful consideration of internal mammary coverage when appropriate, and meticulous technique to reduce cardiopulmonary exposure. For patients undergoing reconstruction, it requires explicit alignment of the radiation plan with reconstructive strategy to minimize complication risk and revision burden. For all patients, it requires acknowledging that one-size-fits-most fields are increasingly incompatible with response-indexed care: the boundaries of elective targets should reflect where residual risk actually resides.

TABLE 3. Practical Response-Guided Algorithm for Right-Sizing Locoregional Radiation After Neoadjuvant Systemic Therapy

Excellent Responders	
Nodal pCR after NAC	Consider omission of RNI (B-51 paradigm) in high-confidence responders[a]
Breast pCR after NAC	Reassess the need for boost radiation: For pCR with favorable biology → boost omission becomes reasonable to study, and trial enrollment should be prioritized where available. For high-risk baseline features or uncertain response → selective boost intensification may remain appropriate, even with strong response, if the pretreatment extent was large or the tumor bed is poorly defined
Breast and nodal pCR after NAC	Trial-based radiation omission strategies (HERO, ROSALIE) where eligible Favor de-escalation when systemic therapy efficacy dominates prognosis and when response assessment is reliable
Residual disease[b]	
Residual nodal disease after NAC	Optimize regional therapy; A011202 may redefine surgical (ALND) *v* radiation escalation in the axilla
Residual breast disease after NAC	Maintain or consider boost; individualize by baseline risk, residual burden, and bed definition; a boost remains appropriate in most cases, particularly when residual burden is meaningful, margins are close, or baseline risk is high
Future directions	
Radiation response	Use radiation response itself as a treatment-selection biomarker (RADAR/ART^2), informed by early biologic readouts such as those demonstrated in P-RAD

Abbreviations: ALND, axillary lymph node dissection; ART^2, adaptive response radiation therapy; NAC, neoadjuvant systemic therapy; pCR, pathologic complete response; RADAR, response-assessed dose-adaptive radiation; RNI, regional nodal irradiation.
[a]Across all scenarios, the common operational rule is that response-guided de-escalation demands high-confidence staging and high-quality multidisciplinary execution. When confidence is low—uncertain baseline nodal status, incomplete nodal evaluation, and ambiguous response in the breast—conservatism remains appropriate.
[b]Escalation guided by biology rather than historical stage alone; emphasize right tissue, right technique, right trade-off.

Radiation as a Biologic Stress Test: RADAR/ART^2 and Neoadjuvant Radiation

An emerging and provocative concept is whether radiation itself can function as a biologic stress test analogous to NAC. Neoadjuvant RT has historically been discussed as a timing

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adjustment. In a response-guided era, it may be more useful to frame it as an assay—an intentional perturbation designed to reveal radiosensitivity and immunogenicity in vivo. Response-assessed dose-adaptive radiation (RADAR) and adaptive response RT (ART²) are terms that may appropriately define this approach.

In a RADAR/ART² model, radiation is delivered upfront in a focused manner, tumor response is assessed biologically and radiographically, and subsequent systemic or surgical decisions are adapted based on radiation sensitivity. The central premise is that the tumor becomes the assay: rather than relying solely on static genomic predictors, response to radiation provides a dynamic, patient-specific readout.

This concept has recently been tested in the randomized neoadjuvant immune-priming phase II radiation trial—P-RAD (TBCRC-053). In this study, the question was whether preoperative radiation to the intact breast tumor, given concurrently with anti–PD-1 therapy, can increase intratumoral immune infiltration in early breast cancer and thus improve pathologic complete response rates. In the hormone receptor–positive/HER2– cohort (node-positive, higher-risk disease; approximately 51 patients across multiple centers), patients were randomly assigned to 0 Gy versus 9 Gy versus 24 Gy delivered preoperatively to the primary tumor, with a mandated 2-week on-treatment biopsy. Dual coprimary end points were (1) 2-week tumor T-cell infiltration (via multiplex immunofluorescence) and (2) nodal pCR at surgery. The key reported signal was that the 24 Gy + pembrolizumab arm produced a statistically significant increase in T-cell infiltration and was associated with induction of tertiary lymphoid structures, supporting the concept that short-course preoperative RT can convert the tumor microenvironment in hormone receptor–positive/HER2– disease. The same regimen increased tertiary lymphoid structures and appeared to remodel the tumor microenvironment in a manner plausibly favorable for immunotherapy responsiveness. Although clinical outcomes remain exploratory and longer follow-up is needed, P-RAD provides a compelling proof-of-concept: preoperative radiation can generate measurable biologic conversion signals on a short timescale.

The longer-term opportunity is to integrate such short-interval response metrics into locoregional decision making. In a RADAR/ART² paradigm, robust immune conversion and early regression could justify selective deintensification of adjuvant targets for some patients, while minimal conversion could justify locoregional optimization and prioritization of systemic escalation strategies. This would represent a true extension of response-guided care: using response to radiation itself to decide how much radiation is needed afterward.

Integrating Radiation With Contemporary Systemic Escalation: Concurrent Versus Sequential Therapy

As systemic options expand, a parallel challenge has become increasingly prominent: how to safely and pragmatically sequence RT with targeted therapy, immunotherapy, and radiosensitizing agents. A core limitation is that most systemic therapy registration trials do not collect comprehensive radiation details or systematically adjudicate radiation-related toxicities. As a result, clinicians often rely on prospective trial subsets where RT was delivered, contemporary retrospective series, and structured sequencing frameworks to guide practice.[31] A widely adopted operational definition considers RT concurrent when delivered within five drug half-lives of systemic therapy, enabling a standardized approach to washout or hold strategies.[32] This definition is useful because it highlights an important clinical reality: for agents with very long half-lives (eg, monoclonal antibodies and some immunotherapies), avoiding concurrency by pharmacokinetic criteria can be impractical, and risk mitigation shifts toward careful selection of RT volumes, dose constraints, and monitoring pathways (Table 4).

Concurrent anti-HER2 monoclonal antibody therapy—particularly trastuzumab—with adjuvant breast/chest wall ± regional nodal RT is generally considered safe, with contemporary meta-analytic data supporting acceptable cardiac safety in the setting of modern heart-sparing techniques and routine cardiac monitoring.[33] In KATHERINE, RT was recommended to start within 60 days of surgery and was delivered concurrently with trastuzumab or ado-trastuzumab emtansine (T-DM1), with low absolute pneumonitis rates but a numerical increase with T-DM1 (1.5% *v* 0.7%).[34] Similar safety was noted in the ATEMPT trial.[35] In DESTINY-Breast05, trastuzumab deruxtecan (T-Dxd) could be given with radiotherapy or sequentially after completion of radiotherapy, with 53.5% of patients receiving radiation concurrently.[36] For patients receiving concurrent therapy, computed tomography (CT) monitoring for asymptomatic or mildly symptomatic therapy-related interstitial lung disease or pneumonitis was recommended at 6 weeks (before cycle 3), followed by every 12 weeks during treatment and at 40-day follow up. For those undergoing sequential therapy, additional low-dose CT of the chest was performed after radiotherapy completion but before first T-Dxd infusion. Notably, the timing of adjuvant radiotherapy had no impact on the incidence of drug-related interstitial lung disease, and the incidence of investigator-reported radiation pneumonitis was similar between the two groups, with a numerically higher incidence in patients who received sequential radiotherapy.[36]

In KEYNOTE-522, pembrolizumab timing relative to RT evolved from a required restart at least 2 weeks after RT to allowance of concurrency, and post hoc analyses suggest that breast/RNI RT with pembrolizumab is generally tolerable with no added toxicity compared to sequential, while underscoring the need for rigorous pneumonitis vigilance and standardized immune-toxicity workflows.[37,38]

Poly (ADP-ribose) polymerase (PARP) inhibitors illustrate how agent selection and regimen details can drive divergent

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TABLE 4. Practical Pharmacokinetic Framing of Concurrent Systemic Therapy With RT (median half-life and 5× half-life)

Systemic Agent	Median Half-Life	5 Half-Lives	Drug and Breast RT Sequencing
PARP inhibitors			
Olaparib	15 hours	75 hours (approximately 3 days)	Sequential after RT supported in OlympiA; metastatic setting: consider RT after approximately 3-day break and avoid during RT. RadioPARP suggests safety as well
Veliparib	5.5 hours	27.5 hours (approximately 1 day)	Concern over increased acute and late toxicity from TBCRC 024
Talazoparib	90 hours	450 hours (approximately 19 days)	Longer PK tail complicates brief holds; favors sequential strategy in early-stage settings
CDK4/6 inhibitors			
Abemaciclib	24.8 hours	124 hours (approximately 5 days)	Short washout allows practical hold strategies around large-field or high-risk RT
Palbociclib	28.8 hours	144 hours (approximately 6 days)	Similar to abemaciclib; marrow/GI exposure drives risk with larger fields
Ribociclib	29.7-54.7 hours	148.5-273.5 hours (approximately 6-11 days)	Longer washout window for some patients; practical to hold during RT when needed, though data of improved efficacy with concurrent adminstration intriguing and evolving
HER2-targeting agents			
T-DM1	96 hours	480 hours (approximately 20 days)	Prospective concurrency in KATHERINE/ATEMPT; pneumonitis/skin toxicity signals warrant plan-dependent caution, but considered reasonable
T-DXd	168 hours	840 hours (approximately 35 days)	Limited breast RT–specific data; class concerns include pneumonitis—volume/overlap critical, but can be considered concurrently
Trastuzumab	456 hours	2,280 hours (approximately 95 days)	Holding by PK is rarely practical; concurrent trastuzumab + RT supported by clinical experience
Immune checkpoint inhibitors			
Pembrolizumab	528 hours (22 days)	2,640 hours (110 days)	Safety with concurrent RT demonstrated in KEYNOTE-522

Abbreviations: HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; RT, radiation therapy; T-DM1, ado-trastuzumab emtansine; T-Dxd, trastuzumab deruxtecan.

outcomes. In OlympiA, RT had to be completed 2-12 weeks before olaparib, supporting a sequential paradigm in early-stage disease.[39] By contrast, TBCRC 024 testing veliparib with concurrent breast/chestwall/RNI RT reported dose-limiting toxicities (including moist desquamation and neutropenia) and severe late fibrosis,[40] whereas RadioPARP reported no dose-limiting toxicities with a more potent PARPi (olaparib) at a much higher dose (up to olaparib 200 mg twice daily) with concurrent locoregional RT and favorable long-term safety.[41] These divergent signals reinforce that PARPi + RT is not a single entity; it is a regimen-dependent construct that should be approached cautiously outside protocols.

In the adjuvant setting, the CREATE-X regimen established the efficacy of capecitabine for residual disease after neoadjuvant chemotherapy, but it was delivered sequentially with local therapy (ie, not as a planned concurrent radiosensitizing strategy, it was completed either before or after radiation treatment), so its results should not be extrapolated to support routine concurrent capecitabine-RT.[42] By contrast, a phase II experience in women with advanced breast cancer tested concomitant capecitabine with radiation and provides the most direct prospective safety signal for concurrency; given the nonadjuvant population and observed acute toxicity profile, many practices still favor

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holding capecitabine during breast/chest wall ± nodal RT and resuming afterward unless a protocol specifically supports overlap.[43]

More recently, with the expanding indications for CDK4/6 inhibitors (eg, palbociclib, ribociclib, and abemaciclib) in the locally advanced, nonmetastatic ER+ breast cancer, there is interest in the timing and sequencing of these drugs with radiation. The best available clinical evidence for CDK4/6 inhibitors with RT remains primarily retrospective (largely in the metastatic/palliative RT setting), suggesting that concurrent administration with RT is often feasible, with expected hematologic suppression and generally low rates of severe nonhematologic toxicity—although rare high-grade GI toxicity has been reported, particularly with pelvic/abdominal fields. Thus, caution is warranted with large fields that include larger volumes of bowel or bone marrow. A previous review and a newer meta-analysis specifically examining CDK4/6i + RT similarly conclude that most series report acceptable acute toxicity, but emphasize heterogeneity, selection bias, and limited long-term follow-up—so routine true concurrency in curative breast RT is not yet evidence-based outside trials.[44] Importantly, prospective nonmetastatic data are emerging, including an actively recruiting phase IB study evaluating ribociclib given concurrently with postoperative adjuvant breast/chest wall ± comprehensive nodal RT in high-risk hormone receptor–positive/HER2– disease (ClinicalTrials.gov identifier: NCT05996107) that will shed additional light on this question. We suggest considering concurrent administration of targeted agents with radiation be done in a context-, volume-, and drug-dependent manner as outlined in Table 5.

RECONSTRUCTION IN CONTEXT: INTEGRATING SURGERY, RADIATION, AND SYSTEMIC THERAPY

Timing Options for Postmastectomy Breast Reconstruction

Breast reconstruction is part of the breast cancer treatment algorithm; however, integrating postmastectomy breast reconstruction with RT remains a clinical challenge. In the setting of immediate breast reconstruction (IMBR), PMRT can lead to capsular contracture and reconstructive failure in implant-based breast reconstruction[45,46] and fat necrosis and flap volume loss in autologous flap reconstruction,[47-50] which may have detrimental effects on patient satisfaction.[51,52] For these reasons, delayed breast reconstruction (DBR) is generally performed after RT is completed.[53,54] Delayed IMBR is an alternative approach whereby a temporary tissue expander (TE) is placed at the time of mastectomy, which can be partially deflated to facilitate RT, with definitive reconstruction performed in delayed fashion. The use of a TE in the setting of PMRT, however, is associated with a high incidence of infective complications, which can result in delay to adjuvant RT and systemic therapy.[55-57]

The many advantages of IMBR include completion of the oncologic and definitive reconstructive procedures in a single operation, improved psychosocial PROs, and avoidance of delays in initiation of targeted therapy if required.[58-61] Experience with performing microsurgical flap reconstruction after preoperative RT, such as in sarcoma and head and neck surgery, has demonstrated technical safety of performing microvascular anastomoses within a recently irradiated surgical field.[62,63] Premastectomy RT (PreMRT) represents a paradigm shift in breast cancer treatment whereby RT is administered before the mastectomy, allowing IMBR to be performed while avoiding the adverse effects of radiation on the autologous flap reconstruction and any risk of delay to adjuvant RT.

Preoperative Radiation Therapy and Microsurgical Immediate Breast Reconstruction

Results from retrospective and prospective studies have demonstrated the novel PreMRT treatment sequence to be feasible and safe with regard to surgical complications and breast reconstructive outcomes when compared with PMRT, as well as for oncologic outcomes.[64-76] The majority of studies of PreMRT followed by mastectomy and immediate breast reconstruction (IBR) have used whole-breast conventionally fractionated (CF) RT with a dose of 50 Gy and pedicled flap or implant-based breast reconstruction. None

TABLE 5. Traffic Light Summary: Concurrent Systemic Therapy With Breast RT

Green (generally acceptable concurrent)	Yellow (caution; plan-/setting-dependent)	Red (avoid concurrent outside protocol)
HER2 mAbs (trastuzumab ± pertuzumab) with breast/chest wall ± RNI RT: clinical experience supports safety and efficacy with standard monitoring and heart-sparing techniques	HER2 ADCs (T-DM1, T-DXd): Prospective concurrency permitted; monitor pneumonitis and skin toxicity; consider fractionation effects with T-DM1 Immunotherapy (eg, pembrolizumab): Generally tolerable with breast/RNI RT but requires pneumonitis vigilance and immune-toxicity workflows CDK4/6 inhibitors: Limited high-level data; short half-lives allow practical hold strategies when field size/marrow exposure is a concern	Capecitabine: Avoid concurrent RT in breast cancer (adjuvant paradigm is nonconcurrent) unless needed for nonresponsive or recurrent disease Veliparib + RT: significant acute and late toxicity reported; avoid concurrency Olaparib + RT: suggestions of safety in RadioPARP, but caution still warranted

Abbreviations: ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; RNI, regional nodal irradiation; RT, radiation therapy; T-DM1, ado-trastuzumab emtansine; T-Dxd, trastuzumab deruxtecan.

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of these studies have reported complete flap failures or inability to complete reconstruction due to the irradiated field. To address concerns regarding the safety of PreMRT on the ability to perform microsurgical reconstruction using the IM recipient vessels in the setting of RNI that includes the internal mammary lymph nodes (IMLNs), two recent prospective studies have investigated outcomes of PreMRT and microsurgical IMBR:

Preoperative Radiotherapy and DIEP Flap (PRADA) Study

The Preoperative Radiotherapy and DIEP Flap (PRADA) Study was a prospective, nonrandomized, feasibility study conducted at two sites in the United Kingdom (ClinicalTrials.gov identifier: NCT02771938).[66,74] Patients with a diagnosis of primary breast cancer requiring mastectomy and RT, who were suitable for deep inferior epigastric artery perforator (DIEP) flap reconstruction, were eligible. Preoperative RT started 3-4 weeks after completion of neoadjuvant systemic therapy (NST) and was delivered to the breast, plus regional nodes as required, at 40 Gy in 15 fractions or 42.72 Gy in 16 fractions. Skin-sparing mastectomy (SSM) and microvascular DIEP flap reconstruction were planned for 2-6 weeks after completion of PreMRT. In total, 33 patients were enrolled, and at 4 weeks after surgery, four (12%) of 33 patients met the primary end point of an open breast wound >1 cm width requiring a dressing at 4 weeks after surgery. There were no complete flap losses or serious treatment-related adverse events, with complication rates comparable to previous studies of PMRT. There were no locoregional recurrences, four patients (12%) developed distant metastatic disease, and two (6%) died from breast cancer at a median follow-up of 23.6 months.

Shortening Adjuvant Photon Irradiation (SAPHIRE) Trial

The SAPHIRE trial was a phase II randomized clinical trial (RCT) conducted at The University of Texas MD Anderson Cancer Center (ClinicalTrials.gov identifier: NCT02912312).[72] Patients with cT0-T3, N0-N3b, M0 breast cancer and a recommendation for RT were eligible. Patients were randomly assigned to receive either CF (50 Gy in 25 fractions) or hypofractionated (HF; 40.05 Gy in 15 fractions) RNI. The PreMRT group was a separate arm within the larger trial for which patients requiring both mastectomy and RT and desiring IMBR were eligible to determine the feasibility and safety of this treatment sequence. The primary outcome was the rate of complete autologous flap failure. In the PreMRT group, RT was started approximately 3-4 weeks after completion of NST. SSM or nipple-sparing mastectomy (NSM) with IMBR was planned for 2-6 weeks after completion of PreMRT. Fifty patients were enrolled, and among 49 evaluable patients, 25 patients received CF RNI, and 24 received HF RNI, including the IMLNs. Forty-eight patients underwent mastectomy with IMBR, at a median of 23 days (IQR, 8.5) after RT. Of these, 41 patients underwent microvascular autologous flap reconstruction, five underwent latissimus dorsi pedicled flap reconstruction, and two had TE placement. There were no complete flap failures and one patient underwent TE explantation for complications.

A separate analysis compared outcomes in the patients who received PreMRT and underwent microvascular autologous flap IMBR with those who underwent PMRT with DBR (n = 103).[71] There were no complete autologous flap losses in either group, and rates of other recipient site complications were similar between the groups. Infection at the recipient site, however, occurred in 20% (13/66) of patients in the PMRT group who underwent TE placement, and nine (14%) required TE explantation due to complications. In the PMRT group, the median time from mastectomy to DBR was 12.8 months, and 108 patients (37%) did not undergo any breast reconstruction. Regarding oncologic outcomes, there were no recurrences in the PreMRT group at a median follow-up of 29.5 months and no locoregional recurrences, and only two patients (2%) with distant metastatic disease in the PMRT group at a median follow-up of 44.7 months.

DISCUSSION

Preoperative RT to allow IBR is an evolving field, and larger prospective trials with longer-term follow-up are needed to establish this new therapeutic sequence as a noninferior standard of care.[77-79] The available studies have established the safety of PreMRT for microsurgical breast reconstruction using the IM recipient vessels in the setting of RNI, which is the standard of care in the United States for patients with node-positive breast cancer,[80,81] including for CF RNI,[82-84] with a time interval of 2-4 weeks after RT found to be optimal before acute radiation injury is clinically apparent. A major advantage of the PreMRT treatment sequence is avoidance of delay to adjuvant RT and targeted therapy (CDK4/6 or PARP inhibitor therapy), which otherwise need to be held for a period before and after surgery to allow healing to occur, with the risk of further therapy delays in the case of surgical complications. Additionally, the overall time taken for breast reconstruction to be completed is reduced, and potentially more patients are able to undergo breast reconstruction.[71] Although, to our knowledge, to date, no RCTs comparing PreMRT with PMRT, as well as comparing outcomes between the different RT fractionation regimens, have been conducted, current active studies will provide further important information regarding this treatment sequence, including implant-based reconstruction:

Trial of Preoperative Radiation (TOPAz)

The Trial of Preoperative Radiation study (ClinicalTrials.gov identifier: NCT05774678) is a phase III RCT of PreMRT conducted at the University of Texas MD Anderson Cancer Center. Patients with T3-T4c or N1-N3; T4d, any N, M1, invasive breast cancer are eligible. In total, 200 patients are randomly assigned to receive HF-PreMRT or CF-PreMRT followed by mastectomy and autologous tissue IBR. The primary goal is to compare outcomes between the different

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RT fractionation regimens, including surgical, oncologic, aesthetic, and PROs, as well as acute and late radiation-related toxicities. A concern regarding PreMRT is the potential to result in a local pCR in patients who would otherwise not have attained it from NST alone,[73] and therefore, patients receive further tumor core biopsy after NST and before PreMRT.

Preoperative Radiotherapy and DIEP Flap Reconstruction (PRADA-II) Trial

The PRADA-II study is a multicenter RCT with a target enrollment of 450 patients with breast cancer identified from 26 trial centers in the United Kingdom. Females with locally advanced breast cancer T3 or T4 and any N stage, or any T stage and N2 or N3 disease, or T2 and/or N1 disease with additional risk factors for local recurrence, and are suitable for microvascular autologous reconstruction are randomly assigned to receive either PreMRT or PMRT and undergo SSM with IMBR. The primary objective is to investigate whether PreMRT leads to improved BREAST-Q satisfaction with immediate autologous reconstruction compared with PMRT at 2 years. The secondary objectives are to determine if the PreMRT sequence improves overall health-related quality of life, attenuates treatment times, reduces fat necrosis, and increases pCR rates.

Preoperative Radiation Therapy and Immediate Breast Reconstruction (PRADAIIBE) trial

The PRADAIIBE trial (ClinicalTrials.gov identifier: NCT06739655) is a multicenter phase III RCT being conducted in Belgium to assess if PreMRT combined with IBR can safely improve both aesthetic and quality-of-life outcomes in patients with breast cancer, compared with PMRT and delayed IMBR. The planned enrollment is 180 patients who are undergoing SSM/NSM for breast cancer and require RT, and autologous, implant-based, and hybrid reconstructions are eligible. The primary outcome is the BREAST-Q satisfaction with breasts score. Secondary outcomes include aesthetic and PROs, treatment duration, adverse events (general or surgical), rate of pCR, and survival compared with PMRT.

CONCLUSIONS

PreMRT is an emerging treatment sequence for breast cancer with similar complication rates to PMRT, which is the current standard approach, a lower risk of delay of initiation of adjuvant therapy, potentially higher patient-reported satisfaction with cosmetic outcome, shorter overall time taken to definitive reconstruction, and the potential to increase the number of patients who undergo postmastectomy breast reconstruction.

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Stage I Triple-Negative Breast Cancer: Moving From One-Size-Fits-All to a Personalized Approach

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OVERVIEW

Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype characterized by lack of estrogen receptor expression, progesterone receptor expression, and human epidermal growth factor 2 overexpression/amplification. Given its generally aggressive biology, current guidelines recommend systemic therapy for most patients, with anthracycline- and taxane-based regimens being historically preferred. However, the clinical outcomes of patients with stage I TNBC and the benefit (or lack thereof) of (neo)adjuvant chemotherapy have not been prospectively evaluated as this population has largely been excluded from prospective randomized clinical trials. As such, management decisions for stage I TNBC are typically extrapolated from trials enrolling patients with stage II or III TNBC or based on retrospective analyses. Currently, the primary factor influencing systemic therapy decisions is the anatomic stage, without other biomarkers clinically used to guide systemic therapy. This review summarizes the existing evidence supporting current and emerging systemic therapy strategies for stage I TNBC, with a special focus on treatment de-escalation and promising biomarkers that can advance personalized treatment selection.

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INTRODUCTION

Triple-negative breast cancer (TNBC) is a distinct subtype of breast cancer characterized by lack of estrogen receptor expression, progesterone receptor expression, and human epidermal receptor 2 (HER2) amplification/overexpression. TNBC accounts for 10%-15% of all breast cancers[1] and is often associated with a more aggressive disease course, characterized by earlier and more frequent relapse and higher mortality.[2] It has a disproportionate occurrence among individuals of African ancestry—particularly west African,[3] carriers of germline *BRCA1*,[4] and women diagnosed before age 40 years.[1]

Given the more aggressive clinical course of TNBC, current clinical practices have predominately focused on treatment intensification strategies. This paradigm remains heavily reliant on anatomic staging, with a notable absence of validated biomarkers to guide individualized treatment selection. Among patients with stage II or III TNBC, the preferred standard of care is the five-drug KEYNOTE-522 regimen administered in the (neo)adjuvant setting, which has demonstrated improvements in pathologic complete response (pCR) rates,[5] event-free survival (EFS),[6] and overall survival (OS)[7] compared with chemotherapy alone. For stage I TNBC, chemotherapy alone with either a two- or three-drug regimen is typically recommended as this cohort was not included in KEYNOTE-522. Patients with stage I TNBC have historically been excluded from randomized clinical trials, resulting in a lack of prospective randomized data to inform optimal systemic therapy options for this population. As such, the clinical management of patients with stage I TNBC often relies on extrapolation of data from studies involving patients with higher-stage disease or from retrospective analysis, leading to widely variable clinical practices.

TNBC encompasses a spectrum of molecularly heterogenous diseases with distinct biology. Studies evaluating the biology of TNBC have identified up to four distinct molecular subtypes, with variable responses to systemic therapy and clinical outcomes.[8-12] These findings highlight that systemic therapy personalization based on predictive biomarkers is feasible and may be a superior strategy compared with the current one-size-fits-all approach. In this review, we will summarize existing clinical data relevant to stage I TNBC, providing an evidence-based framework for therapeutic decision making in the absence of prospective randomized clinical trial data. In addition, we will review subset analyses of clinical trials including patients with node-negative TNBC, offering insight into outcomes that may approximate those for stage I disease. Finally, we will review emerging biomarkers and systemic therapy strategies under investigation as potential tools to personalize treatment in TNBC, which may be especially pertinent to patients with stage I TNBC.

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PRACTICAL APPLICATIONS

- While triple-negative breast cancer (TNBC) is generally an aggressive subtype, it is highly heterogeneous, with a subset of patients having a more favorable biology and high responsiveness to systemic therapy.
- The management of stage I TNBC needs to appropriately balance the underlying risk of recurrence with the short- and long-term risk of treatment-related toxicities.
- Emerging biomarkers such as tumor-infiltrating lymphocytes, tumor proliferation, and dynamic circulating tumor DNA monitoring are promising tools that may enable personalization of systemic therapy.
- Anthracycline-free treatment strategies, targeted therapies for specific subtypes, and immunotherapy approaches may offer further effective treatment options beyond traditional anthracycline- and taxane-based chemotherapy.

CLINICAL OUTCOMES OF STAGE I TNBC WITH AND WITHOUT CHEMOTHERAPY

The role of neoadjuvant or adjuvant systemic therapy in stage I TNBC has not been formally assessed in prospective clinical trials. However, several retrospective analyses have suggested that the key clinical factors affecting survival and disease recurrence of patients with stage I TNBC include tumor size,[13–17] level of tumor-infiltrating lymphocytes (TILs),[18–22] receipt of adjuvant or neoadjuvant chemotherapy, and attainment of pCR (among patients treated with neoadjuvant therapy).[23]

Most retrospective analyses suggest that patients with T1mic and T1a (<0.5 cm) TNBC are likely sufficiently treated with locoregional therapy alone.[14,17,24] In a population-based study using the SEER database, patients with T1mic and T1a TNBC had excellent clinical outcomes regardless of chemotherapy administration, with their respective 5-year breast cancer–specific survival (BCSS) being 99% for T1mic and 98% for T1a (identical rates in the chemotherapy and no-chemotherapy cohorts). The benefit of systemic chemotherapy among T1b tumors has been conflicting, with some retrospective studies reporting benefit,[13,25,26] whereas others do not.[17,24,27] Most studies consistently show that the most pronounced difference in outcomes related to chemotherapy is seen among individuals with T1c tumors.[24,28] In the aforementioned SEER analyses, the 5-year BCSS of patients with T1c N0 TNBC who did not receive chemotherapy was 91%, compared with 95% among those who received chemotherapy,[17] and other studies have reported larger differences.[29]

Beyond tumor and nodal stage, there has been interest in identifying biomarkers that may further stratify risk of recurrence and mortality with and without systemic therapy. As elaborated later in this manuscript, measures of tumor immune infiltration (either by quantification of TILs or through immune expression signatures) are among the most promising biomarkers with potential to identify a subset of patients with favorable outcome who may be candidates for systemic therapy de-escalation or omission.[18–22] Individuals with stage I TNBC and high TILs (particularly ≥50%) have consistently been reported to have excellent long-term prognosis with very low cumulative incidence of distant recurrence or death (5-year distant recurrence-free survival [DRFS] and OS around 95%)[20,22] even when treated without chemotherapy. Conversely, those with stage I TNBC and low TILs (particularly <30%) consistently show a higher cumulative risk of distant metastases or death without chemotherapy, exceeding 20% at 5 years (5-year DRFS and OS of approximately 80%).[20,22] Given that the existing data on TILs in TNBC not treated with chemotherapy are retrospective, this biomarker has not been routinely incorporated into clinical practice. Ongoing clinical trials are prospectively evaluating the use of TILs to inform systemic therapy for stage I TNBC.

TAILORING SYSTEMIC THERAPY FOR STAGE I TNBC

Multiple evidence-based, consensus-driven guidelines (eg, National Comprehensive Cancer Network [NCCN],[30] ESMO,[31] and ASCO[32]) recommend adjuvant or neoadjuvant chemotherapy for patients with stage I TNBC, except for those with T1mic/T1a tumors or rare favorable histologic subtypes. Patients with T1b N0 TNBC are usually treated with up-front surgery followed by adjuvant chemotherapy, whereas neoadjuvant chemotherapy is generally recommended for patients with T1c N0 TNBC (Fig 1).

The standard regimen for early-stage TNBC has traditionally consisted of an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (eg, AC/EC), either followed or preceded by a taxane (T).[33] Efforts to improve the outcomes observed with this 3-drug regimen led to evaluating the addition of carboplatin (Cb)[34–36] and immunotherapy[6,7] for patients with higher-risk stage II-III TNBC. The KEYNOTE-522 trial demonstrated a clear clinical benefit with the addition of pembrolizumab to neoadjuvant TCb followed by AC/EC, establishing it as the current standard of care for this population. This combination resulted in an improvement in pCR (63% *v* 56%), EFS (5-year EFS: 81% *v* 72%, hazard ratio [HR], 0.65 [95% CI, 0.51 to 0.83]), and OS (5-year OS: 87% *v* 82%, HR, 0.66 [95% CI, 0.50 to 0.87]).[6,7] Patients with stage I TNBC were not included in KEYNOTE-522,[7] and as such, the addition of immunotherapy is not currently standard of care for this indication. Similarly, the

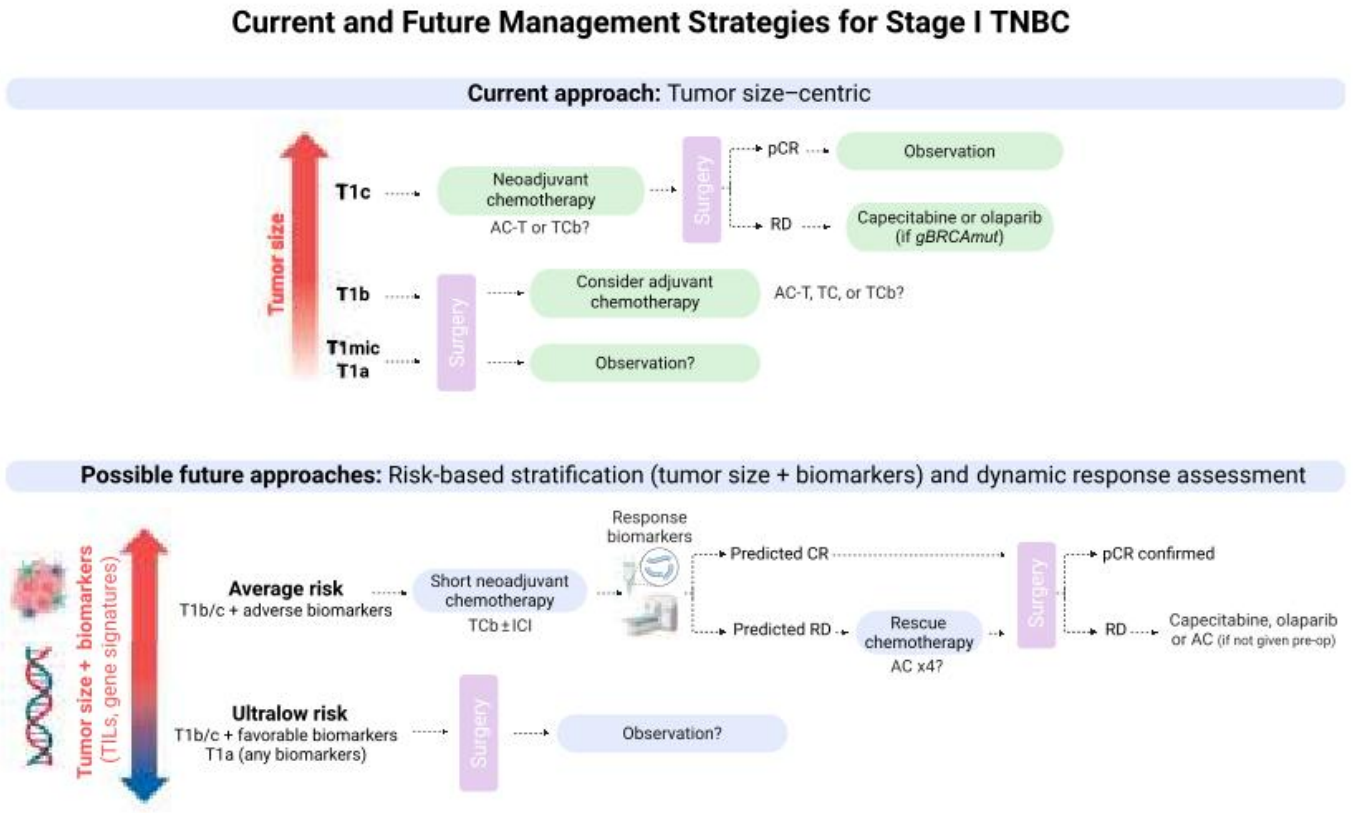

FIG 1. (Top) The current management of stage I TNBC is based nearly exclusively on tumor size, with T1c tumors generally receiving neoadjuvant chemotherapy, while T1mic/a/b generally treated with up-front surgery followed by adjuvant chemotherapy for T1b or observation for T1mic/a. (Bottom) Potential future management strategies may be based not only on tumor size but also on assessment of biological risk of recurrence based on biomarkers (eg, immune biomarkers) and dynamic assessment of response (eg, ctDNA clearance, MRI-based response). AC-T, anthracycline/cyclophosphamide-taxane; CR, complete response; ctDNA, circulating tumor DNA; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; pCR, pathologic complete response; RD, residual disease; TC, docetaxel/carboplatin; TCb, taxane/carboplatin; TILs, tumor-infiltrating lymphocytes; TNBC, triple-negative breast cancer. Created using BioRender. Leon-Ferre R. (2026) https://BioRender.com/g996y2n.

addition of Cb to AC/EC-T in stage I TNBC remains controversial. When chemotherapy is indicated, NCCN recommends either AC/EC-T or the anthracycline-free regimen docetaxel/cyclophosphamide (TC) as preferred options, with Cb plus taxanes listed under other recommended regimens.[30]

Increasingly, there is interest in evaluating anthracycline-free regimens, particularly for patients at lower risk of recurrence. Anthracyclines have historically been a cornerstone in the management of high-risk early-stage breast cancer. While effective, anthracyclines come at the cost of life-threatening long-term cardiac[37] and hematologic[38] toxicities. As both carboplatin and pembrolizumab have demonstrated significant improvements in DFS and OS, there has been interest in exploring opportunities to eliminate the role of anthracyclines in early-stage breast cancer. This approach aligns with the historical evolution of systemic therapy in luminal and HER2-positive breast cancers, where advances in targeted therapies (ie, endocrine and HER2-targeted therapies) have led to the safe de-escalation of cytotoxic chemotherapy, including omission of chemotherapy for low-genomic-risk luminal tumors[39] and the decreased use of anthracyclines in HER2-positive breast cancers.[40]

NONANTHRACYCLINE-BASED REGIMEN: DOCETAXEL + CYCLOPHOSPHAMIDE

TC has been evaluated in several large analyses of prospective clinical trials and, in general, is considered an appropriate alternative regimen for patients with low-risk TNBC, particularly those with node-negative tumors. The data have been somewhat mixed in early-stage TNBC, showing either similar clinical outcomes between TC and anthracycline-containing regimens or showing slight superiority of anthracycline-containing regimens. The results of these analyses are shown in Table 1. In a preplanned joint analysis of the randomized ABC trials which included over 4,000 women with resected early-stage HER2-negative breast cancer, those randomly assigned to anthracycline- and taxane-containing regimens (various concurrent or sequential regimens) had a slightly superior invasive disease-free survival (iDFS) and recurrence-free survival compared with those who received six cycles of TC.[41,42] Exploratory

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TABLE 1. Select Studies Evaluating Adjuvant Anthracycline Versus Nonanthracycline Regimens in Early-Stage Breast Cancer

Trial	No.	Study Type	Regimen	Recurrence	Survival
ABC trials[a]	4,181 (all patients)	Pooled analysis	TC × 6 *v* T/AC regimens	5-year iDFS 85.1% TC *v* 86.7% T/AC HR: 1.14 [0.99 to 1.32], *P* = .08 (noninferiority not demonstrated)	5-year OS 91.8% TC *v* 92.4% HR: 1.05 [0.87 to 1.26], *P* = .64
	TNBC subset (n = 1,304)			5-year iDFS N0: 85.0% TC *v* 88.4% T/AC HR: 1.23 [0.89 to 1.70], *P* = .22 N1: 72.5% TC *v* 79.9% T/AC HR: 1.25 [0.78 to 2.00], *P* = .35 N2/3: 51.9% TC *v* 65.6% T/AC HR: 1.65 [0.83 to 3.27], *P* = .15	5-year OS N0: 91.0% TC *v* 92.9% T/AC HR: 1.17 [0.78 to 1.76], *P* = .45 N1: 82.4% TC *v* 88.2% T/AC HR: 1.30 [0.72 to 2.34], *P* = .38 N2/3: 57.4% TC *v* 75.4% T/AC HR: 1.76 [0.83 to 3.77], *P* = .14
PlanB and SUCCESS C[a]	5,924 (all patients)	Pooled analysis	TC × 6 *v* T/AC regimens	5-year DFS 89.3% TC *v* 90% T/AC HR: 1.05 [0.89 to 1.24], *P* = .57	5-year OS 94.9% TC *v* 95% with T/AC HR: 1.00 [0.80 to 1.26], *P* = 1.00
	TNBC subset (n = 1,279)			5-year DFS 83.1% TC *v* 83.3% T/AC HR: 0.99 [0.76 to 1.30]	5-year OS 89.8% TC *v* 90.5% T/AC HR: 1.08 [0.76 to 1.53]
EBCTCG[b]	18,103 (all patients)	Pooled analysis	TC *v* T + A	10-year recurrence 18.9% TC *v* 16.4% T + A RR:0.86 [0.79 to 0.93], *P* = .0004	10-year breast cancer mortality 12.0% TC *v* 10.4% T + A RR: 0.88 [0.78 to 0.99]
PATTERN[c]	647	Multicenter phase III	TCb *v* CEF-T	5-year DFS 86.5% TCb *v* 80.3% CEF-T HR: 0.65 [0.44 to 0.96], *P* = .03	5-year OS 93.4% TCb *v* 89.8% CEF-T HR: 0.71 [0.42 to 1.22], *P* = .22

Abbreviations: Cb, carboplatin; CEF, cyclophosphamide, epirubicin, and fluorouracil; DFS, disease-free survival; HER2, human epidermal growth factor 2; HR, hazard ratio; iDFS, invasive disease-free survival; OS, overall survival; RR, rate ratio; T + A, taxane + anthracycline; T/AC, taxane/anthracycline/cyclophosphamide; TC, taxane/cyclophosphamide; TNBC, triple-negative breast cancer.
[a]Included patients with HER2-negative breast cancer (hormone receptor–positive and hormone receptor–negative).
[b]Included all breast cancer subtypes.
[c]Included only TNBC.

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subset analyses suggested that patients with TNBC derived the largest iDFS benefit from anthracyclines, particularly those with nodal involvement, with a more modest benefit among those with N0 disease. However, there were no differences in OS, suggesting that the potential small gains in decreasing recurrence were offset by other events, including more cases of leukemia and more non–breast cancer deaths. The results of the ABC trial joint analysis were challenged by the pooled analysis of the PlanB and SUCCESS C trials, which collectively enrolled nearly 6,000 patients with intermediate- or high-risk early HER2-negative breast cancer randomly assigned to receive TC × 6 or sequential anthracycline- and taxane-containing regimens. In this large analysis, there were no differences in DFS or OS (Table 1). Importantly, exploratory subgroup analyses of the TNBC population (representing 20% of the overall population) were consistent, without an apparent benefit from anthracyclines.[43] Finally, a large patient-level EBCTCG meta-analysis of over 100,000 women from 86 randomized trials concluded that the addition of an anthracycline to a taxane-based regimen resulted in both lower recurrence and lower breast cancer–related mortality in all breast cancer subgroups[33] (Table 1). However, the benefit of anthracyclines was primarily driven by trials using a concurrent anthracycline and taxane schedule, with no advantages to the use of anthracyclines when administered in the sequential schedule that is currently considered the standard of care.

Because of these conflicting results, the lack of a survival difference, the small difference in recurrence events in the N0 population, and the lower rate of leukemia, TC has become a viable alternative to AC-T in patients with lower-risk, node-negative early breast cancer and/or potential contraindications to anthracyclines.

NONANTHRACYCLINE-BASED REGIMEN: TAXANES + CARBOPLATIN

Preclinical and clinical evidence has suggested that platinum agents may be particularly active in TNBC compared with other breast cancer subtypes, owing in part to their DNA-damaging effect and the high prevalence of homologous recombination deficiency in TNBC.[44-50] This hypothesis has led to clinical trials incorporating platinums into the AC/EC-T backbone[34-36] and to studies using platinums + taxanes without anthracyclines as a potential anthracycline-sparing strategy.

In the adjuvant setting, the phase III PATTERN trial randomly assigned patients with resected TNBC to an anthracycline- and taxane-based regimen (FEC-D) versus carboplatin + paclitaxel. Interestingly, DFS was superior in the carboplatin + paclitaxel group without a difference in OS (Table 1).[51] While this study did not focus on stage I, the majority (74%) of patients had N0 TNBC and over half (54%) had T1 tumors. In the neoadjuvant setting, platinum- and taxane-based therapy has been associated with high pCR rates (ranging between 46% and 58%) in prospective, single-arm studies and small randomized trials (Table 2).[52-54] Even higher pCR rates have been observed in patients with node-negative disease and those with high TILs, suggesting that these patients may be particularly good candidates for an anthracycline-free neoadjuvant strategy.[53,55] In the Neo-STOP randomized phase II trial, the pCR rate was identical with six cycles of carboplatin plus docetaxel versus carboplatin plus paclitaxel followed by AC[55] (Table 2), with an even higher pCR rate (67%) observed in TNBC with higher TILs (TILs > 20%). There were no differences in EFS or OS between the arms, with patients who obtained a pCR demonstrating a 3-year EFS and OS of 100% for both end points, compared with 81% (95% CI, 69% to 93%) and 86% (95% CI, 75% to 96%), respectively, for patients with residual disease. Importantly, grade 3 and 4 adverse events were more common in the anthracycline-containing arm (73% *v* 21%; $P < .0001$), with the main differences being hematologic toxicities.

Most studies evaluating anthracycline-free regimens have used six cycles of treatment although there is growing interest in evaluating shorter duration regimens, considering that extending AC/EC beyond four cycles did not confer additional benefit and instead added toxicity[56,57] and that four cycles of TC were superior to four cycles of standard-dose AC.[58] In addition to the anticipated improved tolerability of shorter regimens, a four-cycle platinum-/taxane-based approach lends itself well to a response-adapted intensification of treatment. For example, patients achieving pCR after 12 weeks of platinum/taxane could potentially avoid AC without compromising long-term outcomes, whereas those not achieving pCR could still receive AC/EC adjuvantly. This strategy was evaluated in the randomized phase II WSG-ADAPT-TN trial, in which 336 patients with stage I-III TNBC were randomly assigned to four cycles of either neoadjuvant carboplatin + nab-paclitaxel or gemcitabine + nab-paclitaxel.[59] The pCR rate was higher in the carboplatin + nab-paclitaxel arm (Table 2). Among those achieving pCR, approximately half did not receive additional systemic therapy, whereas those with residual disease received four additional cycles of AC/EC either adjuvantly (if residual disease found on surgical pathology) or neoadjuvantly (if residual disease was demonstrated on biopsy after completion of 12 weeks of preoperative therapy). With this approach, the 5-year iDFS in those achieving pCR was 91%, compared with 63% in those with residual disease. For patients achieving pCR, the 5-year iDFS was comparable between those who received additional systemic therapy (91%) and those who did not (90%), suggesting that shorter-duration neoadjuvant therapy without further systemic therapy may not compromise long-term outcomes among those achieving pCR.

TABLE 2. Select Studies Evaluating Neoadjuvant Platinum and Taxane Regimens in Early-Stage Triple-Negative Breast Cancer

Trial	No.	Phase	Stage	Regimen	pCR Rate, %	RCB 0 + 1	pCR (N0)	pCR (high *v* low TILs)
Sharma et al, prospective cohort	190	II	I-III	Carboplatin + docetaxel × 6	55	68	—	—
NeoSTOP	100	II	I-III	Carboplatin + paclitaxel × 4 → AC × 4	54	67	54	67% *v* 49%
				Docetaxel + carboplatin × 6	54	67		
NeoPACT	115	II	I-III	Carboplatin + docetaxel + pembrolizumab × 6	58	69	65	76% *v* 41%
WSG-ADAPT-TN	336	II	I-III	Nab-paclitaxel + carboplatin × 4	46	—	—	—
				Nab-paclitaxel + gemcitabine × 4	29	—	—	—
Neo-N	110	II	I-II	Carboplatin + paclitaxel + nivolumab × 4	53	—	56	67% *v* 46%

Abbreviations: pCR, pathologic complete response; TIL, tumor-infiltrating lymphocyte.

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EMERGING APPROACHES TO PERSONALIZE TREATMENT

There is increasing interest in a priori identification of patients with more favorable disease biology who may be cured with less intensive approaches, potentially reducing both short- and long-term toxicities. In this section, we will explore several promising strategies under investigation for the optimization of therapy in early TNBC that may be particularly relevant for patients with stage I TNBC. These approaches are illustrated in Figures 1 and 2.

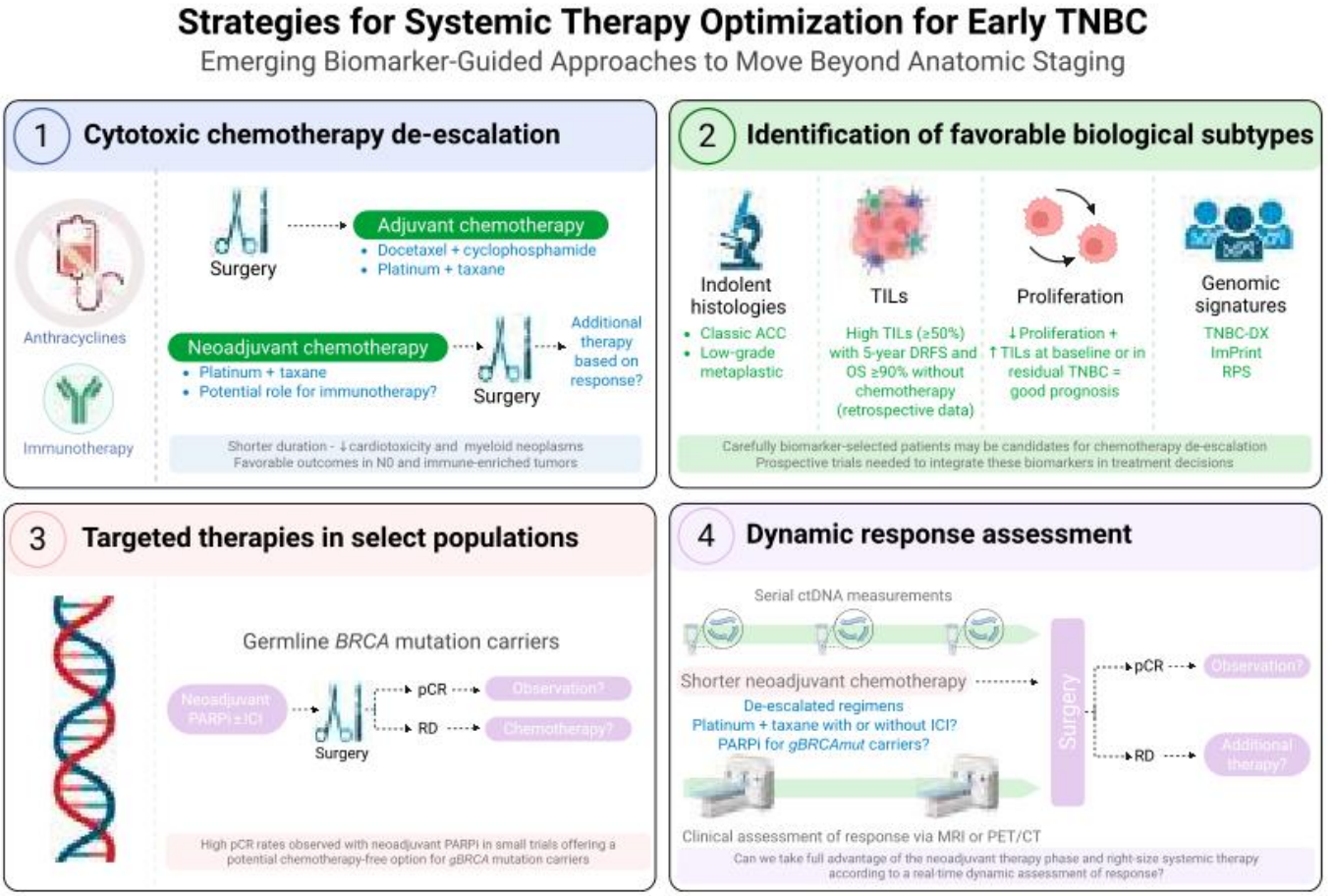

FIG 2. Emerging strategies to optimize systemic therapy in early TNBC focus on cytotoxic chemotherapy de-escalation in the era of immunotherapy, biomarker-based risk stratification, and dynamic biomarkers to assess response to treatment. ACC, adenoid cystic carcinoma; DRFS, distant relapse-free survival; ICI, immune checkpoint inhibitor; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitors; pCR, pathologic complete response; RD, residual disease; RPS, response predictive subtypes; TILs, tumor-infiltrating lymphocytes; TNBC, triple-negative breast cancer. Created using BioRender. Leon-Ferre R. (2026). https://BioRender.com/q2paxz4.

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Optimization 1: Incorporation of Immunotherapy While De-Escalating Cytotoxic Therapy

The addition of pembrolizumab to the neoadjuvant TCb-AC/EC backbone in KEYNOTE-522 has renewed interest in evaluating whether the inclusion of immunotherapy may further facilitate the omission of anthracyclines in early TNBC. Two phase II trials evaluating this strategy include NeoPACT[53] and Neo-N.[60] In NeoPACT, 115 patients with stage I-III TNBC (61% with N0 tumors, and 12% with stage I) were treated with six cycles of pembrolizumab and carboplatin + docetaxel. The overall pCR rate was 58% and was highest among those with N0 disease (pCR 65%) or high TILs (pCR 76% with TILs >30%). Individuals who achieved a pCR had a 2-year EFS of 98% compared with 78% for those with residual disease (HR, 9.12 [95% CI, 1.98 to 41.94]; $P = .001$). Neo-N[60] evaluated a shorter regimen of four cycles of carboplatin + paclitaxel + nivolumab among 110 patients with stage I-II TNBC (one third with stage I and 83% N0). The pCR rate with this abbreviated regimen was 53%. Similar to the NeoPACT study, patients with immune-enriched tumors achieved much higher pCR rates (pCR 71% in PD-L1+ TNBC and 67% in those with TILs ≥30%). These outcomes suggest that over two thirds of patients with stage I TNBC with immune-enriched tumors may safely avoid an anthracycline when immunotherapy is incorporated. The noninferiority of carboplatin + taxane + pembrolizumab versus the full KEYNOTE-522 regimen is currently being studied in the ongoing phase III SCARLET trial (SWOG S2212, ClinicalTrials.gov identifier: NCT05929768), which is enrolling patients with stage II-III TNBC. Furthermore, there are also prospective trials evaluating pCR with neoadjuvant immunotherapy alone among patients with stage I TNBC (eg, POPDurva, ClinicalTrials.gov identifier: NCT05215106).

A key consideration as the field moves forward will be evaluation of the short- and long-term toxicities of anthracycline-free regimens and/or immunotherapy. While it is desirable to avoid anthracycline-related toxicities, the addition of immunotherapy may also result in debilitating and potentially long-term toxicities, significantly affecting quality of life. These toxicities need to be balanced with the nontrivial risk of recurrence of patients with stage I TNBC, particularly among those with larger T1c tumors or adverse biological factors. Whether shorter courses of immunotherapy are associated with decreased risk of severe or persistent immune-related adverse events remains unknown.

Optimization 2: Identification of Early TNBC With Favorable Biology

Favorable Histology

While prospective data are lacking, rare histologic subtypes of TNBC, such as classic adenoid cystic carcinoma, secretory carcinomas of the breast, low-grade forms of metaplastic carcinoma (low-grade adenosquamous carcinoma and fibromatosis-like metaplastic carcinoma), acinic cell carcinoma, tall cell carcinoma with reverse polarity, low-grade mucoepidermoid carcinoma, and others have been shown to be indolent with very low metastatic potential.[61] Tumors classified as such could be effectively treated with locoregional management alone and no chemotherapy, whereas admixed histologies, other atypical variants (eg, solid-basaloid adenoid cystic, high-grade metaplastic tumors), or those with other adverse factors (high-grade or nodal involvement) are generally recommended to receive systemic therapy.

Tumor-Infiltrating Lymphocytes

A growing body of literature suggests that higher levels of pretreatment TILs are associated with favorable prognosis and enhanced chemosensitivity in patients with early TNBC. High TILs measured in residual tumors after neoadjuvant chemotherapy are also associated with improved prognosis and may facilitate further risk stratification beyond calculation of residual cancer burden.[62-64] However, one of the most promising uses of TILs is to identify patients with stage I TNBC with a low risk of recurrence or death who can be managed without chemotherapy.[18-22] In a large international analysis of nearly 2,000 patients with early TNBC who did not receive chemotherapy, patients with pT1c N0 TNBC and TILs ≥50% exhibited 5-year DRFS and OS rates of 92% (95% CI, 89 to 96) and 94% (95% CI, 90% to 97%), respectively. Conversely, patients with pT1c N0 TNBC and low TILs (<30%) had higher risk of distant recurrence (5 years DRFS, 73% [95% CI, 69 to 76]) and death (5 years OS, 77% [95% CI, 73 to 80]). These findings suggest that TIL quantification may allow more precise risk stratification than tumor stage alone, with those with stage I TNBC and high TILs being candidates for studies evaluating systemic therapy de-escalation or omission. In addition, patients with stage I TNBC and low TILs may not only benefit from chemotherapy but may need further systemic therapy despite their low anatomic stage. Ongoing (OPTImal: ClinicalTrials.gov identifier: NCT06476119 and ETNA: ClinicalTrials.gov identifier: NCT06078384) and planned (TIL-CHOICE) clinical trials are designed to prospectively evaluate the use of TILs as an integral biomarker to assign patients to different treatment strategies, including omission of systemic therapy for those with high TILs and immunotherapy-based regimens for those with lower TILs.

A key advantage of using TILs as a biomarker is their ability to be visually assessed on widely available hematoxylin and eosin–stained slides. Despite this, several challenges have hindered their clinical integration, including lack of standardized methods of assessment, interobserver variability, uncertainty regarding the optimal TIL cutoffs for clinical decision making, and lack of prospective studies incorporating TILs for treatment decisions.[65] To address these, the international Immuno-Oncology Biomarker Working Group has developed guidelines to standardize TIL evaluation. Implementation of these guidelines has shown a reduction in

interobserver variability, with intraclass correlation coefficients ranging between 0.81 and 0.93 when using a TIL threshold of 30% and between 0.90 and 0.94 when using a TIL threshold of 75%.[66,67] Ongoing work leveraging automated computational models to evaluate TILs has the potential to further increase reproducibility,[68] which may facilitate clinical implementation. Furthermore, ongoing prospective clinical trials are using TILs as an integral biomarker for treatment decision making and, if positive, may establish their clinical utility.

Tumor Proliferation

Most TNBC tumors are of high histologic grade, highly proliferative, and characterized by abundant mitoses. As such, classic histologic grade determination, manual mitosis counting, or proliferation biomarkers (eg, Ki-67 and mitotic activity index, among others) have not offered meaningful prognostic value in unselected cohorts of early-stage TNBC treated with chemotherapy.[18,69,70] Clinical use has also been hindered by the lack of standardized cutoffs,[71] standardized assays, and the absence of international guidelines for treatment selection. Despite this, emerging data suggest that proliferation measures are valuable as both prognostic and predictive biomarkers. High Ki-67 expression has been correlated with poorer DFS and OS in resected TNBC, particularly when ≥40%.[72] Conversely, retrospective data suggest that the long-term outcomes of individuals with stage I TNBC and low Ki-67 (≤30%) may be similar with or without adjuvant chemotherapy.[73] In addition, dynamic assessment of Ki-67 after neoadjuvant therapy holds prognostic value, with low postneoadjuvant Ki-67 being associated with better BCSS in TNBC.[74] The evaluation of proliferation markers in residual tumors after neoadjuvant chemotherapy provides prognostic information and may facilitate the identification of patients at highest and lowest risk of recurrence, particularly when used in conjunction with TILs (ie, high TILs + low proliferation in residual tumors being associated with the best prognosis, low TILs + high proliferation being associated with the worst prognosis).[53,64] Small studies also suggest that artificial intelligence–based proliferation evaluation in combination with TILs may improve the identification of patients with stage I TNBC at low risk of recurrence in the absence of adjuvant or neoadjuvant chemotherapy.[75-80]

Gene Signatures

Akin to genomic signatures used in hormone receptor–positive breast cancer to inform the use of cytotoxic chemotherapy, there have been efforts to develop prognostic and predictive genomic assays for TNBC. A promising assay is TNBC-DX, which incorporates a 10-gene core immune gene module and a 4-gene tumor cell proliferation signature, along with tumor size and nodal stage.[81] TNBC-DX generates two scores ranging from 0 to 100: a pCR score that predicts the probability of achieving a pCR after neoadjuvant chemotherapy and a risk score that predicts risk of distant recurrence or death. This assay has shown promise in retrospective analyses of prospective clinical trials for both end points. In the stage I TNBC setting, this and other gene signatures would have significant value if validated in the context of up-front surgery without adjuvant systemic therapy.

In addition, promising gene signatures include the response predictive subtypes (RPSs) and the ImPrint signatures developed from pretreatment gene expression profile data from the I-SPY2 clinical trial. RPS categorizes each breast cancer subtype (hormone receptor-positive HER2−, TNBC, and HER2+) into biologically distinct groups with variable responses to neoadjuvant systemic therapy. TNBC is classified into three subtypes: Immune-enhanced (Immune+), Immune-/DNA Repair–Deficient (DRD)+, and Immune-/DRD-. Although evaluable numbers were small, Immune+ tumors were characterized by high responses to immunotherapy (89% pCR), DRD+ tumors by high responses to poly(ADP-ribose) polymerase inhibitors (PARPi)/carboplatin (80% pCR), and Immune-/DRD- by low pCR rates overall (10%-20%).[82] A clinical grade immune classifier (ImPrint) incorporated into the RPS has been used within the I-SPY2 platform to predict response to immunotherapy regimens in the TNBC cohort.[83] While I-SPY only includes stage II/III disease, these signatures might have additional value for stage I TNBC to inform treatment decisions, particularly if prospectively validated in this population.

Optimization 3: Targeted Therapies in Select TNBC Subgroups

A promising treatment de-escalation approach is the use of neoadjuvant PARPi in patients with germline *BRCA* (*gBRCA*) mutations. PARPi are highly active in *gBRCA*-associated breast cancer, improving iDFS and OS in the adjuvant setting.[84] Several innovative studies have evaluated whether neoadjuvant PARPi with or without immunotherapy could offer a chemotherapy-free strategy for *gBRCA* mutation carriers. In a small pilot study (n = 20)[85] and the subsequent larger NEOTALA phase II trial (n = 61),[86] approximately half of patients receiving neoadjuvant single-agent talazoparib for six months achieved a pCR. Similar results were seen with single-agent niraparib[87] and with niraparib plus immunotherapy (dostarlimab) in the TBCRC 056 clinical trial.[88] These studies included patients with stage I-III TNBC. When focusing on patients with earlier-stage TNBC, pCR rates with this strategy have been much higher. In OlympiaN,[89] the pCR rate for patients with T1b/c N0 TNBC treated with 4-6 cycles of olaparib monotherapy was 68%, whereas the pCR rate for patients with T1N1 or T2N0 TNBC treated with 4-6 cycles of olaparib + durvalumab achieved an impressive pCR rate of 80%. Considering that patients with known *gBRCA* mutations undergoing high risk screening are diagnosed at earlier stages,[90-92] this strategy could offer the potential to completely avoid cytotoxic chemotherapy in a large proportion of patients with early-stage *gBRCA*-associated TNBC. Instead, cytotoxic chemotherapy could be reserved for those with

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residual disease after PARPi with or without immunotherapy. However, it is important to note that disease progression during neoadjuvant PARPi treatment has been reported at higher rates (approximately 15%) than typically observed with neoadjuvant chemotherapy,[86] highlighting the need for close monitoring and further investigation of this approach before routine use.

Optimization 4: Dynamic Assessment of Response

ctDNA

Historically, most breast cancer biomarkers have been assessed at isolated time points, either before or after completion of systemic therapy. The advent of minimally invasive and highly sensitive circulating tumor DNA (ctDNA) assays has offered the potential to evaluate the presence or absence of minimal residual disease and to evaluate dynamic changes of ctDNA levels during different phases of treatment. Detectable ctDNA after completion of neoadjuvant systemic therapy is strongly associated with a higher risk of recurrence, whereas clearance is associated with favorable outcomes.[93-95] Prospective studies determining whether acting on those results (ie, offering additional systemic therapy based on the presence or absence of ctDNA) are ongoing. A challenge in stage I TNBC is the anticipated lower rate of ctDNA positivity. In the Safe-De study, 45% of patients with stage I TNBC or HER2+ breast cancer were ctDNA-positive at diagnosis, but most cleared it after surgery.[96] It is unclear whether ctDNA negativity after surgery would allow safe omission of cytotoxic chemotherapy in this context. As more sensitive assays become available, their utility in stage I TNBC may become more prominent.

Imaging Assessment of Response to Neoadjuvant Therapy

In addition to ctDNA, evaluation of response to neoadjuvant systemic therapy using highly sensitive imaging (eg, magnetic resonance imaging [MRI] or positron emission tomography [PET]/computed tomography [CT]) is being evaluated in prospective trials such as I-SPY2.2 (ClinicalTrials.gov identifier: NCT01042379) and NeoADAPT (ClinicalTrials.gov identifier: NCT06245889). In these studies, patients receive an initial abbreviated course of systemic therapy followed by imaging assessment of response with either MRI (I-SPY2.2) or PET/CT (NeoADAPT) to assess likelihood of complete response and guide decisions regarding further neoadjuvant therapy versus surgery. While these studies are focused on stage II-III TNBC, these strategies would also be appealing for patients with T1c N0 treated neoadjuvantly and for whom the role of anthracyclines is still debated.

CONCLUSIONS

TNBC encompasses a range of molecularly distinct subtypes, each with differing responses to systemic therapy and outcomes. The need to tailor treatment approaches for individuals with TNBC is becoming increasingly evident. Notably, the data guiding the management of patients with stage I TNBC are largely derived from retrospective analyses or from prospective trials involving individuals with more advanced disease. Many efforts are underway to personalize and right-size systemic therapy for patients with stage I TNBC by using less intensive systemic therapies, targeted therapies with potentially reduced toxicity, and biomarkers that can inform clinical decision making beyond a simple anatomic stage.

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Personalizing Curative Therapy in Stage II to III Triple-Negative Breast Cancer

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OVERVIEW

The treatment paradigm of stage II to III triple-negative breast cancer (TNBC) is rapidly evolving, with the recent incorporation of pembrolizumab to neoadjuvant chemotherapy improving disease outcomes. Nevertheless, almost one in five patients with early-stage TNBC will relapse in 5 years, underscoring an urgent need to identify and improve outcomes for those at high risk of recurrence. Novel therapeutic strategies including antibody-drug conjugates, anti-vascular endothelial growth factor therapies, dual immune checkpoint blockade, and locoregional therapies to augment the antitumor immune response are being investigated in clinical trials. Biomarker strategies including tumor infiltrating lymphocytes, immune signatures, and circulating tumor DNA are being explored to identify patients at a high risk of relapse and to predict treatment response. In this article, we review recent advances in the management of stage II to III TNBC, highlight emerging investigational therapies and combinations, and explore novel biomarker strategies aimed at personalizing the care for patients with stage II to III TNBC.

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INTRODUCTION

Early-stage triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer with a higher risk of recurrence compared with the other breast cancer subtypes.[1] Treatment of early-stage TNBC involves a multidisciplinary approach incorporating chemotherapy plus immunotherapy, surgery, and possibly radiation therapy (RT). Neoadjuvant therapy is the preferred approach for stage II to III disease to downstage, monitor treatment response, and guide subsequent adjuvant therapies. The addition of pembrolizumab to neoadjuvant chemotherapy (NAC) is standard of care for stage II to III TNBC based on the KEYNOTE-522 trial, which demonstrated that the addition of pembrolizumab improved pathologic complete response (pCR), event-free survival (EFS), and overall survival (OS).[2-4] Despite recent advances in treatment, approximately 20% of patients with stage II to III TNBC will relapse within 5 years, highlighting an urgent need to improve outcomes for these patients.[4]

Novel therapeutic strategies to improve disease outcomes in early-stage TNBC are being investigated with a focus on escalation/de-escalation strategies according to the risk of recurrence. Biomarker strategies including tumor infiltrating lymphocytes (TILs), immune signatures, and circulating tumor DNA (ctDNA) are being explored in clinical trials to identify patients at a high risk of relapse and to predict treatment response. In this article, we review recent advances in the management of stage II to III TNBC, outline emerging investigational therapies and combinations, and highlight novel biomarker strategies aimed at personalizing care for patients with stage II to III TNBC.

ROLE OF IMMUNE CHECKPOINT INHIBITORS IN EARLY-STAGE TNBC

Pembrolizumab

Neoadjuvant and adjuvant pembrolizumab (an anti–PD-1 antibody) is standard of care for stage II to III TNBC based on the phase III KEYNOTE-522 trial.[2] The trial investigated the addition of pembrolizumab to NAC consisting of four cycles of paclitaxel/carboplatin followed by four cycles of an anthracycline (doxorubicin [A] or epirubicin [E]) plus cyclophosphamide (C). After surgery, patients received adjuvant pembrolizumab for up to nine cycles. The trial showed improved pCR rates with the addition of pembrolizumab to NAC (64.8% *v* 51.2%), and subgroup analysis showed benefit regardless of age, tumor size, nodal status, or PD-L1 status.[2] Final survival analyses demonstrated that the addition of pembrolizumab significantly improved 5-year EFS (81.2% *v* 72.2%) and OS (86.6% *v* 81.7%).[4]

Other Immune Checkpoint Inhibitors in the Neoadjuvant Setting

Phase III trials investigating other immune checkpoint inhibitors (ICIs) in the neoadjuvant setting in early TNBC have shown inconsistent long-term survival benefits. The IMpassion031 trial investigated the addition of preoperative

PRACTICAL APPLICATIONS

- Despite the rapidly evolving treatment paradigm of stage II to III triple-negative breast cancer (TNBC), almost one in five patients with early-stage TNBC will relapse in 5 years.
- The addition of pembrolizumab to neoadjuvant chemotherapy improves long-term disease outcomes for patients, regardless of PD-L1 status. However, the benefit of adjuvant pembrolizumab for patients who achieve a pathologic complete response remains unknown, while ongoing studies are examining escalation strategies for those with residual disease.
- Ongoing clinical trials are investigating novel therapeutic strategies including antibody-drug conjugates, anti-vascular endothelial growth factor therapies, dual immune checkpoint inhibitor blockade, and locoregional therapies to augment the antitumor immune response.
- Biomarkers ranging from tumor infiltrating lymphocytes, immune signatures, circulating tumor DNA, and the gut microbiome are being explored to predict treatment response and guide the potential escalation/de-escalation of therapies in early-stage TNBC, offering a promising approach to personalize therapy for patients.

atezolizumab (an anti–PD-L1 antibody) to NAC (nab-paclitaxel → AC) and showed improved pCR rates with the addition of atezolizumab (69% *v* 49%).[5] Numerical improvements in EFS, disease-free survival (DFS), and OS were observed; however, these did not meet statistical significance.[6] The phase III NSABP B-59/GBG-96-Gepar-Douze trial investigated the addition of perioperative atezolizumab to NAC (paclitaxel/carboplatin →AC) and showed improved pCR (63.3% *v* 57.0%) but failed to meet its primary end point of EFS.[7] In addition, the phase III NeoTRIP trial, which investigated the addition of neoadjuvant atezolizumab to carboplatin/nab-paclitaxel for eight cycles, followed by surgery and four cycles of an anthracycline regimen, failed to demonstrate both improved pCR or EFS.[8,9]

The addition of durvalumab (an anti-PD-L1 antibody) to NAC in early TNBC was evaluated in the randomized phase II GeparNuevo trial. Although the trial demonstrated a nonsignificant increase in pCR (53.4% *v* 44.2%), significant differences in 3-year invasive DFS (iDFS), distance DFS (DDFS), and OS were seen.[10,11]

Nivolumab (an anti–PD-1 antibody) was investigated in the phase II Neo-N trial, which compared a 2-week lead-in of nivolumab to concurrent nivolumab plus NAC in early TNBC. The trial showed no difference in pCR with lead-in versus concurrent nivolumab.[12] Notably, a pCR rate of 53% was achieved in all patients despite an anthracycline-free 12-week regimen.

Finally, the addition of the PD-1 inhibitor camrelizumab to NAC in early TNBC was investigated in the phase III CamRelief trial.[13] The trial showed that camrelizumab significantly improved pCR (56.8% *v* 44.7%), with long-term survival outcomes not mature at the time of presentation.[13]

Altogether, the lack of benefit in long-term disease outcomes with the other ICI agents compared with pembrolizumab may reflect differences in trial design, patient populations (eg, inclusion of higher-risk groups), chemotherapy backbones, and the use of adjuvant chemotherapies. Moreover, the various PD(L)-1 targeting agents may confer differential activity in early TNBC because of differences in targets and chemistry.[14] However, to date, there is no direct comparative evidence between the different ICIs in the neoadjuvant setting for TNBC.

Toxicity of ICI in Early-Stage TNBC

Although ICI improves the risk of recurrence and death in patients with early TNBC, ICI causes immune-related adverse events (irAE), which can often result in serious and long-term side effects for patients. In KEYNOTE-522, 35% of patients experienced irAE and 13.1% were grade 3 or higher events, including two deaths due to irAE.[4] Other real-world analyses report even higher rates of irAE ranging from 31% to 72.6%.[15-18] Endocrine irAE occur most frequently in patients with early TNBC, which is often a nonreversible side effect which can require life-long hormone replacement therapy. In the curative-intent setting, in which many patients with early TNBC will survive many years after their diagnoses, the potential long-term toxicities must be weighed against the potential benefit of ICI. Biomarker strategies to predict which patients will benefit from ICI and those which will experience increased toxicity is urgently needed.

Alternative ICI Dosing Strategies

Alternative dosing regimens of pembrolizumab are being explored to minimize toxicity and improve quality of life for patients while maintaining therapeutic efficacy. Weight-based dosing was initially explored in clinical trials and demonstrated similar pharmacokinetic data to flat dosing regimens, with current studies investigating how weight-based dosing may affect efficacy, toxicity, and cost.[19-23] Extended-interval dosing of pembrolizumab (400 mg once every 6 weeks) is also available across solid tumor indications and appears safe and effective in patients with breast cancer.[24,25] In addition, a lower dose of pembrolizumab (50 mg once every 6 weeks) added to NAC in early TNBC was recently evaluated in the phase II PLANeT trial.[26] This study demonstrated a 13.3% absolute benefit in pCR with low-dose

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pembrolizumab, which is a comparable benefit to standard dose (200 mg once every 3 weeks) pembrolizumab in the KEYNOTE-522 trial, suggesting that a lower dose may be possible for patients.

OPTIMIZING THE NEOADJUVANT TREATMENT REGIMEN

Role of Carboplatin

The role of carboplatin in early-stage TNBC has been debated because of inconsistent long-term benefit despite improved pCR rates across trials. In a pooled analysis of three randomized trials (BrighTNess, CALGB 30603, and GeparSixto) evaluating the addition of carboplatin to the neoadjuvant regimen in early TNBC, carboplatin was associated with improved pCR and EFS but not OS.[27] In a randomized, single-center, phase III trial evaluating the addition of neoadjuvant carboplatin to paclitaxel followed by AC in early-stage TNBC, pCR and OS were significantly higher in the carboplatin arm, although no difference in EFS was observed.[29] Interestingly, subgroup analyses reported improved EFS and OS in premenopausal or younger (≤50 years) women with the addition of carboplatin.[29] In the adjuvant setting, most phase III trials evaluating the addition of carboplatin (PATTERN, CITRINE, RJBC-1501, and PEARLY) in early-stage TNBC showed improved DFS, with the exception of NRG-BR003.[30-34] Overall, these data support the use of carboplatin in the treatment of stage II to III TNBC.

Role of Anthracyclines

In the modern era of ICI, the role of anthracyclines in early TNBC remains uncertain. Before ICI, the EBCTCG patient-level meta-analysis demonstrated that the addition of anthracyclines to a taxane-based regimen in early breast cancer reduced recurrence rates by 14%.[35] Similarly, analysis of the ABC study suggested an even greater benefit of anthracycline-containing regimens in TNBC, which confirmed the role of anthracyclines in TNBC.[36] However, anthracyclines cause a small but increased risk of cardiomyopathy and secondary leukemia-myelodysplastic syndrome. As a result, in the ABC trials, no improvement in OS was observed likely because of increases in leukemias and deaths unrelated to breast cancer.[36]

As a tailored chemotherapy strategy in early TNBC, several phase II trials have investigated anthracycline-free neoadjuvant chemo-immunotherapy regimens in early-stage TNBC. For example, the phase II Neo-N trial evaluated nivolumab (both as a lead-in and concurrently) combined with neoadjuvant carboplatin plus paclitaxel for 12 weeks and reported a pCR rate of 53% in all patients.[12] In addition, the single-arm NeoPACT study investigated neoadjuvant pembrolizumab plus carboplatin and docetaxel for six cycles and reported a pCR rate of 58% and 3-year EFS of 86%[37] and informed the ongoing phase III SCARLET trial (ClinicalTrials.gov identifier: NCT05929768) comparing the NeoPACT regimen to the KEYNOTE-522 regimen in early TNBC.

Emerging Combination Strategies in the Neoadjuvant Setting

Antibody-Drug Conjugates

In metastatic TNBC (mTNBC), antibody-drug conjugates (ADCs) have proven more effective compared with conventional chemotherapy. In the phase III ASCENT-03 trial and the TROPION-Breast02 trials, sacituzumab govitecan (SG) and datopotamab-deruxtecan (Dato-DXd), respectively, significantly improved progression-free survival (PFS) compared with chemotherapy in first-line mTNBC in patients ineligible for anti–PD(L)-1 therapy.[38,39] In addition, the phase III ASCENT-04 trial demonstrated improved PFS with SG plus pembrolizumab compared with chemotherapy plus pembrolizumab in first-line PD-L1–positive mTNBC.[40] Collectively, these studies highlight the superior clinical activity of ADCs compared with chemotherapy, supporting their integration earlier in the disease course.

In early-stage human epidermal growth factor receptor 2 (HER2)–negative (HER2–) breast cancer, the phase II multiarm I-SPY2.2 trial investigated neoadjuvant Dato-DXd plus durvalumab.[41] The sequential adaptive trial design included three blocks of treatment: the experimental agent in block A (Dato-DXd plus durvalumab for four cycles), followed by a taxane-based regimen (block B), followed by AC (block C). Overall, the trial resulted in a pCR rate of 50% across all blocks. Notably, of patients with the HER2–immune+ subtype, 54% achieved pCR following Dato-DXd plus durvalumab alone.[41]

ADCs are also being explored to rescue patients from suboptimal responses to standard chemo-immunotherapy. In the phase II NeoSACI-IO trial, patients with stage II to III TNBC who experienced suboptimal responses (≤80% tumor volume reduction) to paclitaxel/carboplatin plus pembrolizumab for four cycles subsequently received SG plus pembrolizumab for four cycles. The trial showed a pCR rate of 48% versus 20% in historical controls.[42]

Together, these studies support several ongoing phase III trials investigating ADCs plus ICI in patients with early TNBC (Table 1).

Anti-Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) plays a key role in tumor angiogenesis and leads to immune suppression within the tumor microenvironment (TME).[43] Preclinical studies demonstrate that anti-VEGF can overcome angiogenesis-induced immunosuppression by promoting immune cell infiltration and activating T cells, thereby improving ICI responses.[44] The combination of ICI plus anti-VEGF is approved for several cancer types, including metastatic renal cell carcinoma (RCC), non–small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), and endometrial cancer, with promising efficacy in mTNBC.[45-50]

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TABLE 1. Ongoing Phase III Trials in Stage II to III TNBC

Trial ID	Population	No.	Regimen	Trial Status	Primary End Point
Neoadjuvant					
SCARLET (NCT05929768)	Stage II to III TNBC	2,400	Carboplatin + docetaxel + pembrolizumab *v* carboplatin + paclitaxel + pembrolizumab followed by AC + pembrolizumab	Recruiting	EFS
TROPION-Breast04 (NCT06112379)	Stage II to III TNBC or HR-low/HER2-negative breast cancer	1,728	Dato-DXd + durvalumab *v* chemotherapy + pembrolizumab	Active, not recruiting	EFS
Trofuse-032 (NCT06966700)	High-risk, early-stage TNBC or HR-low/HER2-negative breast cancer	2,400	Sac-TMT + pembrolizumab *v* chemotherapy + pembrolizumab	Recruiting	pCR, EFS
ADAPT-TN-III (NCT06081244)	Stage I (clinical stage II only if patient does not qualify for neoadjuvant chemo-immunotherapy)	348	SG *v* SG + pembrolizumab	Recruiting	pCR, IDFS
ADAPT-TN-IV (NCT07178730)	Stage II to III TNBC	765	SG + pembrolizumab *v* chemotherapy + pembrolizumab	Not yet recruiting	pCR, EFS
NordicTrip (NCT04335669)	Stage II to III TNBC	325	Platinum-based chemotherapy + pembrolizumab *v* platinum-based chemotherapy with capecitabine + pembrolizumab	Active, not recruiting	pCR
BCTOP-T-N01 (NCT05999149)	Stage II to III TNBC	424	Camrelizumab + chemotherapy + famitinib *v* camrelizumab + chemotherapy	Recruiting	pCR
BCTOP-T-A03 (NCT05909332)	Stage II to III TNBC	764	BP102 + chemotherapy *v* chemotherapy	Recruiting	IDFS
NCT06627712	Stage II to III TNBC	318	SBRT (24 Gy in 3 fx) + PD-1 inhibitor + chemotherapy *v* chemotherapy + PD-1 inhibitor	Recruiting	pCR
NCT04137653	Early-stage TNBC with positive axillary lymph node metastasis	1,498	Nab-paclitaxel + carboplatin *v* paclitaxel + carboplatin	Recruiting	pCR
NCT04301739	Stage II to III TNBC	522	HLX10 + chemotherapy *v* chemotherapy	Not yet recruiting	pCR
Adjuvant					
pCR					
OptimeICE-pCR (NCT05812807)	Stage II to III TNBC with pCR after NAT	1,295	Pembrolizumab *v* observation	Recruiting	RFS
OPT-PEMBRO (NCT06606730)	Stage II to III TNBC with pCR after NAT	2,454	Pembrolizumab *v* observation	Recruiting	RFS
Residual disease					
SWOG 1418 (NCT02954874)	High-risk, early-stage TNBC with residual disease after NAT (no prior immunotherapy)	1,155	Pembrolizumab *v* observation	Active, not recruiting	IDFS
SASCIA (NCT04595565)	HER2-negative breast cancer with residual disease after NAT	1,332	SG *v* chemotherapy	Active, not recruiting	IDFS
ASCENT-05/OptimICE-RD (NCT05633654)	Stage II to III TNBC with residual disease after NAT	1,514	SG + pembrolizumab *v* pembrolizumab ± capecitabine	Recruiting	IDFS
TROPION-Breast03 (NCT05629585)	Stage I to III TNBC with residual disease after NAT	1,174	Dato-DXd + durvalumab *v* investigator's choice (capecitabine, pembrolizumab, or capecitabine + pembrolizumab)	Active, not recruiting	IDFS
TroFuse-012 (NCT06393374)	High-risk, early-stage TNBC with residual disease after NAT	1,530	Sac-TMT + pembrolizumab *v* pembrolizumab ± capecitabine	Recruiting	IDFS

(continued on following page)

TABLE 1. Ongoing Phase III Trials in Stage II to III TNBC (continued)

Trial ID	Population	No.	Regimen	Trial Status	Primary End Point
NCT06313463	Early-stage TNBC with residual disease after NAT and tertiary lymphoid structure	375	Camrelizumab + capecitabine *v* capecitabine	Recruiting	DFS
NCT06533384	Stage II to III TNBC with residual disease after NAT	310	Fuzuloparib (if germline *BRCA1/2* mutation carrier) or capecitabine (if without a germline *BRCA1/2* mutation) + camrelizumab *v* camrelizumab	Recruiting	IDFS
NCT07021261	Early-stage TNBC with residual disease after NAT	440	Utidelone + capecitabine *v* capecitabine	Not yet recruiting	3-year IDFS
Independent of pathologic status after NAT					
BCTOP-T-A02 (NCT05862064)	Stage II to III TNBC with lymph node metastasis (no prior NAT)	606	Camrelizumab + famitinib + chemotherapy *v* chemotherapy	Recruiting	IDFS
GLORIA (NCT03562637)	High-risk, early-stage Globo H-positive TNBC	575	Adagloxad simolenin + OBI-821 + SOC *v* SOC (observation, capecitabine, or ICI)	Active, not recruiting	IDFS
NCT06795503	Early-stage TNBC with low-risk disease according to the mRNA-lncRNA model (no prior NAT)	1,462	TC *v* EC-P	Not yet recruiting	IDFS

Abbreviations: AC, doxorubicin plus cyclophosphamide; Dato-DXd, datopotamab deruxtecan; DFS, disease-free survival; EC-P, epirubicin, cyclophosphamide followed by paclitaxel; EFS, event-free survival; fx, fraction; Gy, gray; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICI, immune checkpoint inhibitor; IDFS, invasive disease-free survival; NAT, neoadjuvant therapy; PARPi, PARP inhibitors; pCR, pathologic complete response; RFS, recurrence-free survival; sac-TMT, sacituzumab tirumotecan; SBRT, stereotactic body radiotherapy; SG, sacituzumab govitecan; SOC, standard of care; TC, docetaxel plus cyclophosphamide; TNBC, triple-negative breast cancer.

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In early-stage TNBC, the single-arm, phase II NeoPanDa03 trial investigated neoadjuvant camrelizumab (anti–PD-1 antibody), apatinib (a VEGFR-2 inhibitor), and chemotherapy and demonstrated that the combination was safe and effective with a pCR rate of 67.6%.[51] Preliminary results from a phase II trial investigating the neoadjuvant combination of anlotinib (an antiangiogenic tyrosine kinase inhibitor), tislelizumab (anti–PD-1 antibody), and chemotherapy in early TNBC demonstrated a similar pCR rate of 68.4%.[52] A window-of-opportunity trial (BRE-03, ClinicalTrials.gov identifier: NCT04427293) is ongoing investigating lenvatinib plus pembrolizumab in early TNBC with the primary end point of infiltration of $CD8^+$ T cells. This study will hopefully shed light on how the anti-VEGF plus ICI combination modulates the TME in early TNBC.

Novel bispecific antibodies targeting PD-1/PD-L1 and VEGF pathways have also demonstrated encouraging activity when combined with chemotherapy in phase II trials in 1L mTNBC.[53,54] A phase II trial of neoadjuvant ivonescimab (a novel bispecific antibody targeting PD-1 and VEGF) combined with carboplatin plus docetaxel in patients with early-stage TNBC is currently enrolling (ClinicalTrials.gov identifier: NCT07017673).

Poly (ADP-ribose) Polymerase Inhibitors

The combination of Poly (ADP-ribose) polymerase (PARP) inhibitors with ICI is being explored given the immunomodulatory effects of PARP inhibition. Specifically, PARP inhibitors induce DNA damage and genomic instability leading to increased neoantigens which promotes a proinflammatory TME.[55,56] Early phase trials investigating PARP inhibitors plus ICI in mTNBC have demonstrated modest synergistic activity, with relatively similar efficacy compared with PARP inhibitor monotherapy.[57,58]

In stage II to III HER2– breast cancer, the I-SPY2 trial investigated the combination of durvalumab/olaparib/paclitaxel (DOP) followed by AC compared with paclitaxel followed by AC.[59] The trial showed that DOP increased pCR rates from 20% to 37% in all patients, with an increase in pCR from 27% to 47% in TNBC.[59] In addition, the phase II TBCRC-056 trial evaluated a chemotherapy-free neoadjuvant regimen of niraparib plus dostarlimab in patients with germline *BRCA1/2* or *PALB-2* mutated early-stage HER2– breast cancer. In the TNBC cohort, the trial showed an encouraging pCR rate of 50% with this chemotherapy-free approach.[60]

Dual ICI

ICIs targeting other immune checkpoint proteins beyond PD-1/PDL-1 have been developed including CTLA-4, LAG-3, and TIGIT, among others. Dual ICI blockade with anti–PD-1/PD-L1 and anti–CTLA-4 antibodies is currently approved in other metastatic solid tumors, including melanoma, RCC, NSCLC, and HCC. In metastatic breast cancer, dual ICI has not resulted in significant benefit, although exceptional responses in select patients have been observed.[61-63]

In early-stage HER2– breast cancer, the I-SPY2 trial demonstrated that the combination of REGN3767 (anti-LAG-3), cemiplimab (anti–PD-1), and paclitaxel followed by AC improved pCR rates compared with the chemotherapy-alone arm, along with the cemiplimab and paclitaxel arm.[64] Notably, patients with an immune+ signature had high pCR rates from both monotherapy and dual ICI combinations (REGN3767 + cempilimab + paclitaxel: 91%; cemiplimab + paclitaxel: 84%). The dual ICI combination showed higher rates of irAE (any-grade: 53%) compared with that seen in monotherapy trials, with 21% of patients developing adrenal insufficiency/hypophysitis.[64]

The phase II adaptive BELLINI trial investigated neoadjuvant dual ICI (ipilimumab/nivolumab) for two cycles without chemotherapy in patients with early TNBC and ≥50% TILs.[65] The trial demonstrated a pCR rate of 33.3% from this chemotherapy-free regimen in this selected cohort.[65] A higher rate of endocrine irAE was also observed, with 40% of patients developing hypothyroidism and 20% developing adrenal insufficiency.

Locoregional Therapies

Preclinical studies demonstrate that local ablative therapies such as RT or cryoablation can transform cold tumors into hot ones to improve ICI efficacy.[66] In a phase II trial of patients with mTNBC unselected for PD-L1 expression, combining pembrolizumab with RT demonstrated modest but encouraging activity, with durable responses observed in a subset of patients.[67]

In early TNBC, the phase Ib/II PEARL trial investigated the addition of preoperative RT to pembrolizumab, followed by NAC in early HER2– breast cancer.[68] Despite the lack of pembrolizumab during NAC, the combination of preoperative RT with pembrolizumab followed by NAC demonstrated a pCR rate of 59.2% in TNBC and 33.3% for hormone receptor–positive (HR+)/HER2– breast cancer.[68] The phase II P-RAD trial (ClinicalTrials.gov identifier: NCT04443348) is currently ongoing investigating the addition of two dosing strategies of RT to pembrolizumab followed by NAC with pembrolizumab.

The use of cryoablation (the process of freezing cancer cells to destroy them) also has immunologic effects.[69] Specifically, the freeze-thaw process of cryoablation releases nondenatured tumor neoantigens triggering an antitumor effect.[69] The combination of cryoablation combined with ICI was evaluated in a phase II study in patients with early TNBC with residual disease following NAC.[70] Patients received one dose of dual ICI (ipilimumab/nivolumab) before cryoablation, followed by adjuvant nivolumab for three cycles. The trial demonstrated an improved 3-year EFS of 66.7% compared with the historical landmark of chemotherapy

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alone. This suggests that local ablative therapies may boost ICI responses, allowing for potential ICI de-escalation strategies.

PERSONALIZING THERAPY IN THE ADJUVANT SETTING

De-escalation Strategies for pCR

A pCR following NAC is a robust prognostic marker of improved DFS and OS in early-stage TNBC.[71] In KEYNOTE-522, patients who achieved a pCR had a 36-month EFS rate of 94.4% compared with 67.4% for those with residual disease.[3] As such, pCR is often used as a surrogate end point in clinical trials indicating improved long-term disease outcomes, allowing for the potential de-escalation of adjuvant therapy.

In KEYNOTE-522, patients received neoadjuvant pembrolizumab followed by adjuvant pembrolizumab regardless of pCR status, leading to improved EFS.[72] However, the benefit of the neoadjuvant versus adjuvant portion of pembrolizumab remains unclear. Preclinical studies demonstrate that neoadjuvant administration of ICI with the tumor intact enhances the tumor antigen reservoir and promotes antitumor immunity.[73] Accordingly, a phase II trial in resectable melanoma demonstrated decreased recurrence with neoadjuvant-adjuvant pembrolizumab compared with an adjuvant-only strategy.[74]

In breast cancer, trials investigating neoadjuvant-only ICI (eg, GeparNuevo) have demonstrated improved EFS, while several trials investigating adjuvant-only ICI (eg, IMpassion030 and A-BRAVE) have failed to show improved IDFS.[11,75,76] These findings suggest that adjuvant ICI may not be necessary for patients following neoadjuvant chemo-immunotherapy, particularly in patients who achieve a pCR. Several phase III trials are investigating the de-escalation of adjuvant pembrolizumab in patients who achieve pCR following neoadjuvant chemo-immunotherapy, including OptimeICE-pCR (ClinicalTrials.gov identifier: NCT05812807) and Opt-PEMBRO (ClinicalTrials.gov identifier: NCT06606730).

Escalation Strategies for Residual Disease

In KEYNOTE-522, patients with residual disease had significantly worse prognoses compared with those with pCR, with the extent of disease as measured by the residual cancer burden (RCB) correlating with recurrence risk. Specifically, patients with RCB-1, RCB-2, and RCB-3 had 36-month EFS of 84.4%, 75.7%, and 26.2%, respectively, following neoadjuvant chemo-immunotherapy.[77] Given the high risk of recurrence with residual disease, escalation strategies with additional therapies are needed to improve disease outcomes.

Oral capecitabine is standard of care for patients with TNBC and residual disease following NAC based on the phase III CREATE-X trial.[78] The trial investigated adjuvant capecitabine in patients with HER2− breast cancer and showed improved DFS and OS in all patients; however, subgroup analysis demonstrated that the benefit in DFS and OS was largely driven by TNBC.[78] Although KEYNOTE-522 did not allow for adjuvant capecitabine (as it was not standard therapy at the time of trial design), it is common practice to combine adjuvant pembrolizumab with capecitabine for patients with residual disease. Two phase II trials demonstrated that the combination of pembrolizumab plus capecitabine in the metastatic setting is safe to use.[79,80]

Patients with *BRCA1* or *BRCA2* mutations are also eligible to receive adjuvant olaparib based on the phase III OlympiA trial.[81,82] The trial investigated adjuvant olaparib for 1 year in high-risk *BRCA1/2* mutation carriers with HER2− breast cancer and demonstrated a significant reduction in recurrence and death, with the benefit consistent across HR+ and TNBC. Given the combination of pembrolizumab and olaparib is also considered safe, pembrolizumab plus olaparib can be combined in the adjuvant setting.[57–59] The optimal strategy with respect to olaparib versus capecitabine for *BRCA1/2* mutation carriers with residual disease is not known. Nevertheless, sequencing olaparib first is often recommended because of the survival benefit observed in *BRCA1/2* mutation carriers.

For patients who received up-front NAC or those with presumed stage I TNBC who were upstaged at the time of surgery, the question remains whether these patients benefit from adjuvant ICI. Impassion030 investigated the addition of adjuvant atezolizumab to chemotherapy in patients with stage II to III TNBC and showed no improvement in IDFS.[75] Similarly, the A-BRAVE trial investigated adjuvant avelumab in patients with early TNBC who received (neo)adjuvant chemotherapy and demonstrated no improvement in the primary end point of DFS.[76] However, avelumab was associated with a significant improvement in DDFS and OS.[76] The phase III SWOG S1418 (ClinicalTrials.gov identifier: NCT02954874) trial is ongoing to investigate the benefit of adjuvant pembrolizumab in patients with early TNBC with residual disease following NAC.

In addition to ADCs ± ICIs being explored in the neoadjuvant setting, several ongoing phase III trials are evaluating the combination of ADC ± ICI as an escalation strategy in the adjuvant setting for patients with residual disease to improve the risk of recurrence (Table 1).

Biomarker Strategies

While the KEYNOTE-522 regimen is standard of care for all patients with stage II to III TNBC, some individuals may be overtreated by this regimen resulting in unnecessary toxicity, while others may benefit from additional therapies to further decrease recurrence risk. Currently, there is no US Food and Drug Administration–approved biomarker to predict which patients with early-stage TNBC will benefit from the addition of immunotherapy to chemotherapy nor to refine the specific treatment regimen for patients. Ongoing

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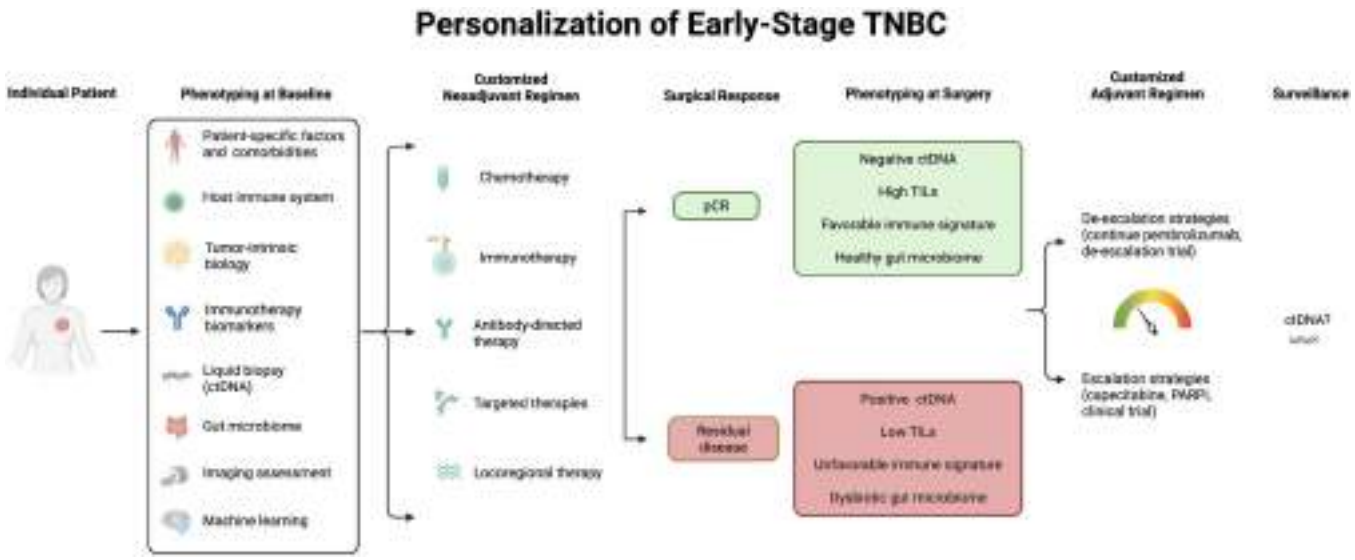

FIG 1. Personalizing therapy in neoadjuvant and adjuvant setting. Figure created with BioRender (Toronto, Canada). ctDNA, circulating tumor DNA; PARPi, poly (ADP-ribose) polymerase inhibitors; pCR, pathologic complete response; TILs, tumor-infiltration lymphocytes; TNBC, triple-negative breast cancer.

studies are exploring novel biomarkers in early-stage TNBC to better individualize neoadjuvant and adjuvant therapy regimens for patients (Fig 1).

PD-L1

Although PD-L1 positivity (combined positive score ≥ 10) is predictive of pembrolizumab benefit in mTNBC,[83] the KEYNOTE-522 trial demonstrated improved outcomes with pembrolizumab in early TNBC regardless of PD-L1 expression.[2] However, higher rates of pCR were observed for PD-L1–positive tumors following NAC with or without immunotherapy.[2] Similarly, trials of other ICIs (eg, Impassion031 and GeparNuevo) in early TNBC also demonstrated benefit of ICI regardless of PD-L1 expression.[5,11] The differential value of PD-L1 as a biomarker in early TNBC compared with mTNBC may be due to its more immunogenic TME, potentially allowing for a more robust ICI response.[84] The reliability of PD-L1 to predict ICI benefit may also be affected by the utilization of different scoring criteria among the various PD-L1 assays.[85]

Tumor Mutational Burden

Tumor mutational burden (TMB) is approved as a tissue-agnostic biomarker for pembrolizumab based on the association of high TMB (≥10 mutations/megabase) with ICI responses.[86] TMB is a marker of genomic instability, which leads to increased neoantigens resulting in a stronger antitumor immune response.[87] In an exploratory analysis of KEYNOTE-522, although TMB-high was rare (<5% of patients) in early-stage TNBC, TMB-high was associated with improved pCR and EFS in those who received pembrolizumab.[88] Conversely, TMB-high did not predict EFS in the chemotherapy alone arm. Likewise, the GeparNuevo trial of neoadjuvant durvalumab in early TNBC also demonstrated an association with a higher TMB and pCR.[89]

Tumor Infiltrating Lymphocytes

High baseline TILs are strongly prognostic in early TNBC. In a pooled analysis of patients with early TNBC treated with chemotherapy, each 10% increment in TILs was associated with decreased recurrence and improved OS.[90] High TILs is also associated with improved prognosis in patients with early TNBC treated without chemotherapy, with patients with TILs ≥ 50% demonstrating 5-year OS rates of 95%.[91] Furthermore, TILs has been shown to predict pCR following NAC with or without immunotherapy.[37,92,93]

TILs are currently being investigated as a biomarker strategy to guide intensification of therapy. For stage I TNBC, the EORTC 2275/OPTImal (ClinicalTrials.gov identifier: NCT06476119) and ETNA (ClinicalTrials.gov identifier: NCT06078384) trials are evaluating the role of TILs to potentially omit adjuvant chemotherapy. For stage I (T > 1 cm) to III TNBC, the phase II neoTRACT trial is investigating the use of TILs to guide neoadjuvant chemo-immunotherapy. Specifically, for TILs ≥ 30%, patients will receive carboplatin/docetaxel + pembrolizumab for 4-6 cycles depending on treatment response. For TILs 5%-29%, patients will receive carboplatin/docetaxel + pembrolizumab for six cycles. For TILs <5%, patients will receive the KEYNOTE-522 regimen.

Among patients with residual disease following NAC, TILs in the residual tissue (RD-TILs) also holds prognostic value. In a pooled analysis of the GBG/AGO-B trials in early TNBC, the combination of high RD-TILs and low Ki67 in the residual tumor was associated with improved DDFS and OS.[94] In

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addition, the A-BRAVE trial demonstrated that both baseline and RD-TILs predicted efficacy of adjuvant avelumab.[95] Avelumab improved 3-year DDFS in patients with baseline TILs ≥30%, but not in those with baseline TILs <30%. However, in patients with baseline TILs <30%, avelumab improved DDFS in RD-TILs <10% but not RD-TILs ≥10% (although DDFS events were small in this group).[95] Together, these studies highlight the prognostic and predictive value of both baseline and RD TILs, supporting their potential use as a biomarker to tailor neoadjuvant and adjuvant therapies.

Circulating and Intratumoral Immune Profiling

Circulating and intratumoral immune compositions beyond TIL density may further inform treatment responses in early TNBC. Peripheral markers, such as absolute lymphocyte count (ALC) and neutrophil-to-lymphocyte ratio (NLR), may reflect systemic immune status and have been associated with improved prognosis in patients with early TNBC.[96–98] Peripheral immune profiling of patients with early TNBC undergoing neoadjuvant chemoimmunotherapy also demonstrates that proinflammatory profiles characterized by higher levels of $CD4^+$ and $CD8^+$ T cells, regulatory T cells, and B cells are associated with higher rates of pCR.[99–101] Similarly, within the TME, multiomics analyses show that an abundance of proinflammatory immune subsets is associated with pCR.[102] Furthermore, spatial organization and proximity of immune cells relative to tumor cells also plays a critical role in influencing antitumor immune responses.[103] Overall, these studies demonstrate that comprehensive profiling of the systemic and intratumoral immune landscape may further enhance prediction modeling in early TNBC.

Immune Signatures

Several immune gene signatures have been developed to predict ICI responses in breast cancer including the DetermaIO, ImPrint, and TcellingGEP signatures. DetermalIO is a 27-gene RT-qPCR–based assay that was validated as a biomarker of ICI responses in early breast cancer using data from the neoTRIP and I-SPY2 randomized trials.[104] In both trials, DetermalIO predicted pCR rates from neoadjuvant immunotherapy rather than chemotherapy alone. The mRNA-based 53-gene ImPrint assay is another immune signature developed through the I-SPY2 trial.[105] In patients with HER2– breast cancer treated with pembrolizumab, the ImPrint assay demonstrated a sensitivity of 94% and specificity of 84% for predicting pCR.[105] Finally, the 18-gene T-cell–inflamed gene expression profile (TcellinfGEP) was evaluated as a predictor of pCR in an exploratory biomarker analysis of KEYNOTE-522.[88] The trial showed that TcellinfGEP was associated with improved pCR and EFS in both treatment arms (eg, with and without pembrolizumab), suggesting that TcellinfGEP is prognostic but not predictive of pembrolizumab benefit.[88]

Circulating Tumor DNA

In patients with early TNBC undergoing neoadjuvant therapy, clearance of ctDNA is associated with improved survival outcomes and can further refine risk stratification beyond pCR status.[6,106–113] In the Impassion-031 trial, 94% of patients with stage II to III TNBC were ctDNA-positive at baseline and 87% cleared ctDNA after neoadjuvant therapy.[6] All patients who achieved pCR had negative ctDNA at surgery. Among those with residual disease, ctDNA positivity at surgery was associated with worse prognosis. Similarly, in an ancillary ctDNA study using samples from the I-SPY2 trial, patients with residual disease and ctDNA-positivity had a significantly increased risk of recurrence, whereas clearance of ctDNA among those with residual disease was associated with improved survival outcomes similar to those who achieved pCR.[113]

In the adjuvant setting, ctDNA positivity is also associated with worse prognosis and often signals metastatic disease at the time of detection. In the phase II randomized OXEL trial, which investigated adjuvant nivolumab, capecitabine or the combination in patients with residual TNBC following NAC, clearance of ctDNA during adjuvant therapy was associated with improved prognosis, whereas all patients with persistent ctDNA positivity developed distant recurrence.[114] In the phase II c-TRAK trial, which included moderate- and high-risk TNBC to assess the utility of ctDNA surveillance in guiding therapy, a high rate of metastatic disease (72%) was identified at the time of ctDNA detection.[115] Likewise, the phase III randomized ZEST trial, which enrolled patients with early-stage breast cancer and positive ctDNA after the completion of curative intent therapy, was terminated early because of a low rate of ctDNA positivity (12%) and a high rate of metastatic disease (49%) at the time of ctDNA positivity.[116]

Several ongoing trials in early TNBC including ASPRIA (ClinicalTrials.gov identifier: NCT04434040), Apollo (ClinicalTrials.gov identifier: NCT04501523), and Artemis (ClinicalTrials.gov identifier: NCT04803539) are exploring whether intensification of therapy can improve outcomes in patients with positive ctDNA.

Gut Microbiome

Emerging studies have shown that the gut microbiome can affect cancer outcomes by influencing gut barrier integrity, modulating the immune system, and producing gut-derived microbial metabolites.[117] The gut microbiome also influences ICI efficacy by playing a critical role in the development of both the innate and adaptive immune system. Studies across multiple cancer types demonstrate that the gut microbiome can predict ICI responses, with specific bacteria such as *Akkermansia muciniphila* associated with improved ICI responses.[118]

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In early breast cancer, bacterial diversity and specific bacterial species before treatment have been shown to influence pCR to chemotherapy.[119,120] Several preclinical and clinical studies have also found a link between specific gut microbial compositions and improved ICI responses in early breast cancer.[121-125] Additional studies are needed to better understand the role of the gut microbiome as a biomarker and potential therapeutic strategy to improve treatment responses in early TNBC.

Early Imaging to Predict pCR

Imaging during neoadjuvant therapy can be an early indicator of treatment response and guide subsequent therapies. In early TNBC, midtreatment magnetic resonance imaging (MRI) has been shown to predict pCR following chemotherapy alone.[126-130] In a prespecified exploratory analysis of KEYNOTE-522, an objective response on midtreatment MRI during neoadjuvant chemo-immunotherapy was associated with more than 14-fold (by RECIST v1.1) and 9-fold (by functional tumor volume) increase in the odds of pCR.[131] Given the strong association with midtreatment MRI and pCR, the adaptive I-SPY2 trial incorporates midtreatment MRI with core biopsy to determine response and guide subsequent treatment strategies.

Machine Learning

The advent of artificial intelligence technology such as machine learning offers a promising approach to personalize cancer therapy. Deep learning, a type of machine learning, extracts patterns from complex data using layered neural networks to train itself and make future predictions. This technology holds the potential to incorporate numerous clinical factors and biomarkers in prediction models to guide treatment decision making. Studies are exploring the role of machine learning to predict treatment response in early TNBC. For example, studies using MRI imaging were able to predict histologic components and treatment response using deep learning models.[129,132-138] In addition, machine learning analysis can recognize certain biomarker features within the TME from digitized hematoxylin and eosin tissue slides and predict treatment response.[135-137] Models incorporating multimodalities including imaging assessments and clinicopathologic biomarkers are being explored, offering the potential to fully individualize treatment plans for patients.[138]

CONCLUSION

The addition of pembrolizumab to NAC significantly improved disease outcomes for patients with early-stage TNBC. However, there remains an urgent need to identify and improve disease outcomes for patients with high-risk TNBC while minimizing treatment-related toxicity. Ongoing trials are investigating novel combination strategies both in the neoadjuvant and adjuvant setting, with a focus on tailoring therapy according to recurrence risk. Biomarker strategies including TILs, ctDNA, and immune signatures are being explored to guide the selection and intensification of therapy. Ultimately, a multimodality biomarker-driven approach to predict treatment response holds the potential to fully personalize therapy and improve outcomes for patients with early-stage TNBC.

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

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Advanced Triple-Negative Breast Cancer: Emerging Therapies and a Changing Treatment Landscape

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OVERVIEW

Triple-negative breast cancer (TNBC) is characterized by the lack of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 overexpression. Historically, treatment options for TNBC have been limited, because of the absence of actionable targets. The addition of immune checkpoint inhibitors to chemotherapy improved outcomes for a subset of patients with metastatic PD-L1–positive disease; however, a critical need for more effective therapies remains. Antibody-drug conjugates (ADCs) have been a promising advance in the management of advanced TNBC and are reshaping the landscape as they move earlier into the treatment algorithm. A greater understanding of the molecular heterogeneity of TNBC has enabled the pursuit of more targeted and personalized therapeutic strategies. Despite this, TNBC continues to have the least favorable outcomes compared with other breast cancer subtypes. This review highlights current evidence and future challenges in advanced TNBC, including optimizing therapeutic sequencing and the ongoing need for predictive biomarkers and novel agents.

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INTRODUCTION

Triple-negative breast cancer (TNBC) represents approximately 15% of breast cancer diagnoses and is defined by the absence of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) overexpression.[1] Clinically, TNBC is associated with an aggressive disease course and inferior outcomes compared with other breast cancer subtypes, with a disproportionate burden of early relapse and mortality.[1,2] For decades, the management of metastatic TNBC relied almost exclusively on cytotoxic chemotherapy, because of the lack of actionable targets available. Advances in the molecular characterization of TNBC have since revealed distinct biologic subtypes, resulting in the development and approval of targeted therapies for certain patient populations, such as poly(ADP-ribose) polymerase inhibitors (PARPi) for patients with germline *BRCA* (gBRCA) mutations.[3-6] The addition of immune checkpoint inhibitors (ICIs) to chemotherapy in the frontline setting represented a further advance for a subset of patients with PD-L1–positive metastatic TNBC.[7] Despite these developments, improvements in overall survival (OS) for metastatic TNBC have remained limited relative to other metastatic breast cancer subtypes, driving efforts to further improve outcomes.[8] Antibody-drug conjugates (ADCs), particularly trophoblast cell-surface antigen 2 (TROP2)-targeted agents, have emerged as an important therapeutic class in metastatic TNBC and are moving into the first-line space.[9-13] In this review, we discuss recent advances and evolving therapeutic strategies for advanced TNBC.

IMMUNOTHERAPY IN METASTATIC TNBC

Previous studies demonstrated only modest activity of ICI monotherapy in metastatic TNBC, with overall response rates (ORR) of approximately 20% when used in the first line, and lower response rates in subsequent lines of therapy.[14,15] This provided the rationale for investigating ICI therapy in combination with chemotherapy, with the goal of enhancing efficacy. The pivotal KEYNOTE-355 trial evaluated pembrolizumab combined with chemotherapy versus chemotherapy alone and demonstrated significant improvements in progression-free survival (PFS; 9.7 *v* 5.6 months) and OS (23 *v* 16.1 months; hazard ratio [HR], 0.73) with the combination.[7] In contrast to the early-stage setting, this survival benefit was confined to PD-L1–positive tumors, defined as a combined positive score (CPS) ≥ 10.[7,16] Based on these results, pembrolizumab combined with chemotherapy became the standard of care for the first-line treatment of advanced PD-L1–positive TNBC.

Atezolizumab, an anti–PD-L1 agent, is another approved ICI internationally, based on the phase III IMpassion130 trial which showed survival benefits with first-line nab-paclitaxel plus atezolizumab in patients with PD-L1–positive advanced TNBC (defined as ≥1% PD-L1 expression by Ventana SP142 assay).[17] However, the approval was

PRACTICAL APPLICATIONS

- Antibody-drug conjugates (ADCs) have redefined the management of advanced triple-negative breast cancer (TNBC), with trophoblast cell-surface antigen 2-targeting ADCs becoming the new frontline standard of care, marking a shift away from conventional chemotherapy.
- As the landscape continues to evolve, the identification of predictive biomarkers to inform therapy selection and sequencing is a key research priority.
- Emerging therapeutic strategies include novel ADC designs and bispecific antibodies.
- An improved understanding of the molecular heterogeneity of TNBC is enabling more targeted and personalized therapeutic approaches.
- Despite recent advances, overall survival remains modest compared with the other breast cancer subtypes, and a critical need to improve outcomes remains.

withdrawn in the United States in 2021, after the negative phase III IMpassion 131, which had a similar design to IMpassion130 but with a paclitaxel backbone.[18,19]

To date, no clinical trials have demonstrated improvements with immunotherapy for patients with PD-L1 negative metastatic TNBC. For these patients, who make up approximately 60% of cases,[7,18,19] chemotherapy has been the mainstay of treatment in the first-line setting and is associated with cumulative toxicity and short durations of response. These challenges have prompted interest in alternative approaches and innovative therapies.

RATIONALE FOR ADCs

Among these, ADCs represent a novel therapeutic class, composed of a monoclonal antibody targeting a specific tumor antigen linked to a cytotoxic payload.[20] ADCs bind selectively to cell-surface antigens on tumor cells, enabling targeted delivery of highly potent cytotoxic agents, which are internalized and released intracellularly, leading to tumor cell death.[21] This targeted mechanism allows improved efficacy compared with conventional chemotherapy (Table 1).

TROP2 is a transmembrane protein that is overexpressed in TNBC and represents a novel therapeutic target.[22] Early clinical studies established the activity of TROP2-directed ADCs in metastatic TNBC. Sacituzumab govitecan (SG) is a TROP2-targeting ADC conjugated to the topoisomerase-1 inhibitor SN-38.[23] In the phase III ASCENT trial, SG demonstrated superior clinical outcomes compared with standard chemotherapy in heavily pretreated metastatic TNBC, resulting in its approval as a second-line therapy.[9] Datopotamab deruxtecan (Dato-DXd) is a next-generation TROP2-directed antibody conjugated to a potent topoisomerase-I inhibitor payload (an exatecan derivative) via a cleavable linker.[24] Similarly, the phase I TROPION-PanTumor01 study demonstrated encouraging antitumor activity of Dato-DXd in patients with heavily pretreated advanced TNBC (Table 2).[25]

Further supporting the therapeutic relevance of TROP2 targeting, sacituzumab tirumotecan (sac-TMT), an anti-TROP2 ADC with a novel topoisomerase-1 inhibitor payload, has been approved in China for metastatic TNBC. Sac-TMT demonstrated improved disease outcomes versus treatment of physician's choice (TPC) chemotherapy in metastatic TNBC treated with at least two lines of prior chemotherapy in the OptiTROP-Breast01 trial with a PFS of 6.7 versus 2.5 months (HR, 0.32); OS not reached versus 9.4 months (HR, 0.53).[26] Subsequently, the phase II OptiTROP-Breast05 study explored the use of sac-TMT in the first-line metastatic setting.[27] Among 32 patients with PD-L1 CPS < 10, the ORR was 71.9%, and the median PFS was 13.1 months.

TROP2 ADCs MOVING TO THE FRONTLINE

Building on the activity of TROP2-directed ADCs in later lines of therapy for advanced TNBC, two phase III trials, ASCENT-03 and TROPION-Breast02, investigated whether TROP2-ADCs could replace chemotherapy as first-line treatment for patients with advanced TNBC who are not candidates for ICI.[11,12]

ASCENT-03 evaluated SG compared with TPC chemotherapy in patients with previously untreated, locally advanced inoperable or metastatic TNBC, ineligible for PD-L1 inhibitors.[12] The trial met its primary end point, with the SG arm demonstrating a significant improvement in PFS (9.7 *v* 6.9 months; HR, 0.62), establishing SG as an effective first-line option and challenging the historical paradigm of standard chemotherapy in this setting.

Similarly, TROPION-Breast02 randomly assigned patients with immunotherapy-ineligible metastatic TNBC to receive first-line Dato-DXd or TPC chemotherapy.[11] The trial observed significant improvements in ORR (62.5% *v* 29.3%), PFS (10.8 *v* 5.6 months; HR, 0.57), and OS (23.7 *v* 18.7 months; HR, 0.79), favoring Dato-DXd over chemotherapy.[28] This is one of the first reports of an OS benefit for an ADC used in this context, with OS data from ASCENT-03 immature at present.

Collectively, these studies support the use of TROP2-directed ADCs as a first-line treatment option for

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TABLE 1. Key Characteristics of Approved ADCs in Breast Cancer

Feature	T-DXd	SG	Dato-DXd	Sac-TMT[a]
Antibody	HER2-directed hRS7 humanized IgG1 mAb	TROP2-directed hRS7 humanized IgG1 mAb	TROP2-directed MAAP-9001a humanized IgG1 mAb	TROP2-directed RS7 humanized IgG1 mAb
Payload	DXd (DNA Topo I inhibitor)	SN38 (DNA Topo I inhibitor)	DXd (DNA Topo I inhibitor)	KL610023 (DNA Topo I inhibitor derived from belotecan)
Linker	Cleavable	Hydrolyzable	Cleavable	Cleavable
DAR	8	7.6	4	7.4
Bystander effect	Yes	Yes	Yes	Yes
Common side effects	Neutropenia, anemia, nausea, vomiting, fatigue, alopecia, ILD/pneumonitis	Neutropenia, anemia, diarrhea, alopecia	Oral mucositis/stomatitis, nausea, vomiting, fatigue, alopecia, ocular toxicity	Anemia, neutropenia, thrombocytopenia, stomatitis, transaminitis
Dosing schedule	q3wk	D1, D8 of 21d cycle	q3wk	D1, D15 of 28d cycle

Abbreviations: ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; Dato-DXd, datopotamab deruxtecan; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; mAB, monoclonal antibody; Sac-TMT, sacituzumab tirumotecan; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TROP2, trophoblast cell-surface antigen 2.
[a]Approved for use in China.

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metastatic TNBC, marking a significant shift away from conventional chemotherapy (Fig 1). Accordingly, the National Comprehensive Cancer Network guidelines have been updated based on the results from ASCENT-03 and TROPION-Breast 02.[29] Additional phase III studies are ongoing, including a randomized trial comparing sac-TMT with chemotherapy in first-line PD-L1 negative advanced TNBC (ClinicalTrials.gov identifier: NCT06279364), which will further inform the role of ADCs in this setting.

CLINICAL CONSIDERATIONS IN THE USE OF TROP2-DIRECTED ADCs

As multiple effective TROP2-directed ADCs enter the first-line space for metastatic TNBC, how to most optimally select among these agents becomes an important clinical question. ASCENT-03 and TROPION-Breast02 differed in several ways, including eligibility criteria, baseline risk, control arm composition, built-in cross-over, and follow-up duration.[11,12]

Notably, TROPION-Breast02 enrolled a higher-risk population by allowing patients with any disease-free interval following curative-intent therapy, resulting in a greater number of patients with early relapse; 15% of patients had a recurrence within 6 months of adjuvant treatment versus 0% in ASCENT-03.[12,28] TROPION-Breast02 also had a higher prevalence of brain metastases and allowed enrollment of PD-L1–positive patients in regions without access to pembrolizumab.[11,28]

These differences are important when interpreting efficacy outcomes. The higher ORR observed with Dato-DXd in TROPION-Breast02 (62.5% *v* 29.3%) compared with SG in ASCENT-03 (48% *v* 46%) should be considered in the context of these differences in patient populations and eligibility criteria. The inclusion of patients with early relapse in TROPION-Breast02 suggests a more chemotherapy-refractory cohort, with more aggressive biology, which may have influenced observed outcomes. Consistent with this, the control arm of TROPION-Breast02 had a numerically shorter median PFS compared with ASCENT-03 (5.6 *v* 6.9 months).[12,28] Differences in the chemotherapy received in the control arm may also have contributed, with less use of platinum agents and no doublet therapy in TROPION-Breast02. Performance of the control arm is important to take into account, as poorer outcomes in the control arm may widen the observed differences in ORR and PFS between study arms. Additionally, the higher proportion of PD-L1–positive patients in TROPION-Breast02 (10% *v* 0.4%) suggests differences in underlying tumor biology between the study populations and may have contributed to variations in outcomes.

Importantly, subsequent receipt of ADC after progression in the control arm differed between the trials, further complicating interpretation of survival outcomes.[11,12] In TROPION-Breast 02, crossover to Dato-DXd was not permitted, as it is not approved in later-line metastatic TNBC, and many patients in the control arm had limited access to a subsequent ADC after study discontinuation, reflecting the geographic areas in which the study was conducted. By contrast, crossover to SG was permitted in ASCENT-03, with most patients on the control arm (approximately 80%) ultimately receiving SG. Although OS data for ASCENT-03 is immature, the impact of postprogression therapy and trial design on survival end points must be considered, and cross-trial comparisons should be undertaken with caution.

In addition, there are clinically meaningful differences in the toxicity profiles of TROP2-directed ADCs, which may influence treatment selection, tolerability, and patient-preference in real-world clinical practice. SG is associated with neutropenia requiring growth factor support, diarrhea,

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TABLE 2. Pivotal Phase III Clinical Trials in Metastatic TNBC

Phase III Clinical Trial	Participants (No.)	Eligibility Criteria	Treatment Arms	Median PFS, HR (95% CI)	Median OS, HR (95% CI)	ORR
First-line PD-L1 positive						
Keynote 355	847	Previously untreated locally recurrent inoperable or metastatic TNBC Any PD-L1 status DFI > 6 months Treated and stable brain mets included	Pembro + chemo *v* Placebo + chemo (paclitaxel, nab-paclitaxel, gem/carbo)	9.7 *v* 5.6 months[a] 0.66 (0.50 to 0.88)	23.0 *v* 16.1 months[a] 0.73 (0.55 to 0.95)	53% *v* 41%
ASCENT-04	443	Metastatic TNBC PDL-1 positive No prior chemo DFI > 6 months Treated and stable brain mets included	SG + pembro *v* chemo + pembro (paclitaxel, nab-paclitaxel, gem/carbo)	11.2 *v* 7.8 months 0.65 (0.51 to 0.84)	NR (immature) 0.89 (0.62 to 1.29)	60% *v* 53%
First-line PD-L1 negative						
ASCENT-03	558	Metastatic TNBC No prior chemo; not a candidate for immunotherapy DFI > 6 months Treated and stable brain mets included	SG *v* TPC (paclitaxel, nab-paclitaxel, gem/carbo)	9.7 *v* 6.9 months 0.62 (0.50 to 0.77)	NR (immature)	48% *v* 46%
TROPION-Breast02	644	Metastatic TNBC No prior chemo; not a candidate for immunotherapy (including no pembro access) Any DFI allowed Stable, asymptomatic brain mets included	Dato-DXd *v* TPC (paclitaxel, nab-paclitaxel, capecitabine, carbo, eribulin)[b]	10.8 *v* 5.6 months 0.57 (0.47 to 0.69)	23.7 *v* 18.7 months 0.79 (0.64 to 0.98)	62.5% *v* 29.3%
Subsequent line trials						
ASCENT	529	Metastatic TNBC Received 2+ prior chemo regimens (including taxane) Stable brain mets for 4 weeks were enrolled but not included in analysis	SG *v* TPC (eribulin, vinorelbine, capecitabine, gem)	5.6 *v* 1.7 months 0.29 (0.31 to 0.49)	12.1 *v* 6.7 months 0.48 (0.39 to 0.59)	35% *v* 5%
OptiTROP-Breast01	262	Locally recurrent or metastatic TNBC Received 2+ prior therapies, including 1 for metastatic disease	Sac-TMT *v* chemo (eribulin, vinorelbine, capecitabine, gem)	6.7 *v* 2.5 months 0.32 (0.24 to 0.44)	NR[c] *v* 9.4 months 0.53 (0.36 to 0.78)	45.4% *v* 12.0%

Abbreviations: Dato-DXd, datopotamab deruxtecan; DFI, disease-free interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Sac-TMT, sacituzumab tirumotecan; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.
[a]Outcomes for the PD-L1 positive (CPS > 10) subset.
[b]Paclitaxel/nab-paclitaxel if no prior taxane or DFI >12 months, or cape/carbo/eribulin if prior taxane and DFI ≤12 months.
[c]At the treatment group protocol-specified interim analysis.

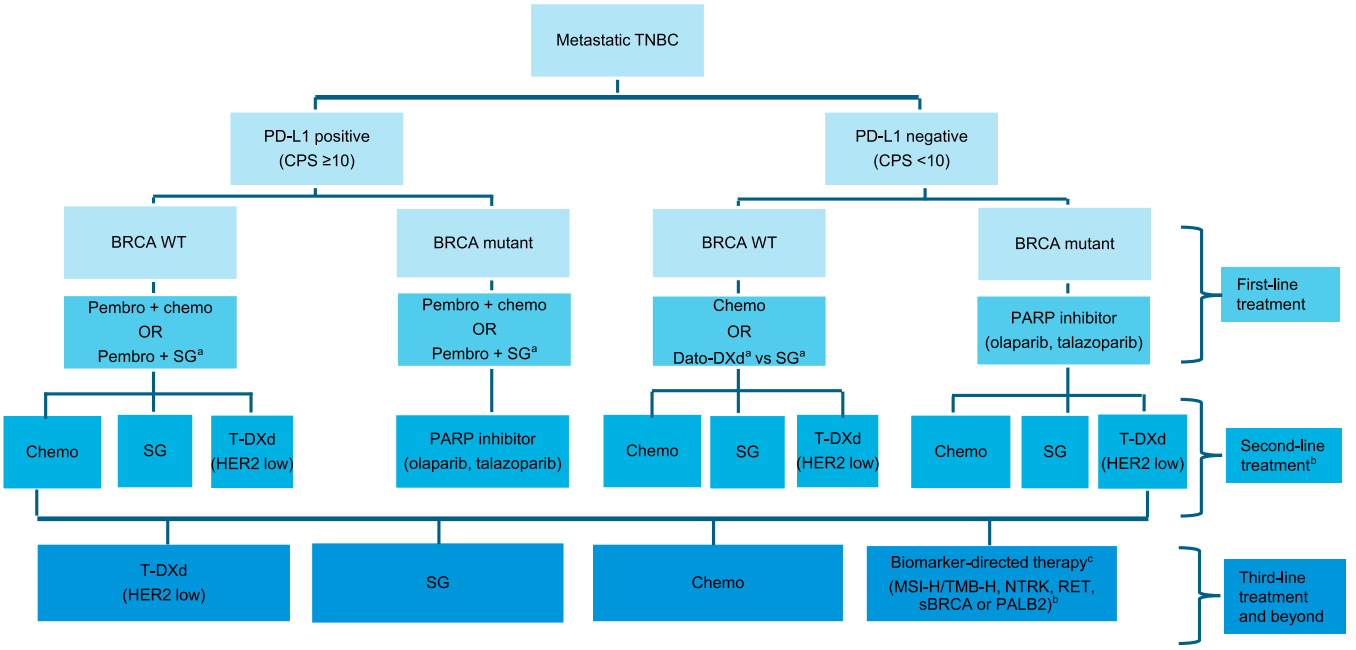

FIG 1. Treatment algorithm for management of metastatic triple negative breast cancer. [a]If approved/available. [b]Therapies not received in a prior line may be considered in subsequent lines, as clinically appropriate. [c]Such targetable biomarkers include MSI-H/dMMR (corresponding therapy: pembrolizumab or dostarlimub-gxly); TMB-H (corresponding therapy: pembrolizumab); NTRK fusion (corresponding therapy: larotrectinib, entrectinib, or repotrectinib); RET fusion (corresponding therapy: selpercatinib); PALB2/sBRCA1/2 mutation (corresponding therapy: olaparib). BRCA, breast cancer gene; Chemo, chemotherapy; CPS, combined positive score; Dato-DXd, datopotamab deruxtecan; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; RET, rearranged during transfection; s, somatic; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TMB-H, tumor mutational burden-high; TNBC, triple negative breast cancer; WT, wild type.

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and alopecia, whereas classic toxicities of Dato-DXd include oral mucositis/stomatitis, ocular surface toxicity, as well as a recognized though uncommon risk of interstitial lung disease/pneumonitis.[30] Another consideration is the dosing schedule of these agents, with Dato-DXd being administered every 21 days and SG administered on day 1 and day 8 of a 21-day cycle.[9,25] In the absence of predictive biomarkers to guide management, selection among these TROP-2–directed ADCs will require an individualized approach, taking the above factors into account.

ADC-ICI COMBINATIONS IN 1L PD-L1–POSITIVE ADVANCED TNBC

For those with PD-L1–positive TNBC, the idea of combining an ADC with immunotherapy to replace the chemotherapy backbone has been explored, with the goal of improving efficacy while also reducing chemotherapy-associated toxicity. SG in combination with pembrolizumab has emerged as a potential new frontline treatment option, based on the ASCENT-04 trial which enrolled patients with advanced TNBC who were PD-L1 positive with a CPS ≥10.[13] Participants (N = 443) were randomly assigned to receive either SG plus pembrolizumab or TPC chemotherapy plus pembrolizumab, and a significant improvement in median PFS was observed in the experimental group (11.2 *v* 7.8 months, HR, 0.65).[13]

Meanwhile, TROPION-Breast05 (ClinicalTrials.gov identifier: NCT06103864) is an ongoing multicenter phase III study of Dato-DXd in combination with durvalumab versus TPC chemotherapy plus pembrolizumab in patients with PD-L1–positive advanced or metastatic TNBC, further investigating the concept of ADC-based immunotherapy combinations in the first-line setting.[31]

ADC-ICI COMBINATIONS IN 1L PD-L1–NEGATIVE ADVANCED TNBC

Whether adding an ADC to ICI could be efficacious in PD-L1–negative metastatic TNBC is currently under investigation, with the goal of extending the benefit of immunotherapy beyond PD-L1–positive metastatic TNBC. In the phase Ib/II BEGONIA trial, the combination of Dato-DXd with durvalumab achieved an ORR of 79% and median PFS of 14 months, with benefit seen irrespective of PD-L1 status.[32] In fact, the vast majority (87.1%) of tumors were PD-L1 negative. Building on these findings, the DIAMOND phase II trial (ClinicalTrials.gov identifier: NCT06954480) is now evaluating Dato-DXd alone or in combination with

durvalumab in patients with advanced PD-L1–negative (CPS < 10) TNBC and will provide further insights. Similarly, SG is being investigated either alone or in combination with pembrolizumab in the phase II Saci-IO TNBC trial, also in PD-L1–negative metastatic TNBC.[33] In addition, TroFuse-011 (ClinicalTrials.gov identifier: NCT06841354) is a phase III study in the same advanced PD-L1–negative setting, with three arms investigating either sac-TMT alone, sac-TMT with pembrolizumab or TPC chemotherapy.

T-DXD IN HER2-LOW/ULTRA-LOW TNBC

Other ADCs that have been investigated in metastatic TNBC include T-DXd, a HER2-targeted ADC composed of trastuzumab linked to a highly potent topoisomerase-1 inhibitor payload.[34] T-DXd has demonstrated activity across a spectrum of HER2 expression, because of a bystander effect whereby the membrane-permeable payload diffuses into neighboring tumor cells, leading to cell death even in tumors with low HER2 expression.[10]

Approximately one third of patients with TNBC have HER2-low tumors, defined as immunohistochemistry (IHC) 1+ or IHC 2+/in situ hybridization (ISH)−. The phase III Destiny-Breast04 trial randomly assigned patients with HER2-low metastatic breast cancer previously treated with 1-2 lines of chemotherapy to either T-DXd or TPC chemotherapy.[10] A small subset of patients with hormone receptor–negative/HER2-low breast cancer (n = 58, 12%) were included and a significant PFS and OS benefit was noted for T-DXd compared with chemotherapy (PFS: 8.5 *v* 2.9 months; OS: 18.2 *v* 8.3 months), supporting its activity in patients with HER2-low TNBC.

The ongoing Destiny-Breast15 trial is expanding on these findings by further evaluating T-DXd in HER2 ultra-low (IHC 0 with faint, incomplete membrane staining in ≤10% of cells) or HER2-null (IHC 0 with no membrane staining) metastatic breast cancer.[35] The study will include a cohort of patients with hormone receptor–negative disease, and therefore, if positive, these findings may further extend the use of T-DXd in metastatic TNBC.

MECHANISMS OF ADC RESISTANCE AND SEQUENCING

As a growing number of ADCs with similar payloads and similar targets become available, the optimal sequencing strategy remains unclear and is of increasing clinical importance. With SG, Dato-DXd and T-DXd all containing topoisomerase-1 inhibitor payloads, there is a concern for cross-resistance and reduced efficacy if used in sequence.[36] Several retrospective studies have demonstrated that sequential ADC use is associated with reduced clinical benefit of the second ADC used. For example, a retrospective multicenter evaluation of sequential use of T-DXd and SG for HER2-low metastatic breast cancer showed that the first ADC administered consistently had a longer time-to-treatment failure than the second ADC.[37] This was irrespective of ADC sequence order, age, presence of visceral disease, or use of an intervening treatment. A complementary analysis of a large real-world data set evaluating the efficacy of subsequent therapy post–T-DXd showed that SG post–T-DXd had a short real-world PFS (≤3.4 months), implying some degree of cross-resistance among topoisomerase-1 ADCs.[38]

Preclinical and translational efforts to better understand mechanisms of resistance have shown that resistance can develop because of alterations of either the antibody binding target or the payload.[39] The emergence of distinct TOP1 mutations at the time of progression has been described in patients treated with topoisomerase-1–based ADCs, suggesting that TOP1 mutations are likely to contribute to cross-resistance when ADCs with topoisomerase-1 inhibitor payloads are used in sequence and that payload switching may be critical for optimizing efficacy.[40] A recent preclinical study further supports the concept of payload diversification, demonstrating that resistance to T-DXd and SG in breast cancer cell lines was largely mediated by payload-specific factors rather than loss of antigen expression and that antitumor activity was restored by switching to ADCs with different payloads.[41] Further efforts to identify biomarkers of ADC response and resistance are needed, and several prospective studies have now been designed to specifically address the issue of optimal ADC sequencing.

The TRADE-DXd (TBCRC064) study is a randomized phase II trial evaluating sequential use of T-DXd and Dato-DXd in patients with HER2-low metastatic breast cancer. Patients are randomly assigned to receive either ADC as initial therapy, followed by crossover to the alternate ADC at progression, with serial tumor biopsies and blood-based correlative studies incorporated. This study will help to determine whether switching targets while maintaining a similar payload is an effective strategy. In parallel, ENCORE (TBCRC067) is a prospective multicenter registry designed to capture real-world outcomes, safety, and sequencing patterns of ADCs in HER2-negative metastatic breast cancer.[42] Patients are enrolled when initiating their first or second ADC as per standard of care, with biomarker analyses integrated, including circulating tumor DNA, spatial profiling and patient-reported outcomes. Finally, the phase II SERIES trial is evaluating SG after progression on T-DXd with longitudinal blood and tissue-based sampling.[43] Although this study is being conducted in ER-positive, HER2-low metastatic breast cancer, the insights generated will likely have broader relevance and inform ADC sequencing strategies across tumor subtypes. Overall, these prospective efforts represent an important step toward defining evidence-based ADC sequencing, a highly clinically relevant question, as ADCs move earlier in the treatment algorithm.

PARP INHIBITORS

Defective DNA damage repair is a defining biologic feature noted in a subset of TNBC, most commonly involving

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impairment of homologous recombination repair (HRR). g*BRCA1/2* mutations are the most common cause of HRR deficiency and are present in approximately 10% of patients with TNBC.[44,45] These tumors are highly sensitive to DNA repair-targeting therapies, including PARPi that exploit synthetic lethality.[3]

Two PARPi are approved in metastatic g*BRCA*-mutated TNBC having demonstrated superiority over chemotherapy in pivotal trials. Olaparib received approval based on the phase III OlympiAD trial, which demonstrated a PFS benefit (7 *v* 4 months) compared with TPC chemotherapy (capecitabine, eribulin, vinorelbine) in patients with g*BRCA*-mutated metastatic TNBC. Although no statistically significant OS benefit was observed with olaparib compared with TPC, there was a suggestion of a meaningful OS benefit for those who received olaparib in the frontline setting.[5,46] Another PARPi, talazoparib, was approved following the phase III EMBRACA trial, in which talazoparib demonstrated a PFS benefit of 8.6 versus 5.6 months compared with TPC chemotherapy (gemcitabine, capecitabine, vinorelbine, eribulin) in the same TNBC population, although again without significant improvement in OS.[6,47] As our treatment options expand, and because these studies were conducted before the emergence of ADCs, the optimal positioning of PARPi within the current, increasingly complex treatment landscape is an important consideration.

Moving beyond g*BRCA*, Olaparib Expanded (TBCRC048) was a phase II investigator-initiated study that assessed use of olaparib in patients with metastatic breast cancer and mutations in other HRR-related genes, such as *PALB2*, *ATM*, *CHEK2*, and somatic (s) *BRCA1/2*.[48] Among 54 patients with germline (g) *PALB2* (n = 24) or s*BRCA* (n = 30), 13% had TNBC, with the remainder representing other breast cancer subtypes.[49] The study demonstrated that PARP inhibition was effective in patients with g*PALB2* and s*BRCA1/2* mutations, whereas limited activity was observed in tumors harboring mutations in other HRR genes such as *ATM* or *CHEK2*.[48,49] These findings highlight the relevance of HRR deficiency as a therapeutic biomarker and expand the population likely to benefit from PARPi beyond those with gBRCA mutations.

TARGETING THE PI3K/AKT/PTEN PATHWAY

The PI3K/AKT/PTEN pathway regulates critical cellular processes including cell survival, metabolism, and proliferation.[50] This pathway is frequently dysregulated in TNBC and is associated with poor prognosis and resistance to therapy, making it an attractive therapeutic target.[51] Capivasertib is a potent AKT inhibitor approved for metastatic hormone receptor–positive breast cancer,[52] and preclinical studies in TNBC have demonstrated synergistic activity between capivasertib and taxane-based chemotherapy.[53]

These findings provided the motivation for the randomized phase II LOTUS and PAKT trials, which evaluated AKT inhibition in combination with chemotherapy in metastatic TNBC. Both studies showed improvements in PFS and OS, particularly in the PI3K/AKT/PTEN-altered subgroups, generating enthusiasm for this therapeutic approach.[54,55] However, these promising results unfortunately did not translate into benefit in the later phase III trials. In IPATunity130, there was no improvement in PFS with the addition of the AKT inhibitor ipatasertib to paclitaxel for first-line treatment of metastatic TNBC.[56] Similarly, the CAPItello-290 trial did not show a significant benefit in adding the AKT inhibitor capivasertib to first-line paclitaxel in metastatic TNBC, either in the overall population or in the PIK3CA/AKT1/PTEN-altered subgroup, despite a numerical trend toward improved PFS.[57]

AR-DIRECTED TARGETED THERAPIES

The heterogeneity of TNBC has made the identification of actionable targets and development of targeted therapies particularly challenging. Lehmann et al[58] described six subtypes of TNBC based on gene expression, mesenchymal stem-like (MSL), mesenchymal (M), immunomodulatory (IM), basal-like 1, basal-like 2, and luminal androgen receptor (LAR), in an attempt to help identify molecular-based therapies.

The LAR molecular subtype represents approximately 10%-15% of TNBC and is driven by androgen receptor (AR) signaling, with a luminal gene expression profile, low proliferation rates, and relative chemoresistance.[58] These features led to interest in exploring AR inhibition as a potential therapeutic strategy for this subgroup of TNBC. Challenges in implementing AR-directed strategies include the absence of standardized AR IHC testing, uncertainty around the optimal AR threshold for positivity and the lack of predictive biomarkers to reliably identify the population most likely to benefit. Several trials have investigated AR inhibitors as monotherapy, including bicalutamide, enzalutamide, and abiraterone; however, these studies yielded modest results, with median PFS of approximately 3-4 months.[59-61]

One explanation may be the development of resistance mechanisms to AR-inhibition via activation of the glucocorticoid receptor (GR). Approximately 60% of AR-positive TNBCs coexpress high levels of GR, providing the rationale for combined AR and GR blockade.[62] This approach is being evaluated in the randomized phase II TBCRC058 trial comparing enzalutamide alone, enzalutamide plus the GR antagonist mifepristone, and chemotherapy in advanced AR-positive TNBC.[63] The primary end point is PFS, and the trial is designed to assess whether enzalutamide either alone or in combination with GR inhibition can improve outcomes compared with standard chemotherapy in this biomarker selected population.

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EMERGING THERAPIES AND FUTURE DIRECTIONS

TROP2-directed ADCs have changed the treatment landscape of advanced TNBC, and efforts are now increasingly focused on the development of ADCs targeting different antigens and delivering different payloads, to overcome resistance and enhance antitumor activity. Emiltatug ledadotin (Emi-Le) is a novel ADC targeting B7-H4, a cell-surface protein that is highly expressed across solid tumors, including breast cancers, with limited expression in normal healthy tissue. It delivers an auristatin-based microtubule inhibitor payload.[64] Early data from an ongoing phase I trial demonstrated clinical activity and acceptable safety in a heavily pretreated population of patients with advanced TNBC, all of whom had received at least one prior topoisomerase-1 based ADC.[64] Tumors were assessed for B7-H4 expression by IHC and stratified into B7-H4 TPS "high" and B7-H4 TPS "low" cohorts. At interim analysis, the ORR was 23% in the B7-H4 high group, whereas no confirmed responses were observed in the B7-H4 low tumors.[64] These findings suggest that Emi-Le may offer biomarker-enriched clinical activity in patients with metastatic TNBC and high B7-H4 expression, including in those previously treated with topoisomerase-1 ADCs.

Zelenectide pevedotin belongs to a new class of investigational agents called bicycle toxin conjugates. It consists of a bicyclic peptide targeting nectin-4 conjugated to a monomethyl auristatin E payload via a cleavable linker.[65] Advantages of this agent over ADCs, are its lower molecular weight and shorter half-life, allowing enhanced tumor penetration, shorter systemic exposure, and potentially less toxicity in nontarget tissues. Nectin-4 is a cell adhesion molecule that has emerged as a predictive biomarker of response to nectin-4 targeted therapy in metastatic urothelial cancer. Nectin-4 amplification, assessed by fluorescence in situ hybridization, is thought to be present in approximately 23% of TNBCs and may represent a predictive biomarker for this novel agent.[65]

The ongoing phase I/II study BT8009-100/Duravelo-1 (ClinicalTrials.gov identifier: NCT04561362) is evaluating zelenectide pevedotin in advanced solid tumors, including a TNBC cohort. In a post hoc analysis, pretreated patients with nectin-4–amplified TNBC achieved an ORR of 57.1% versus 13.3% in the biomarker-unselected population.[65] These findings indicate that nectin-4 amplification may have clinical utility in identifying patients with TNBC who derive benefit from zelenectide pevedotin. Building on these results, the ongoing duravelo-3 (ClinicalTrials.gov identifier: NCT06840483) trial is further evaluating this agent in patients with advanced nectin-4–amplified breast cancer.

Other approaches are focusing on PD-L1 signaling and VEGF-mediated angiogenesis, both of which play central roles in immune evasion and tumor progression in TNBC. Bispecific antibodies that simultaneously target PD-1 and VEGF are emerging as a new therapeutic strategy, designed to act synergistically to overcome these mechanisms. For example, ivonescimab is a novel PD-1/VEGF bispecific antibody that has demonstrated encouraging activity. In a phase II trial conducted in first-line advanced TNBC (N = 36), ivonescimab plus chemotherapy led to an ORR of 80.0% in the overall population, with similar responses in PD-L1 CPS ≥ 10 (83.3%) and PD-L1 CPS < 10 (79.3%) subgroups.[66] The median PFS was 9.36 months (95% CI, 6.24 to NE), with comparable results observed in the subgroups with CPS < 10 and CPS < 1. The combination of ivonescimab and nab-paclitaxel versus nab-paclitaxel alone is now being evaluated in the ongoing phase III HARMONi-BC1 trial (ClinicalTrials.gov identifier: NCT06767527), enrolling patients with treatment naïve PD-L1–negative metastatic TNBC.

Similarly, the PD-L1/VEGF-A bispecific antibody pumitamig (PM8002/BNT327) demonstrated promising results in a phase Ib/II study (n = 42) in combination with nab-paclitaxel in a cohort of patients with untreated metastatic TNBC. An ORR of 73.8% was reported with a median PFS was 13.5 months (95% CI, 9.4 to 19.3), and findings overall showed similar activity regardless of PD-L1 status.[67] The toxicity profile for pumitamig includes immune-related adverse events, hypertension, and proteinuria. Based on these encouraging data, the ROSETTA Breast-01 (ClinicalTrials.gov identifier: NCT07173751) phase III study is underway, investigating chemotherapy with or without pumitamig in first-line PD-L1–negative TNBC. These early-phase clinical data are exciting, and we eagerly await further studies of this dual-targeting strategy, particularly in PD-L1–negative metastatic TNBC, which has not benefited from ICI to date.

CONCLUSIONS

Significant advances have been made in the management of advanced TNBC over the past decade. ADCs have come to the forefront and are changing the treatment paradigm for metastatic TNBC, improving outcomes compared with conventional chemotherapy. The biologic heterogeneity of TNBC is widely recognized and efforts to personalize therapy with novel targeted therapies and biomarker-selected strategies are under investigation. Innovative agents, such as PD-1/VEGF bispecific antibodies, are promising approaches to expand the activity of immunotherapy beyond PD-L1 positive disease, and are showing encouraging early clinical results, with phase III studies ongoing. Critical questions remain regarding the optimal sequencing of therapies and mechanisms of resistance. Further areas of need include improved therapeutic options for patients who relapse after neoadjuvant chemoimmunotherapy for early-stage disease, as well as for those with disease progression following first-line ADC therapy. Ongoing and future studies will be essential to shed light on these scenarios and help inform how to optimally integrate therapies for patients with metastatic TNBC, with the goal of further improving survival outcomes and quality of life.

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

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Tailoring Management for Invasive Lobular Carcinoma: Imaging, Surgical Treatment, and Systemic Therapy Considerations

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OVERVIEW

Invasive lobular carcinoma (ILC) represents the most common special subtype of breast cancer. Studies show challenges with imaging, surgical therapy, and systemic therapy selection, arguing for the need for improved treatment personalization for this histologic subtype of breast cancer. While standard imaging tools have decreased sensitivity for ILC, newer imaging approaches may be more effective in both early and advanced disease settings. Surgical treatment is notable for high rate of positive margins and need for more extensive surgery; this may be mitigated by improved imaging and incorporation of particular techniques. While endocrine therapy remains the mainstay of treatment for most patients with ILC, the unique molecular characteristics of this tumor type may provide targets for new therapeutic approaches. The preponderance of data supports the need for ILC specific studies and trials.

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INTRODUCTION

Invasive lobular carcinoma (ILC) is the most common special histologic subtype of breast cancer accounting for 10%–15% of all breast cancers. The hallmark of ILC is the loss of E-cadherin (encoded by the gene *CDH1*), resulting in discohesive cell growth and decreased disruption of the stroma. Between 30,000 and 40,000 women are diagnosed with ILC annually in the United States. Over the past decade, the incidence rate of ILC (2.8%) has increased more steeply compared with all other breast cancer subtypes.[1]

At diagnosis, ILC presents with a higher tumor burden compared with breast cancer of no special type (NST), also known as invasive ductal carcinoma. A recent meta-analysis of patients with early-stage breast cancer who received anthracycline-based adjuvant chemotherapy in National Surgical Adjuvant Breast and Bowel Project randomized phase III clinical trials showed that patients with ILC presented with a higher proportion of tumors that are larger than 4 cm and with ≥4 involved lymph nodes compared with those with NST.[2] This is likely due, at least in part, to the challenges in breast imaging of primary ILC, particularly since ILC tends not to form a distinct mass. The confluence of higher stage at diagnosis and decreased sensitivity of imaging lead to suboptimal outcomes with surgical treatment for those with ILC. In addition, ILC has a lower rate of early recurrences (<5 years) but higher risk of late recurrences (after 5 years).

In the metastatic setting, ILC has a higher propensity to metastasize to the GI tract, ovaries, and leptomeninges. Biologically, ILC has a unique genomic landscape, and emerging studies are revealing distinct features of the tumor microenvironment.[3–6] Despite the clinical and biological data supporting the notion that ILC is a unique breast cancer subtype, most of the clinical guidelines for imaging, surgical management, and systemics treatments in ILC are extrapolated from clinical studies in which most of the patients had NST breast cancer. This highlights the unmet need for prospective clinical studies of ILC and particular attention to the unique features of this tumor during clinical management.

IMAGING CONSIDERATIONS IN ILC

Evaluation of Primary and Locoregional Metastatic Disease

ILC can be difficult to detect with conventional imaging because its infiltrative, single-file growth pattern often lacks a central mass or desmoplastic response.[7–10] Standard mammography, including digital breast tomosynthesis, is frequently limited by low sensitivity, which can drop as low as 10% to 30% in patients with dense breast tissue.[8,11–13] Breast ultrasound serves as a valuable supplementary tool, demonstrating an improved sensitivity and assisting in the evaluation of dense tissue and palpable abnormalities. Contrast-enhanced breast magnetic resonance imaging (MRI) remains the current gold standard for primary ILC detection and local staging because of its higher sensitivity, which is between 83% and 100%.[14–17] However, MRI is associated with high costs and a higher rate of false positives,

PRACTICAL APPLICATIONS

- Recognize that standard imaging tools like mammogram, ultrasound, and fluorodeoxyglucose-positron emission tomography may underestimate disease extent in patients with invasive lobular carcinoma (ILC).
- Surgical treatment of patients with ILC is notable for high rates of positive margins and upstaging on pathology.
- Oncoplastic surgery is safe and may reduce positive margins.
- The use of neoadjuvant or adjuvant chemotherapy in ILC may improve surgical outcomes and survival outcomes in select populations, but ILC-specific treatment selection tools are needed.
- The unique molecular features of ILC could lead to differential response to standard endocrine therapies; further research stratified by histology is needed.

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and it may overestimate tumor size, which can potentially lead to more extensive surgeries such as unnecessary mastectomies.[18] While contrast-enhanced mammography is promising for detection of sites of primary ILC, this method is limited compared with MRI for assessment of locoregional metastatic disease given the narrow field of view of mammography.[19]

Positron Emission Tomography/Computed Tomography Evaluation of Metastatic ILC

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) detects metabolic activity via glucose uptake; however, its effectiveness in ILC can be limited.[9,20,21] Compared with NST, ILC primary tumors and metastases are frequently less FDG-avid, leading to a higher rate of false-negative results.[22] While it is valuable for identifying distant disease in many cancers, ILC often spreads to serosal surfaces, the GI tract, and the peritoneum—sites where FDG PET/CT frequently fails to show significant uptake above background levels.[23]

Despite these limitations, FDG PET/CT remains a standard-of-care tool for systemic staging and can provide important prognostic information.[24] High FDG uptake (SUVmax >5.0), while less common in ILC, is typically associated with more aggressive disease and a poorer prognosis, whereas FDG-indolent lesions are more characteristic of the typical, strongly estrogen receptor (ER)–positive ILC phenotype and correlate with longer survival.[25] Because of its known weaknesses in this subtype, experts often recommend supplementing FDG scans with ER-targeted (fluoroestradiol [FES]) PET or, potentially in the future, other radiopharmaceuticals such as fibroblast activation protein-targeted (FAPI) PET to achieve a more accurate assessment of the true disease burden.[26–30]

^{18}F-FES PET/CT is a molecular imaging technique that uses a radiolabeled estradiol analog to noninvasively visualize tissues expressing ERs. This modality is especially relevant for ILC because approximately 95% of ILC cases are ER-positive.[31] In clinical practice, FES PET/CT has demonstrated the ability to alter clinical staging in up to 32% of patients with ILC by identifying occult metastatic disease missed by conventional imaging.[27] It is particularly effective at detecting bone metastases, which in ILCs are frequently sclerotic and may appear false-negative on FDG scans.[32] Beyond its diagnostic utility, FES PET/CT serves as a powerful predictive and prognostic biomarker. High tracer uptake generally correlates with a better response to endocrine therapy, whereas the presence of FES-negative or heterogeneous lesions often indicates endocrine resistance and a shorter duration of progression-free survival.[29,33] Despite these benefits, the technique has notable limitations: high physiologic uptake in the liver and bowel can obscure metastases in those regions, and patients must undergo a washout period if they are taking ER-blocking agents like tamoxifen or fulvestrant to ensure accurate tracer binding.[34]

Several additional PET radiopharmaceuticals show potential to improve detection and staging of ILC. ^{68}Ga-FAPI agents highlight cancer-associated fibroblasts and may be useful in ILC given its prominent stromal component, showing high tumor-to-background ratios and improved detection of infiltrative and occult metastases.[35,36] ^{18}F-fluciclovine targets amino acid transport and may outperform standard imaging in identifying primary and metastatic ILC, whereas PSMA-based PET has shown more limited sensitivity but retains theranostic potential.[37] Receptor-targeted tracers such as ^{68}Ga-NeoB (GRPR) also demonstrate promising early results for staging and metastatic detection, particularly in hormone receptor–positive disease.[38] In addition, ^{18}F-sodium fluoride (NaF) PET provides highly sensitive detection of osseous metastases by targeting osteoblastic activity.[39,40]

Whole-Body Diffusion-Weighted MRI Evaluation of Metastatic ILC

Whole-body diffusion-weighted MRI (WB-DWI/MRI) is an emerging, potentially highly sensitive functional imaging tool with promise for the staging and response assessment of ILC because of the tumor's unique biological and metastatic patterns.[41,42] WB-MRI may be superior at identifying characteristic ILC metastatic sites that are frequently occult on standard imaging, such as the peritoneum, retroperitoneum, and GI tract, while also proving to be more reliable for assessing bone-only or bone-predominant disease.[43]

Clinical data indicate that WB-MRI can identify additional sites of disease, leading to significant changes in systemic anticancer treatment for nearly half of the patients with ILC evaluated.[44]

Radioligand Therapy for ILC

Radioligand therapy (RLT) is an emerging precision oncology approach that uses theranostic pairs to deliver targeted radiation directly to cancer cells and may be well-suited for ILC given its radiation sensitivity, stromal biology, and potential to aid in cases of endocrine resistance.[45,46] Investigational targets include FAP (eg, 177Lu-FAP agents), GRPR (177Lu-NeoB), SSTR2 (Ac225-DOTATATE, 177Lu-DOTATOC), and human epidermal growth factor receptor 2 (HER2) mutations in metastatic ILC (^{177}Lu-trastuzumab and radioiodinated nanobodies), with molecular imaging used to confirm target expression before therapy.[46-48] Although largely in early-phase trials, RLT offers the potential of a personalized, multidisciplinary strategy for refractory disease, with ongoing challenges including biological heterogeneity and isotope cost.

SURGICAL APPROACH TO PRIMARY ILC

In principle, the surgical management of ILC does not differ from that of NST. In practice, however, surgery for those with ILC is fraught with unexpected findings, positive margins, and nodal upstaging.[49-54] ILC grows in so-called single file lines of tumor cells, presumably because of its lack of the adhesion protein E-cadherin.[55,56] This growth pattern is thought to underlie the challenges with detection on imaging and clinical staging.

Consequently, patients with ILC experience greater rates of second surgeries including re-excisions, completion mastectomies, axillary dissections, and higher rates of escalated locoregional treatment such as postmastectomy radiotherapy (PMRT).[57,58] While inadequate locoregional therapy can predispose to recurrence, more extensive treatment and repeated operations can lead to morbidity such as surgical site infection, seromas, negative psychological impact, lymphedema, tissue fibrosis, and chronic pain.[59-61] Thus, improving our approach to maximize the likelihood of success and right-size locoregional therapy for those with ILC is of critical importance and an area of unmet need in the treatment of breast cancer.[62]

Breast Conservation and Margins in ILC

Several studies demonstrate the safety of breast-conserving surgery in those with ILC; however, these studies assume that negative margins are achieved.[63-66] Since the publication of joint guidelines from the Society of Surgical Oncology and the American Society for Radiation Oncologists, adequate surgical margin width for invasive breast cancer including ILC is defined as "no ink on tumor," meaning that there is no reduction in the risk of recurrence with obtaining wider margins.[67] These guidelines result from a meta-analysis involving over 28,000 patients, of whom fewer than 10% had ILC. While patients with ILC were not highly represented in this analysis, there are no data suggesting that patients with ILC should be treated with different margin guidelines. Indeed, since the publication of these guidelines in 2014, re-excisions for patients with ILC have decreased, with no concomitant increase in recurrence reported in the literature thus far.[68]

Given the diffuse growth pattern and greater rates of multifocality observed in tumors with lobular histology, it is possible that the use of adjuvant radiotherapy adequately compensates for what is potentially a greater risk of residual microscopic disease in those with ILC. A small institutional series supports this hypothesis, demonstrating higher than expected rates of recurrence in patients with ILC who omitted radiation after lumpectomy, with such omission notably being associated with recurrence within the first five years of treatment, rather than the late recurrences for which ILC is known.[69,70] Interestingly, some data suggest that ILC might be biologically more radiosensitive than other tumor types.[71] While the increased use of PMRT in those with ILC is driven by higher stage, recently presented data also showed a statistically significant greater relative benefit of PMRT in those with ILC compared with those with NST when adjusting for stage.[72]

Achieving negative margins, even when defined as no ink on tumor, can be challenging in the setting of ILC. Multiple studies show that risk of positive margins in ILC is two-fold that of NST and can be as high as 30%-55%.[52-54,73] While the use of preoperative breast MRI has not consistently shown associations with improved outcomes in those with ILC, there are some data suggesting that re-excision rates may be reduced in those undergoing breast MRI.[74,75] In addition, the techniques of routine shave margin use and incorporation of oncoplastic surgery have also been shown to be associated with significant reduction in the risk of positive margins.[76-79] For those with larger ILC tumors, mastectomy is also not a guarantee of negative margins, with data showing that positive margin rates after mastectomy for those with ILC tumors measuring 5 cm or larger can be close to 20%.[80] These data suggest both a need for improved imaging and surgical techniques and also argue for the need for effective neoadjuvant therapy to optimize surgical outcomes. While inconsistent, there are data to support the notion that preoperative systemic therapy can lead to decrease in tumor burden, both to increase rates of successful breast conservation and to potentially downstage the axilla even in those with ILC.[81-86] A major challenge in studying the impact of neoadjuvant therapy in those with ILC is our inability to accurately clinically assess tumor burden; some studies suggest that pathologic stage can be higher than clinical stage after neoadjuvant therapy in those with ILC, suggesting that treatment was ineffective.[87] However, clinical tumor stage is often underestimating true disease burden; accordingly, other markers of response should be developed specifically for ILC.[88,89]

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Of note, a not uncommon clinical scenario is the finding of lobular carcinoma in situ (LCIS) at a surgical margin in the setting of resection for invasive breast cancer. Data suggest that there is no benefit of re-excision for either classic or nonclassic LCIS at the margin, provided that negative margins for the invasive component have been achieved.[90,91]

Axillary Management in ILC

As with management of the primary tumor, patients with ILC also experience higher rates of nodal involvement than those with NST.[92] While imaging and clinical examination may underestimate nodal burden, studies evaluating findings at surgery consistently demonstrate that lobular histology is a significant risk factor for having N2 or greater disease.[93,94] While this does not mean that the use of sentinel node surgery for axillary staging, omission of axillary lymph node dissection, or even omission of all axillary surgery cannot be applied for those with ILC, it does mean that ILC-specific analyses must be conducted to ensure the safety of these approaches for this unique histologic subtype of breast cancer.[95] Indeed, reduction in the extent of axillary surgery is important for reducing patient morbidity, particularly if such axillary surgery will not reduce recurrence or improve survival. However, we must consider how our ability to detect high burden of nodal disease clinically might differ in those with ILC compared with those with NST, potentially affecting both local disease control and the utilization of newer systemic therapies such as CDK4/6 inhibitors.

In the setting of clinically node-negative disease, sentinel node surgery remains the standard of care for staging the axilla in patients with ILC. Series suggest acceptable false-negative rate of sentinel node surgery in ILC although the use of frozen section for intraoperative evaluation can be more challenging than for other tumor types.[96,97] For patients with ILC and low burden of nodal disease (1-2 positive nodes), completion axillary lymph node dissection can be omitted provided that patients will receive adjuvant radiotherapy.[98]

Recent data from the SOUND, INSEMA, and BOOG 2013-08 trials demonstrated the safety of omitting all surgical staging of the axilla in carefully selected patients with favorable tumor biology and low clinical stage.[99-101] There is considerable debate about the safety of applying these data to patients with ILC, with several series showing that unexpected nodal involvement occurs at a greater rate in patients with ILC than those with NST, potentially altering the risk benefit ratio of axillary surgery omission in patients with ILC.[102] In addition, because most lobular tumors are biologically less aggressive, as evidenced by lower grade and proliferation rates, nodal involvement is a common indication for adjuvant treatment with CDK4/6 inhibitors in those with ILC.[103,104] While more data are needed before routinely applying criteria for omitting sentinel node surgery to the general patient population with ILC, there may be certain subgroups where omission is appropriate, such as patients older than 70 years with clinically small tumors and clinically negative axillae, using the principles of shared decision making.[105,106]

SYSTEMIC THERAPIES FOR ILC

ILC is predominantly ER-positive and commonly of the luminal A subtype.[55] Accordingly, endocrine therapy is the cornerstone of treatment for ER-positive (ER+) ILC in both early-stage and advanced diseases. Endocrine therapies include selective ER modulators (tamoxifen), aromatase inhibitors (AIs) and selective ER degraders (SERDs), including next-generation oral SERDs recently approved in the metastatic setting for ESR1-mutant breast cancer.[107,108] Large, randomized adjuvant trials in ER+ breast cancer have shown superior long-term outcomes with AIs compared with tamoxifen, irrespective of histology.[109,110] However, there is evidence that differences between specific ET may be more pronounced in ILC. A retrospective prespecified analysis of the BIG-1-98 phase III randomized adjuvant trial reported a larger magnitude of benefit of an AI versus tamoxifen in ILC compared with NST.[111] In the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 study, sequential adjuvant AI followed by tamoxifen compared with tamoxifen alone was associated with a survival advantage in ILC, but not in NST.[112] Similarly, a more recent retrospective analysis of the phase III SOFT and TEXT trials in premenopausal women found that the magnitude of benefit with an AI plus ovarian suppression versus tamoxifen was greater in ILC than in NST.[113] By contrast, a meta-analysis of three large adjuvant clinical trials in postmenopausal patients with central histopathology review confirmed AI superiority over tamoxifen but did not identify a differential effect between ILC and NST.[114]

Biologically, ILC has a higher frequency of FOXA1 mutations and lower frequency of GATA3 mutations compared with NST. Both genes encode transcription factors that play key roles in the ER transcriptional axis. Preclinical studies indicate that the ER transcriptional activity differs in ILC versus NST, and this is linked to a unique chromatin state driven by FOXA1. Persistent FOXA1-associated ER chromatin binding has been proposed as a potential mechanism of relative resistance to tamoxifen in ILC.[115]

Two preclinical window of opportunity trials evaluating tamoxifen and an AI in ILC have recently been completed. In TBCRC 037 (ClinicalTrials.gov identifier: NCT02206984), patients with ILC were randomly assigned to tamoxifen, letrozole, and fulvestrant.[116] Ki67 reduction was greater with fulvestrant compared with tamoxifen, but there was no difference between tamoxifen and an AI or between an AI and fulvestrant. In the Palbociclib and Endocrine Therapy for Lobular Breast Cancer Preoperative Study (PELOPS, ClinicalTrials.gov identifier: NCT02764541), AI resulted in an enhanced decrease in Ki67 with an AI when compared with tamoxifen in both ILC and NST, without significant interaction by histologic subtype. However, a more comprehensive analysis of the cell cycle using RNAseq showed a

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significant difference between tamoxifen and an AI effect on the inhibition of cell cycle gene sets in ILC, but not in NST.[117] Overall, these data support the notion that the ER axis in ILC differs from NST and may affect clinical benefit from specific endocrine therapies. Nevertheless, there is no definitive evidence in the adjuvant setting that clinical benefit from tamoxifen versus an AI differs in ILC versus NST.

Next-generation oral SERDs are emerging as superior agents in certain contexts, particularly in the metastatic setting in the presence of an *ESR1* mutation.[108,118] Whether ILC, a breast cancer that is highly ER-dependent, derives particular benefit from next-generation oral SERDs or from the combination of an oral SERD with an AI relative to older endocrine therapies remains unclear. Several ongoing large trials of next-generation oral SERDs do not stratify patients by histologic subtype, and dedicated prospective studies in ILC may be needed to generate robust breast cancer subtype-specific data.

CDK4/6 inhibitors (CDK4/6is) are pivotal components of treatment in ER+ breast cancer in metastatic disease and, more recently, in the adjuvant setting. Subgroup analyses from metastatic trials suggest that the magnitude of benefit from CDK4/6is is similar in ILC and NST.[119,120] To date, there are no dedicated analyses specifically evaluating the benefit of combining abemaciclib or ribociclib to adjuvant endocrine therapy in ILC. However, in the adjuvant setting, improvement in invasive disease-free survival (iDFS) with abemaciclib has been observed across molecular subtypes of ER+ breast cancers, including luminal A, which comprises most ILCs.[121] PALLAS, a phase III randomized trial of adjuvant palbociclib, did not demonstrate improved outcomes with the addition of palbociclib. However, an exploratory subgroup analysis suggested a numerically greater benefit in ILC (hazard ratio [HR], 0.76) than in NST (HR, 0.97) although the interaction test by histology was not statistically significant.[122] Similarly, in PENELOPE-B, the addition of adjuvant palbociclib for 1 year did not improve long-term outcomes overall; however, exploratory analyses showed a trend toward improved iDFS in patients with ILC who received palbociclib.[123]

CHEMOTHERAPY IN EARLY-STAGE DISEASE

Neoadjuvant chemotherapy in ER+ breast cancer is used primarily in high-stage disease to downstage tumors, facilitate margin negative resection, and increase the feasibility of breast-conserving surgery. An early prospective study investigating neoadjuvant chemotherapy in ILC and NST reported lower rates of pathologic complete response (pCR) and lower rates of breast-conserving surgery in patients with ILC. However, not all patients in the study had ER+ disease, and the proportion of patients with ER-negative disease was higher among patients with NST.[124] Since then, multiple prospective studies have similarly shown lower pCR rates and lower breast-conserving surgery rates in ILC, suggesting that neoadjuvant chemotherapy may be less effective for downstaging in this breast cancer subtype and that neoadjuvant endocrine therapy may be a preferable approach.[125] However, most of these studies did not incorporate molecular risk stratification to chemotherapy benefit, highlighting the need to better define the specific subgroups of ILC that may derive benefit from neoadjuvant chemotherapy.

Several cohort studies have reported that adjuvant chemotherapy is not associated with improved 10-year overall survival.[126,127] A more recent meta-analysis of eight clinical trials also showed that chemotherapy was not associated with improved long-term outcomes.[128] In addition, a study restricted to patients with Oncotype DX score ≥26 did not demonstrate improved overall survival with the addition of chemotherapy.[129] By contrast, other analyses suggest that patients with high-risk ILC tumors derive long-term benefit from chemotherapy. In one study, factors associated with high-risk disease included age, tumor size, nodal status, and lymphovascular invasion.[130]

Overall, the studies investigating adjuvant chemotherapy specifically in ILC are largely retrospective and data are conflicting. Collectively, the data suggest lower chemotherapy efficacy in ILC than NST overall, with a likely benefit in high-risk subgroups. It is unclear how well the genomic risk stratification tools predict outcomes and benefit from chemotherapy ILC. Oncotype DX risk scores in ILC are most often low or intermediate. High-risk scores occur in about 10% of ILC tumors and are more frequently observed in the pleomorphic variant.[131–133] An exploratory subgroup analysis of the MINDACT trial, which included central pathology review and used the MammaPrint 70 gene signature, found that about 16% of ILC tumors in this subgroup analysis were classified as genomic high-risk tumors, with a higher proportion among nonclassic ILCs. After accounting for genomic risk, overall survival was comparable between ILC and NST.[134] LobSig is an ILC-specific gene expression signature that is prognostic of survival, but its role in predicting benefit from chemotherapy remains unclear.[135] Additional studies are needed to evaluate existing and novel molecular tools for risk stratification and prediction of chemotherapy benefit in ILC.

In addition to unique patterns of presentation and metastatic spread, ILC has a unique constellation of genomic alterations. Several of these alterations have targeted treatments approved for their treatment, and others hold promise as opportunities for development of future targeted therapies.

CDH1 alteration is the hallmark of ILC, and while it is not felt to be directly druggable, it leads to increased dependence on alternate pathways that have been investigated as targets in breast cancer.[136] Bosutinib, a tyrosine kinase inhibitor of *BCR-ABL* and *SRC*, a pathway upregulated in *CDH1*-deficient models, is approved for the treatment of chronic myeloid leukemia and has been studied in combination with fulvestrant and palbociclib in a phase I trial in breast cancer. The

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combination was found to be tolerable with an encouraging 6-month clinical benefit rate of 50%.[137]

ROS1 has been identified as another target whose inhibition leads to synthetic lethality in E-cadherin–deficient preclinical models.[138] A trial investigating *ROS1* inhibition in the metastatic setting failed to meet its primary end point (ROLo),[139] but the ROSALINE trial of neoadjuvant endocrine therapy + *ROS1* inhibitor entrectinib found an encouraging objective response rate of 49% on preoperative MRI, and the REPLOT trial is ongoing.[140,141]

PI3K/AKT/mTOR pathway alterations are identified in 35%-60% of patients with ILC,[142-145] but the benefit of agents targeting this pathway may be independent of mutation status as loss of E-cadherin has been shown to lead to aberrant activation of *PI3K/AKT* signaling and results in susceptibility to inhibition of this pathway.[146,147] Inhibitors of this pathway are approved in the metastatic setting; the *PIK3CA* inhibitors alpelisib and inavolisib are approved in patients with *PIK3CA* mutation, the *AKT* inhibitor capivasertib is approved in patients with alteration in *AKT/PIK3CA/PTEN*, and the mTOR inhibitor everolimus is approved in this population regardless of mutation status.[148-152] Studies of novel agents targeting this pathway in patients with pathway-mutated cancers in the early setting (ClinicalTrials.gov identifier: NCT05306041) and mutation-agnostic studies targeting this pathway in the advanced setting hold promise for patients with ILC.[153]

While *ERBB2* amplification leading to HER2-positive disease is rare in ILC, mutations in *ERBB2* are enriched in this population, having been identified in 7%-9% of tumors from patients with early-stage ILC[142,154] and 6%-27% of patients with metastatic disease.[155-157] Neratinib and trastuzumab-deruxtecan, medications targeting *ERBB2* mutation, have demonstrated benefit of targeting this mutation in patients with hormone receptor–positive, HER2-negative, HER2-mutant metastatic breast cancer[158] or *ERBB2*-mutated solid tumors,[159] and a neoadjuvant trial specific for patients with ILC is ongoing investigating the benefit of neratinib in combination with standard endocrine therapy in patients with *ERBB2*-mutated stage I-III ILC with a primary end point of preoperative endocrine prognostic index score (ClinicalTrials.gov identifier: NCT05919108).[160,161]

In conclusion, as the treatment of breast cancer continues to move toward personalization, accumulating data show that lobular histology confers unique clinical and molecular features warranting recognition of ILC as a specific subtype of breast cancer that requires a nuanced diagnostic and treatment approach. Studies continue to identify areas of suboptimal outcomes for patients with ILC, ranging from worse sensitivity of imaging studies in the screening setting, suboptimal diagnostic tool performance, worse surgical outcomes, decreased responsiveness to standard therapies, and worse long-term outcomes in both early and late-stage settings. While we are currently in the beginning stages of identifying ILC specific approaches, there is a clear unmet need to conduct ILC-specific studies and report on histology-specific outcomes in clinical trials. By doing so, we can hopefully improve outcomes for all patients with ILC by tailoring treatment approaches to its distinct biological features.

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Tailoring Management for Invasive Lobular Carcinoma: Imaging, Surgical Treatment, and Systemic Therapy Considerations

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OVERVIEW

Invasive lobular carcinoma (ILC) represents the most common special subtype of breast cancer. Studies show challenges with imaging, surgical therapy, and systemic therapy selection, arguing for the need for improved treatment personalization for this histologic subtype of breast cancer. While standard imaging tools have decreased sensitivity for ILC, newer imaging approaches may be more effective in both early and advanced disease settings. Surgical treatment is notable for high rate of positive margins and need for more extensive surgery; this may be mitigated by improved imaging and incorporation of particular techniques. While endocrine therapy remains the mainstay of treatment for most patients with ILC, the unique molecular characteristics of this tumor type may provide targets for new therapeutic approaches. The preponderance of data supports the need for ILC specific studies and trials.

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INTRODUCTION

Invasive lobular carcinoma (ILC) is the most common special histologic subtype of breast cancer accounting for 10%–15% of all breast cancers. The hallmark of ILC is the loss of E-cadherin (encoded by the gene *CDH1*), resulting in discohesive cell growth and decreased disruption of the stroma. Between 30,000 and 40,000 women are diagnosed with ILC annually in the United States. Over the past decade, the incidence rate of ILC (2.8%) has increased more steeply compared with all other breast cancer subtypes.[1]

At diagnosis, ILC presents with a higher tumor burden compared with breast cancer of no special type (NST), also known as invasive ductal carcinoma. A recent meta-analysis of patients with early-stage breast cancer who received anthracycline-based adjuvant chemotherapy in National Surgical Adjuvant Breast and Bowel Project randomized phase III clinical trials showed that patients with ILC presented with a higher proportion of tumors that are larger than 4 cm and with ≥4 involved lymph nodes compared with those with NST.[2] This is likely due, at least in part, to the challenges in breast imaging of primary ILC, particularly since ILC tends not to form a distinct mass. The confluence of higher stage at diagnosis and decreased sensitivity of imaging lead to suboptimal outcomes with surgical treatment for those with ILC. In addition, ILC has a lower rate of early recurrences (<5 years) but higher risk of late recurrences (after 5 years).

In the metastatic setting, ILC has a higher propensity to metastasize to the GI tract, ovaries, and leptomeninges. Biologically, ILC has a unique genomic landscape, and emerging studies are revealing distinct features of the tumor microenvironment.[3–6] Despite the clinical and biological data supporting the notion that ILC is a unique breast cancer subtype, most of the clinical guidelines for imaging, surgical management, and systemics treatments in ILC are extrapolated from clinical studies in which most of the patients had NST breast cancer. This highlights the unmet need for prospective clinical studies of ILC and particular attention to the unique features of this tumor during clinical management.

IMAGING CONSIDERATIONS IN ILC

Evaluation of Primary and Locoregional Metastatic Disease

ILC can be difficult to detect with conventional imaging because its infiltrative, single-file growth pattern often lacks a central mass or desmoplastic response.[7–10] Standard mammography, including digital breast tomosynthesis, is frequently limited by low sensitivity, which can drop as low as 10% to 30% in patients with dense breast tissue.[8,11–13] Breast ultrasound serves as a valuable supplementary tool, demonstrating an improved sensitivity and assisting in the evaluation of dense tissue and palpable abnormalities. Contrast-enhanced breast magnetic resonance imaging (MRI) remains the current gold standard for primary ILC detection and local staging because of its higher sensitivity, which is between 83% and 100%.[14–17] However, MRI is associated with high costs and a higher rate of false positives,

PRACTICAL APPLICATIONS

- Recognize that standard imaging tools like mammogram, ultrasound, and fluorodeoxyglucose-positron emission tomography may underestimate disease extent in patients with invasive lobular carcinoma (ILC).
- Surgical treatment of patients with ILC is notable for high rates of positive margins and upstaging on pathology.
- Oncoplastic surgery is safe and may reduce positive margins.
- The use of neoadjuvant or adjuvant chemotherapy in ILC may improve surgical outcomes and survival outcomes in select populations, but ILC-specific treatment selection tools are needed.
- The unique molecular features of ILC could lead to differential response to standard endocrine therapies; further research stratified by histology is needed.

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and it may overestimate tumor size, which can potentially lead to more extensive surgeries such as unnecessary mastectomies.[18] While contrast-enhanced mammography is promising for detection of sites of primary ILC, this method is limited compared with MRI for assessment of locoregional metastatic disease given the narrow field of view of mammography.[19]

Positron Emission Tomography/Computed Tomography Evaluation of Metastatic ILC

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) detects metabolic activity via glucose uptake; however, its effectiveness in ILC can be limited.[9,20,21] Compared with NST, ILC primary tumors and metastases are frequently less FDG-avid, leading to a higher rate of false-negative results.[22] While it is valuable for identifying distant disease in many cancers, ILC often spreads to serosal surfaces, the GI tract, and the peritoneum—sites where FDG PET/CT frequently fails to show significant uptake above background levels.[23]

Despite these limitations, FDG PET/CT remains a standard-of-care tool for systemic staging and can provide important prognostic information.[24] High FDG uptake (SUVmax >5.0), while less common in ILC, is typically associated with more aggressive disease and a poorer prognosis, whereas FDG-indolent lesions are more characteristic of the typical, strongly estrogen receptor (ER)–positive ILC phenotype and correlate with longer survival.[25] Because of its known weaknesses in this subtype, experts often recommend supplementing FDG scans with ER-targeted (fluoroestradiol [FES]) PET or, potentially in the future, other radiopharmaceuticals such as fibroblast activation protein-targeted (FAPI) PET to achieve a more accurate assessment of the true disease burden.[26–30]

^{18}F-FES PET/CT is a molecular imaging technique that uses a radiolabeled estradiol analog to noninvasively visualize tissues expressing ERs. This modality is especially relevant for ILC because approximately 95% of ILC cases are ER-positive.[31] In clinical practice, FES PET/CT has demonstrated the ability to alter clinical staging in up to 32% of patients with ILC by identifying occult metastatic disease missed by conventional imaging.[27] It is particularly effective at detecting bone metastases, which in ILCs are frequently sclerotic and may appear false-negative on FDG scans.[32] Beyond its diagnostic utility, FES PET/CT serves as a powerful predictive and prognostic biomarker. High tracer uptake generally correlates with a better response to endocrine therapy, whereas the presence of FES-negative or heterogeneous lesions often indicates endocrine resistance and a shorter duration of progression-free survival.[29,33] Despite these benefits, the technique has notable limitations: high physiologic uptake in the liver and bowel can obscure metastases in those regions, and patients must undergo a washout period if they are taking ER-blocking agents like tamoxifen or fulvestrant to ensure accurate tracer binding.[34]

Several additional PET radiopharmaceuticals show potential to improve detection and staging of ILC. ^{68}Ga-FAPI agents highlight cancer-associated fibroblasts and may be useful in ILC given its prominent stromal component, showing high tumor-to-background ratios and improved detection of infiltrative and occult metastases.[35,36] ^{18}F-fluciclovine targets amino acid transport and may outperform standard imaging in identifying primary and metastatic ILC, whereas PSMA-based PET has shown more limited sensitivity but retains theranostic potential.[37] Receptor-targeted tracers such as ^{68}Ga-NeoB (GRPR) also demonstrate promising early results for staging and metastatic detection, particularly in hormone receptor–positive disease.[38] In addition, ^{18}F-sodium fluoride (NaF) PET provides highly sensitive detection of osseous metastases by targeting osteoblastic activity.[39,40]

Whole-Body Diffusion-Weighted MRI Evaluation of Metastatic ILC

Whole-body diffusion-weighted MRI (WB-DWI/MRI) is an emerging, potentially highly sensitive functional imaging tool with promise for the staging and response assessment of ILC because of the tumor's unique biological and metastatic patterns.[41,42] WB-MRI may be superior at identifying characteristic ILC metastatic sites that are frequently occult on standard imaging, such as the peritoneum, retroperitoneum, and GI tract, while also proving to be more reliable for assessing bone-only or bone-predominant disease.[43]

Clinical data indicate that WB-MRI can identify additional sites of disease, leading to significant changes in systemic anticancer treatment for nearly half of the patients with ILC evaluated.[44]

Radioligand Therapy for ILC

Radioligand therapy (RLT) is an emerging precision oncology approach that uses theranostic pairs to deliver targeted radiation directly to cancer cells and may be well-suited for ILC given its radiation sensitivity, stromal biology, and potential to aid in cases of endocrine resistance.[45,46] Investigational targets include FAP (eg, 177Lu-FAP agents), GRPR (177Lu-NeoB), SSTR2 (Ac225-DOTATATE, 177Lu-DOTATOC), and human epidermal growth factor receptor 2 (HER2) mutations in metastatic ILC (^{177}Lu-trastuzumab and radioiodinated nanobodies), with molecular imaging used to confirm target expression before therapy.[46-48] Although largely in early-phase trials, RLT offers the potential of a personalized, multidisciplinary strategy for refractory disease, with ongoing challenges including biological heterogeneity and isotope cost.

SURGICAL APPROACH TO PRIMARY ILC

In principle, the surgical management of ILC does not differ from that of NST. In practice, however, surgery for those with ILC is fraught with unexpected findings, positive margins, and nodal upstaging.[49-54] ILC grows in so-called single file lines of tumor cells, presumably because of its lack of the adhesion protein E-cadherin.[55,56] This growth pattern is thought to underlie the challenges with detection on imaging and clinical staging.

Consequently, patients with ILC experience greater rates of second surgeries including re-excisions, completion mastectomies, axillary dissections, and higher rates of escalated locoregional treatment such as postmastectomy radiotherapy (PMRT).[57,58] While inadequate locoregional therapy can predispose to recurrence, more extensive treatment and repeated operations can lead to morbidity such as surgical site infection, seromas, negative psychological impact, lymphedema, tissue fibrosis, and chronic pain.[59-61] Thus, improving our approach to maximize the likelihood of success and right-size locoregional therapy for those with ILC is of critical importance and an area of unmet need in the treatment of breast cancer.[62]

Breast Conservation and Margins in ILC

Several studies demonstrate the safety of breast-conserving surgery in those with ILC; however, these studies assume that negative margins are achieved.[63-66] Since the publication of joint guidelines from the Society of Surgical Oncology and the American Society for Radiation Oncologists, adequate surgical margin width for invasive breast cancer including ILC is defined as "no ink on tumor," meaning that there is no reduction in the risk of recurrence with obtaining wider margins.[67] These guidelines result from a meta-analysis involving over 28,000 patients, of whom fewer than 10% had ILC. While patients with ILC were not highly represented in this analysis, there are no data suggesting that patients with ILC should be treated with different margin guidelines. Indeed, since the publication of these guidelines in 2014, re-excisions for patients with ILC have decreased, with no concomitant increase in recurrence reported in the literature thus far.[68]

Given the diffuse growth pattern and greater rates of multifocality observed in tumors with lobular histology, it is possible that the use of adjuvant radiotherapy adequately compensates for what is potentially a greater risk of residual microscopic disease in those with ILC. A small institutional series supports this hypothesis, demonstrating higher than expected rates of recurrence in patients with ILC who omitted radiation after lumpectomy, with such omission notably being associated with recurrence within the first five years of treatment, rather than the late recurrences for which ILC is known.[69,70] Interestingly, some data suggest that ILC might be biologically more radiosensitive than other tumor types.[71] While the increased use of PMRT in those with ILC is driven by higher stage, recently presented data also showed a statistically significant greater relative benefit of PMRT in those with ILC compared with those with NST when adjusting for stage.[72]

Achieving negative margins, even when defined as no ink on tumor, can be challenging in the setting of ILC. Multiple studies show that risk of positive margins in ILC is two-fold that of NST and can be as high as 30%-55%.[52-54,73] While the use of preoperative breast MRI has not consistently shown associations with improved outcomes in those with ILC, there are some data suggesting that re-excision rates may be reduced in those undergoing breast MRI.[74,75] In addition, the techniques of routine shave margin use and incorporation of oncoplastic surgery have also been shown to be associated with significant reduction in the risk of positive margins.[76-79] For those with larger ILC tumors, mastectomy is also not a guarantee of negative margins, with data showing that positive margin rates after mastectomy for those with ILC tumors measuring 5 cm or larger can be close to 20%.[80] These data suggest both a need for improved imaging and surgical techniques and also argue for the need for effective neoadjuvant therapy to optimize surgical outcomes. While inconsistent, there are data to support the notion that preoperative systemic therapy can lead to decrease in tumor burden, both to increase rates of successful breast conservation and to potentially downstage the axilla even in those with ILC.[81-86] A major challenge in studying the impact of neoadjuvant therapy in those with ILC is our inability to accurately clinically assess tumor burden; some studies suggest that pathologic stage can be higher than clinical stage after neoadjuvant therapy in those with ILC, suggesting that treatment was ineffective.[87] However, clinical tumor stage is often underestimating true disease burden; accordingly, other markers of response should be developed specifically for ILC.[88,89]

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Of note, a not uncommon clinical scenario is the finding of lobular carcinoma in situ (LCIS) at a surgical margin in the setting of resection for invasive breast cancer. Data suggest that there is no benefit of re-excision for either classic or nonclassic LCIS at the margin, provided that negative margins for the invasive component have been achieved.[90,91]

Axillary Management in ILC

As with management of the primary tumor, patients with ILC also experience higher rates of nodal involvement than those with NST.[92] While imaging and clinical examination may underestimate nodal burden, studies evaluating findings at surgery consistently demonstrate that lobular histology is a significant risk factor for having N2 or greater disease.[93,94] While this does not mean that the use of sentinel node surgery for axillary staging, omission of axillary lymph node dissection, or even omission of all axillary surgery cannot be applied for those with ILC, it does mean that ILC-specific analyses must be conducted to ensure the safety of these approaches for this unique histologic subtype of breast cancer.[95] Indeed, reduction in the extent of axillary surgery is important for reducing patient morbidity, particularly if such axillary surgery will not reduce recurrence or improve survival. However, we must consider how our ability to detect high burden of nodal disease clinically might differ in those with ILC compared with those with NST, potentially affecting both local disease control and the utilization of newer systemic therapies such as CDK4/6 inhibitors.

In the setting of clinically node-negative disease, sentinel node surgery remains the standard of care for staging the axilla in patients with ILC. Series suggest acceptable false-negative rate of sentinel node surgery in ILC although the use of frozen section for intraoperative evaluation can be more challenging than for other tumor types.[96,97] For patients with ILC and low burden of nodal disease (1-2 positive nodes), completion axillary lymph node dissection can be omitted provided that patients will receive adjuvant radiotherapy.[98]

Recent data from the SOUND, INSEMA, and BOOG 2013-08 trials demonstrated the safety of omitting all surgical staging of the axilla in carefully selected patients with favorable tumor biology and low clinical stage.[99-101] There is considerable debate about the safety of applying these data to patients with ILC, with several series showing that unexpected nodal involvement occurs at a greater rate in patients with ILC than those with NST, potentially altering the risk benefit ratio of axillary surgery omission in patients with ILC.[102] In addition, because most lobular tumors are biologically less aggressive, as evidenced by lower grade and proliferation rates, nodal involvement is a common indication for adjuvant treatment with CDK4/6 inhibitors in those with ILC.[103,104] While more data are needed before routinely applying criteria for omitting sentinel node surgery to the general patient population with ILC, there may be certain subgroups where omission is appropriate, such as patients older than 70 years with clinically small tumors and clinically negative axillae, using the principles of shared decision making.[105,106]

SYSTEMIC THERAPIES FOR ILC

ILC is predominantly ER-positive and commonly of the luminal A subtype.[55] Accordingly, endocrine therapy is the cornerstone of treatment for ER-positive (ER+) ILC in both early-stage and advanced diseases. Endocrine therapies include selective ER modulators (tamoxifen), aromatase inhibitors (AIs) and selective ER degraders (SERDs), including next-generation oral SERDs recently approved in the metastatic setting for ESR1-mutant breast cancer.[107,108] Large, randomized adjuvant trials in ER+ breast cancer have shown superior long-term outcomes with AIs compared with tamoxifen, irrespective of histology.[109,110] However, there is evidence that differences between specific ET may be more pronounced in ILC. A retrospective prespecified analysis of the BIG-1-98 phase III randomized adjuvant trial reported a larger magnitude of benefit of an AI versus tamoxifen in ILC compared with NST.[111] In the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 study, sequential adjuvant AI followed by tamoxifen compared with tamoxifen alone was associated with a survival advantage in ILC, but not in NST.[112] Similarly, a more recent retrospective analysis of the phase III SOFT and TEXT trials in premenopausal women found that the magnitude of benefit with an AI plus ovarian suppression versus tamoxifen was greater in ILC than in NST.[113] By contrast, a meta-analysis of three large adjuvant clinical trials in postmenopausal patients with central histopathology review confirmed AI superiority over tamoxifen but did not identify a differential effect between ILC and NST.[114]

Biologically, ILC has a higher frequency of FOXA1 mutations and lower frequency of GATA3 mutations compared with NST. Both genes encode transcription factors that play key roles in the ER transcriptional axis. Preclinical studies indicate that the ER transcriptional activity differs in ILC versus NST, and this is linked to a unique chromatin state driven by FOXA1. Persistent FOXA1-associated ER chromatin binding has been proposed as a potential mechanism of relative resistance to tamoxifen in ILC.[115]

Two preclinical window of opportunity trials evaluating tamoxifen and an AI in ILC have recently been completed. In TBCRC 037 (ClinicalTrials.gov identifier: NCT02206984), patients with ILC were randomly assigned to tamoxifen, letrozole, and fulvestrant.[116] Ki67 reduction was greater with fulvestrant compared with tamoxifen, but there was no difference between tamoxifen and an AI or between an AI and fulvestrant. In the Palbociclib and Endocrine Therapy for Lobular Breast Cancer Preoperative Study (PELOPS, ClinicalTrials.gov identifier: NCT02764541), AI resulted in an enhanced decrease in Ki67 with an AI when compared with tamoxifen in both ILC and NST, without significant interaction by histologic subtype. However, a more comprehensive analysis of the cell cycle using RNAseq showed a

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significant difference between tamoxifen and an AI effect on the inhibition of cell cycle gene sets in ILC, but not in NST.[117] Overall, these data support the notion that the ER axis in ILC differs from NST and may affect clinical benefit from specific endocrine therapies. Nevertheless, there is no definitive evidence in the adjuvant setting that clinical benefit from tamoxifen versus an AI differs in ILC versus NST.

Next-generation oral SERDs are emerging as superior agents in certain contexts, particularly in the metastatic setting in the presence of an *ESR1* mutation.[108,118] Whether ILC, a breast cancer that is highly ER-dependent, derives particular benefit from next-generation oral SERDs or from the combination of an oral SERD with an AI relative to older endocrine therapies remains unclear. Several ongoing large trials of next-generation oral SERDs do not stratify patients by histologic subtype, and dedicated prospective studies in ILC may be needed to generate robust breast cancer subtype-specific data.

CDK4/6 inhibitors (CDK4/6is) are pivotal components of treatment in ER+ breast cancer in metastatic disease and, more recently, in the adjuvant setting. Subgroup analyses from metastatic trials suggest that the magnitude of benefit from CDK4/6is is similar in ILC and NST.[119,120] To date, there are no dedicated analyses specifically evaluating the benefit of combining abemaciclib or ribociclib to adjuvant endocrine therapy in ILC. However, in the adjuvant setting, improvement in invasive disease-free survival (iDFS) with abemaciclib has been observed across molecular subtypes of ER+ breast cancers, including luminal A, which comprises most ILCs.[121] PALLAS, a phase III randomized trial of adjuvant palbociclib, did not demonstrate improved outcomes with the addition of palbociclib. However, an exploratory subgroup analysis suggested a numerically greater benefit in ILC (hazard ratio [HR], 0.76) than in NST (HR, 0.97) although the interaction test by histology was not statistically significant.[122] Similarly, in PENELOPE-B, the addition of adjuvant palbociclib for 1 year did not improve long-term outcomes overall; however, exploratory analyses showed a trend toward improved iDFS in patients with ILC who received palbociclib.[123]

CHEMOTHERAPY IN EARLY-STAGE DISEASE

Neoadjuvant chemotherapy in ER+ breast cancer is used primarily in high-stage disease to downstage tumors, facilitate margin negative resection, and increase the feasibility of breast-conserving surgery. An early prospective study investigating neoadjuvant chemotherapy in ILC and NST reported lower rates of pathologic complete response (pCR) and lower rates of breast-conserving surgery in patients with ILC. However, not all patients in the study had ER+ disease, and the proportion of patients with ER-negative disease was higher among patients with NST.[124] Since then, multiple prospective studies have similarly shown lower pCR rates and lower breast-conserving surgery rates in ILC, suggesting that neoadjuvant chemotherapy may be less effective for downstaging in this breast cancer subtype and that neoadjuvant endocrine therapy may be a preferable approach.[125] However, most of these studies did not incorporate molecular risk stratification to chemotherapy benefit, highlighting the need to better define the specific subgroups of ILC that may derive benefit from neoadjuvant chemotherapy.

Several cohort studies have reported that adjuvant chemotherapy is not associated with improved 10-year overall survival.[126,127] A more recent meta-analysis of eight clinical trials also showed that chemotherapy was not associated with improved long-term outcomes.[128] In addition, a study restricted to patients with Oncotype DX score ≥26 did not demonstrate improved overall survival with the addition of chemotherapy.[129] By contrast, other analyses suggest that patients with high-risk ILC tumors derive long-term benefit from chemotherapy. In one study, factors associated with high-risk disease included age, tumor size, nodal status, and lymphovascular invasion.[130]

Overall, the studies investigating adjuvant chemotherapy specifically in ILC are largely retrospective and data are conflicting. Collectively, the data suggest lower chemotherapy efficacy in ILC than NST overall, with a likely benefit in high-risk subgroups. It is unclear how well the genomic risk stratification tools predict outcomes and benefit from chemotherapy ILC. Oncotype DX risk scores in ILC are most often low or intermediate. High-risk scores occur in about 10% of ILC tumors and are more frequently observed in the pleomorphic variant.[131–133] An exploratory subgroup analysis of the MINDACT trial, which included central pathology review and used the MammaPrint 70 gene signature, found that about 16% of ILC tumors in this subgroup analysis were classified as genomic high-risk tumors, with a higher proportion among nonclassic ILCs. After accounting for genomic risk, overall survival was comparable between ILC and NST.[134] LobSig is an ILC-specific gene expression signature that is prognostic of survival, but its role in predicting benefit from chemotherapy remains unclear.[135] Additional studies are needed to evaluate existing and novel molecular tools for risk stratification and prediction of chemotherapy benefit in ILC.

In addition to unique patterns of presentation and metastatic spread, ILC has a unique constellation of genomic alterations. Several of these alterations have targeted treatments approved for their treatment, and others hold promise as opportunities for development of future targeted therapies.

CDH1 alteration is the hallmark of ILC, and while it is not felt to be directly druggable, it leads to increased dependence on alternate pathways that have been investigated as targets in breast cancer.[136] Bosutinib, a tyrosine kinase inhibitor of *BCR-ABL* and *SRC*, a pathway upregulated in *CDH1*-deficient models, is approved for the treatment of chronic myeloid leukemia and has been studied in combination with fulvestrant and palbociclib in a phase I trial in breast cancer. The

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combination was found to be tolerable with an encouraging 6-month clinical benefit rate of 50%.[137]

ROS1 has been identified as another target whose inhibition leads to synthetic lethality in E-cadherin–deficient preclinical models.[138] A trial investigating *ROS1* inhibition in the metastatic setting failed to meet its primary end point (ROLo),[139] but the ROSALINE trial of neoadjuvant endocrine therapy + *ROS1* inhibitor entrectinib found an encouraging objective response rate of 49% on preoperative MRI, and the REPLOT trial is ongoing.[140,141]

PI3K/AKT/mTOR pathway alterations are identified in 35%-60% of patients with ILC,[142-145] but the benefit of agents targeting this pathway may be independent of mutation status as loss of E-cadherin has been shown to lead to aberrant activation of *PI3K/AKT* signaling and results in susceptibility to inhibition of this pathway.[146,147] Inhibitors of this pathway are approved in the metastatic setting; the *PIK3CA* inhibitors alpelisib and inavolisib are approved in patients with *PIK3CA* mutation, the *AKT* inhibitor capivasertib is approved in patients with alteration in *AKT/PIK3CA/PTEN*, and the mTOR inhibitor everolimus is approved in this population regardless of mutation status.[148-152] Studies of novel agents targeting this pathway in patients with pathway-mutated cancers in the early setting (ClinicalTrials.gov identifier: NCT05306041) and mutation-agnostic studies targeting this pathway in the advanced setting hold promise for patients with ILC.[153]

While *ERBB2* amplification leading to HER2-positive disease is rare in ILC, mutations in *ERBB2* are enriched in this population, having been identified in 7%-9% of tumors from patients with early-stage ILC[142,154] and 6%-27% of patients with metastatic disease.[155-157] Neratinib and trastuzumab-deruxtecan, medications targeting *ERBB2* mutation, have demonstrated benefit of targeting this mutation in patients with hormone receptor–positive, HER2-negative, HER2-mutant metastatic breast cancer[158] or *ERBB2*-mutated solid tumors,[159] and a neoadjuvant trial specific for patients with ILC is ongoing investigating the benefit of neratinib in combination with standard endocrine therapy in patients with *ERBB2*-mutated stage I-III ILC with a primary end point of preoperative endocrine prognostic index score (ClinicalTrials.gov identifier: NCT05919108).[160,161]

In conclusion, as the treatment of breast cancer continues to move toward personalization, accumulating data show that lobular histology confers unique clinical and molecular features warranting recognition of ILC as a specific subtype of breast cancer that requires a nuanced diagnostic and treatment approach. Studies continue to identify areas of suboptimal outcomes for patients with ILC, ranging from worse sensitivity of imaging studies in the screening setting, suboptimal diagnostic tool performance, worse surgical outcomes, decreased responsiveness to standard therapies, and worse long-term outcomes in both early and late-stage settings. While we are currently in the beginning stages of identifying ILC specific approaches, there is a clear unmet need to conduct ILC-specific studies and report on histology-specific outcomes in clinical trials. By doing so, we can hopefully improve outcomes for all patients with ILC by tailoring treatment approaches to its distinct biological features.

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Innovation, Evidence, Compassion, and Hope: Delivering Outcomes That Matter

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OVERVIEW

Over the past 50 years, advances in systemic therapy, radiotherapy, surgery, and supportive care have dramatically improved cancer outcomes. Yet, growing concern exists that in our race for biomedical innovation, the metrics used to evaluate progress have drifted away from the outcomes that matter most to people living with cancer. In addition, we have not built health care systems that adequately recognize the psychosocial, relational, and existential dimensions of illness. Many medical therapies approved through regulatory pathways in the past decade offer modest clinical benefit while imposing substantial burdens on patients and the sustainability of health systems globally. These patterns reflect the convergence of global structural forces—including clinical trial design, regulatory standards, practice guidelines, and reimbursement systems—that often prioritize innovation and access over greater certainty that therapies meaningfully improve clinically relevant outcomes. In this review, we examine how these interconnected forces influence patients' experiences of cancer care worldwide. We argue that sustaining meaningful progress requires a reanchoring of oncology to outcomes that reflect what patients consistently value: longer survival, preserved function, improved quality of life, and timely access to high-value care.

Since the declaration of the War on Cancer more than 5 decades ago, oncology has pursued progress with a collective urgency that has led to many new treatments and steadily improving outcomes in many areas of our field. In this time, we have witnessed remarkable scientific and therapeutic advances. Alongside these gains, however, there is growing recognition that the metrics we use to evaluate, celebrate, and communicate benefit have drifted from what matters most to those living with cancer.[1,2] In addition, many treatments that are approved by regulatory agencies contribute only marginally to improving clinical outcomes while adding substantial physical and nonphysical toxicities at high cost.[3-6] These challenges do not reflect a lack of commitment to improving outcomes; rather, they arise from multiple factors including the inherent difficulty of balancing speed and certainty, access and equity, and hope and realism. The clinical, education, and research ecosystems of oncology are deeply intertwined with the pharmaceutical industry, which has contributed both to the major advances in our field, and also some of the challenges. Outside of high-income health systems, resource constraints limit access to new therapies and amplify the consequences of evidentiary uncertainty for patients and clinicians alike. The resulting misalignment can complicate treatment decision making, amplify prognostic uncertainty, widen inequities in care access, and contribute to care that may be experienced as burdensome without commensurate benefit.

The recent Lancet Commission on the Human Crisis of Cancer Care also challenges us to confront an equally difficult truth: despite extraordinary scientific progress in the biomedical domain, we have not built systems of care that adequately recognize the psychosocial, relational, and existential dimensions of illness (Fig 1).[7] This dissonance reflects not only gaps in access but also what our systems measure and reward. When end points, approval standards, and clinical care drift from patient priorities, the result can be a system that appears to move forward while failing to relieve suffering. Our central question is not whether the science of oncology is progressing, but whether it is progressing in ways that reliably reduce suffering, improve lives, and remain sustainable and scalable across diverse health systems.

The theme of this ASCO Annual Meeting—*The Science and Practice of Translation: Improving Cancer Outcomes Worldwide*—captures both the extraordinary success of modern oncology and the challenges it now confronts. Advances in cancer biology and therapeutics have accelerated the movement of discovery from bench to bedside, yet translation is incomplete if evidence cannot be meaningfully applied in clinics around the world. True translation extends beyond attaining statistical significance or regulatory approval; it requires that the outcomes that we measure, report, and prioritize support informed, person-centered decision making across diverse

PRACTICAL APPLICATIONS

- Oncology should define progress not only by scientific and technological advances, but also by whether improvements are meaningful, equitable, and accessible for patients.
- Clinical trials should be designed to demonstrate meaningful gains in patient-centered outcomes, rather than primarily to support regulatory approval of drugs and technologies.
- Clinicians, researchers, and policymakers should evaluate treatments in light of their overall impact on patients, including physical, financial, time, and logistical burdens, especially when benefit is uncertain or marginal.
- Health systems, reimbursement models, and regulatory frameworks should support supportive, behavioral, and system-level interventions alongside pharmacologic innovation.
- Evidence generation, policy, and clinical practice should be aligned with outcomes that patients consistently value: longer survival, better quality of life, preserved function, and attention to psychosocial, relational, and existential dimensions of care.

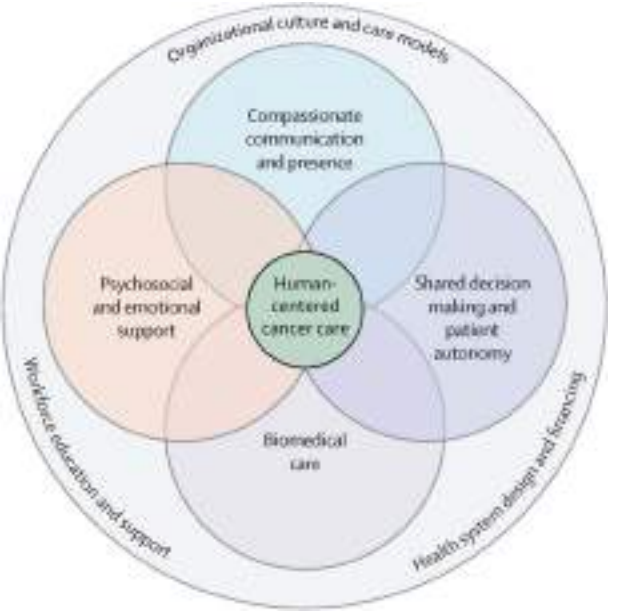

FIG 1. The four domains of cancer care, as described by the Lancet Commission on the Human Crisis in Cancer; used with permission, Lancet Oncology Elsevier Ltd.[7]

clinical and health system contexts. As oncology trials are increasingly globalized, aligning evidentiary standards and health systems with patient priorities becomes central to both ethical care and sustainable progress. Importantly, reanchoring oncology does not require abandoning progress but remembering who treatments ought to benefit. Our challenge is to refine how benefit is defined, measured, studied, and communicated so that clinical trials and regulatory pathways more consistently support person-centered decision making at the bedside. In this ASCO Educational Book Chapter, we examine how misalignment arises across (1) clinical care and communication, (2) evidence generation in trials, and (3) health systems and policy and propose practical solutions to address each (Table 1).

ACHIEVING THE GOALS OF ONCOLOGIC CARE

If the success of translation is ultimately judged at the bedside, then questions about evidence and measurement return us to a more fundamental question: What are the goals of cancer care? We propose that the answer to this question—indeed, the aim of medicine broadly—is to alleviate human suffering and to prolong life in the face of illness.[8,9] In oncology parlance, this is generally taken to mean improving length and quality of life. However, providing this care transcends the delivery of anticancer treatments. Scientific and technical excellence are indeed central to the physician's craft, but the practice of oncology has always involved something more—the relational, interpretive, and moral work of caring for patients facing serious illness. It is this art—helping patients navigate uncertainty and walk a path aligned with their values amid the chaos of illness—which drew many of us into oncology in the first place.

At our best, oncologists embody this dual commitment to science and person-centered care. Our craft, for all its modern tools and technologies, still rests on ancient moral foundations. The Hippocratic Corpus, and its modern articulation by Louis Lasagna,[10,11] emphasizes a primary commitment to the sick, providing care that avoids the dual traps of overtreatment and therapeutic nihilism, but above all, recognizing that medicine is ultimately a technology of kindness:

> "That our warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug."[10]

Importantly, the modern Hippocratic corpus also calls for epistemic humility and stewardship. We are reminded of the limits and changeability of knowledge and our obligation to be stewards to those in our communities as readily as we might care for our own patients.

These ethical commitments converge most clearly in the process of informed consent. Conventionally, informed

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TABLE 1. Aligning Clinical Practice, Evidence Generation, and Health Policy With Outcomes That Matter to Patients and Society

Domain	Current Gap	Actionable Step
Practice	Limited training in SDM and communication of uncertainty	Increase emphasis on SDM and communication training in medical education and CPD
	Insufficient infrastructure to support SDM	Systems should accommodate longer consultation time when needed; use of decision aids for complex care, integrate multidisciplinary supportive care
	Overstatement of treatment benefit (eg, PFS without OS/QoL gain)	Emphasize absolute benefit, patient-relevant outcomes, and degree of uncertainty
	Understatement of therapy-related toxicities	Allow time to inform patients on expected acute and persistent adverse events and their severity
Trials	Inadequate measurement of time toxicity	Mandate reporting of time toxicity in clinical trial reporting
	Restrictive eligibility criteria	Broaden inclusion criteria to reflect real-world practice
	Reliance on unvalidated surrogate end points	Use of clinical end points or validated surrogate
	Emphasis on relative rather than absolute benefit	Report absolute risk differences
	Poor interpretability of PROs	Use responder-based PRO analyses
	Focus on novel therapies over optimization	Prioritize de-escalation, dose optimization, comparative-effectiveness of existing strategies, pragmatic and clinically relevant trials
Policy	Misalignment between approval, reimbursement, and patient value	Align regulatory frameworks with patient-centered outcomes, including QoL and time burden
	Limited context-specific prioritization	Develop locally relevant prioritization frameworks in LMICs
	Slow adoption and deadoption	Implement value-based adoption and deadoption strategies
	Underuse of nonpharmacologic care	Streamline funding pathways for nonpharmacological interventions eg, supportive care, navigation, exercise
	Underinvestment in prevention	Prioritize public health and screening alongside treatment

Abbreviations: CPD, continuing professional development; LMICs, low- and middle-income countries; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; QoL, quality of life; SDM, shared decision making.

consent is framed around the disclosure of benefits, risks, alternatives, and uncertainties in appropriate terms to a willing individual with capacity to understand and appreciate consequences.[12] However, autonomous decision making by a sovereign, rational individual, can be threatened when patients' agency is constrained by the existential threat of life-limiting illness.[13–15] In this context, conveying complex information to emotionally overwhelmed patients with cancer, often within time-pressured clinical encounters, may further undermine the conditions required for meaningful understanding and voluntary choice.

The difficulty of achieving informed consent through shared treatment decision making is no reason to abandon its lofty goals. What may be more achievable in practice, as *Scanlan and colleagues* suggest, is a frank recognition of the complexity of this process and a refocus on its core elements. Namely, the aim becomes achieving some shared understanding of the goals of treatment, the outcomes hoped for, and the rationale for the choices being made. Most importantly, throughout this process, we must convey through our words and actions "*a promise that (we) will support the patient as they struggle to survive, and if this is not possible, as they die.*"[13] This is the art of oncology.

We have all cared for patients in whom these ideals play out as intended. Often, these encounters are characterized by longitudinal relationships, sufficient time for human connection, and space for patients and their care partners to ask questions and reflect. It is often easier when treatments on offer provide clear and clinically meaningful extension of life or quality of life. When patients and families are supported to engage in these discussions, and when conversations about prognosis and the end of life are welcomed as appropriate and compassionate, discussing treatments can move beyond a procedural requirement toward a shared understanding of goals, expectations, and trade-offs that meaningfully guide care.

However, these conditions are increasingly difficult to achieve in contemporary oncology practice. In busy clinics and increasingly industrialized health systems, care is frequently reduced to a set of efficiencies—optimizing for flow, metrics, and throughput—rather than the relational work of understanding what matters most to patients.[16] Training in core skills such as communicating with seriously ill patients is uncontroversially vital to the practice of oncology, yet can easily be marginalized in favor of keeping up with changing treatment paradigms. Strengthening communication and shared decision-making capabilities through structured training, protected time for serious conversations, and decision supports are essential to ensuring that patient-centered care can be consistently delivered in practice (Table 1).

Contemporary regulatory frameworks aim to improve access to innovative drugs or technologies by prioritizing rapid access over certainty that therapies meaningfully extend life or improve its quality.[17–19] Pharmaceutical sponsors operate rationally within this system—responding to the incentives that exist—and their role in therapeutic progress is indispensable. However, preferencing speed over certainty has a downside: when evidentiary thresholds drift toward plausibility rather than certainty, the interests of patients, payers, and sponsors may compete in subtle but consequential ways. In the clinic, oncologists and patients are left

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to speculate about how improvements in intermediate end points will translate into outcomes that matter in lived experience. Once incorporated into standard-of-care pathways, these therapies acquire normative force, making it easier to defer difficult conversations in favor of the next guideline-directed step.

All of this unfolds against a backdrop of hyper-optimistic therapeutic narratives, in which the science of discovery is framed solely through innovation and promise, fostering unrealistic expectations, and eroding trust when outcomes are questioned or benefits fall short.[20] In this context, patients may consent to treatments with uncertain, limited, or no benefits, with guaranteed physical, time, and financial toxicities which disproportionately affects those with limited survival times. Of course, each patient will view the value offered by each treatment through the lens of their own goals and preferences. However, we can collectively seek to raise the bar on the trials we design, the treatments we offer, and the quality of our discussions. One of our core duties as oncologists is to empower patients with the knowledge and understanding they need to make the treatment decision that makes the most sense for them. This raises a central challenge for oncology: How should we design our systems of innovation and care to support patients and clinicians at the bedside, and how should clinicians balance the obligation to sustain hope while preparing patients to face the more difficult realities of their illness?

MEANINGFUL EVIDENCE FOR PATIENTS

The difficulty of balancing hope and realism is compounded when the evidence itself is based upon putative surrogate endpoints rather than clinical realities. From the patient's perspective, this uncertainty is rarely apparent. Regulatory approvals shape what clinicians offer, and insurers will cover, but they also shape what patients reasonably believe that they should receive. For patients and families, these endorsements are often understood as affirmations that a treatment offers meaningful benefit. In this way, the trialist's choice of end points, use of words in reporting, presentations, or press releases or the policymaker's decision about evidentiary thresholds can structure patient expectations even before the clinical encounter takes place.[21]

At the bedside, clinicians must translate trial-level findings into individual recommendations. Putative surrogate end points such as progression-free survival or response rates must be translated into plain language and patient-centered terms—to avoid well-intentioned vagaries such as 'this may help', 'could slow things down' or 'buy some time'. These expressions are not intentionally evasive; they reflect genuine epistemic limits. Yet, they tend to obscure both the likelihood and magnitude of treatment benefit while completely overlooking the burden of treatment-related harms on remaining life quality. When layered onto the value signal of regulatory approval, conditional evidence can be internalized as probable benefit.

It is therefore unsurprising that prognostic misunderstanding in oncology is common. Ample data suggest that people living with advanced cancer frequently misunderstand the intent or impact of treatments, a phenomenon often attributed to coping strategies, cultural narratives of survivorship, or failures of physician communication.[22,23] However, to locate problems with prognostic awareness solely at the level of bedside dialog risks overlooking deeper sources of uncertainty. When evidentiary standards prioritize measures of plausible benefit over measures of clinical benefit, the information substrate upon which prognostic understanding rests is itself incomplete.

In such a context, both patients and clinicians are asked to make highly consequential decisions without clear insights into how treatment will affect how a person will feel, function, or live. Prognostic ambiguity is not merely a communicative problem; it is a structural feature of how modern oncology evidence is generated and what evidence our regulatory bodies accept. If prognostic understanding is constrained by how we generate and report evidence, then the outcomes we choose to measure—and omit—become ethically decisive.

It is often argued that patients prefer rapid access to novel therapies even if evidence of benefit is uncertain. This perspective implies that the hope of a treatment response outweighs other reasonable hopes, such as preservation of quality of life or goal-concordant end-of-life care. While this may be valid for some individuals, emerging empirical data complicate this narrative. In a recent discrete choice experiment, US-based respondents with lived experience of cancer expressed a preference for greater certainty of survival benefit over faster access to therapies supported by limited evidence, with a substantial proportion willing to wait up to 2 years for more robust data.[24] Similarly, survey-based preference research demonstrates that diverse groups of patients consistently prioritize benefits in clinical outcomes such as survival time over putative surrogates such as response rate or progression-free survival (PFS).[17,25–31] Together, these findings suggest that while timely access to innovation matters, it should not be assumed to outweigh confidence in meaningful outcomes. Patients certainly want timely access to new cancer treatments—but they also want to know if these treatments will really help them.

For many patients, the central question is not simply whether a treatment delays radiographic progression, but how their decision to accept treatment will shape their remaining life. In addition to measures of treatment effectiveness, many studies demonstrate that patients consistently prioritize quality of life, preservation of function, cognitive clarity, independence, and time with family.[32–34] A recent secondary analysis of the GAP70+ trial strongly supports this preference hierarchy, with 71.7% of older adult study participants prioritizing maintaining quality of life, compared with 8.4% prioritizing prolonging survival.[35] Yet, despite the importance of health-related quality of life in

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determining treatment value to people with cancer, these domains are variably captured and inconsistently reported in registration trials.[36–39] When patient-reported outcomes are collected, they are often summarized as aggregate differences that are often difficult to apply to individual circumstances. As a field, we must do better to capture this information in clinical trials and consistently ask "what really matters" in our clinical practice.

Moreover, the lived burden of treatment extends beyond what is conventionally classified as "toxicity." Time toxicity—the cumulative hours spent traveling to, waiting for, and receiving care—represents time diverted from work, caregiving, rest, and relationships.[40] Financial toxicity functions as a clinical harm, associated with distress, treatment nonadherence, and worsened outcomes.[41,42] Administrative complexity, fragmented systems, and repeated appointments further compound these pressures. These burdens intersect: time spent seeking care may generate lost income; financial strain may restrict access to supportive services; and logistical demands may erode quality of life even when disease is radiographically stable (Fig 2).[43] When benefits are modest and burdens substantial, the moral stakes of our treatment decisions, and the evidence which informs them, intensify. In the absence of improvement in clinical end points and transparent reporting of how treatments affect how patients feel, function, and live, the calculus of trade-offs remains obscured. In such circumstances, the language of benefit risks floating free from the realities of lived experience.

The difficulty is not only what we measure, but how we report it. Much of modern oncology evidence is summarized through medians, hazard ratios, and mean changes—statistics that are scientifically rigorous yet experientially abstract. Patients, however, reason in probabilities and narratives: "What are the chances this will help me?" "How likely is it that I will feel worse?" Group averages can conceal heterogeneity, masking whether benefit is concentrated in a minority while most derive little change.

We propose several solutions to these issues in our field (Table 1). First, patient-centered metrics of treatment burden—such as health care contact days—should be routinely reported alongside traditional clinical outcomes in trials. Emerging evidence suggests that time required for treatment may influence patient preferences and decision making.[44] Reporting these metrics is unlikely to impose substantial additional burden on trial sponsors, but may help contextualize treatment benefits in relation to the time required to receive care. More broadly, measuring and reporting time toxicity may have important downstream effects by incentivizing innovations that reduce unnecessary health care contact. These include less frequent infusion schedules, greater use of telehealth or decentralized trial models, and increased prioritization of de-escalation or perioperative trials that define the minimal effective contribution of each treatment component.

Second, clinical trials should continue adopting approaches to outcome reporting that are meaningful to both patients and clinicians in practice. Existing strategies such as prioritizing clinical end points (or well-validated surrogates), reporting absolute risk differences, presenting distributional curves, and highlighting numbers at risk can vastly improve the interpretability of data. In addition, greater emphasis should be placed on collecting and reporting quality-of-life data, patient-reported outcomes or experience measures, and using responder-based analyses where possible. These approaches provide decision-relevant information for patients asking not only "how long can I live?" but "how long can I live like this?" or "how will this make me feel?"

FIG 2. The intersecting burdens of cancer treatments. When the clinical benefit of treatments are modest or uncertain, there is a greater potential for net harm because of overlapping burdens from physical, financial, time, and logistical burdens of treatment.

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Aligning trial design and reporting with outcomes that matter to patients is not a cosmetic refinement. It is a precondition for meaningful informed consent. Clinicians and patients cannot align on treatment decisions if the outcomes most relevant to lived experience are poorly measured or ambiguously presented.

Reanchoring oncology evidence to what patients value does not require abandoning innovation. It requires refining how we define, measure, and communicate benefit so that statistical significance is matched by the lived experience of people with cancer. Table 1 highlights practical changes to trial design, end point selection, and reporting standards to ensure that evidence meaningfully informs patient-centered decision making.

FROM GUIDELINES AND TRIALS TO FRONTLINE CARE

Clinical practice guidelines occupy a uniquely authoritative position in oncology. They do not merely summarize evidence; they communicate standards and shape reimbursement decisions, regulatory policies, and clinical care pathways. In many settings, adherence to guidelines is equated with high-quality cancer care.[45] As such, guidelines function not only as advisory documents but also as normative instruments that define what counts as appropriate cancer care.

However, clinical practice guidelines face a generalizability problem. Most influential guidelines are developed in high-income countries where drug availability is broad and costs are rarely central—or effectively absent—from deliberation. The evidentiary and economic assumptions embedded within these recommendations may therefore not reflect the realities of frontline care in much of the world. Despite the globalization of cancer trials, the evidence base informing guidelines is largely generated from well-resourced, often industry-sponsored clinical trials, reflecting infrastructure, supportive care capacity, and financing models that may not exist elsewhere. Although some organizations attempt to contextualize benefit—such as through the ASCO Value Framework or the ESMO Magnitude of Clinical Benefit Scale—most recommendations remain anchored to statistically positive trials, even when absolute gains are modest.[46,47] When exported globally, the structural and economic assumptions underlying these recommendations often travel unexamined, with downstream consequences for patients, clinicians, and health systems.

Even methodologically rigorous trials may therefore produce guidance that is difficult to operationalize outside well-resourced systems. A statistically significant improvement in PFS achieved with high-cost agents and intensive monitoring requirements may be absorbable in one setting yet destabilizing in another. Many novel treatment strategies, such as antibody-drug conjugates, are highly sophisticated, and some have delivered considerable survival improvements.[48,49] However, these medicines often come at very high costs and rely upon rigorous biomarker testing, secure supply chains, frequent and lengthy infusions, and the availability of diagnostic and supportive care facilities in the event of toxicity. As medicines become increasingly targeted and higher in cost, they also deliver benefit to an increasingly select group of the population at greater expense to payers.[50] These requirements strain all oncology budgets, but the strain is felt most in low- and middle-income countries, where cancer spending competes with broader public health priorities, such as communicable disease prevention. Therefore, the opportunity costs of adopting marginal or high-cost innovations can be substantial. In such contexts, guidelines that equate innovation with quality risk widening disparities rather than reducing them. And when such treatments are not provided, patients and oncologists from such settings may become frustrated, feeling they are receiving or delivering suboptimal care.

The problem is not that guidelines are inherently flawed but that they are insufficiently contextualized. When standards are defined without explicit consideration of affordability, substitution options, and health system capacity, implementation gaps become inevitable. Bridging this gap requires structured adaptation to local realities. For example, the Brazilian Prioritization Index incorporates magnitude of clinical benefit, degree of unmet medical need, availability of substitution, and locally generated cost-effectiveness analyses to guide adoption decisions.[51] In this framework, a therapy supported by a positive phase III trial does not automatically translate into high implementation priority.

Beyond formal prioritization tools, pragmatic adoption strategies can also mitigate implementation gaps. Where therapeutically comparable agents exist within a pharmacologic class, procurement policies may favor the selection of a single representative agent to enable price negotiation and sustainable supply. Lower-cost—but equally effective options, such as paclitaxel in place of nab-paclitaxel—may achieve clinically comparable outcomes in many settings. Given the proliferation of so-called me-too agents across high-cost pharmacologic classes such as PD-1/L1 inhibitors and targeted agents, substitution strategies are relevant in all systems to ensure health budget sustainability. Similarly, convenience-driven innovations, including subcutaneous formulations of agents traditionally administered intravenously, warrant careful scrutiny when incremental logistical advantages are accompanied by substantial cost premiums (such as patent extension and deferral of biosimilar incorporation).[52] Across health systems, the cost of convenience must be weighed against broader population-level opportunities to save costs.

Resource stewardship extends beyond drug selection. Diagnostic and surveillance strategies frequently migrate from trial protocols into routine practice without reassessment of their incremental value. While intensive monitoring may be appropriate in early-phase or registration trials—where the safety profile and magnitude of benefit of an agent remain

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incompletely defined—the routine use of high-cost imaging, serial tumor markers, or overly intensive follow-up schedules in clinical practice may compound financial strain without demonstrable clinical benefit.

These adaptation strategies, however, address downstream consequences of a more fundamental issue: the way trials themselves are designed and how drug prices are set around the world. If clinical trials are designed to detect marginal gains, use suboptimal comparators, and surrogate end points that are poorly linked to patient-centered outcomes, the evidence that they generate will reflect these outcomes. This is not merely a problem for low- and middle-income countries; it is a problem for the sustainability of health systems everywhere. Efforts to improve global access to innovation must therefore begin with clinical trials that incorporate clinically meaningful effect sizes in clinical end points—such as overall survival and patient-reported quality-of-life outcomes, appropriate and globally relevant control arms, inclusive eligibility criteria, and pragmatic research questions that reflect real-world care delivery (Table 1).

The clinical trials landscape already contains ample examples of design approaches that prioritize clinical relevance and system sustainability. Pragmatic trials evaluating shorter durations of therapy, such as the IDEA collaboration assessing 3 versus 6 months of adjuvant chemotherapy in colorectal cancer, demonstrate how noninferiority frameworks can reduce cumulative toxicity and cost without compromising clinically meaningful outcomes.[53] Similarly, dose-optimization strategies with immunotherapy in breast cancer and head and neck cancer,[54,55] perioperative trials evaluating treatment contribution by component,[56] and studies evaluating the deferred use of CDK4/6 inhibitors in advanced breast cancer offer substantial potential to align efficacy with affordability and have shown promise in several settings.[57] Notably, guidelines may be powerful tools to endorse these strategies. Beyond mere cost-saving, these approaches generate opportunities to optimize care in other domains, such as enabling the use of a new drug or supportive care strategy.

More broadly, near-equivalence and noninferiority randomized designs, incorporation of time to treatment failure as a clinically pragmatic end point, and systematic inclusion of patient-reported outcomes and time toxicity measures can generate evidence that is not only internally valid but also implementable across diverse health systems. Trials that employ globally relevant standard-of-care comparators, enroll broader patient populations reflective of real-world practice, and prespecify clinically meaningful effect size assumptions in relevant trial end points are more likely to produce results that can be translated equitably.[58] In this way, methodologic decisions made at the design stage directly shape not only regulatory approval and guideline inclusion but also the feasibility of sustainable implementation.

DESIGNING HEALTH SYSTEMS WITH COMMON SENSE

If clinical trials and guidelines define what is possible in oncology, health systems are the final common pathway determining what is delivered to patients. Health technology assessment, reimbursement models, workforce distribution, cancer prevention policy, and hospital infrastructure collectively shape what clinicians offer, what patients can access, and what becomes labeled standard care in different contexts. These forces are often so embedded in day-to-day practice that they can escape scrutiny. Drug reimbursement decisions signal what is acceptable to payers and influence upstream drug development, design, and pricing. Although much attention is focused on cancer treatments, equally important are supportive services. For instance, underresourced or maldistributed diagnostic services may delay diagnosis more than any modern therapy could remedy, while limited reimbursement of hospice or palliative services constrain timely referral regardless of clinician intent.[59] Importantly, there is a distinction between access and availability: Formal reimbursement may grant theoretical access to treatment, but geography, workforce shortages, supply chains, and administrative complexity determine whether care is truly available.

Contemporary systems often reward activity more readily than outcomes. Clinical throughput—for example, treatments delivered, visits completed, and fractions administered—is easier to measure than the outcomes delivered by such care. In radiation oncology, fee-for-service reimbursement has historically incentivized longer fractionation schedules even when shorter regimens are clinically equivalent.[60,61] Maintenance systemic therapy may continue by default despite modest incremental benefit, reinforced by performance metrics oriented toward volume. Clinic key performance indicators frequently emphasize waiting times or case numbers rather than goal-concordant care. These structures did not arise maliciously; they have reflected what is easily measured. Yet, when outputs substitute for outcomes, the system risks conflating busyness with benefit.

In parallel, health systems frequently underinvest in interventions with the greatest population-level impact. Prevention and early detection remain less visible than therapeutic innovation, despite often yielding greater reductions in cancer mortality. Tobacco taxation and regulation, for example, have probably saved many more lives than all systemic cancer therapies combined, yet they face sustained resistance from lobby groups, with less political will and financial commitments.[62] Screening programs, where effective, often do not reach the most at-risk groups, including rural populations, Indigenous peoples, and ethnic minorities.[63,64] Similarly, uneven geographic distribution of radiotherapy facilities, surgical services, and oncology workforce capacity can exert a greater influence on outcomes than incremental drug innovations.[65] Technological advances cannot compensate for gaps in foundational infrastructure.

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Health systems also generate harms independent of drug toxicity. Financial and time burdens are often byproducts of system design, rather than treatments alone. Uncoordinated health system contacts, complex reimbursement paperwork, and high copayments can impose substantial strain on patients and families.[43,66,67] Commercial enthusiasm for emerging technologies, such as multicancer blood tests, broad use of positron emission tomography-computed tomography scans and surgical robots, may outpace demonstration of clinical utility. Although these technologies hold promise, their broad adoption should be guided by demonstrated improvements in patient-centered outcomes rather than technical capability alone.

If adopting new interventions is challenging, deimplementing low-value care is often harder. Shorter durations of therapy were supported by evidence, avoidance of tests that are not likely to alter management, and earlier integration of supportive or palliative services may free resources for higher-value services. Yet, withdrawing established practices can be politically and professionally uncomfortable. Innovation attracts attention and funding; deimplementation requires deliberate restraint. For sustainable oncology systems, both are essential.

To deliver higher-value care while remaining sustainable, systems must be anchored to outcomes that matter: improving survival, quality of life, functional independence, and patient-reported outcomes. They must reward value, not volume, aligning incentives with meaningful benefit rather than activity alone. They must also prioritize and invest in prevention, equitable screening, workforce capacity, and early supportive care—recognizing that a sustainable cancer control strategy depends more on these measures than on new drugs or technologies. These systems would evaluate technologies, services, and infrastructure with comparable rigor, expanding assessment beyond drugs and technologies to critiquing the broader architecture of care. Finally, they must put equal emphasis on the equitable distribution of high-value treatments as the discovery of new ones. Together, this reorientation has been described as an oncology groundshot.[68-70]

Designing such systems does not require reinventing the wheel or abandoning scientific progress—we have examples of systems that prove that meaningful reform is feasible (Table 1). First, structured health technology assessment, although imperfect, can help align reimbursement decisions with magnitude of benefit and opportunity cost for a population, rather than equating approval with routine adoption. As drugs and technologies rapidly change, it is more important than ever that health technology assessment is structured and resourced by governments to keep pace with evolving evidence. Second, adoption of hypofractionated radiotherapy schedules in line with clinical evidence illustrates how reimbursement models can evolve in response to evidence, reducing patient burden without compromising outcomes.[60,61,71] Third, sustained tobacco control efforts in countries such as Australia and the United Kingdom highlight the impact of upstream prevention relative to downstream treatment expansion. Last, investing in systems redesign and services that provide quality care, such as geriatric assessment and hospice care, often fall outside of these systems and remain challenging, although not impossible, to implement. Collectively, these examples suggest that aligning reimbursement, regulation, and service delivery with meaningful outcomes is not aspirational—it is achievable. In doing so, oncology can ensure that innovation serves not only those within well-resourced systems but also patients and communities worldwide.

CONCLUSION

Oncology stands at a critical juncture. Scientific progress has taken us forward in leaps and bounds, yet the structures through which we generate evidence, define standards, and deliver care are under increasing strain. Health systems and oncologists around the world are struggling to balance quality and access, speed and certainty, innovation and sustainability, and hope with realism, while absorbing escalating costs, expanding indications, and the cumulative burdens placed on patients and clinicians alike. To remain sustainable, recalibration is required. Care must be realigned with its central purpose: improving how long and how well people live. This means recognizing that high-quality cancer care extends beyond tumor control to the psychosocial, relational, and existential realities of living with cancer. By anchoring trials, guidelines, and reimbursement systems to outcomes that matter most to patients, we can generate evidence that is not only scientifically rigorous but also delivers equitable, sustainable and high-value care to all patients—regardless of where they live.

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Importance of and Strategies for Implementing *DPYD* Testing to Prevent Severe Fluoropyrimidine Chemotherapy Toxicity in Health Care Systems

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OVERVIEW

Recent regulatory and guideline changes have established pretreatment *DPYD* genotyping as a critical strategy to prevent severe fluoropyrimidine toxicity. Following earlier European leadership by the European Medicines Agency, the US Food and Drug Administration added boxed warnings to capecitabine and 5-fluorouracil labels recommending genetic testing before therapy. Concurrent updates from the National Comprehensive Cancer Network and ASCO align US with European practice supporting universal testing. Fluoropyrimidines remain foundational treatments across multiple cancers but can cause life-threatening toxicity in patients with dihydropyrimidine dehydrogenase (DPD) deficiency, most commonly because of inherited *DPYD* variants. *DPYD* variant carriers receiving standard doses experience markedly increased risk of severe toxicity and treatment-related mortality, emphasizing the clinical importance of *DPYD* testing and genotype-guided dosing. Evidence demonstrates that dose individualization based on guidance from the Clinical Pharmacogenetics Implementation Consortium reduces toxicity risk while maintaining treatment effectiveness and potentially reducing overall costs. Patient advocacy, particularly efforts led by Advocates for Universal DPD/*DPYD* Testing, has accelerated policy change, increased clinician awareness, and highlighted ethical implications of preventable harm. Despite growing adoption, implementation challenges persist, including workflow integration, clinician education, and equitable access. Integrated health systems such as the Veterans Health Administration demonstrate how centralized infrastructure and clinical decision support can facilitate uptake. Barriers are more pronounced in resource-constrained settings, where limited infrastructure, reimbursement uncertainty, and insufficient pharmacogenomic education hinder implementation. Regional initiatives illustrate education-focused, context-adapted strategies to expand testing and address population-specific variant knowledge gaps. Collectively, emerging evidence, regulatory alignment, and advocacy efforts position *DPYD* genotyping as a patient-safety imperative necessary to achieve safer, more equitable fluoropyrimidine therapy worldwide.

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INTRODUCTION

In 2020, the European Medicine's Agency (EMA) released guidance that all patients should be tested for dihydropyrimidine dehydrogenase (DPD) deficiency before initiating systemic fluoropyrimidine chemotherapy,[1] making Europe the first to officially adopt DPD deficiency testing, including *DPYD* genotype testing. In October 2025, the FDA added a boxed warning to the Xeloda (capecitabine) drug label stating, "Test patients for genetic variants of *DPYD* prior to initiating XELODA unless immediate treatment is necessary."[2] A similar update was added to the 5-fluorouracil (5-FU) label in February 2026.[3] The National Comprehensive Cancer Network (NCCN) updated their treatment Guidelines for Colon Cancer (Version 5.2005) to include the recent FDA guidance and explicitly stated that "this recommendation applies to patients receiving 5-FU as well."[4] ASCO guidelines that include fluoropyrimidine chemotherapy have also recently been updated to explicitly endorse *DPYD* testing.[5] These recent actions by FDA, NCCN, and ASCO align the United States with Europe to support universal pretreatment DPD/*DPYD* testing for all patients before starting systemic fluoropyrimidine treatment. Although phenotypic DPD testing is used by some European health care systems,[6] it is not currently available in the United States and many other regions, and therefore, this article will focus on *DPYD* genetic testing. The immediate need to implement pretreatment *DPYD* testing in all cancer treatment centers is the basis for the ASCO 2026 Annual Meeting Education Session: Updated Guidance on *DPYD* Testing to Prevent Severe and Fatal Toxicity from Fluoropyrimidine Chemotherapy—Is it Time to be Universal?

PRACTICAL APPLICATIONS

- Pretreatment *DPYD* genotyping should be incorporated into routine oncology workflows for all patients receiving fluoropyrimidines, consistent with recommendations from the US Food and Drug Administration, National Comprehensive Cancer Network, and ASCO to reduce preventable severe toxicity and treatment-related mortality.
- Genotype-guided fluoropyrimidine dose selection using guidance from the Clinical Pharmacogenetics Implementation Consortium enables individualized therapy that minimizes toxicity risk while preserving treatment effectiveness through careful dose titration.
- Multidisciplinary collaboration among oncologists, pharmacists, genetic specialists, and laboratory teams is essential to select appropriate testing panels, interpret results accurately, and implement clinical decision support for ongoing medication management.
- Oncology practices can improve safety and efficiency by embedding *DPYD* testing into electronic medical record order sets, automated alerts, and standardized chemotherapy pathways rather than relying on individual clinician recall.
- Expansion of education initiatives, patient advocacy partnerships such as Advocates for Universal DPD/*DPYD* Testing, and implementation strategies tailored to resource-limited settings will be critical to achieving equitable access to *DPYD* testing and preventing disparities in fluoropyrimidine safety.

CONSEQUENCES OF FLUOROPYRIMIDINE TOXICITY IN DPD-DEFICIENT PATIENTS

Fluoropyrimidines are standard chemotherapy treatment commonly used in colorectal, breast, and pancreatic cancers, among other tumor types.[4,7–9] Three systemic fluoropyrimidines are FDA-approved in the United States, intravenous 5-FU infusion, its oral prodrug capecitabine, and trifluridine/tipiracil, whereas additional fluoropyrimidines are commonly used outside of the United States including tegafur (S-1). These approvals are based on evidence of tumor response and improvements in survival, but treatment can also cause severe toxicity including myelosuppression, gastrointestinal toxicity, and hand and foot syndrome. Fluoropyrimidine[10] toxicity can be life-threatening, requiring costly hospitalizations and leading to fatality in an estimated one in 1,000 patients.[11,12]

Fluoropyrimidines are metabolized by a series of intracellular enzymes into active metabolites that interfere with DNA replication, leading to cellular apoptosis.[13] Importantly, an alternative catabolic pathway catalyzed by the DPD enzyme is responsible for approximately 80% of systemic fluoropyrimidine elimination.[14] The DPD enzyme is encoded by the polymorphic *DPYD* gene, which has hundreds of reported germline variants. Among these, four variants are most well-established to reduce DPD enzyme function and cause DPD deficiency.[15] Administering standard fluoropyrimidine doses to patients with partial or complete DPD deficiency constitutes an overdose that leads to supratherapeutic systemic exposure[16] and unacceptably high risk of severe toxicity.

Evidence from retrospective genotyping of prospective clinical trials[17] and meta-analyses[10,18] indicates that partially DPD-deficient patients receiving standard fluoropyrimidine doses have >50% risk of severe toxicity, which primarily presents as hematologic and/or gastrointestinal toxicity. This severe systemic toxicity necessitates hospitalizations in an estimated 30% of partially deficient patients, which are extremely costly.[11] In addition, approximately 3% of partially DPD-deficient patients experience treatment-related fatal toxicity.[12] The increased toxicity risk in DPD-deficient patients is comparable between fluoropyrimidine regimens, including in patients receiving 5-FU or capecitabine.[10] Although precise estimates are not available because of its infrequency, the risks of severe toxicity, hospitalization, and death are assumed to be much higher in patients with complete DPD deficiency.

For patients who experience severe fluoropyrimidine toxicity indicative of DPD deficiency, regardless of whether their DPD status is known, fluoropyrimidine treatment should be held and supportive care should be initiated immediately. If fluoropyrimidine treatment had been initiated <72 hours ago, treatment with uridine triacetate,[19] the FDA-approved antidote for fluoropyrimidine overdose, is strongly recommended. Although the efficacy of uridine triacetate beyond this 72-hour window has not been established, treatment could be considered even outside of this window. Of note, uridine triacetate is expensive and is not stocked by all hospitals although the drug company has an expedited delivery system in the United States. Many clinicians order *DPYD* testing after severe toxicity has occurred although the usefulness of this information after toxicity may be limited. Resuming fluoropyrimidine treatment at a lower dose, under the assumption that the patient might have a DPD deficiency, can be considered after toxicity resolution.

In addition to the direct costs of toxicity and hospitalization, there is a demonstrated risk of medical liability from failing to test for DPD deficiency before starting fluoropyrimidine treatment. In 2022, Oregon Health Sciences University paid a $1 million US dollars settlement for a wrongful death

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lawsuit.[20] This settlement predates the updates to the FDA drug label and oncology guidelines, which have established *DPYD* testing as the standard of care in the United States and likely dramatically increase medical liability for failure to offer testing. Despite this, some sites and many clinicians still fail to discuss *DPYD* testing, which has led to continued legal cases. While several lawsuits have been settled out of court and are therefore not part of public record, a news article from March 5, 2026, states that another lawsuit has been filed in Connecticut.[21]

An Advocacy View of the Patient and Caregiver Experience

In the absence of routine *DPYD* testing, patients and families have borne devastating consequences of severe, preventable toxicities. The patient experience of DPD deficiency frequently begins with standard 5-FU or capecitabine doses without DPD/*DPYD* testing being discussed or conducted. Within days, the patient becomes severely ill—extreme diarrhea, mucositis, neutropenia, sepsis, or multiorgan failure.

Karen Merritt's experience, similar to that of many patient advocates, began with the sudden and devastating decline of a loved one who was treated with 5-FU without any mention of risks of DPD deficiency or *DPYD* testing. Karen's mother, Linda, began her 5-FU infusion fully aware that chemotherapy might bring discomfort, but never imagining that it could take her life. By Day 6, Linda was unable to keep down food or fluids and went to the emergency department seeking hydration. The opportunity to recognize early signs of fluoropyrimidine overdose and administer the antidote uridine triacetate[19] was tragically missed. Linda was sent home still severely ill, and over the following days, her condition worsened—unrelenting mucositis and profound weakness. When she collapsed on Day 10, her husband called 911, beginning a harrowing hospitalization. Her medical team suggested her condition was likely due to DPD deficiency. By Day 17, Linda was comatose. What followed was an excruciating vigil of hope and heartbreak as her white blood cell count remained near zero, her organs strained under the burden of toxicity, and her loved ones watched her slip further away. As a caregiver of an individual with this toxicity, a critical question still lingers, "Is there a way to protect my family?"

On Day 24, despite supportive measures, Linda's body could no longer withstand the overwhelming effects of 5-FU overdose. Her blood pressure and oxygen levels collapsed, and she passed away leaving behind a devastated family. Losing a loved one to cancer is heartbreaking; losing a loved one to a *preventable* chemotherapy toxicity is shattering. The trauma is compounded by the realization that neither the patient nor their caregivers were informed that a genetic test existed. Testing results could have guided evidence-based dose reductions that likely would have spared her from enduring horrible, prolonged toxicity and spared her family from the grief of losing their loved one.

More than 50 years after the introduction of 5-FU, stories like Linda's and others are far too common. Patient and caregiver narratives reveal a consistent, tragic pattern of preventable harm:

- Patients and caregivers are not informed of DPD deficiency and toxicity risks by clinicians
- Patients and caregivers suffer the horrendous consequence of unnecessary toxicity
- Oncology teams fail to detect fluoropyrimidine overdose early enough to intervene
- Clinicians claim that severe toxicity is idiosyncratic and unpredictable
- DPD/*DPYD* testing is discussed only after catastrophic harm—if at all

In addition to the consistent pattern of profound physical, psychological, and financial harms to patients and caregivers, the consequences of failing to test may carry ethical and legal consequences. A legal precedent was set in a settlement in a wrongful death liability case involving fatal capecitabine toxicity in the absence of pretreatment *DPYD* testing.[20]

DPYD TESTING TO IMPROVE FLUOROPYRIMIDINE TREATMENT OUTCOMES

The recent action by FDA, NCCN, and ASCO establishes that all patients should undergo *DPYD* testing before fluoropyrimidine chemotherapy to prevent avoidable toxicity. However, *DPYD* genetics and available tests can be somewhat complicated for those who have not followed this area closely. Over 100 germline *DPYD* variants that are recurrent in human populations have been documented.[22] The four variants that have been most extensively studied include two that result in complete loss of DPD activity (c.1905+1G>A *DPYD**2A, rs3918290 and c.1679T>G, *DPYD**13, rs55886062) and two that result in reduced activity (c.1129-5923C>G, *DPYD* HapB3, rs75017182 and c.2846A>T, *DPYD* p.D949V, rs67376798). Considering only these four variants, approximately 6% of people of European ancestry carry at least one validated *DPYD* allele[23] although carrier frequencies can vary dramatically based on ancestral populations. Most retrospective association[10,24] and prospective dosing[25] studies have focused on these four variants. However, many other recurrent alleles, many of which are found more commonly in non-European populations, also reduce DPD activity in vitro, ex vivo, or in silico[15,26,27] and have been reported in cases of severe fluoropyrimidine toxicity.[28,29] Recently, the Association for Molecular Pathology (AMP) led a consensus effort to review data for all germline *DPYD* variants and published a guideline including two tiers of validated variants based on the strength of evidence of their association with reduced activity and increased toxicity risk, their reported allele frequencies, and the existence of reference materials for validating genotyping assays.[30] AMP classified seven variants, including the four previously described, as Tier 1 variants that should be included in all *DPYD* testing, and six Tier 2 variants that should also be considered for inclusion on testing panels (Table 1).

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TABLE 1. AMP Tier 1 and 2 *DPYD* Variants

Tier	Variant	Legacy Name	Protein Change	rsID	Activity Value[b]
1	c.1905+1G>A	*2A	NA	rs3918290	0.0
1	c.1679T>G	*13	I560S	rs55886062	0.0
1	c.1129-5923C>G[a]	HapB3	NA	rs75017182	0.5
1	c.557A>G	NA	Y186C	rs115232898	0.5
1	c.868A>G	NA	K290E	rs146356975	0.5
1	c.2279C>T	NA	T760I	rs112766203	0.5
1	c.2846A>T	NA	D949V	rs67376798	0.5
2	c.299_302del	*7	F100(FS)	rs72549309	0.0
2	c.703C>T	*8	R235W	rs1801266	0.0
2	c.1475C>T	NA	S492L	rs72549304	0.0
2	c.1774C>T	NA	R592W	rs59086055	0.0
2	c.2639G>T	NA	G880V	rs55674432	0.0
2	c.1314T>G	NA	F438L	rs186169810	0.5

NOTE. Information adapted from the AMP guidelines.[30]
Abbreviations: AMP, Association for Molecular Pathology; NA, not applicable.
[a]Variant is in strong but incomplete linkage with the tag SNP c.1236G>A (rs56038477). Genotyping for the causal variant is recommended.
[b]Activity values assigned by PharmGKB/CPIC are likely to change with the updated CPIC guidelines in 2026.

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DPYD genotyping results need to be translated into fluoropyrimidine dosing recommendations. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines use an activity scoring system to translate genotype into activity phenotype and dosing recommendations, similar to that commonly used for other pharmacogenes.[31] In this system, each *DPYD* allele is assigned an activity value (AV), with a reference allele (ie, wild-type) by default assigned AV = 1.0, no-function alleles assigned AV = 0.0, and reduced function alleles assigned AV = 0.5,[23] although some other pharmacogenes such as *CYP2D6* have additional AV assignments including 0.25.[31] A patient's DPD metabolic activity score (AS) is calculated by adding the AV of their two alleles, resulting in an AS that ranges from 0.0 (no activity) to 2.0 (normal activity). These AS can be translated into metabolizer activity phenotypes including poor metabolizer (AS = 0.0-0.5), intermediate metabolizer (AS = 1.0-1.5), or normal metabolizer (AS = 2.0), and dosing recommendations are made on the basis of metabolic phenotype or AS.

Dose recommendations from the original CPIC guideline published in 2017[23] are included in Table 2. As more data have been generated, these guidelines have undergone informal revisions cataloged at the CPIC website.[32] Importantly, CPIC is currently updating their systematic review, AV and AS classifications, and dosing recommendations; the updated CPIC guidance was not available at the time of publication. Until these new guidelines are available, these authors recommend a modified dosing strategy described in a recent editorial by Hertz et al in which patients with AS = 1.5 because of carrying c.1129-5923C>G, (*DPYD* HapB3) receive a 25% starting dose reduction and patients with AS = 1.0-1.5 carrying any other variant receive a 50% starting dose reduction.[34] As explicitly stated in the CPIC guideline and reiterated in the FDA drug label and NCCN guideline, all patients initiating treatment with a *DPYD*-guided dose reduction should be carefully monitored and doses should be titrated up in the next cycle based on tolerability, to ensure that all patients receive maximally tolerated and effective doses. Additional guidance for dose reduction and titration should be available in the updated CPIC guideline, which are anticipated to be released in 2026.

Prospective single-arm trials have confirmed that dose reduction according to CPIC guidelines in *DPYD* variant carriers normalizes toxicity risk with wild-type patients[25] and reduces toxicity as compared with historical control cohorts of *DPYD* variant carriers receiving standard doses.[35] In addition, this strategy has been estimated to be approximately cost-neutral, with several recent real-world analyses suggesting direct cost savings from reduced hospitalization and use of uridine triacetate[36,37] and clearly satisfying standard thresholds for cost utility.[38-40] However, retrospective secondary analyses suggest that dose reduction without proper titration in carriers of some *DPYD* alleles may reduce progression free-survival[41] and recent pharmacokinetics data indicate that some *DPYD* variant carriers may be underdosed.[42] Nevertheless, pretreatment *DPYD* testing and dose reduction is a treatment safety strategy[33] supported by prevailing regulatory and clinical guidelines.

PATIENT ADVOCACY AS A CATALYST FOR IMPROVING PATIENT CARE

Patient advocates and caregivers have transformed their personal loss into sustained public action, particularly the Advocates for Universal DPD/*DPYD* Testing (AUDT, of which coauthor KM is a member). These efforts have been a major

TABLE 2. Recommendations for Fluoropyrimidine Dosing Based on *DPYD* Activity Score

Activity Score	CPIC DPD Metabolizer Phenotype	Example *DPYD* Genotype	Original CPIC-Recommended Starting Dose[a]	Current CPIC-Recommended Starting Dose[b]	Recommended Starting Dose Until CPIC Update[c]
2.0	Normal metabolizer	**1/*1*	Label-recommended dose	Label-recommended dose	Label-recommended dose
1.5	Intermediate metabolizer	**1*/c.1129-5923C>G (HapB3 only)	Reduce 25%-50%	Reduce 50%	Reduce 25%
1.5	Intermediate metabolizer	**1*/c.2846A>T (all other alleles with AV = 0.5)	Reduce 25%-50%	Reduce 50%	Reduce 50%
1.0	Intermediate metabolizer	**1*/c.1905+1G>A or c.2846A>T/c.2846A>T	Reduce 50%	Reduce 50%	Reduce 50%
0.5	Poor metabolizer	c.1905+1G>A/c.2846A>T	Avoid use or strongly reduce dose (>75%)	Avoid use or strongly reduce dose (>75%)	Avoid use or strongly reduce dose (>75%)
0.0	Poor metabolizer	c.1905+1G>A/ c.1905+1G>A	Avoid use	Avoid use	Avoid use

NOTE. See Table 1 for AV for all AMP Tier 1 and 2 alleles.
Abbreviations: AMP, Association for Molecular Pathology; AV, activity value; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPD, dihydropyrimidine dehydrogenase.
[a]Original CPIC recommendations based on 2017 guidelines.[23]
[b]Current CPIC recommendations based on the CPIC website.[32]
[b]Recommended starting doses based on expert opinion and anticipated CPIC update in 2026.[33]

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contributor to the dramatic changes in the landscape surrounding *DPYD* testing in the United States:

Raising Awareness Through Lived Experience

Advocates have publicly shared their stories—through media interviews, conference presentations, social media, and grassroots outreach—to illuminate the urgent need for *DPYD* testing to ensure patient safety. This has led to a perceptional shift of severe toxicity from an idiosyncratic, unpredictable occurrence to a predictable and preventable harm.

Driving Regulatory and Policy Change

Caregivers submitted citizen petitions,[43] communicated directly with FDA officials, and presented evidence of the preventable harm from fluoropyrimidine treatment in DPD-deficient patients. Their persistence contributed to FDA's addition of the capecitabine box warning, which was a key milestone in the United States. Advocates also engaged extensively with guideline groups including NCCN and ASCO, contributing to the updated clinical guidelines that recommend testing. Advocates continue working toward updates across all relevant guidelines.

Partnering With Health Systems

Advocates have collaborated with academic centers, community oncology networks, and integrated systems to encourage the adoption of system-wide pretreatment testing. Many hospitals and cancer centers implemented *DPYD* testing only after a patient experienced severe toxicity locally or after advocates reached out to quality leaders and shared the scientific and human urgency of the issue.

Supporting Other Families

A vital component of advocacy has been creating a community where families affected by DPD deficiency can find support, validation, and education. For many, advocacy transforms sorrow into purpose; for others, it provides a path toward healing. In addition, patient advocacy has connected several families to medical liability law firms to facilitate wrongful death lawsuits.

Progress and Ongoing Success: The Impact of Advocacy on Clinical Care

The cumulative effect of these grassroots and national efforts has been profound:

- FDA action: A boxed warning establishing pretreatment *DPYD* testing as essential for safe treatment.
- Guideline alignment: NCCN, ASCO, and scientific organizations have updated guidelines to recommend testing, with more updates expected.
- Rising institutional adoption: Increasing numbers of US cancer centers now perform routine pretreatment *DPYD* testing.
- Growing clinician awareness: Pharmacists, oncologists, and nurses are more familiar with DPD deficiency, *DPYD* testing, and genotype-guided dosing to prevent severe toxicity.
- Emerging equity efforts: Advocacy has highlighted disparities in testing access, prompting new initiatives to make *DPYD* assays and care more equitable.[44]

This progress reflects the powerful synergy between evidence-based medicine and patient-driven advocacy. The voices of patients and caregivers have fundamentally reshaped how the

oncology community understands and addresses fluoropyrimidine safety.

Ensuring That No Patient is Harmed by a Preventable Toxicity

The story of DPD deficiency illustrates a simple but profound truth: when patients' experiences are heard and taken seriously, clinical care improves for everyone. The personal consequences of receiving fluoropyrimidines without *DPYD* testing are devastating and preventable. Through their persistence, caregivers and advocates have elevated *DPYD* testing to a recognized standard of care, catalyzing meaningful change across regulatory, guideline, and clinical practice domains. As *DPYD* testing becomes increasingly integrated into oncology workflows, the ultimate goal is clear: to ensure that no patient suffers or dies from a toxicity that could have been prevented.

UPTAKE OF *DPYD* TESTING

A 2021 survey of US medical oncologists found extremely low rates of *DPYD* testing, with <5% of medical oncologists reporting that they had conducted pretreatment testing.[45] As more data have emerged and the concern about preventable deaths has gained more attention, more oncologists and cancer centers have adopted pretreatment *DPYD* testing.[46-48] A 2023 survey identified 24 US sites that had implemented *DPYD* testing.[49] Of these, 67% only tested a subset of fluoropyrimidine-treated patients, sometimes based on the tumor type (eg, colorectal cancer only) or which medical oncologist treated the patient. In addition, nearly half of sites (46%) stated that it was the responsibility of the clinician (ie, medical oncologist) to remember to order testing. The majority of sites ordered *DPYD* testing from a commercial provider that included four or five *DPYD* variants (ie, the four validated variants with or without c.557A>G, *DPYD p.Y186C*). Sites reported mean turnaround times of <10 days for most commercial laboratories. Results were typically reported to the patient within the patient portal and stored in the electronic medical record (EMR). A more recent survey, also conducted before the FDA boxed warning, including US and international sites, found generally similar findings.[50]

This ASCO Educational Book article describes recommended practices for establishing a *DPYD* testing strategy; however, clinicians and sites should review the recent publication from Ho et al that includes a more detailed description of the entire process, starting with the exploration and preparation phases and continuing through implementation and sustainment.[51] Rigorous implementation science studies are needed to generate evidence-based best practices for *DPYD* testing, particularly in under-resourced health systems (Section 7).[52]

With the updated guidance from FDA and clinical guidelines organizations, all oncology sites in the United States should implement pretreatment *DPYD* testing for all patients receiving systemic fluoropyrimidine treatment, except for rare patients who must start treatment immediately or who make an informed decision to refuse testing.[53] Rapid uptake in United States is expected, similar to the rapid uptake in Europe following the 2020 EMA guidance.[54]

An important determination in establishing a *DPYD* genetic testing program is how and when to identify fluoropyrimidine-treated patients. Best practice is to establish system-level infrastructure that supports *DPYD* testing without relying on clinicians remembering to order testing. This could include interruptive alerts in the EMR that remind clinicians to test when placing fluoropyrimidine orders or including *DPYD* testing within institutional order sets or other standard workflows. *DPYD* testing should be ordered as soon as fluoropyrimidine treatment is determined to be appropriate, if not earlier, such as at the time of diagnosis of a tumor type that is likely to receive systemic fluoropyrimidine treatment (eg, stage III colon cancer).

The next important decision is how testing will be conducted. Large academic medical centers might have the capability of establishing an in-house testing panel, whereas community sites may rely on commercial testing vendors. The AMP guidelines, combined with the rapid uptake of testing because of FDA and clinical guideline updates, has led to a rapid expansion in testing options and coverage (Table 3). Therefore, sites and clinicians should work with pathology, genetic medicine, and/or pharmacogenetics colleagues to identify a comprehensive test (ie, all AMP Tier 1 and Tier 2 variants included) with a turnaround time that will not delay treatment. Guideline updates have also led to widespread payer coverage of *DPYD* testing, overcoming one of the logistical barriers to adoption, although prior authorization requirements from some payers continue to add unnecessary hurdles.[55] Sites may also consider alternative approaches to obtaining *DPYD* genetic data. Specifically, some US sites have implemented pre-emptive panel genetic testing of all patients[56] and other sites have institutional genetic data repositories with *DPYD* genotype data.[57,58] Finally, clinicians should be aware that several tumor genetic testing companies including Tempus, Caris, and Guardant use genetic panels that include *DPYD* genetic determination and return these results either by default or if requested as an add-on test.

After genotype results have been obtained, clinicians will need to determine the appropriate treatment for the patient. As described earlier, CPIC provides expert consensus guidance on initial dosing and titration for patients with available *DPYD* genotype (Table 2).[32] CPIC guidance should be consulted for up-to-date dosing recommendations, which can also be incorporated into active clinical decision support within the EMR. Developing system-wide infrastructure will be particularly helpful for storing *DPYD* genetic information that can be used for clinical decision support alerts, especially in situations in which the information is generated from pre-emptive panel testing, a genetic data repository, or

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TABLE 3. Allele Coverage of *DPYD* Tests Commercially Available in the United States

Laboratory	Test Name	Turnaround Time (Days)	AMP Tier 1 (n = 7)	AMP Tier 2 (n = 6)	Extended Variants
Comprehensive coverage					
Helix	Pharmacogenomics (PGx) fluoropyrimidines *DPYD* test	7-10	All	All	Yes
Mayo Clinic Labs	DPYDZ (sequencing)	5-10	All	All	Yes
Mira Precision Health	TOXNAV advantage	5-10	All	All	Yes
Sanford Medical Genetics	*DPYD* Genotyping LBOR0159	7-10	All	All	—
Extended coverage					
ARUP Laboratories	Dihydropyrimidine dehydrogenase (*DPYD*)	5-10	All	Partial (1)[a]	Yes
Quest diagnostics	Pharmacogenomics panel with report (14271)	7-14	All	Partial (2)[b]	Yes
Legacy coverage					
AccessDx	AccessDx PGx profile	7-10	Partial (5)	—	—
Clinical Pathology Laboratories	Dihydropyrimidine dehydrogenase (4,458)	12	Partial (5)[c]	—	—
LabCorp	#512275 *DPYD* genotyping	7-10	Partial (5)	—	—
Mayo Clinic Labs	DPYDQ (genotyping)	7-10	Partial (5)	Partial (2)[b]	—
OneOme	RightMed Oncology *DPYD* Single Gene Tests	4-5	Partial (5)	—	—
RPRD Diagnostics, LLC	Precision Health PGx Panel	14	Partial (5)[c]	Partial (2)[b]	Yes
SinoChips diagnostics	*DPYD* Genotyping	Unk	Partial (5)	Partial (2)[b]	Yes

NOTE. Information is current as of December 2025, based on information sourced from the NIH Genetic Testing Registry and on laboratory test information retrieved from company websites. Laboratories including *DPYD* genotyping as part of germline disease testing and cancer somatic testing (eg, Tempus, Guardant, Caris) are not included. AMP Tiers are based on AMP *DPYD* genotyping recommendations. Comprehensive coverage test covers all Tier 1 variants and Tier 2 variants; extended coverage tests cover all Tier 1 plus some of the Tier 2 variants; minimum coverage tests cover all AMP Tier 1; Legacy coverage tests cover the four extensively studied variants (c.1905+1G>A (*2A), c.1679T>G (*13A), c.2846A>T, HapB3) plus c.557A>G (Y186C). "All" indicates the test covers all variants within the tier. "Partial" indicates test covers some but not all variants within the tier; the number in parentheses indicates the number of variants included. "—" indicates no coverage. Turnaround times estimated from company websites or test users. For laboratories offering multiple tests, the test with more comprehensive *DPYD* variant coverage was included.
Abbreviations: AMP, American Association for Molecular Pathology; NIH, National Institutes of Health; PGx, Pharmacogenomics; Unk, unknown.
[a]Test includes c.1774C>T.
[b]Test includes c.299_302del (*7) and c.703C>T (*8).
[c]Test includes c.1236G>A (rs56038477) as a proxy for HapB3 but does not include causal variant c.1129-5923C>G.

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tumor genetic testing that is completed before fluoropyrimidine treatment is indicated for that patient.

One remaining barrier to widespread adoption is the lack of health care professional awareness and education around pharmacogenetics generally and *DPYD* specifically.[45,59,60] Pharmacogenomics education should be a core competency across health-related training programs, including *DPYD*-specific education for clinicians entering oncology practice.

IMPLEMENTATION OF *DPYD* TESTING IN VETERANS HEALTH ADMINISTRATION

Standardization of Clinical Practice: Early Adoption of Genomic Sequencing

Because of its integrated nature, the US Veterans Affairs (VA) health care system can reduce traditional barriers to access for emerging technologies. The VA has a longstanding history of standardizing comprehensive genomic profiling (CGP) in medical oncology including programmatic leadership from the National Precision Oncology Program.[61] Barriers in the care of patients with cancer can result in health care disparities by social and racial barriers[33] for which recent VA reports have shown that standardizing access can result in normalized access to testing.[62,63] In the case of both CGP and pharmacogenetic testing, the cost is supported at the national level based on clinical pathway guidance. This process avoids unnecessary time delays in prior authorization[33] or having to go through insurance companies for reimbursement. Implementation into practice is also assisted by an appointed site champion to guide genomic profiling efforts. In addition, pharmacists with additional training in pharmacogenomics are available to consult on alterations to pharmacotherapy regimens based on the results of genomic sequencing through the Pharmacogenomic Testing for Veterans (PHASER) program.[64]

As the VA is the largest integrated health care system in the United States, ensuring coverage of novel treatments and practices is more straightforward than it is in non-VA health care systems. Unlike non-VA health care systems, which typically develop clinical standards at the individual institution level, VA develops system-wide clinical pathways as a decision support tool to support faster adoption of novel research into standard clinical practice. These pathways are developed and implemented by a diverse panel of experts in medical oncology, radiation oncology, surgical oncology, pathology, and pharmacy, published on the National VA Oncology Sharepoint website, and directly implemented into the VA EMRs.[65]

Pragmatic Expectation in Clinic

Current implementation of *DPYD* testing in clinical practice involves a risk/benefit conversation between the clinician and the patient. After shared decision making, testing should ideally be performed at the first visit. At locations with access to a centralized testing center, sequencing results should be expected within 2 weeks. *DPYD* sequencing can often be paired with next-generation sequencing of cancer driver mutations to aid in therapy selection for specific cancers (eg, *EGFR* in colorectal cancers). Finally, testing results should be uploaded into the VA EMR for future access.

Limitations of Pharmacogenetics Testing

Pharmacogenomics testing, particularly sequencing, can reveal incidental findings of variants of unknown significance (VUS) within the tested gene (ie, *DPYD*) or other genes. Although *DPYD* VUS may not currently have sufficient data to be used in therapeutic decision making, it is possible that these variants may be actionable in the future. In addition, panel pharmacogenomics testing may uncover variants that affect other pharmacotherapies that will be relevant for future treatment of the patient. For example, some *DPYD* testing panels may reveal alterations in *CYPD6* that affects the efficacy or toxicity of other agents commonly used in patients with cancer including ondansetron, antidepressants, or opioids.[66-68]

IMPLEMENTATION OF *DPYD* TESTING IN LOWER-RESOURCED SETTINGS

Much of the *DPYD* test implementation literature has focused on large academic centers in well-resourced countries that have integrated molecular diagnostics and robust pharmacogenomics infrastructure.[47-49] However, the majority of patients worldwide receive cancer care in lower-resourced settings, including both community oncology clinics within high-income countries and health care systems in low- and middle-income regions globally. Administering fluoropyrimidines without considering *DPYD* status is particularly dangerous in lower-resourced systems, in which delayed toxicity recognition, limited intensive care availability, and constrained pharmacologic rescue options (eg, uridine triacetate) magnify the clinical consequences. However, the implementation of *DPYD* genotyping poses unique challenges in lower-resourced and fragmented health systems, including Latin American countries. In these systems, implementation barriers are not limited to financial constraints, but instead reflect a complex interaction between regulatory, economic, structural, and educational factors.

Barriers to Implementing *DPYD* Testing in Lower-Resourced Settings

Most Latin American drug agencies rely on FDA or EMA labeling without adapting recommendations to local implementation contexts. While local regulatory authorities acknowledge *DPYD* deficiency as a risk factor for fluoropyrimidine toxicity, explicit regulatory recommendations for pretreatment testing are generally absent. This regulatory ambiguity contributes to clinician uncertainty and limits institutional willingness to invest in testing infrastructure.

In contrast to top-down policy adoption seen in parts of Europe[1] and recently in United States,[2] *DPYD* implementation efforts in Latin America have largely emerged from bottom-up initiatives led by academic groups, clinical pharmacologists, and professional networks. Combined with the implementation barriers, this has contributed to the heterogeneous and fragmented uptake of *DPYD* testing across Latin America. In this context, *DPYD* testing in Latin America should be understood not as lagging behind international standards, but as operating within distinct structural and economic constraints that require tailored implementation strategies.

Cost is one of the most cited barriers to implementing *DPYD* testing. In lower-resourced settings that do not have national health systems with centralized reimbursement, pharmacogenetic tests are viewed as add-on expenses rather than cost-saving interventions. In addition, short-term cost visibility often outweighs longer-term economic and clinical benefits in clinical and regulatory decision making. Policy analyses reveal that pharmacogenomic testing is often evaluated in isolation, without accounting for downstream cost savings associated with avoided hospitalizations, intensive care admissions, and treatment interruptions.[38] This narrow economic framing disproportionately disadvantages preventive interventions such as *DPYD* testing.

Limited access to testing infrastructure is another structural constraint to implementing *DPYD* testing. Test availability is typically confined to isolated academic centers, private health care systems, or research-driven initiatives, resulting in highly unequal access. When testing is available, turnaround times are often longer than in well-resourced settings. Strategies such as testing immediately on diagnosis, pre-emptive panel-based pharmacogenomics, or integration with tumor genetic testing can mitigate this issue even in constrained environments.[69,70]

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Insufficient clinician education in pharmacogenomics consistently emerges as one of the most significant obstacles to *DPYD* testing implementation across settings.[45,59,60] These challenges are particularly pronounced in lower-resourced settings where pharmacogenomics education is generally absent from undergraduate curricula, residency training, and continuing medical education. This is further exacerbated by the lack of institutional infrastructure to integrate testing recommendations into EMR alerts or clinical workflows. Reliance on clinician memory and personal expertise disproportionately disadvantages systems with high staff turnover, limited subspecialty training, and heavy clinical workloads.

RELIVAF as a Regional Implementation and Education Model

In response to these challenges, the Latin American Network for the Implementation and Validation of Pharmacogenomic Clinical Guidelines (RELIVAF)[71] together with the Latin American Society of Pharmacogenomics and personalized Medicine (SOLFAGEM)[72] has developed a multilevel educational and implementation strategy tailored to resource-constrained settings. RELIVAF survey respondents endorsed the previously described barriers to implementing *DPYD* testing including lack of regulatory recommendations, uncertainty regarding reimbursement, and insufficient education and training.[73,74] RELIVAF is working to increase *DPYD* test adoption by incorporating implementation feasibility into development of guidelines around pharmacogenetic testing.

Rather than focusing solely on laboratory infrastructure, RELIVAF has prioritized education as the foundational element of sustainable pharmacogenomic adoption. The RELIVAF model integrates pharmacogenomics education at multiple levels: undergraduate training for health professionals, structured continuing medical education for practicing clinicians, pharmacist-led implementation initiatives within health systems, and patient-facing educational materials designed to support informed consent and shared decision making. Importantly, RELIVAF's approach recognizes that pharmacogenomics implementation is not a single event, but a longitudinal process requiring reinforcement, interdisciplinary collaboration, and institutional commitment.

Experience within RELIVAF has demonstrated that when clinicians understand the biological rationale, clinical evidence, and ethical implications of *DPYD* testing, resistance to implementation decreases markedly, even in the absence of ideal infrastructure. Education empowers clinicians to advocate for testing within their institutions, to engage administrators using patient safety and cost-effectiveness arguments, and to adapt international guidelines to local realities.

In addition, RELIVAF is overcoming one additional implementation barrier in Latin America that applies to many other under-resourced settings. Most pharmacogenetics research, similar to other fields of biomedical science, has been conducted in predominantly European patients.[44] This has led to the discovery and validation of actionable *DPYD* variants that are primarily carried by patients of European ancestry, with limited information about variants carried in other ancestral populations. Latin America is characterized by highly admixed populations who carry *DPYD* variants that are understudied and are therefore not considered to be actionable or recommended for inclusion on *DPYD* testing panels.[30]

RELIVAF is working to overcome this challenge by determining local allele frequencies for important pharmacogenes, including *DPYD*.[74] This important work will identify the common variants for dedicated research efforts to determine which variants increase toxicity risk and should be included on *DPYD* testing panels. In parallel, national-level translational efforts are emerging; for example, in Chile, a policy brief on *DPYD* genotyping for implementation in the public health care system has recently been submitted to health authorities although it remains unpublished.

Practical Strategies and Emerging Opportunities to Expand *DPYD* Testing

Drawing from international experience and regional initiatives, several practical strategies can facilitate *DPYD* testing in lower-resource health systems. First, prioritization of high-risk gene-drug pairs, such as *DPYD* and fluoropyrimidines, allows systems to focus limited resources where clinical impact is greatest. Second, leveraging existing laboratory capacity, including regional reference laboratories or shared testing agreements, can reduce duplication and cost. Third, embedding *DPYD* testing into clinical workflows through EMR alerts, standardized order sets, and clear delineation of responsibility can overcome educational and staffing challenges. Even simple interventions, such as default test orders triggered when fluoropyrimidine therapy is planned, can dramatically increase testing rates without requiring extensive new training or infrastructure. Finally, integrating *DPYD* testing into broader pharmacogenomic panels may improve economic efficiency and future-proof implementation as additional gene-drug pairs become clinically relevant.

Other trends in the oncology and health care industry will facilitate *DPYD* testing uptake in Latin America and other resource-constrained settings. As molecular diagnostic capacity expands, driven by oncology genomic profiling, the availability of *DPYD* testing will increase, particularly if *DPYD* is included in somatic cancer testing panels.[70] In addition, increased regional collaboration to build shared infrastructure and generate context-adapted pharmacogenomic guidelines will create opportunities for more systematic adoption. Combining these strategies and trends with dedicated work of regional organizations like RELIVAF will overcome the particular barriers in under-resourced systems to increase adoption of *DPYD* testing.

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CONCLUSION

Across all health care systems, the question is no longer whether *DPYD* testing is scientifically justified, but whether health care systems are willing to accept preventable harm in the absence of implementation. Ethical considerations, clinical evidence, and real-world experience converge on the conclusion that *DPYD* genotyping represent a patient safety intervention rather than a luxury of precision medicine. By leveraging implementation strategies tailored to the local context, all oncology systems, including those that are resource-constrained, can move toward safer fluoropyrimidine prescribing and more equitable cancer care.

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Value, Access, and High-Quality Medical Oncology Care: Can We Have It All?

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OVERVIEW

Health systems, oncologists, and patients face a crisis in value of cancer care that has several components: interpretation of meaningful benefit, cost, and affordability that limits access to treatment and effective delivery of evidence-based care. Value in health care has several definitions but can be defined as benefit/cost, which can be explicitly measured using cost-effectiveness analyses and used to shape coverage decisions for health systems. In addition to drug costs, costs can also include physical costs (ie, clinical toxicities and harm), productivity losses (from inability to work because of treatment effects), and time away from family and friends. Low-value treatments include those that offer limited clinical benefit and score poorly on scales such as the European Society of Medical Oncology Magnitude of Clinical Benefit Scale and the overuse, misuse, or underuse of therapies that provide clinical benefit. Opportunity costs are what is given up when one intervention is chosen over another. Opportunity costs of low-value care translate into patient and societal harm and limit access to more effective treatments. Solutions to the value crisis require recognition of low-value care and quality improvement programs to prevent its use and support high-level care. Drug substitution and dose and schedule reduction when supported by evidence can also improve the value of care.

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INTRODUCTION

Box 1 describes the organization of the ASCO presentation and of this article. We emphasize drug treatment for cancer as this is the major driver of costs of treatment and is most relevant to the ASCO audience. Our value crisis is driven by three factors:

1. A crisis in the interpretation of meaningful benefit.
2. A crisis in cost and affordability that limits access to treatment
3. A crisis in the effective delivery of evidence-based care

Providing reliable access to high-value and high-quality cancer care is a priority for health systems. However, the rising costs of cancer drugs, the growing number of drug approvals in oncology of uncertain benefit to patients, and the provision of low-quality low-value care are growing public health challenges that threaten our cancer systems globally. Oncologists have an ethical responsibility to advocate for the delivery of high-value cancer care, which includes equitable access to affordable treatments that meaningfully improve the lives of patients, and the avoidance of low-value care which is harmful to both patients and health systems. To be effective advocates and to develop potential solutions, it is not sufficient to recognize a value crisis in cancer care—oncologists must understand what constitutes high- (and low-) value care, the key economic drivers behind this crisis, and the opportunity costs of providing low-value care.

IDENTIFYING HIGH- AND LOW-VALUE CANCER TREATMENTS

The value of a cancer treatment can be expressed as a ratio of the net benefit to the accompanying cost,[1] where costs can include financial costs (including direct and indirect costs of treatment and clinical care), physical costs (ie, clinical toxicities or harms), and time away from home and family to receive the treatment.[2] There are only two ways a drug may benefit patients, by either improving their overall survival (OS) or their quality of life (QoL). New treatments often increase toxicity, and consensus methods for assessing the meaningful benefit of new drug treatments have been developed which indicate their likely value to a health system, with respect to achieving gains in OS or QoL, and their toxicities. For example, the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) considers OS, QoL, and toxicity and rate benefits on a scale of A-C (curative) or 5 to 1 (palliative), with levels A and 5 conveying the greatest benefit.[3]

Accelerated approvals and emphasis by registration agencies on rapid access to new treatments can impair the rigorous evaluation of clinical benefit. Even once a beneficial

PRACTICAL APPLICATIONS

- Oncologists should recognize low-value care that offers limited benefit to patients (ie, no or minimal improvements in survival or its quality) and avoid such treatments.
- Low-value care includes underuse, misuse, or overuse of therapies that provide benefit.
- Oncologists should know the cost of treatments that they are prescribing and recognize that low-value treatments include those with minimal benefit in relation to cost.
- Oncologists should recognize that within resource-limited environments (essentially all), there is an opportunity cost of using high-cost/low-value treatments since resources could be used to support more effective treatments.
- Incorporating quality improvement strategies into practice deserves priority.

BOX 1. Main Themes of the Article

Value in cancer treatment

- Definition of value
  Value as benefit/cost
  Value as benefit/harm
- Crisis in providing value in cancer treatment
  Interpretation of meaningful benefit
  Cost and affordability that limit access
- Identifying low-value treatments
  European Society of Medical Oncology Magnitude of Clinical Benefit Scale
  Overuse, misuse, or underuse of treatment

Economics of cancer care

- Causes of Economic Crisis in Cancer Care
- Cost-Effectiveness and Willingness to Pay
- Cancer Drug Price Elasticity
- Legislative and Regulatory Environment

Opportunity cost

- What we give up when we choose one intervention over another
  Opportunity cost of low-value care translates into patient harm and system-level consequences, even when care is guideline-concordant
- Opportunity costs amplifies inequity and limits access to treatment

Potential solutions to the value crisis

- Recognizing overuse, misuse, and underuse as low-value care
- Quality improvement programs to support high-value care and prevent low-value care
- Drug substitution (generics and biosimilars)
- Dose and schedule reduction when supported by evidence

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treatment is identified, many factors, including the drug development process, drug pricing, regulatory systems, and health systems, can limit access to it. Drug development is dominated by the pharmaceutical industry (henceforth Pharma), which now sponsors more than 90% of randomized controlled trials (RCTs).[4] While Pharma has been instrumental in developing several highly effective drugs, their primary goal—to bring profitable drugs to market—is not always aligned with public interests. Many registered drugs have minimal clinical benefit and/or high toxicity[5,6] and are therefore of low value to patients and health systems. With prices set by Pharma, unlike most other products, there is no relationship between the clinically meaningful benefit of a drug and its cost.[7,8] High costs limit access for patients, especially, but not only, in low- and middle-income countries (LMICs). Even when drugs are affordable, optimal care demands the prescription of treatments that are of high value (high benefit/low harm).

Complementary to the concept of high-value care is the recognition that some treatments represent low-value care. Low-value care should include the overuse and misuse of care,[9,10] and the 2025 European Commission on Health Performance Assessment included the underuse of evidence-based care.[11] Therefore, low-value care may encompass the suboptimal use of resources (human or financial) that results from services not being provided in the right sector (eg, reliance on inpatient versus outpatient care) by the right professional (non-accredited oncology care provision) or that could have been provided with equally effective but more environmentally friendly alternatives (eg, short *v* longer course of radiotherapy). In this article, we consider low-value care as any health care that lacks efficacy has not been found to be cost-effective, where the risks or harms to the patient outweigh the benefit and where health care resources are overused, misused, underused, or not delivered in the most appropriate setting.

ECONOMIC FACTORS CONTRIBUTING TO THE VALUE CRISIS IN CANCER CARE

The high costs of cancer drugs are a dominant factor in the cancer value crisis and a key determinant of what constitutes high- versus low-value care. The Organization for Economic Co-operation and Development (OECD)'s 2026 report on low-value cancer care[12] highlights the increased spending on cancer care over the past three decades: direct costs have doubled from $54 billion US dollars (USD) in 1995 to $120 billion USD in 2023, with a further expected increases

of 59% in European Union (EU) countries and 67% in OECD countries between 2023 and 2050. The micro- and macroeconomic factors contributing to the unsustainable rise in costs are numerous and complex. Herein, we focus on three key economic principles that are important for clinicians to understand: cost-effectiveness and willingness-to-pay (WTP) thresholds, the legislative and regulatory environment, and cancer drug price inelasticity.

The patient and societal WTP is the maximum price the consumer (or health system) is prepared to spend on a product—such as a cancer drug—and will vary across health care systems and countries. It indirectly reflects the value that the payer places on a product relative to other goods and is a key economic concept in drug pricing. In societies with robust Health Technology Assessment (HTA) programs, WTP is the monetary value placed on a quality-adjusted life year (QALY) or a life year saved. The incremental cost-effectiveness ratio (ICER) then measures cost per additional QALY compared with the current standard of care. Society's WTP for cancer drugs is often higher than that for drugs for other conditions even when they provide the same QALY—termed the "cancer premium." For example, Serra-Burriel et al[13] compared the price of new drugs approved across three jurisdictions between 2011 and 2020, finding that cancer drugs were approximately three times more expensive compared with noncancer drugs. WTP and ICERs have also been shown to vary depending on the type of cancer, the political context (democracy *v* non-democracy), and the culture and society, in addition to the effectiveness of the drug.[14] For example, since 2020, the Canadian Agency of Drugs and Technologies in Health has been using a WTP threshold of $36,000 USD per QALY for both oncology and nononcology drugs,[15] whereas National Institute for Health and Care Excellence (NICE) recently increased its ICER to $47,000 USD. Other jurisdictions such as France do not have defined WTP thresholds and instead evaluate cost-effectiveness on a case-by-case basis. Importantly, WTP does not necessarily equate to ability to pay and this gap may be a source of financial toxicity.

Behavioral economics suggests that cognitive biases may also affect WTP thresholds. Patients and policymakers often overvalue marginally effective cancer drugs, where life-extending treatments are framed as essential regardless of cost-effectiveness. Known as Prospect theory, the knowledge that failure to receive treatment will lead to certain death, while treatment provides the possibility of improvement even if that possibility is very small, may inflate WTP.[16] Few studies have explored whether cancer premiums and high WTP thresholds are truly in line with societies' priorities. In one study,[17] respondents were asked to allocate funds to purchase a drug to manage cancer or a noncancerous condition, where the drugs provide equal clinical value for the two conditions. The majority (64%) of respondents allocated the funds equally between the listed conditions, challenging the notion that the public places higher value on cancer treatments. It is uncertain, therefore, whether a higher WTP for cancer drugs reflects societal desires or whether this is due to market and political pressures.

Despite these concerns, WTP thresholds can still positively affect HTA processes by limiting the adoption of low-value drugs. More concerning are instances where health systems, for political expediency, have tried to bypass HTA processes, ignoring WTP thresholds to achieve quicker access to innovation, or where HTA programs do not exist. An example of bypassing HTA processes is the UK Cancer Drugs Fund (CDF), established in 2010. In the first five years, the CDF approved 47 drugs at a cost of 1.3 billion dollars. The approved drugs either were awaiting HTA review or were not considered cost-effective, and only one in five met ESMO criteria for meaningful benefit, leading to lost opportunity costs in the setting of scare resources.[18]

The most concerning example of a lack of HTA process is the US cancer drug system. Legal barriers prevent the US Food and Drug Administration (FDA) from considering price when deciding whether to approve a new treatment, and the Medicare Prescription Drug, Improvement, and Modernization act of 2003 prohibits Medicare from directly negotiating with manufactures, leaving Pharma to freely dictate price. In other jurisdictions, price negotiations between public payers and industry take place confidentially and final negotiated prices are rarely publicized. The lack of HTA programs in the United States and the inability to negotiate transparently and report final drug prices have negative consequences on negotiating power in all jurisdictions contributing to the global value crisis in cancer care. The US cancer system also incentivizes the prescription of higher-cost drugs—clinicians derive income from the prescription and delivery of cancer drugs, and payments from Pharma to physicians may influence prescribing patterns.[19] Cancer drug monopolies stemming from patent protections and a lack of market competition further amplify the crisis in cancer drug costs. This constellation of macroeconomic policies create a precedence for high pricing which has trickle-down effects on all health systems but especially in LMICs where cancer drugs are often least affordable after adjusting for purchasing power.

Related to WTP is the concept of price elasticity, calculated as the % change in demand divided by the % change in price. Cancer drugs have relatively inelastic pricing: changes to price have little effect on demand. Goldman et al[20] have demonstrated using US data that if an insurance plan were to double the cost sharing for a rheumatoid arthritis drug, demand would decrease by 21%; by contrast, doubling the cost share of a cancer drug would decrease its demand by only 1%. Among Medicare enrollees, Jung et al[21] found that every $100 USD increase in the initial price of a cancer drug would result in only a 0.07% decrease in demand. This price inelasticity is driven by several factors, including limited competition for cancer drug indications, the perception that cancer medicines are lifesaving, insurance coverage or public

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reimbursement which can insulate patients' decisions to accept therapy, and clinicians' willingness to prescribe, from the true value of a drug. Failure to inform patients of the option of best supportive care could also increase price inelasticity. In a study of 118 patients with incurable cancer, only 44% were provided with the option of no treatment.[22] This price inelasticity enables Pharma to set high prices with little impact on demand, maximizing profits sometimes at the expense of individuals and health systems.

OPPORTUNITY COSTS AND THE CANCER VALUE CRISIS

The opportunity cost of a medical intervention is what we give up when we choose one intervention over another (Fig 1).[23] Opportunity costs can describe the economic resources needed to provide one intervention over an alternative or can be framed as what we stand to lose in one health domain relative to what we gain in another. In a system with a limited budget, committing resources (be it medications, human resources, or time slots for a linear accelerator) to a specific purpose means that they may not be available for other uses.[24,25] When new interventions are introduced into health systems with fixed resources, assets must be redirected from other services or interventions to meet the new demands.

Opportunity costs exist in all health care decisions and are a natural consequence of resource scarcity. However, they become more evident—and more consequential—when resources are used for low-value interventions. High-cost cancer medications with limited clinical benefit may reduce the resources available for alternative high-value cancer services, such as radiotherapy, pathology, and essential supportive care, which often deliver larger aggregate health gains at the population level.[24] Performing frequent surveillance computed tomography scans in asymptomatic patients in scenarios for which no meaningful survival benefit has been proven could affect wait times for imaging for patients requiring urgent imaging for a suspected disease recurrence or for those on treatment requiring timely response assessment.[26]

The harm of low-value care lies in what patients and health systems stand to lose through opportunity costs. For a health care system, including high-cost medications (defined here as those whose ICER exceeds the public WTP threshold to gain a QALY) in a public funding scheme can render other effective interventions becoming less affordable within a fixed budget, resulting in a net health loss at the population level. This has been demonstrated in an analysis of new drug appraisals in England between 2000 and 2020, of which 45% corresponded to oncology indications. In this study, oncology drugs accounted for most of the net health loss, with an estimated 0.87 million QALYs forgone at a population level in association with cancer medications.[27] Health systems with fewer available resources, and consequently a lower WTP threshold, may be more vulnerable to the consequences of opportunity cost. An analysis of several high-cost medications from the perspective of the Thailand health care system estimated the opportunity cost in terms of QALYs forgone by comparing the budget impact of these medicines with the health gains that could have been

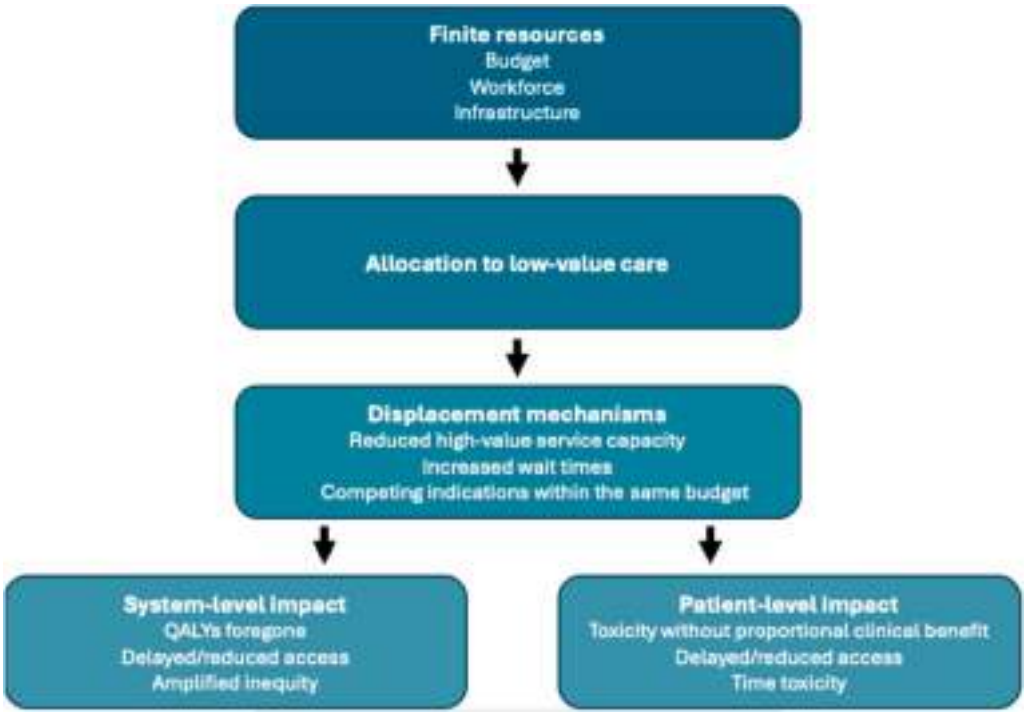

FIG 1. Opportunity costs. QALY, quality-adjusted life year.

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achieved if the same resources had been allocated to interventions at the WTP threshold of 160,000 Thai Baht (approximately $5,000 USD) per QALY.[28] Their results showed that several high-cost medicines were associated with a substantial net loss of QALYs at the population level. For example, although funding lenalidomide (with an ICER of approximately $380,000 USD/QALY) produced an estimated gain of 14 QALYs, accounting for its opportunity cost led to a net loss of 1,031 QALYs. In a high-income country example, the opportunity cost of treating advanced cervical cancer with bevacizumab in Italy in 2012 was evaluated. The authors found that the yearly cost of bevacizumab in this setting was higher than that incurred by fully vaccinating a cohort of twelve-year-old girls.[29] This scenario raises the question of whether the addition of immunotherapy for advanced cervical cancer is viable from the perspective of opportunity cost compared with other preventive or curative interventions.[30] These examples demonstrate the magnitude of resource trade-offs that health systems may face when allocating funding within a fixed budget across the disease trajectory, considering interventions with different cost profiles and population-level impacts.

The approval of indications with low clinical benefit can increase demand for a medication and place pressure on available supply and budgets, thereby limiting access for patients with conditions for which the same medication provides greater clinical benefit. As an example, trastuzumab-deruxtecan (T-Dxd) as second- or later-line therapy for advanced human epidermal growth factor 2 (HER2)–positive breast cancer has an ESMO-MCBS score of 4 with substantial benefit in both progression-free survival and OS.[31] However, the use of T-Dxd in combination with pertuzumab as a first-line treatment for advanced HER2-positive breast cancer obtained an ESMO-MCBS score of 2 because of an increase in serious and disabling adverse events.[32] Both indications have been approved by the FDA, but in the context of a limited budget, patients who stand to benefit the most from this medication may face delays or reduced access if both indications place competing demands on limited resources. Moreover, fast timelines to approval, the rapid expansion of indications, and overlapping indications across medications with the same mechanism of action can complicate the ability of health systems to anticipate and manage the budgetary impact of a medication and its resulting opportunity cost.

The time that patients spend receiving cancer treatment represents a significant opportunity cost.[2] In addition to opportunity costs related to health, patients must weigh the time spent in traveling, attending appointments, receiving infusions, and managing treatment-related toxicities against maintaining education or employment (with potential loss of income if unable to work) or pursuing other personal priorities. These opportunity costs may be magnified in patients at risk for higher time toxicity, such as those with productivity losses from being unable to work,[33] those living in underserved areas, or those who require more complex care coordination, such as older adults. While some patients may reasonably accept the risks of treatments with limited clinical benefit, the time required to receive these treatments is under-recognized. For interventions with limited clinical value, time opportunity costs may become a decisive factor for some individuals and should be explicitly considered when discussing treatment options with patients and caregivers.

In addition to established cost of illness studies, the Oncology Opportunity Cost Assessment Tool quantifies how medical oncology care generates patient and caregiver opportunity costs, for example, time spent on travel and appointments, effects on work and home responsibilities, and care coordination challenges. Validation of the tool is ongoing, but it may prove to be useful to inform both treatment discussions and system-level interventions.[34]

POTENTIAL SOLUTIONS REDUCING THE USE OF LOW-VALUE CARE

Improving value in cancer care requires examination of the efficiency and quality of care delivery, shifting from a focus on drug development, trial design, regulation, and reimbursement policy to evaluating and optimizing downstream processes and practices. Several factors must be considered to achieve the best outcomes with available resources (technical value) and equitable resource distribution across all patient groups (allocative value). Box 2 applies the European Commission definition of low-value care to medical oncology.[35] Reducing low-value care is a major goal of health systems research, designed to improve the sustainability, equity, and quality of cancer services by targeting the overuse, misuse, and underuse of medical oncology care.

Reducing low-value care within medical oncology practice starts with understanding the scale of the problem. Although lagging behind surgical[36] and radiation oncology care,[37] there are several indicators in medical oncology for the evaluation of quality of care at a regional or national level, which are part of quality management or audit programmes.[38] These programs have identified evidence of poor adherence to guidelines and underuse of evidence-based systemic therapies in clinical practice. For example, in England, on average, only 40% of eligible patients with primary metastatic hormone-sensitive prostate cancer received treatment intensification beyond ADT[39] and only 60% received adjuvant chemotherapy for stage III colon cancer.[40] In both studies, there is large variation between hospitals and for patient groups. Lower rates of utilization were associated with older age (adjusted for comorbidities), Black ethnicity, and lower socioeconomic status.

Quality management programs have also identified evidence for the overuse of treatments, with high 30-day mortality from systemic anticancer therapy evident across hospitals in the United Kingdom and Canada,[41,42] suggesting inappropriate use of drug treatments toward the end of life. There is

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BOX 2. Application of the Four Pillars From European Commission Definition of low-value care to Medical Oncology

Overuse:
- End-of-life treatment/late-line chemotherapy when not indicated, or when palliative care is indicated, is linked to hospitalizations and reduced quality of life
- Use of drugs lacking meaningful patient benefit
- Inpatient delivery of systemic therapy that can be safely delivered in the ambulatory setting
- Using branded drugs where approved generics available

Misuse:
- Off-label use of drugs or use of wrong drug combinations
- Inconsistent guideline adherence such as cotesting for molecular markers
- High rates of adverse events because of inappropriate prescribing, poor assessment of fitness, and inadequate care systems to manage complications

Underuse:
- Evidence-based treatments not delivered to eligible populations

Unwarranted variation:
- Different rates of treatment by socioeconomic status/provider status/geography

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also evidence of a large variation in rates of severe toxicities after administration of cytotoxic therapies for bowel cancer, with rates of severe toxicity requiring overnight hospital admission averaging 50%, but ranging between 25% and 67% among hospitals.[43] These substantial differences point to suboptimal or misuse of evidence-based therapies or inadequate outpatient support for early toxicity management, which could be improved.

To address practices with low-value care, a system of quality assurance according to agreed indicators is critical.[44] There are several international initiatives designed to monitor and report on low-value cancer care within and between countries. For example, the OECD report on low-value cancer care in 2026 includes all 27 EU member states and selected OECD member countries including Australia, Canada, and the United States.[12] Although not primarily focused on medical oncology care, they demonstrate substantial overuse in practices of care across the EU and OECD countries, such as the overdiagnosis of prostate cancer because of opportunistic screening and overtreatment of low-risk prostate cancer. National and regional cancer audit and quality management programs provide rigorous population-level data intelligence related to various low-value care domains to target quality improvement: they tend to use large registry data sets linked to administrative data which report on procedures and outcomes of care[45,46] and provide in-depth insights across a wide range of cancers. For example, the National Cancer Audit Collaborating Centre in the United Kingdom covers nine cancer types across the spectrum of care from diagnosis to treatment and survivorship.[47]

Developing solutions to reduce low-value care is a major challenge. Reporting indicators need to be coupled with rigorous attention as to how the data are fed back to clinicians, service managers, and policy makers to achieve a maximum impact. A recent Cochrane review of some 293 audit and feedback studies[48] described approaches to harnessing feedback, through education programs, adjusting reporting frequency, applying expected targets, or changing how the data are reported, such as benchmarking with other hospitals.

While audit and feedback can encourage behavior change, to improve the value of care requires focused quality improvement interventions, but there is scant evidence in this area. For example, a systematic review designed to identify intervention to address inequalities in access to cancer care from screening to diagnosis and treatment found that 90% of papers focus on the screening pathway, with only two of the 57 studied identified to be focused on treatment delivery.[49] Another systematic review found that only 27 studies focused on improving the quality of medical oncology care.[50] Among these studies, 50% focused on timeliness of treatment and only 11 focused on low-value care, such as excess 30-day mortality, adverse events, and prescribing errors. While work is ongoing to move the dial in improving quality of care globally,[51] increased funding and improvement in quality training are required.

One approach to improving the quality of care that continues to gain traction is Choosing Wisely,[52-54] which, in tandem with the OECD report,[12] provides consensus-based definitions of low-value care in medical oncology, such as avoiding the use of cancer-directed therapy for patients with poor performance status and promoting early integration of palliative care. Incorporating patient-reported outcomes and QoL measures into value assessments further strengthens the discussion of high-value care. Another approach is through behavioral or economic incentives that adapt the reimbursement system to nudge clinical care to higher-value pathways and provide disincentives for low-value care.[55]

OTHER INITIATIVES TO IMPROVE THE VALUE OF MEDICAL CARE

Long-term solutions to reduce low-value cancer care will require changes in regulation at national or international levels. Allowing the FDA and the European Medicines Agency (EMA) to set price limits based on the clinical value of new

treatments would be a logical reform to their mandate and would be consistent with the value-based pricing that influences everything else that we purchase.[56] Many countries have a two-step process in approving drugs, involving HTA after drug approval by the registration agency. After approval by the EMA, NICE in the United Kingdom (and HTA bodies in other European countries) assesses the value of new treatments, based partly on cost-effectiveness, and can bargain with Pharma companies as part of their decision to fund (or not) treatments as part of the National Health Service. HTA may reject low-value treatments and reduce the cost of high-value treatments. Increasing use of HTA, and its introduction in the United States and allowing Medicare and Medicaid to negotiate drug prices, could reduce the cost of new medications and link that cost to clinical value.

Procedures leading to registration of new drugs varies among countries, and delays in regulatory approval are a cause of limited access to new treatments. However, effective registration and HTA are unlikely to bring the cost of new effective drugs to a range that is affordable for most patients in LMICs. Ideally, the price of drugs in individual countries should reflect their gross domestic product—especially as global RCTs in cancer drug development are now often sponsored by Pharma. It is unethical to recruit patients in a LMIC to a clinical trial that leads to marketing of a drug but deny that treatment to patients in the same country when the trial is completed. While there have been efforts by foundations in collaboration with Pharma companies to provide universal coverage for a few drugs (eg, imatinib for chronic myelogenous leukemia), new drugs are not available to most people in LMICs because of cost.

Other strategies can reduce costs and improve access to high-value treatment. Generic drugs and biosimilars that have undergone appropriate chemical and clinical testing offer substantial savings. In addition, many drugs can be used at lower doses, in shorter courses or given less often than in the trials that led to their approval.[57,58] For example, adjuvant trastuzumab is a high-value therapy for women with HER2-positive breast cancer but is not available to many patients in LMICs because of cost. Several trials and a meta-analysis have shown that 6 months of treatment give similar outcomes to 1 year, and two studies have shown similar outcomes for 9 weeks of adjuvant trastuzumab.[59] Some of these studies may not satisfy formal non-inferiority criteria, but the benefits of showing similar survival outcomes with less toxicity and cost in near-equivalence studies far outweigh that concern.[60] Acceptance of 9 weeks of a trastuzumab biosimilar as effective high-value adjuvant treatment for women with HER2-positive breast cancer would allow markedly greater access to this effective treatment.

Most targeted agents have undergone phase 1 evaluation in the same way as chemotherapy—the dose is increased for small groups of patients until toxicity is observed. The maximum tolerated dose (MTD) is then used in phase II and III trials and, if the drug is effective, becomes the registered dose. But for targeted agents, the optimum dose is that which maximally inhibits its target, often much lower than the MTD. The FDA has mandated dose-finding studies for new drugs,[61] but many drugs are used at doses that are far higher, or given more often, than needed to inhibit their target. For example, abiraterone, an effective drug for men with prostate cancer was registered at 1000 mg once daily fasting, but 250 mg once daily after breakfast gives equivalent blood levels and clinical effects[62] and is now accepted by the National Comprehensive Cancer Network as an alternative. A survey in India indicates how the lower dose can improve access.[63]

Multiple studies have shown that inhibitors of PD1 and PD-L1, which are effective in improving OS for patients with many types of cancers, are used at much higher doses and are given more often than is necessary.[64,65] In a 168-patient phase 2 trial for patients with renal cell carcinoma, there was no significant difference in any outcome between patients receiving nivolumab at 0.3, 2, and 10 mg/kg every 3 weeks,[66] yet the dose taken forward into phase III trials was 3 mg/kg (or 240 mg) every 2 weeks—15 times the lowest effective dose. Oncologists in India have recognized the possibility of expanding access to effective immunotherapy by sharing vials between patients and evaluating ultralow doses of nivolumab (20 mg every 2-3 weeks).[67,68] Strategies to reduce dose, use less-frequent dosing, or shorten the course represent appropriate strategies and improve access of patients to high-value treatments.

In other areas of medicine, similar effects of different drugs within a class (eg, statins, angiotensin converting enzyme inhibitors) are often used interchangeably, allowing hospitals to bargain for a lower price by giving preference to one drug of a class. Drug development in oncology has tried to establish niche effects for given members of a class of drugs, but there is evidence of similar benefits from drugs of the same class.[69] As more drugs within a class are developed, drug substitution may allow substantial cost savings, thereby improving access to effective treatment. This is already happening with PD-1 inhibitors in China.

CONCLUSIONS

Oncologists cannot afford to remain silent on the value crisis in cancer care and the economic consequence and financial toxicities that cancer care has on our patients, their families, and our health systems. We must have honest conversations with patients and the public regarding the true value of treatments and avoid hyperbole and rhetoric that overstates clinical benefits. We must invest in quality management and auditing systems that provide data on use of low-value care and support steps to improve it. We must recognize the opportunity costs associated with the provision of low-value

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interventions and shift resources toward those treatments that are most meaningful for our patients. Finally, public benefit rather than private profit must be central to future drug development and must include investment in studies evaluating alternative treatments and lower doses of effective drugs.

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Translating Cancer Science Into Cancer Care: Using Serious Illness Communication Frameworks to Deliver High-Quality Person-Centered Care in Neuro-Oncology

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OVERVIEW

People with CNS cancer and their caregivers need and deserve not only innovative cancer-directed care but also high-quality person-centered care for navigating living their lives in the face of their cancer diagnosis and treatment. Palliative care aims to be an extra layer of support for people with cancer and their caregivers by focusing on what matters most to them and helping people live as well as they can for as long as they can. Palliative care is appropriate starting from time of diagnosis when many palliative care needs begin and is most beneficial when integrated earlier in the disease trajectory, yet the provision of palliative care remains underutilized in neuro-oncology. Centered on illness experience and the multidimensional composition of a person's biological, psychological, and social factors, palliative care is an approach to person-centered care focused on optimizing management of distress arising from physical, psychological, social, existential, and spiritual concerns to reduce and mitigate suffering while promoting coping, patient autonomy, choice, and access to information per the values, goals, priorities, beliefs, and culture of the patient, caregiver, and family members. Fundamental aspects of palliative care, referred to as primary palliative care, should be provided by all clinicians, with specialty palliative care clinicians augmenting as needed where available. In this article, teachable, learnable, and adaptable serious illness communication frameworks leveraged in the palliative care approach are featured in two vignettes. The use of these serious illness communication frameworks actualizes the translation of cancer science into high-quality person-centered cancer care.

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OVERVIEW

In this article the underutilized provision of palliative care as an extra layer of support for people with CNS cancer and their caregivers, which focuses on optimizing quality of life through managing and mitigating distress and suffering, is explored including a brief discussion of the biomedical versus biopsychosocial models of medicine and concept of total pain. In addition primary palliative care (PPC) versus specialty palliative care (SPC) is outlined and serious illness communication frameworks are featured within two clinical vignettes; a middle-age man diagnosed with glioblastoma whose wife wants to know different information from the neuro-oncology team than the patient and a teacher in the adolescent and young adult (AYA) age range diagnosed with a low-grade glioma who is experiencing social and existential distress in conceptualizing her uncertain future. The vignettes demonstrate how these serious illness communication frameworks actualize the translation of cancer science into high-quality person-centered cancer care.

Vignette 1: David is a 58-year-old retired engineer diagnosed with glioblastoma six weeks ago following a seizure at home. He has undergone surgical resection and is midway through 6-weeks of concurrent radiotherapy and temozolomide. His wife, Carol, attends every appointment. David is quiet during consultations, deflecting questions with dark humor. Carol emails the clinical nurse specialist between appointments with detailed questions about prognosis, recurrence rates, and what the end will look like.

The neuro-oncology team is experienced, but the dynamic is becoming strained as David doesn't want to discuss prognosis, yet Carol is desperate for information so that she can plan, making sure that she has everything in place for what lies ahead. The clinicians feel caught between them.

INTEGRATING MODELS OF MEDICINE IMPROVES OUTCOMES

Western medicine, including modern oncology with its continuously evolving scientific advances in cancer-directed treatment, is based on the biomedical model which considers health to be the absence of disease. The

PRACTICAL APPLICATIONS

- Palliative care is a person-centered approach that aims to optimize management of distress arising from physical, psychological, social, spiritual, and existential concerns while supporting the individual's needs, values, priorities, beliefs, culture, autonomy, and access to health care information and choice, delivered concurrently with cancer-directed care.
- People with CNS cancer and their caregivers often have unmet palliative care needs from the time of diagnosis.
- Palliative care is appropriate at any stage in the disease trajectory with people living with CNS cancer and their caregivers benefiting sooner when palliative care is integrated earlier.
- Primary palliative care (PPC) provided by oncology teams entails basic symptom management, discussions about code status, health care surrogate designation, prognosis, treatment intent, and timely referral to hospice.
- Specialty palliative care clinicians who have expertise in serious illness communication augment PPC for those patients and caregivers who have palliative care needs such as high and/or complex symptom burden; moderate to severe distress arising from social, emotional, spiritual, and/or existential concerns; conflicts between or among patient/caregiver/family members/health care staff; and complex hospice transitions.

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biomedical model of medicine is centered on disease: elucidating its pathophysiology and risk factors and identifying how it can be diagnosed and treated. Inherent in biomedical medicine is the premise that elimination or attenuation of the disease results in restoration of health. In contradistinction to the biomedical model's disease-focused medicine, the focus of the biopsychosocial model of medicine is improving how a person living with an illness feels and functions. The biopsychosocial model is centered on the illness experience and its multidimensional phenomenology that arises from an individual's unique biological, psychological, and social factors (Fig 1).[1] Examples of health care specialties informed by the biopsychosocial model include palliative medicine, physical and rehabilitation medicine, nursing, and psychology. They aim to optimize how people diagnosed with disease are feeling and functioning within the context of their unique individual illness experience harmonized with their disease-directed treatment.

People with cancer and their caregivers need and deserve the biomedical and biopsychosocial models of medicine delivered concurrently within their comprehensive cancer care to have the best possible outcomes for their cancer and their lives. Given the incurable nature of many primary and secondary cancers involving the CNS, palliative-intent cancer-directed treatment aims to slow disease progression, prolong survival, reduce disease symptoms, and maintain quality of life. Yet, people with CNS cancer and their caregivers have expressed wanting support for emotional distress, social and relationship issues, existential concerns, coping with uncertainty and neurobehavioral changes, and navigating health care in addition to cancer-directed treatment.[2] AYAs, including those with CNS cancer, might also have unmet symptom control and psychosocial and spiritual needs. Many express wanting care focused on palliation and quality of life aligned with palliative care especially late in the disease course.[3,4] Palliative care is an approach to person-centered care focused on optimizing symptom control, addressing informational needs and multidimensional suffering according to the beliefs, culture, values, goals, and priorities of the person with serious illness and their caregiver.[5] Suffering may not be limited to physical symptoms. Suffering may arise from psychological distress and loss or change of social roles. Suffering may also encompass existential and/or spiritual concerns. The combination of all these factors related to suffering was conceptualized as total pain by Cicely Saunders (Fig 2).[6] Given that suffering may arise throughout the disease trajectory and not only at the end of life, palliative care is appropriate at any time starting from diagnosis concurrent with cancer-directed treatment. This approach is especially crucial for people with CNS tumors.

Robust evidence from randomized trials investigating palliative care for people with advanced cancer concurrent with cancer-directed care resulted in ASCO and multiple other professional organizations issuing guidelines or recommendations for concurrent palliative care as the standard of care for patients with advanced cancer (Table 1).[5,7-10,14,15] Guidelines specifically addressing the role of palliative care for adults with CNS cancer include the National Comprehensive Cancer Network (NCCN) and the European Association for Neuro-Oncology (EANO).[5,8] EANO designated three main areas of palliative care for adults with glioma: symptom management, patient and caregiver needs, and palliative care including but not limited to care in the end-of-life phase and provides concrete clinical and management interventions.[8] The National Institute of Health and Care Excellence (NICE) issued committee-level recommendations on the diagnosis and management of primary brain tumors and brain metastases and determined that people with brain tumors have very specific needs that are often not met and issue guidance on improving supportive and palliative care for adults with brain cancer.[9] The NCCN CNS tumor panel recommends that "palliative and pain management should be integrated into management of neuro-oncology patients early in the course of their treatment."[10] A

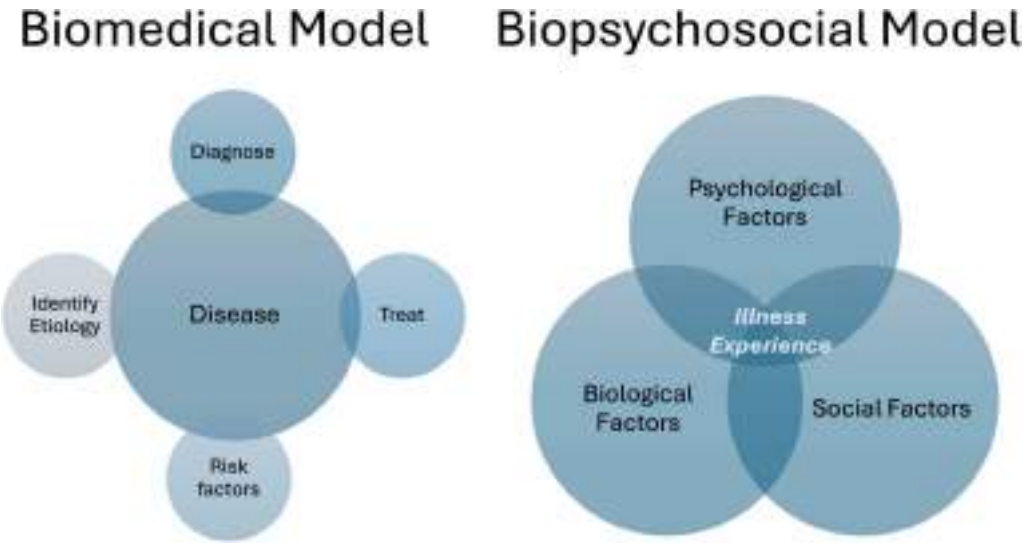

FIG 1. Comparison of the biomedical model of medicine focused on disease and the biopsychosocial model of medicine focused on the illness experience.

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recently published prospective randomized trial evaluating early palliative care for adults with glioblastoma provides evidence that early palliative care integration improves quality of life, mood, communication, and coping with neurologic functions among surviving participants.[16] Overall, SPC consultations are underutilized for people with primary brain tumors.[17] Underlying factors range from neurocognitive dysfunction, psychiatric and behavioral changes from time of diagnosis, limiting communication and engagement in serious illness communication, to avoidant coping strategies such as denial, and the prevailing misconception among clinicians, patients, and caregivers alike that palliative care is only for people who are at end of life or is synonymous for hospice care.[18-20]

All oncology clinicians should provide palliative care, often referred to as "primary" palliative care, in collaboration with SPC experts per evidence-based guideline cancer care pathways and based on based patients' palliative care needs. NCCN recommends that all patients with cancer should be screened for palliative care needs at their initial clinic visit and at subsequent visits as clinically indicated, and ASCO recommends early engagement in palliative care for adults with advanced cance.[5,7] In addition to people with cancer themselves, their caregivers and family members should also be informed that palliative care is an integral part of comprehensive cancer care from time of diagnosis and palliative care provides an extra layer of support, reinforcing the message that it is not end-of-life care. Vierhout et al

FIG 2. Concept of total pain as first described by Dame Cicely Saunders.

TABLE 1. Professional Organizations With Issued PC Guidelines or Recommendations

Organization	Guideline Specifically Addresses PC for People with CNS Cancer (Y/N)	Summary of Recommendations
American Society for Clinical Oncology (ASCO)[7]	N	Formal guidelines recommending PC for all patients with solid cancers
European Association for Neuro-Oncology (EANO)[8]	Y	Designated three main areas of PC for adult patients with glioma: symptom management, patient and caregiver needs, and PC (including but not limited to care in the end-of-life phase). Provides concrete clinical and management interventions for patients
National Institute of Health and Care Excellence (NICE)[9]	Y	Committee-level recommendations acknowledge that people with brain tumors have very specific needs that are often not met and provide general guidance on improving supportive and PC for adults with brain cancer
National Comprehensive Cancer Network (NCCN)[5,10-13]	Y	(1) Evidence-based recommendations addressing the integration of PC in oncology are available to both (a) clinicians and (b) patients
		(2) Specific recommendations for early PC in patients with CNS cancers
		(3) Patient-facing guidelines specifically for glioma
European Society for Medical Oncology (ESMO)[13,14]	N	Formal clinical practice guidelines for communication and support of patients and caregivers in chronic cancer care
European Association of Palliative Care (EAPC)[15]	N	Formal guidelines recommending PC for patients with cancer and noncancer diagnoses

Abbreviations: N, no; PC, palliative care; Y, yes.

concluded that "patients believe that palliative care would contribute to their emotional well-being" and that patients want health care clinicians to "aim to educate brain cancer patients about palliative care early and in a sensitive manner."[20]

Clinicians, patients, and caregivers should understand the concept of PPC versus SPC and their key differences (Table 2).[21] Briefly, PPC is provided by all clinicians, including a patient's primary oncologist. By contrast, SPC is provided by an interdisciplinary team with specific training to address complex patient and caregiver needs. SPC clinicians are experts in serious illness communication, which supports patients and caregivers navigating complex emotions and multidimensional distress that arise because of serious illness. PPC and SPC are intended to address needs beyond the typical therapeutic interactions that focus on imaging results and cancer-directed medications. For people with CNS cancer, PPC can and should be delivered by any of the specialists involved in their day-to-day care (Table 2). Although clinicians, patients, and caregivers may perceive advantages and disadvantages of PPC versus SPC implementation, SPC demand will continue to outweigh its availability as the global burden of cancer and other serious health-related suffering is estimated to double by 2060.[22]

LEVERAGING SERIOUS ILLNESS COMMUNICATION

Vignette 1. Continued

Carol is exhausted and frightened. She knows the median survival for glioblastoma is approximately 12-15 months from diagnosis. Within this disease trajectory, David's clinicians know there is often a period of relative functional stability following initial treatment—a window clinically underutilized for the kinds of conversations that would be beneficial for Carol and David.

TABLE 2. Comparison of PPC and SPC

PPC	SPC
Performed by all clinicians. For example Medical oncologist Neuro-oncologist Radiation oncologist Surgeon Primary care physician Physiatrist Oncology nurse, nurse practitioner, physician assistant	Performed by an interdisciplinary team of palliative care specialists that includes any of the following: Board-certified palliative medicine physician Advanced practice provider Nurse Social worker Psychologist Chaplain Pharmacist
Standard skills and competencies expected of all clinicians, including Basic symptom management of pain, nausea, anxiety, and depression Basic goals of care conversations Establishing code status Advance care planning especially to establish health care surrogate Timely hospice referrals	Specialized palliative care addresses Complex (and/or uncontrolled) symptom management Evaluation and management of moderate to severe distress (social, emotional, spiritual, existential) Conflicts between or among patient/caregiver/family members/healthcare staff Needs for expert communication and goal setting Complex hospice transitions
Occurs in any health care setting (inpatient, outpatient, etc)	Occurs in any health care setting *where available*
Provided along with standard treatments	Provided along with standard treatments

Abbreviations: PPC, primary palliative care; SPC, specialty palliative care.

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The Conversations

Carol says: "*He won't talk about it. He acts like everything is fine. And I'm the one holding all of this on my own.*" She wants to know how long he has and what the time they have left will look like. She wants to plan—for the children, for finances, and for herself.

David, when contacted separately through the clinical team, is initially resistant. He eventually says: "*I know what's coming. I just don't want to spend whatever time I have talking about it.*"

This is not denial in the clinical sense. This is an individual making an active, values-based choice about how to live with a life-limiting disease—what Cicley Saunders would have recognized as part of the existential, social, and psychological dimensions of total pain: the suffering that arises not from physical symptoms alone, but from loss of meaning, role, and future.[6,23] David is a person who has lost control of almost everything, and this is one of the few things he can still control.

COMMUNICATION FRAMEWORK: THE SERIOUS ILLNESS CONVERSATION GUIDE

The Serious Illness Conversation Guide (SICG), developed by Ariadne Labs, provides a structured but flexible approach to exploring what matters most to patients facing life-limiting illness.[24] It moves through four domains, using questions designed to open rather than foreclose:

- illness understanding,
- information preferences,
- goals and fears, and
- what gives life meaning.

Rather than leading with prognosis, clinicians ask first: "*How much do you understand about where you are with your illness*?" and "*How much information would be helpful for you*?"

This framing is particularly valuable in person-centered conversations about navigating life with glioblastoma, where patients and caregivers often differ substantially in their information needs and coping styles.[25] In David and Carol's case, using SICG-structured conversations (held separately from each other) allows the clinical team to meet each person where they are, rather than defaulting to the most information-hungry partner setting the agenda for both.

In the clinical consultation, the SPIKES protocol offers a practical structure: establishing the Setting, exploring Perception, obtaining Invitation to share information, providing Knowledge, responding to Emotion, and Summarizing with a strategy (Table 3).[26] Responding to emotion is often the step most abbreviated or omitted, yet it is where trust is built or lost; it is where deep emotional processing is done.[27] When Carol says "*I just need to know what I'm preparing for*," the response that helps her is not immediately informational; it is the one that names and validates her experience before anything else is offered.

COMMUNICATION USING A COACHING MINDSET AND RESPONDING TO EMOTION HELPS

With Carol, serious illness conversation does not start with information; it starts with exploring what she actually needs that underpins her information-seeking. The GROW model—Goal, Reality, Options, Will (Table 3)—provides a useful structure here, and in practice, it is important to identify the goal before moving onto the reality: *what is happening for Carol right now*, in her own words.[28] Through careful questioning, she realizes that what she needs most is not a timeline but to address her social suffering by feeling less alone in carrying the knowledge she already has. She needs practical help—with financial planning, with having age-appropriate conversations with her children, and with building her own support network so that David is not her only source of connection.

The NURSE framework—Naming, Understanding, Respecting, Supporting, Exploring—for responding to emotions (Table 3) is a learnable communication skill that

TABLE 3. Frameworks for Coaching and Communication

Framework	Acronym	Elements and Examples
SPIKES protocol for delivering news	Setting Perception Invitation Knowledge Emotions Strategy and summary	Ensure private space without interruptions Elicit knowledge of the current situation Obtain permission to give news Provide information in short statements, checking for comprehension Respond empathically to emotions Review main points, strategize next steps, and summarize the plan
GROW model for problem-solving and decision making	Goal Reality Options Will	What do you want? What is happening now? How do you feel? What are your options? What could you do? What will you do? How will you do it?
NURSE statements for empathically responding to emotion	Naming Understanding Respecting Supporting Exploring	It sounds like you might be feeling overwhelmed Hearing this helps me better understand I can see how much this means to you I will be here for you no matter what happens Could you say more what you are concerned about?

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clinicians can use to compassionately express their understanding which facilitates emotional processing.[29] When a clinician says: "*It sounds like you're carrying an enormous amount and doing it largely invisibly*" (Naming and Understanding), Carol's response is to exhale and say: "*Yes. Exactly that.*" Something shifts. The subsequent conversation about what support might look like becomes possible in a way it was not before.

With David, the serious illness conversation centers on what matters to him right now. The Ask-Tell-Ask approach—asking what he already knows, offering information only in response to what he actually wants, and checking what he has taken from the exchange—allows him to remain in control of what enters the conversation (Table 4).[30] He is helped to articulate what a good day is for him, aiming to help him have as many as possible. He says: "*I want to go to the rugby. I want decent coffee. I don't want everyone looking at me like I'm already gone.*" This is, within the emotional intelligence–focused realm of serious illness communication, an expression of his values and his goals, along with acknowledgment of his poor prognosis and mortality. He conveyed information that is clinically and humanly vital, but that would likely never have emerged from a prognosis-led conversation.

Using serious illness communication frameworks allows Carol to get what she needs through a private conversation with the palliative care team, whereas David gets to set the terms of his remaining time. Their relationship, under extraordinary pressure, is given room to breathe.

THE CLINICAL LESSON

Because of cognitive dysfunction in those living with glioblastoma, the caregiver frequently becomes the primary interlocutor with the clinical team. Caregiver information needs and the patient's coping style can be in direct tension, a dynamic well-documented in the literature.[31,32] Integrating palliative care within a few weeks to months of the diagnosis creates the conditions in which these conversations can happen without crisis forcing them, or they may not happen at all. The principle applies with equal relevance in neuro-oncology: by using serious illness communication frameworks, individual and collective wants, needs, values, and priorities are elicited so patients, caregivers, and their clinicians can navigate next steps in the patient's care.

TABLE 4. Key Communication Skills

Skill	Example
"Tell me more"	"Tell me more about what is most important to you."
Ask-Tell-Ask	"What do you want to know about….?"
	"The information I hear you are seeking is…"
	"Does this information help you?"
"I wish…."	"I wish more chemotherapy would change what is happening right now."
"I worry…"	"I worry that more chemotherapy will cause you feel sicker from more side effects without changing the cancer's growth."
Silence	Holding space for strong emotion with compassion by remaining silent and holding the person expressing emotion with unconditional positive regard

Low-Grade Glioma—The Uncertain Wait

> **Vignette 2:** Priya is a 34-year-old teacher, diagnosed with a WHO grade 2 IDH-mutant astrocytoma 18 months ago after presenting with new onset headaches with what Priya described as "odd sensations". She underwent resection and is currently on active surveillance with regular MRIs. She is back at work. To colleagues and her students, she looks well. To herself, she is waiting. She is articulate and organized, having created a list of questions and a spreadsheet of symptoms she has been tracking. She has read grade 2 IDH-mutant gliomas carry a median survival that has improved significantly with modern molecular testing and targeted therapy, with many now living 10 years or longer, though the disease eventually transforms to higher grade in most cases. This is not, as it is sometimes characterized by clinicians to patients, a reassuring prognosis to Priya. Rather it is a different kind of prognosis--one that requires a different kind of support over a far longer timeframe.

THE CONVERSATIONS

Priya's challenges though different from someone living with glioblastoma are no less profound. She describes living in a state of *suspended animation*—too well to claim the identity of someone who is seriously ill and too ill to reclaim the future she had planned. She had expected to be promoted. She had expected to start a family. Now, every decision feels contingent on something she cannot name.

She is also managing the exhaustion of other people's relief. "*Everyone keeps saying how well I'm doing. And I am. But I also have a brain tumor, and nobody seems to want to acknowledge both of those things at once.*"

Her partner, Sanjay, is loving but avoidant. He does not want to talk about the tumor. He says that talking about it makes it more real. Priya finds this isolating.

This pattern—the person living with the tumor diagnosis carrying existential awareness that those around her cannot tolerate—is well-recognized in the qualitative medical literature. Cavers and colleagues describe the social and existential isolation experienced by people with glioma as distinct from other cancer diagnoses, partly because cognitive and personality changes, when they occur, can alter the very relational capacity on which support depends.[31] Even in the absence of overt symptoms, the anticipatory grief and identity disruption are present from diagnosis.

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COMMUNICATION FRAMEWORK: EXPLORING INFORMATION PREFERENCES AND FUTURES

For Priya, the clinical challenge is not acute. She is not in a medical crisis. But the absence of medical crisis should not be misread as the absence of need. The SICG question "*What are your biggest fears or worries about the future*?"—asked not in a moment of deterioration but in a routine surveillance consultation—opens a conversation that transforms her engagement with her own care.[24] She says that her biggest fear is not death, but cognitive change: losing her ability to teach, to think quickly, and to be herself in a classroom. This is information her clinical team did not have, and it changes the conversation about when to initiate treatment.

The Ask-Tell-Ask approach is again valuable here.[30] Rather than offering information about transformation rates and treatment timelines (Tell), the clinician first asks: "*What would be most helpful to understand about what the next few years might look like*?" (Ask). Priya says that she wants to understand what signs to watch for and what control she has over timing. The information that follows is calibrated to that question, not to a generic prognostic summary (Tell). Checking what she has understood and what she wants to do with it (Ask) closes the loop and returns agency to her.

WHERE PALLIATIVE CARE'S EXTRA LAYER OF SUPPORT HELPS

For Priya, the palliative care clinician relationship provides the one space where she does not have to manage other people's feelings. This matters. The emotional labor of protecting others from distress, a burden disproportionately carried by patients with nonvisible illness, is itself exhausting and isolating.[33]

Using the GROW framework, the conversations begin with an honest exploration of reality: not the medical reality, which Priya understands well, but her lived reality and the decisions she has frozen, the relationships she is navigating with insufficient support, and the sense of purposelessness that has crept into her working days.[28] The goal that sits behind this is not dramatic: she wants to feel like she is living her life again, not waiting to see what happens to it.

By contemplating her options framed in the GROW model, Priya conceptualizes ideas and thoughts she had not allowed herself to consider. She had stopped applying for promotion because it seemed pointless. She had stopped discussing children with Sanjay because the conversation felt impossible. Priya's catalyst was the opportunity to separate the practical questions (which are answerable, with the right information and support), from the existential ones, which require a different kind of holding. She approaches her fertility specialist. She applies for the promotion and gets it.

The SICG framework again proves to be useful, this time in helping Priya to have a different conversation with Sanjay.[24] Rather than approaching him with information, which he is known to avoid, she approaches him with a named need of what is most important to her: "*I don't need you to know what's going to happen. I just need to not be alone with it*." The palliative care clinician helps her find this formulation. It is, in the language of serious illness communication, an expression not of prognosis but of relational need and navigating social distress. This expression of Priya's need is one Sanjay can respond to.

Priya also prepares differently for her next magnetic resonance imaging (MRI) review. Rather than arriving with a spreadsheet, she arrives with two questions that matter to her. The consultation shifts from data-gathering to dialogue about her disease status to a meaningful conversation. She leaves feeling that she has been seen and heard in addition to informed about her stable surveillance MRI.

THE CLINICAL LESSON

Low-grade glioma presents a distinct and often underrecognized challenge: the patient is well enough to be largely invisible to supportive care services but is living with a chronic existential threat that permeates every major life decision across a horizon of many years. Systematic reviews of supportive care needs in patients with brain tumor consistently identify unmet psychological and social needs even in patients who appear to be functioning well.[33-35] Palliative care, in this context, is defined by the WHO as the active total care of patients whose disease is not responsive to curative treatment and is applicable from the point of diagnosis.[36] The palliative care approach of being person-centered on their illness experience and what is most important is particularly well-suited to the long trajectory of low-grade glioma. It meets patients where they are, over time, without requiring them to be in crisis to access support. For clinicians, this vignette illustrates that the absence of acute distress is not evidence of absent need and that the most important conversations are often the ones that happen before anything has gone wrong.

CONCLUSION

For people with CNS cancer, their disease may affect every aspect of their physical, cognitive, and emotional well-being—the core of who they are as a human being. They face a highly uncertain future and need as much support as possible, as do their caregivers and family members. David's case depicts what happens when the patient and the caregiver have profoundly different needs and coping styles. Serious illness communication did not resolve that tension by forcing engagement with prognosis. It resolved it by meeting each person where they were in their emotional processing of the cognitive information about the cancer. Priya's case makes the harder argument: that a patient who

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is functioning well by every clinical measure can simultaneously be living with a chronic existential threat that is quietly foreclosing her future. The absence of acute distress is not evidence of absent need. The featured vignettes highlight how people like David and Priya present with different diagnoses, different disease trajectories, and different palliative care needs, yet both illustrate the same core proposition: that people with CNS cancer need and deserve care focused on their illness experience and optimizing how they are feeling and functioning concurrently with their cancer-directed care. Together, these cases make the case for communication that is built into care from diagnosis, not grafted on when clinical deterioration emerges. The frameworks described here—SICG, SPIKES, NURSE, Ask-Tell-Ask, and GROW—are teachable, learnable, and adaptable communication skills. The use of these serious illness communication frameworks actualizes the translation of cancer science into high-quality person-centered cancer care. The science of neuro-oncology has made extraordinary advances. Translating those advances into health care that is truly person-centered requires clinicians to bring the same rigor and intentionality to communication that they bring to cancer treatment.

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Precision Immunotherapy: Revolutionizing Cancer Treatment With Targeted Innovations

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OVERVIEW

While immune checkpoint inhibitors have transformed treatment for many cancers, their benefit remains limited across all tumor types and is constrained by immune-related toxicity. Targeted immunotherapies, including T-cell engagers (TCEs), offer a more selective strategy by directing immune activity toward tumor-associated antigens. TCEs have achieved major success in hematologic malignancies and now show promise in selected solid tumors, with the approvals of tebentafusp and tarlatamab in uveal melanoma and small cell lung cancer, respectively, establishing proof of concept that durable benefit is possible. However, TCE efficacy is balanced by class-specific toxicities such as cytokine release syndrome and neurotoxicity, as well as on-target off-tumor effects. Antibody-drug conjugates (ADCs) can also enhance the specificity of cancer treatment by directing cytotoxic activity toward tumor cells via specific targets. ADC-checkpoint inhibitor combinations are similarly reshaping solid tumor therapy, most notably in urothelial carcinoma, where enfortumab vedotin plus pembrolizumab has demonstrated substantial survival gains. Across both strategies, efficacy may be influenced by antigen density, tumor heterogeneity, microenvironmental suppression, and treatment sequencing. Emerging drug engineering approaches and biomarker-driven patient selection aim to improve efficacy while limiting toxicity. Together, these advances support a new era of precision immuno-oncology, but broader success will require improved biomarkers, rational combinations, and an understanding of resistance mechanisms.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have had a profound impact in the past two decades, with US Food and Drug Administration (FDA) approvals for many tumor types and response rates surpassing 50% in metastatic melanoma for combination ICI.[1-5] However, not all cancers harbor sufficient pre-existing tumor antigen–specific T-cells or have suppressive microenvironments leading to ICI insensitivity, such as the case in microsatellite stable colorectal cancer and pancreatic cancers, where the potential of immunotherapy has not yet been realized.[6,7] In addition, many of the risks associated with ICI are related to the nonspecific mechanism of T-cell activation by checkpoint blockade, in which immune responses to healthy tissues lead to organ damage and dysfunction.[8] Therefore, additional immunotherapies with activity in cancer types that initially exhibit refractoriness or develop resistance to ICI, and which spare healthy tissues, are an ongoing need in cancer treatment.

An alternate approach to harnessing the power of the immune system against cancer is to use targeted immunotherapy which can focus attack on specific tumor antigens (Fig 1). This idea is not entirely novel as some of the earliest immunotherapies approved were cancer vaccines, such as sipuleucel-T, a vaccine made of ex vivo–expanded antigen-presenting cells targeting prostatic acid phosphatase in prostate cancer.[9] More recently, chimeric antigen receptor (CAR) T-cells and bispecific T-cell engagers (TCEs) are examples of immunotherapies developed to activate T-cells against specific targets known to be overexpressed or selectively expressed in tumors.[10-12] The success of these therapies is demonstrated by seven CAR T-cell approvals (all within hematologic malignancies), one T-cell receptor (TCR) T-cell therapy approval for sarcoma, and multiple TCE approvals across hematologic and solid tumors.[10,13-17] The advantages of the targeted immunotherapy strategy include fewer nonspecific immune effects as ICI, but can increase the risk of other toxicities because of the specific recognition of the target on healthy cells (on-target off-tumor [OTOT] toxicity).[18] This is notable with B-cell depletion that occurs with CD19-targeted CAR T-cell therapy for hematologic malignancies, which is generally thought to be an acceptable risk, whereas other solid tumor CAR T-cell programs have led to fatal toxicity (eg, pneumonitis and respiratory distress related to recognition of the antigens CEACAM5 and human epidermal growth factor receptor 2 [HER2] in the lungs).[14,19,20] Targeted therapies inducing potent immune responses can also lead to inflammatory syndromes (cytokine release syndrome [CRS], neurotoxicity) as a result of

PRACTICAL APPLICATIONS

- Targeted immunotherapy is a new direction in precision cancer therapy, with many approvals for T-cell engagers (TCEs) in hematologic malignancies. The recent approvals of tebentafusp and tarlatamab demonstrate that TCEs can also produce meaningful benefit in solid tumors and encourage oncologists to think beyond tumor histology toward target-driven therapy selection.
- Combination targeted therapy and immunotherapy regimens are becoming the standard in some diseases. The success of enfortumab vedotin plus pembrolizumab in urothelial cancer suggests that antibody-drug conjugate-checkpoint inhibitor combinations could be successful in additional tumor types.
- Targeted immunotherapy and combination regimens provide additional rationale for the importance of biomarker testing. Future practice decisions may rely more on factors such as antigen expression, human leukocyte antigen type, circulating tumor, and immune signatures to decide who should receive targeted regimens.
- As targeted combinations move earlier in therapy, clinics will need stronger workflows for managing on-target off-tumor toxicities and other documented adverse events such as cytokine release syndrome and neurotoxicity, including step-up dosing, early monitoring, and rapid intervention pathways.
- Treatment sequencing and resistance remain major clinical questions. Future oncology practice will need to better define when to use targeted therapy, immunotherapy, or both and how to overcome antigen loss, immune exclusion, and exhaustion—likely through rational combinations.

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immune activation downstream of a targeted attack. These therapies have ushered in a new era of immunotherapy in which the modality (ie, vaccine, cell therapy, monoclonal antibody) is equally as important as the target of the therapeutic agent and requires integration with other immunotherapies such as ICI, chemotherapy, and other molecularly targeted cancer drugs.

In addition, as immunotherapy has become a pillar of cancer treatment, combination regimens are increasingly common. For example, many solid tumors are treated with chemotherapy and immunotherapy combination regimens that have superior efficacy to either monotherapy.[21-23] Cytotoxic therapies such as chemotherapy and radiation may be synergistic with immunotherapy because of induction of immunogenic cell death and release of tumor antigens, activating dendritic cells and subsequently T-cell responses.[24,25] Similarly, targeted therapies capable of inducing immunogenic cell death may achieve similar effects on T-cell activation.[26,27] Another theoretical advantage is using immunotherapy in combination to induce adaptive and long-lived immune responses to overcome the challenge of short-lived responses because of targeted therapy resistance. Beyond tumor cell death, targeted therapies can also have immunostimulatory effects on dendritic cells, T-cells, and natural killer cells[28,29] and relieve tumor-induced immune suppression by decreasing suppressive cytokine production,[30] inhibiting regulatory T-cells,[31,32] normalizing tumor vasculature by vascular endothelial growth factor (VEGF) inhibition,[33,34] and repolarizing or inhibiting tumor-associated myeloid cells.[34,35] These effects of targeted therapies may synergize with immunotherapy, providing potential mechanisms for the increased efficacy of combination regimens.[36-39] As ADCs are more widely used across malignancies, they are also being investigated for their efficacy as part of combination regimens.[40]

The use of both targeted immunotherapy and combination targeted/immunotherapy in regimens has several FDA-approved uses which we will review in detail, with a focus on the benefits and specific risks associated with these. The potential benefits and challenges of this new mode of cancer treatment are addressed, including the process of selecting personalized targets and therapies.

ADVANCED TCE STRATEGIES

Structure, Mechanism, and Engineering of TCEs

TCEs are bispecific or multispecific antibody-based molecules designed to physically link tumor cells and T-cells.[41] Structurally, they consist of antigen-binding domains recognizing tumor-associated antigens (TAAs) on cancer cells and a CD3-binding domain targeting the TCR complex, often arranged within IgG-like architectures that may include an engineered Fc region.[41-45] Through this modular antibody design, TCEs act as molecular bridges that forcibly redirect T-cells toward tumor cells, initiating immune synapse formation and cytotoxic activity independent of native T-cell antigen specificity.

The structural modality of TCEs is defined by their binding valency (1 + 1, 2 + 1, or 1 + 1 + 1) and molecular platform (immunoglobulin G [IgG]–like *v* non–IgG-like), which dictate their pharmacokinetic and safety profiles.[46] The simplest binding valency is the conventional 1 + 1 bispecific format, defined by a single tumor-binding arm paired with a single CD3-binding arm. The configuration efficiently redirects polyclonal T-cells toward antigen-expressing tumor cells through high-affinity monovalent interactions. Clinically established examples include blinatumomab (CD19×CD3) in B-cell acute lymphoblastic leukemia and teclistamab (BCMA × CD3) in multiple myeloma.[47-49] To

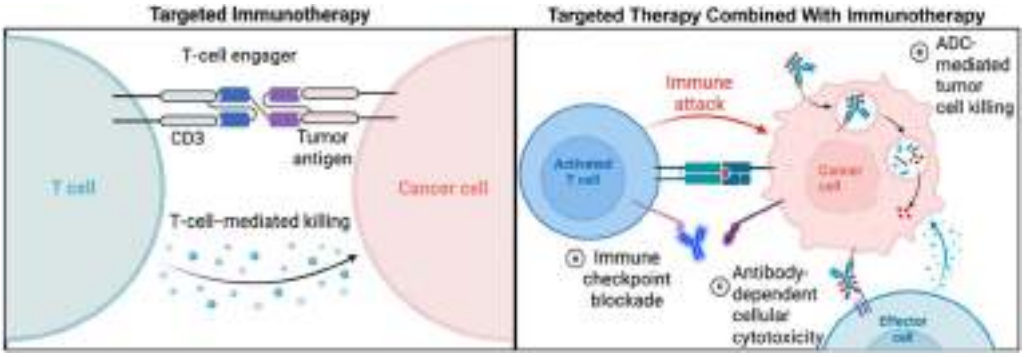

FIG 1. Targeted immunotherapy and combination immunotherapy plus targeted therapy mechanisms. Targeted immunotherapy includes novel therapeutics such as T-cell engagers, which activate and physically localize T-cells to cancer cells via dual T-cell and tumor antigen binding, resulting in T-cell–mediated killing of cancer cells (left panel). ADC can be combined with immunotherapy, such as immune checkpoint inhibitors, to increase tumor cell killing (right panel). (A) Immune checkpoint blockade leads to T-cell activation, (B) whereas ADC targeting of tumor cells via tumor antigens results in delivery of the chemotherapy payload. (C) ADCs can also mediate immune activation via the release of tumor antigens and by antibody-dependent cellular cytotoxicity. ADC, antibody-drug conjugates. Created using BioRender. Keenan. 2026. https://BioRender.com/v3b8lsf.

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enhance tumor selectivity and reduce off-tumor toxicity, 2 + 1 formats have been developed, incorporating two tumor-binding domains and a single CD3-binding arm. Representative agents include glofitamab (CD20 × CD3) in B-cell non-Hodgkin lymphoma and tarlatamab (DLL3 × CD3) in small cell lung cancer (SCLC).[10,50]

Beyond binding format, the molecular platform of Fc region constitutes a second major structural determinant of TCE behavior. Fragment-based platforms such as bispecific T-cell engagers (BiTEs) exemplified by blinatumomab or dual-affinity retargeting antibody lack an Fc region. As a result, these constructs exhibit superior tissue penetration but a short circulating half-life that necessitates continuous intravenous infusion.[51] By contrast, IgG-like TCEs, including teclistamab and tarlatamab, incorporate an engineered Fc region that preserves neonatal Fc receptor (FcRn) binding. This design enables prolonged half-life and convenient intermittent dosing, whereas Fcγ receptor interactions are silenced to prevent nonspecific immune activation and mitigate the risk of CRS.

Functionally, the structural features of TCEs translate into potent antitumor efficacy by enforcing direct physical proximity between T-cells and tumor cells, resulting in rapid immunologic synapse formation.[52] Of note, TCEs activate T-cells independent of their native TCR specificity and without reliance on major histocompatibility complex (MHC)–restricted antigen presentation.[53] Activated T-cells then induce direct tumor cell killing through the immediate proliferation and secretion of inflammatory cytokines, primarily perforin and granzymes.[45] Perforin forms transmembrane pores in the tumor cell membrane, facilitating granzyme entry and triggering apoptosis. This MHC-independent mechanism is particularly relevant in tumors that evade immune surveillance through MHC class I downregulation.[54] Consequently, TCEs retain activity against immunologically inactive tumors and can restore effective immune-mediated tumor control. In addition, the destruction of the tumor cell can lead to epitope spreading, where the release of new tumor antigens further stimulates the broader immune system to recognize and attack the cancer.

Beyond structural optimization, dosing strategy has emerged as a critical determinant of T-cell fitness. Continuous stimulation by TCEs can lead to T-cell exhaustion and activation-induced cell death. Translational data from the pasritamig (prostate-specific membrane antigen [PSMA]xCD3) trial in prostate cancer revealed that extending the dosing interval from every 3 weeks to every 6 weeks preserved a stem-like $TCF1^+$ T-cell phenotype and reduced exhaustion markers such as $CD69^+$, potentially improving long-term efficacy.[55]

Safety Profiles and Management

The potent, MHC-independent T-cell activation that underlies TCE efficacy also drives their characteristic immune-mediated toxicities, most notably CRS and immune effector cell–associated neurotoxicity syndrome (ICANS).[56,57] CRS results from rapid and widespread T-cell activation after immunologic synapse formation, leading to excessive release of proinflammatory cytokines such as interleukin-6 and interferon-γ.[58,59] Clinically, CRS manifests as fever, hypotension, hypoxia, and organ dysfunction, with severity influenced by tumor burden, antigen density, and dosing kinetics.[56] ICANS, although less frequent than with CAR-T therapies, may occur through cytokine-mediated endothelial activation and blood-brain barrier disruption, presenting as encephalopathy, confusion, aphasia, or seizures.[57]

Management of TCE-related toxicities relies on proactive prevention, early recognition, and grade-adapted intervention. Most cases of CRS occur during the first treatment cycle and correlates with tumor burden and initial T-cell activation kinetics. Preventive strategies include step-up dosing, inpatient close monitoring, and premedication with corticosteroids and antipyretics. Grade 1 CRS is generally managed with supportive care alone, whereas grade ≥2 events warrant temporary treatment interruption and early interleukin-6 (IL-6) blockade such as tocilizumab, with prompt corticosteroid escalation for persistent or progressive symptoms. Severe cases may require vasopressor support, oxygen supplementation, or intensive care. ICANS requires close neurologic monitoring and is primarily treated with corticosteroids as IL-6 inhibition has limited efficacy for isolated neurotoxicity. Importantly, most events are early, transient, and reversible, allowing safe rechallenge after resolution.

Success in Hematologic Malignancies

The clinical proof of concept for TCEs was established in hematologic malignancies, where targets are often lineage-specific with manageable off-tumor toxicity. Blinatumomab (CD19×CD3) is the first established proof of concept in relapsed/refractory B-cell precursor acute lymphoblastic leukemia, producing a complete remission (CR) rate of 43% (95% CI, 33 to 53) and minimal residual disease (MRD) negativity in 78% of responders, with a median overall survival (OS) of 7.7 months (95% CI, 5.6 to 9.6) in heavily pretreated patients.[47,60] Among CD20-directed bispecifics, mosunetuzumab demonstrated an objective response rate (ORR) of 80% (95% CI, 70 to 88) and a CR of 60% (95% CI, 49 to 70) in relapsed/refractory follicular lymphoma, with a median duration of response (DOR) of 22.8 months (95% CI, 9.7 to not estimable [NE]) and mostly low-grade CRS.[61,62] Epcoritamab achieved similarly robust activity, with an ORR of 63% (95% CI, 52 to 72) and a CR of 39% (95% CI, 29-49) in diffuse large B-cell lymphoma[63] and an ORR of 82% (95% CI, 72 to 89) and a CR of 60% (95% CI, 49-70) in follicular lymphoma.[64] The median DOR was 12.0 months (95% CI, 9.7 to 15.1), with mostly grade 1-2 CRS (49%). In multiple myeloma, teclistamab (BCMA × CD3) produced an ORR of 63% (95% CI, 55 to 70) and CR in 39% (95% CI, 31 to 47) after more than three prior lines, with sustained benefit (median DOR, 18.4 months [95% CI, 14.9 to NE]) and manageable CRS (72%, mostly grade 1-2).[49] By contrast, early-phase CD33- or CD123-targeted TCEs in AML have yielded more modest activity (ORR, 10%-30%) with higher inflammatory toxicity.[65-68] Collectively, these data confirm that TCEs deliver high response rates, deep remissions, and durable disease control in relapsed/refractory B-cell malignancies, establishing a therapeutic benchmark that is now being extended into earlier-line and combination strategies.

Clinical Development Landscape in Solid Tumors

Translating the success of TCEs to solid tumors has been challenging because of the scarcity of highly specific tumor antigens and the immunosuppressive tumor microenvironment (TME). However, two landmark approvals and emerging data marked a significant turning point (Table 1). The first approval was tebentafusp, an ImmTAC (immune-mobilizing monoclonal TCR against cancer). Tebentafusp uses a high-affinity engineered TCR specific for the gp100 peptide presented by HLA-A*02:01, fused to an anti-CD3 effector domain.[69] Phase I dose-escalation and dose-expansion studies established the recommended phase II dose (RP2D) using a step-up regimen, demonstrating manageable toxicity and early signals of efficacy.[70] The most frequent adverse events were pyrexia (91%), rash (83%), pruritus (83%), nausea (74%), and chills (69%), with toxicity attenuating after the first three doses. In a pivotal phase III trial in previously untreated metastatic uveal melanoma, tebentafusp significantly improved OS compared with investigator's choice therapy. The 1-year OS was 73% with tebentafusp versus 59% in the control arm (hazard ratio [HR], for death 0.51), and with extended follow-up, the survival benefit remained durable with a median OS of 21.6 versus 16.9 months (HR, 0.68 [95% CI, 0.54 to 0.87]) and a 3-year OS of 27% versus 18%, despite only modest RECIST responses (ORR 11% *v* 5%, median progression-free survival [PFS] 3.4 *v* 2.9 months).[15,71] This dissociation between response rate and survival benefit underscores the unique immunobiology of TCEs and suggests durable immune control beyond radiographic tumor shrinkage. In metastatic cutaneous melanoma, the phase Ib combination of tebentafusp and durvalumab with or without tremelimumab showed tolerability and encouraging efficacy (ORR, 14%, tumor shrinkage 41%, 1-year OS 76% [95% CI, 70% to 81%]) even after prior checkpoint inhibitors.[72] Translational data further show that tebentafusp reprograms suppressive macrophages and a high $CD163^{+}$ TAM-to-T-cell ratio predicted worse OS (HR, 2.09 [95% CI, 1.31 to 3.33]), supporting IL-2–based combinations to overcome myeloid suppression.[73]

Toxicity of tebentafusp is dominated by on-target immune effects related to gp100 expression in normal melanocytes and cytokine release. CRS was observed in over 80% of patients, but events were mostly grade 1 or 2, occurring early during treatment and diminishing with subsequent dosing.[74] Skin-related adverse events, including rash and pruritus, occurred in approximately 70%-80% of patients, reflecting melanocyte targeting. However, these were generally manageable with topical or systemic corticosteroids. Grade 3 or higher treatment-related adverse events occurred in about 40%, but treatment discontinuation because of toxicity was infrequent.[71] Importantly, no severe neurotoxicity was observed, highlighting differences in safety profiles between ImmTACs and CAR T-cell therapies.

Ongoing trials include multiple phase II and phase III studies in uveal melanoma, spanning neoadjuvant, adjuvant, and metastatic settings (Table 2). In parallel, tebentafusp is being explored in combination approaches, including with pembrolizumab (TEBE-AM phase III trial), radiation therapy, and immune-modulatory or cytotoxic agents such as

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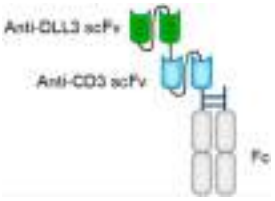
TABLE 1. FDA-Approved T-Cell Engagers in Solid Tumors

Antibody (trade name)	Target/Structure	Format and Features	Indications	Year of Approval
Tebentafusp (Kimmtrak)	GP100 × CD3	ImmTAC (TCR × scFv) Lacks Fc MW: approximately 75-77 kDa Half-life: 6-8 hours	Uveal melanoma	2022
Tarlatamab (Imdelltra)	DLL3 × CD3 	HLE-BiTE Two scFvs linked together and an IgG1 Fc domain MW: approximately 105 kDa	SCLC	2024

Abbreviations: DLL3, delta-like ligand 3; HLE-BiTE, half-life extended bispecific T-cell engager; Ig, immunoglobulin; scFv, single-chain variable fragment; SCLC, small cell lung cancer; TCR, T-cell receptor.

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sargramostim (granulocyte-macrophage colony-stimulating factor) and BCNU. Beyond uveal melanoma, phase II studies are extending tebentafusp to advanced cutaneous melanoma and clear cell sarcoma, with growing interest in gp100-directed T-cell redirection across melanocytic and translocation-associated sarcomas.

Tarlatamab is a BiTE targeting delta-like ligand 3 (DLL3), a Notch pathway ligand highly and selectively expressed in SCLC with minimal normal tissue expression.[75,76] In the phase I/II DeLLphi-301 study enrolling heavily pretreated patients with relapsed or refractory SCLC, tarlatamab demonstrated robust antitumor activity.[10] At the selected 10 mg dose administered every 2 weeks (n = 100), the confirmed ORR was 40% (97.5% CI, 29 to 52), with a median PFS of 4.9 months (95% CI, 2.9 to 6.7) and a median OS of 14.3 months (95% CI, 10.8 to NE). Long-term follow-up data presented in late 2024 updated the median OS to 15.2 months. Patient-reported outcomes (PROs) showed significant improvements in cough and dyspnea, with the median time to deterioration for these symptoms exceeding 6 months. Confirmatory phase III data from DeLLphi-304 demonstrated a significant survival advantage over standard chemotherapy in the second-line setting (median OS 13.6 *v* 8.3 months; HR, 0.60; ORR 35% *v* 20%), leading to traditional regulatory approval.[77] Consistent findings were observed in an earlier phase I dose-escalation/dose-expansion study (N = 107), where heavily pretreated patients achieved an ORR of 23.4% (95% CI, 15.7 to 32.5), a disease control rate of 51.4% (95% CI, 41.5 to 61.2), a median DOR of 12.3 months (95% CI, 6.6 to 14.9), a median PFS of 3.7 months (95% CI, 2.1 to 5.4), and a median OS of 13.2 months (95% CI, 10.5 to NE), further demonstrating durable benefit even in refractory disease.[78]

The toxicity profile of tarlatamab is consistent with class-specific immune activation. CRS occurred in approximately 50%-55% of patients, with the majority being grade 1-2. Grade 3 or higher CRS was 1%-3%, which mostly occurred during the first cycle and resolved with supportive care and IL-6 blockade. ICANS was rare, reported in <5% of patients, and predominantly low grade. Importantly, step-up dosing, premedication, and early intervention strategies enabled outpatient administration after initial monitoring, supporting real-world feasibility.[79]

More recently, earlier-line integration has shown encouraging signals (Table 2). In DeLLphi-303, a phase Ib multicenter maintenance study, tarlatamab combined with atezolizumab or durvalumab after platinum-etoposide chemoimmunotherapy achieved a median OS of 25.3 months (95% CI, 20.3 to NE) among 88 patients with ES-SCLC, with manageable toxicity.[80] Grade 3-4 adverse events included hyponatremia (10%), anemia (8%), and neutropenia (7%), and serious adverse events were most commonly CRS (24%), pyrexia (7%), ICANS (5%), and pneumonia (5%), with no treatment-related deaths. In parallel, phase III DeLLphi-305[81] (ClinicalTrials.gov identifier: NCT06211036) is evaluating maintenance tarlatamab plus durvalumab versus durvalumab alone after four cycles of carboplatin-etoposide, with durvalumab as first-line therapy with OS, PFS, and PRO end points, whereas phase III DeLLphi-306[82] (ClinicalTrials.gov identifier: NCT06117774) is assessing tarlatamab in limited-stage SCLC after concurrent chemoradiation.

TABLE 2. Selected Ongoing Clinical Trials of Two Approved T-Cell Engagers in Solid Tumors

Target	Agent	Clinical Trial/Phase (enrollment)	Indications	Study Arms	Status (study ID)
DLL3 × CD3	Tarlatamab	NCT03319940 Phase I (269)	SCLC	Tarlatamab Tarlatamab + pembrolizumab Tarlatamab + CRS mitigation strategies	Active, not recruiting (DeLLphi-300)
		NCT050560016 Phase II (222)	Relapsed/refractory SCLC	Tarlatamab	Active, not recruiting (DeLLphi-301)
		NCT05361395 Phase I (184)	ES-SCLC	Tarlatamab + atezolizumab/durvalumab + carboplatin + etoposide Tarlatamab + atezolizumab/durvalumab	Active, not recruiting (DeLLphi-303)
		NCT05740566 Phase III (509)	SCLC	Tarlatamab SOC (lurbinectedin/topotecan/amrubicin)	Active, not recruiting (DeLLphi-304)
		NCT06211036 Phase III (563)	ES-SCLC	Tarlatamab + durvalumab Durvalumab	Active, not recruiting (DeLLphi-305)
		NCT06117774 Phase III (400)	LS-SCLC	Tarlatamab Placebo	Recruiting (DeLLphi-306)
		NCT06502977 Phase II (32)	ES-SCLC	Tarlatamab	Active, not recruiting (DeLLphi-307)
		NCT06598306 Phase1 (220)	ES-SCLC	Tarlatamab (subcutaneous)	Recruiting (DeLLphi-308)
		NCT06745323 Phase II (240)	SCLC	Tarlatamab	Recruiting (DeLLphi-309)
		NCT07037758 Phase I (380)	ES-SCLC	Tarlatamab + AB248	Recruiting (DeLLphi-311)
		NCT07005128 Phase III (330)	ES-SCLC	Tarlatamab + durvalumab + carboplatin + etoposide Durvalumab + carboplatin + etoposide	Recruiting (DeLLphi-312)
		NCT06898957 Phase I (200)	SCLC	Tarlatamab + YL201 Tarlatamab + YL201 + anti-PDL1 (atezolizumab/durvalumab)	Recruiting
		NCT06788938 Phase II (29)	Advanced DLL3-expressing tumors	Tarlatamab	Recruiting
		NCT06893783 Phase II (60)	NEC NEC of pancreas NEC of prostate	Tarlatamab	Recruiting (DeLLight)
		NCT07111507 Phase II (32)	Metastatic prostate cancer	Tarlatamab	Recruiting (TIDAL)
		NCT07016230 Phase II (40)	Metastatic/locally advanced SCLC, poorly differentiated NEC, high-grade MTC	Tarlatamab	Recruiting
		NCT06957314 Phase I/II (30)	Melanoma, MTC, bladder cancer, GBM, NSCLC, cervical cancer, and so on	Tarlatamab Tarlatamab + concurrent radiation therapy Tarlatamab + sequential radiation therapy	Recruiting (RABBIT)
		NCT06776250 Phase II (44)	Astrocytic tumor Oligodendroglial tumor	Tarlatamab	Recruiting
		NCT07243470 Phase I/II (70)	Glioma CNS tumor	Tarlatamab + temozolomide	Recruiting

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TABLE 2. Selected Ongoing Clinical Trials of Two Approved T-Cell Engagers in Solid Tumors (continued)

Target	Agent	Clinical Trial/Phase (enrollment)	Indications	Study Arms	Status (study ID)
GP100 × CD3	Tebentafusp	NCT05315258 Phase II (850)	Melanoma Uveal melanoma	Tebentafusp	Active, not recruiting
		NCT07057596 Phase II (19)	Metastatic uveal melanoma	Tebentafusp (neoadjuvant)	Recruiting
		NCT06246149 Phase III (290)	Uveal melanoma	Tebentafusp (adjuvant)	Recruiting
		NCT06070012 Phase II (44)	Uveal melanoma	Tebentafusp	Recruiting (TARGET-tebe)
		NCT006414590 Phase II (19)	Locally advanced unresectable uveal melanoma	Tebentafusp (neoadjuvant)	Recruiting
		NCT05549297 Phase III (540)	Advanced melanoma	Tebentafusp Tebentafusp + pembrolizumab Investigator's choice	Recruiting (TEBE-AM)
		NCT06942442 Phase II (47)	Clear cell sarcoma	Tebentafusp Physician's choice	Recruiting
		NCT06627244 Phase II (30)	Metastatic uveal melanoma	Tebentafusp + radiation	Recruiting
		NCT066626516 Phase I/II (109)	Metastatic uveal melanoma	Tebentafusp Tebentafusp + sargramostim (GM-CSF) Tebentafusp + BCNU	Recruiting

Abbreviations: CRS, cytokine release syndrome; ES-SCLC, extensive-stage small cell lung cancer; GBM, glioblastoma multiforme; GM-CSF, granulocyte-macrophage colony-stimulating factor; LS-SCLC, limited-stage small cell lung cancer; MTC, medullary thyroid carcinoma; NEC, neuroendocrine carcinoma; NHL, non-Hodgkin lymphoma; NSCLC, non–small cell lung cancer; SOC, standard of care.

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DeLLphi-312[83] is evaluating tarlatamab added to durvalumab plus carboplatin-etoposide versus durvalumab plus chemotherapy alone in treatment-naïve extensive-stage SCLC. Dosing and schedule optimization is being explored first in the phase II DeLLphi-309[84] (ClinicalTrials.gov identifier: NCT06745323) to minimize toxicities including CRS, whereas a more convenient subcutaneous formulation of tarlatamab is being evaluated in the phase I DeLLphi-308[85] (ClinicalTrials.gov identifier: NCT06598306). These designs reflect confidence in the predictable and manageable CRS profile and aim to further extend clinical benefit into earlier-line settings.

DLL3 expression across high-grade neuroendocrine malignancies has prompted broader application of tarlatamab beyond SCLC (Table 2), including phase II expansion into extrapulmonary neuroendocrine carcinomas (DeLLight,[86] ClinicalTrials.gov identifier: NCT06893783), DLL3-positive metastatic and neuroendocrine prostate cancer (TIDAL,[87] ClinicalTrials.gov identifier: NCT07111507), and tissue-agnostic DLL3-expressing tumors[88] or mixed solid tumors[89] (ClinicalTrials.gov identifiers: NCT06788938, NCT07016230). In parallel, novel combination strategies are being explored to enhance T-cell fitness and overcome resistance, including pairing with the CD8-selective IL-2 agonist AB248 to augment T-cell expansion and persistence (DeLLphi-311,[90] ClinicalTrials.gov identifier: NCT07037758) and with the B7-H3–targeted ADC YL201 (DeLLphi-310,[91] ClinicalTrials.gov identifier: NCT06898957), reflecting a move toward rational immunologic and dual-targeting combinations.

INTEGRATING IMMUNOTHERAPY AND TARGETED THERAPY IN THE FORM OF ADC

Rationale for Combined Targeted Therapy and Immunotherapy

ICIs have transformed cancer therapy by restoring T-cell–mediated antitumor activity.[92] Yet, their efficacy depends on the presence of an inflamed TME with adequate antigen presentation and immune infiltration—features absent in many cold tumors. Targeted therapies can reshape this environment by creating biological conditions that favor immune activation.[93] Agents such as ADCs induce immunogenic cell death and release tumor antigens,[94] whereas HER2-targeted and FGFR-directed therapies enhance antigen visibility and modify oncogenic signaling that drives immune resistance.[95,96] VEGF and poly(ADP-ribose) polymerase inhibitors normalize vasculature, reduce immunosuppressive cytokines, and increase T-cell trafficking.[97,98] Together, these mechanisms can heighten immune recognition and overcome adaptive resistance to ICIs (Fig 1). Clinically, this rationale underpins emerging successes such as enfortumab vedotin combined with pembrolizumab in metastatic urothelial carcinoma (UC) and anti-HER2 therapy paired with checkpoint inhibition in breast, gastric, and urothelial cancers (Table 3).[99-102] These combinations

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TABLE 3. Ongoing Clinical Trials of Combination Targeted Therapy and Immunotherapy in Ongoing or Planned Clinical Trials (cutoff date: March 20, 2026)

Target and Drug Conjugate	Agent	Clinical Trial/Phase (enrollment)	Indications	Treatment Arm	Status (study ID)
HER2 SN-38	Sacituzumab govitecan	NCT06991790 phase II (51)	Advanced TNBC	Sacituzumab govitecan + toripalimab	Recruiting
HER2 SN-38	Sacituzumab govitecan	NCT06161532 phase II (60)	Rare genitourinary tumors (including bladder SCC, adenocarcinoma/urachal, neuroendocrine carcinoma, renal medullary carcinoma, penile SCC)	Sacituzumab govitecan with or without atezolizumab	Recruiting
TROP2, KL610023	Sacituzumab tirumotecan (MK-2870)	NCT06841354 phase III (TroFuse-011) (1000)	Advanced TNBC	ADC + pembrolizumab-based combinations	Recruiting
HER2, deruxtecan	Trastuzumab deruxtecan	NCT04379596 phase Ib/II (DESTINY-Gastric03) (450)	HER2-positive advanced/metastatic gastric or gastroesophageal junction adenocarcinoma	Trastuzumab deruxtecan + chemotherapy or immunotherapy (pembrolizumab, durvalumab, volrustomig, rilvegostomig)	Recruiting
B7-H3, deruxtecan	Ifinatamab deruxtecan (I-DXd)	NCT06362252 phase Ib/II (IDeate-Lung03) (123)	Extensive-stage small cell lung cancer (first-line)	I-DXd + atezolizumab with or without carboplatin (induction and/or maintenance)	Recruiting
Nectin-4, MMAE	Enfortumab vedotin	NCT06041503 phase II (E-VIRTUE) (68)	Rare genitourinary tumors (urinary tract adenocarcinoma, squamous cell carcinoma, refractory testicular germ cell tumors)	Enfortumab vedotin with or without pembrolizumab	Recruiting
Folate receptor alpha (FRα), DM4	Mirvetuximab soravtansine (IMGN853)	NCT03835819 phase II (18)	Recurrent or persistent endometrial cancer (FRα-positive)	Mirvetuximab soravtansine + pembrolizumab	Active
EGFR × HER3, topoisomerase I inhibitor	Izalontamab brengitecan	NCT05983432 phase I (470)	NSCLC and other solid Tumors	BL-B01D1	Recruiting
HER2 × HER3, topoisomerase I inhibitor	BL-B16D1	NCT06475131 phase I (21)	HER2-expressing solid tumors	BL-B16D1	Recruiting
HER2 × HER2, camptothecin	JSKN033	NCT0728319, phase II (160)	NSCLC	JSKN033	Not yet recruiting
TROP2, topoisomerase I inhibitor, and RNA polymerase II inhibitor	KH815	NCT0688564, phase I (30)	Advanced solid Tumors	KH815	Not yet recruiting
CD33, GSPT1 degrader	BMS-986497	NCT0641963, phase I (105)	Relapsed or refractory acute myeloid leukemia or myelodysplastic syndrome	BMS-986497 Azacitidine Venetoclax	Recruiting

Abbreviations: GSPT1, G1 to S phase transition 1; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; MMAE, monomethyl auristatin E; NSCLC, non–small cell lung cancer; SCC, squamous cell carcinoma; SN-38, 7-ethyl-10-hydroxycamptothecin; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2.

exemplify a convergent strategy: integrating tumor-targeted precision with systemic immune activation to achieve deeper, more durable responses across multiple tumor types.

Structure, Mechanisms, and Immune Effects of ADCs

ADCs are composed of a monoclonal antibody specific for a TAA, a chemical linker, and a cytotoxic payload. The antibody directs the payload to target-expressing cells, the linker (cleavable or non-cleavable) governs where and how the payload is released, and the payload (such as microtubule-disrupting monomethyl auristatin E [MMAE] or topoisomerase I inhibitors) mediates targeted cytotoxicity against tumor cells (Fig 1). After antigen binding, ADCs are internalized and trafficked to lysosomes, where proteolytic degradation or linker cleavage liberates the active drug. This results in microtubule disruption or DNA damage, direct tumor cell death, and, for some constructs, a bystander effect through diffusion of released payload into neighboring cells with lower or heterogeneous antigen expression.[103]

Beyond direct cytotoxicity, several ADCs induce immunogenic cell death with release of danger-associated molecular patterns, enhanced dendritic cell activation, and increased antigen presentation, often accompanied by upregulation of PD-L1 on tumor and immune cells.[94] These changes provide a strong biological rationale for combining MMAE- and topoisomerase I–based ADCs with checkpoint inhibitors. Key pharmacologic considerations of ADCs include drug-to-antibody ratio, which influences potency and clearance; linker stability, which balances systemic safety against intratumoral release; and the risk of on-target/off-tumor toxicity in normal tissues that express the antigen.[103] Clinically, this translates into characteristic safety profiles—peripheral neuropathy for MMAE-based ADCs, cutaneous reactions, and a classwide risk of pneumonitis—overlapping with immune-related adverse events when combined with ICIs. Careful monitoring and early intervention for neuropathy, skin toxicity, liver enzyme elevation, pneumonitis, and other immune-mediated events are therefore essential when integrating ADCs with immunotherapy.[104]

ADC-ICI Combinations Reshaping Solid Tumor Treatment

UC has emerged as a leading model for combining ADCs with ICI. Enfortumab vedotin plus pembrolizumab (EVP) is the first ADC-ICI doublet to demonstrate a definitive OS benefit over platinum-based chemotherapy in previously untreated locally advanced or metastatic UC. In EV-302/KEYNOTE-A39, EVP doubled median PFS compared with gemcitabine-platinum (12.5 *v* 6.3 months; HR for progression or death, 0.48 [95% CI, 0.41 to 0.57]) and more than doubled median OS (33.8 *v* 15.9 months; HR for death, 0.51 [95% CI, 0.43 to 0.61]). The confirmed ORR was approximately 68% with EVP versus 44% with chemotherapy, with complete responses in 29% and 12% of patients, respectively, and median DOR was prolonged (23.3 *v* 7.0 months).[99,105] Treatment-related adverse events with EVP were common (97% any grade), with grade ≥3 events in about 56% of patients. EV-associated toxicities were dominated by skin reactions, peripheral neuropathy, and hyperglycemia. Skin reactions occurred in roughly 70% of patients and are managed with skincare and topical steroids for grade 1-2, escalation to treatment interruption and systemic corticosteroids for grade ≥3, and permanent discontinuation for severe bullous or exfoliative events. Peripheral sensory neuropathy is frequent and typically managed with EV dose interruption and reduction based on severity, with discontinuation in persistent grade 3 neuropathy. Hyperglycemia (any grade approximately 13%, grade 3-4 approximately 9%) requires baseline risk assessment, regular glucose monitoring, initiation or intensification of antihyperglycemic therapy, and EV dose modification or interruption in uncontrolled grade ≥3 cases.[106]

KEYNOTE-905/EV-303 compared perioperative EVP with radical cystectomy alone in cisplatin-ineligible or cisplatin-declining muscle-invasive bladder cancer. The combination improved event-free survival (EFS; median not reached *v* 15.7 months; HR for events or death, 0.40 [95% CI, 0.28 to 0.57]) and OS (2-year OS 79.7% *v* 63.1%; HR for death, 0.50 [95% CI, 0.33 to 0.74]). Pathologic complete response rates were higher with perioperative EVP (57.1% *v* 8.6%), and cystectomy completion rates were similar between arms, indicating that the regimen did not compromise surgical feasibility.[107] KEYNOTE-B15/EV-304 compares perioperative EVP with cisplatin-based neoadjuvant chemotherapy in cisplatin-eligible muscle-invasive bladder cancer. In the first prespecified interim analysis (median follow-up 33.6 months), EVP significantly improved EFS versus cisplatin-gemcitabine (median not reached [NR] *v* 48.5 months; 24 month estimated EFS rate 79.4% *v* 66.2%; HR, 0.53 [95% CI, 0.41 to 0.70]). OS was also improved (median NR *v* NR; 24-month estimated OS rate 86.9% *v* 81.3%; HR, 0.65 [95% CI, 0.48 to 0.89]). The pathologic complete response rate was higher with EVP than with cisplatin-gemcitabine (55.8% *v* 32.5%; 95% CI, 16.7 to 29.8).[108] Together, these studies support EVP as an emerging perioperative systemic option across cisplatin-ineligible and cisplatin-eligible muscle-invasive bladder cancer.

Beyond Nectin-4–targeted EV, HER2-directed disitamab vedotin combined with toripalimab has shown encouraging activity and manageable toxicity in pretreated metastatic UC, and a phase III trial compares disitamab vedotin plus pembrolizumab with platinum chemotherapy in the first-line setting.[102,109] Collectively, these data cement UC as a paradigm for rational ADC-ICI integration across metastatic and perioperative disease states.

In breast cancer, ADC-ICI combinations are also under active evaluation although most data remain in earlier phases. Trastuzumab deruxtecan plus nivolumab has shown promising activity in HER2-expressing metastatic breast cancer in the phase Ib DS8201-A-U105 study, supporting the

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biological rationale for combining HER2-directed topoisomerase I ADCs with PD-1 blockade.[100] More mature randomized data are emerging with trophoblast cell surface antigen 2 (TROP2)–directed sacituzumab govitecan plus pembrolizumab in PD-L1–positive metastatic triple-negative breast cancer, where a phase III trial has demonstrated superior PFS and longer DOR compared with chemotherapy plus pembrolizumab, and regulatory submissions are anticipated.[110] Additional phase III programs, such as neoadjuvant datopotamab deruxtecan plus durvalumab in TROPION-Breast04, will clarify the role of ADC-ICI doublets in early-stage triple-negative and HR-low/HER2-negative disease.[111]

Biomarkers for ADC Combination Regimens

Biomarker development for ADC-ICI combinations is increasingly focused on precision selection rather than indiscriminate use of doublet therapy. PD-L1 remains an imperfect predictor of benefit, limited by assay variability, dynamic expression, and inconsistent performance across tumor types and treatment settings; it is rarely sufficient as a standalone decision tool.[112] Tumor antigen expression is more directly actionable for ADCs, with Nectin-4, HER2, TROP2, and HER3 serving as key targets in urothelial, breast, gastric, and other solid tumors. Quantitative and qualitative measures of antigen expression, along with genomic amplifications and splice variants, are being explored to refine patient selection although clear thresholds for clinical decision making are still evolving.[113] As an example, the newly developed Quantitative Continuous Scoring-Normalized Membrane Ratio score was predictive of PFS and ORR in non–small cell lung cancer (NSCLC) treated with datopotamab deruxtecan (Dato-DXd, a TROP2-directed ADC), whereas traditional immunohistochemistry did not correlate with response.[114] Broader genomic and immune biomarkers provide complementary information. Tumor mutational burden and interferon-gamma–related signatures may enrich for ICI benefit but lack standardized assays and prospective validation for guiding ADC-ICI doublets.[115] Circulating tumor DNA offers a dynamic readout of MRD and early treatment response, with circulating tumor DNA (ctDNA) positivity and clearance patterns correlating with recurrence risk and survival in multiple malignancies, including UC, but its role in selecting or adapting ADC-ICI therapy remains investigational.[116] Spatial and temporal heterogeneity—between primary and metastatic sites and over the course of therapy—further supports integrating tissue and liquid biopsies rather than relying on a single sampling time point.

THE FUTURE OF PERSONALIZED IMMUNOTHERAPY

Given the progress with targeted immunotherapy and combination immunotherapy/targeted therapy in the past few years as highlighted in this text, we anticipate an exponential increase in the coming years of additional combination targeted immunotherapy regimens. Examples of different targeted and combination strategies for immunotherapy are given in Tables 2-4 as evidence of the already large and growing number of clinical trials for these agents. In addition to the focus on novel TCE and ADC-ICI strategies, there are many ongoing efforts to develop other targeted immunotherapies including CAR and TCR T-cell therapy beyond the scope of this review.

New Targets for TCE in Solid Tumors

PSMA is overexpressed in 85%-100% of metastatic castration-resistant prostate cancer and remains the most extensively studied TCE target in solid tumors.[117] First-generation PSMA-directed TCEs showed limited efficacy (ORR 0%-7.4%) despite PSA50 declines in approximately 30% of patients.[118,119] By contrast, next-generation masked or protease-activated constructs demonstrated markedly improved activity, with PSA50 declines in 58% of patients treated with VIR-5500 and 100% of those treated with JANX007, and an ORR of 50% in patients with measurable disease.[120] STEAP1 has emerged as one of the most clinically validated prostate cancer differentiation antigens. In a phase I study of xaluritamig, ORRs reached 24% overall and 41% at target doses, with PSA50 declines in approximately half of treated patients and a median OS of 17.4 months.[121,122] Although CRS was frequent, grade ≥3 events occurred in only 16%, supporting STEAP1 expression as a robust enrichment biomarker with an acceptable safety profile. Other prostate lineage antigens, such as TMEFF2 and KLK2, have shown only modest activity (ORR 15.2%), indicating that not all lineage-restricted antigens are equally actionable.[123] TYRP1, despite melanocyte specificity, failed to demonstrate clinical activity (ORR 0%), largely because of antidrug antibody formation and loss of exposure, underscoring the importance of pharmacokinetic durability in antigen selection.[124]

Broadly expressed epithelial antigens pose intrinsic safety challenges because of normal tissue expression, making spatial restriction of T-cell activation central to clinical success. Accordingly, biomarker strategies in this category emphasize tumor-localized activation. EGFR is broadly expressed across epithelial malignancies, and protease-activated EGFR-directed constructs have shown encouraging early signals. CX-904 achieved an ORR of 33% and disease control in all evaluable patients with pancreatic cancer.[125] By contrast, EGFRvIII, a tumor-specific mutant in glioblastoma, demonstrated limited efficacy (ORR approximately 12%) with significant toxicity,[126] highlighting that tumor specificity does not overcome challenges posed by antigen heterogeneity and immune exclusion. Early unmasked HER2-directed TCEs showed minimal activity, but masked designs improved tolerability and efficacy. VIR-5818 led to tumor shrinkage in approximately 50% of patients with an ORR of 33% in small colorectal cancer cohorts.[127] Quantitative HER2 expression, rather than amplification status alone, appears to be more relevant for patient selection.

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TABLE 4. Ongoing Clinical Trials of Newly Developed T-Cell Engagers in Solid Tumors (cutoff date: January 15, 2026)

Target	Agent	Clinical Trial/Phase (enrollment)	Indications	Treatment Arm	Status (study ID)
B7-H4 × CD3	GEN1047	NCT05180474 Phase I/II (179)	Breast cancer, endometrial cancer, ovarian cancer, squamous NSCLC	GEN1047	Active, not recruiting
B7-H6 × CD3	BI 765049	NCT04752215 Phase I (67)	Malignant solid tumors expressing B7-H6	BI 765049 BI 765049 + ezabenlimab	Completed
		NCT06091930 Phase I (97)	Asian patients with malignant solid tumors expressing B7-H6	BI 765049 BI 765049 + ezabenlimab	Recruiting
		NCT06882746 Phase I (135)	Advanced cancer of the colon, rectum, stomach, or pancreas	BI 765049	Active, not recruiting
B7-H6 × CD3	TGI-6	NCT06374173 Phase I (123)	Advanced/metastatic solid tumors	TGI-6	Recruiting
CD276 × CD3	CC-3	NCT05999396 Phase I (89)	Breast carcinoma, colorectal cancer, penile carcinoma, sarcoma	CC-3	Recruiting
CDH17 × CD3	Cabotamig (ARB202)	NCT05411133 Phase I (68)	Advanced gastrointestinal cancer	Cabotamig	Recruiting
CEACAM5 × CD3	NILK-2301	NCT06663839 Phase I (25)	Metastatic colorectal cancer	NILK-2301	Recruiting
CEACAM5 × CD3	BA1202	NCT05909241 Phase I (78)	Advanced solid tumors	BA1202	Recruiting
CLDN6 × CD3	XmAb541	NCT06276491 Phase I (212)	Advanced solid tumors	XmAb541	Recruiting
CLDN6 × CD3	CTIM-76	NCT06515613 Phase I(80)	Recurring ovarian cancer, other advanced solid tumors	CTIM-76	Recruiting
CLDN6 × CD3	BGB-B455	NCT06803680 Phase I (90)	Advanced/metastatic solid tumors	BGB-B455 BGB-B455 with or without chemotherapy	Recruiting
CLDN6 × CD3	BNT142	NCT05262530 Phase I/II (73)	CLDN6+ solid tumors	BNT142	Active, not recruiting
CLDN18.2 × CD3	ASP2138	NCT05365581 Phase I (398)	Stomach cancer, gastroesophageal junction cancer, pancreatic cancer	ASP2138 ASP2138 + pembrolizumab + mFOLFOX6 ASP2138 + ramucirumab + paclitaxel	Recruiting
		NCT07024615 Phase I (25)	Pancreatic ductal cancer	Neoadjuvant ASP2138	Recruiting
CLDN18.2 × CD3	AZD5863	NCT06005493 Phase I/II (280)	Advanced/metastatic solid tumors	AZD5863	Recruiting
CLDN18.2 × CD3	QLS31905	NCT06446388 Phase II (360)	CLDN18.2+ advanced malignant solid tumors	QLS31905 with or without chemotherapy QL1706 with or without chemotherapy	Not yet recruiting
DLL3 × CD3	Gocatamig (MK-6070, HPN328)	NCT06780137 Phase Ib/II (242)	SCLC	Gocatamig Gocatamig + ifinatamab deruxtecan (I-DXd) Gocatamig + durvalumab	Recruiting
		NCT04471727 Phase I/II (232)	SCLC, neuroendocrine carcinoma	Gocatamig Gocatamig + ifinatamab deruxtecan (I-DXd) Gocatamig + atezolizumab	Recruiting
		NCT07227597 Phase Ib/II (170)	ES-SCLC	Gocatamig + ifinatamab deruxtecan (I-DXd) Gocatamig + I-DXd → gocatamig + atezolizumab Carboplatin + etoposide + atezolizumab → atezolizumab	Not yet recruiting

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TABLE 4. Ongoing Clinical Trials of Newly Developed T-Cell Engagers in Solid Tumors (cutoff date: January 15, 2026) (continued)

Target	Agent	Clinical Trial/Phase (enrollment)	Indications	Treatment Arm	Status (study ID)
DLL3 × CD3	Obrixtamig (BI 764532)	NCT04429087 Phase I (300)	SCLC, neuroendocrine neoplasms	BI 764532	Recruiting
		NCT05879978 Phase I (45)	SCLC, neuroendocrine neoplasms	Obrixtamig + ezabenlimab	Active, not recruiting
		NCT05882058 Phase II (174)	SCLC, neuroendocrine carcinoma	BI 764532	Recruiting (DARE-ON™-5)
		NCT05916313 Phase I (18)	Glioma	BI 764532	Active, not recruiting
		NCT05963867 Phase I (12)	SCLC, neuroendocrine neoplasms	BI 764532	Recruiting
		NCT05990738 Phase I (90)	SCLC	BI 764532 + topotecan/single-agent chemotherapy	Recruiting (DARE-ON™-9)
		NCT06132113 Phase I (55)	Neuroendocrine neoplasms	BI 764532 + carboplatin + etoposide	Recruiting (DARE-ON™-7)
		NCT06077500 Phase I (45)	SCLC	BI 764532 + carboplatin + etoposide + atezolizumab BI 764532 + carboplatin + etoposide + durvalumab	Active, not recruiting (DAREON™-8)
DLL3 × CD3	RO7616789 (RG6524)	NCT05619744 Phase I (41)	SCLC, neuroendocrine carcinoma	RO7616789	Completed
DLL3 × DLL3 × CD3	Alveltamig (ZG006)	NCT05978284 Phase I/II (54)	SCLC, neuroendocrine carcinoma	ZG006	Recruiting
		NCT06283719 Phase I/II (265)	SCLC, neuroendocrine carcinoma	ZG006	Recruiting
		NCT06440057 Phase I/II (78)	Neuroendocrine carcinoma	ZG006	Recruiting
		NCT06592638 Phase I (30)	SCLC	ZG006	Recruiting
		NCT07024277 Phase II (60)	Neuroendocrine prostate cancer	ZG006	Not yet recruiting
		NCT07038096 Phase Ib/II (350)	SCLC, neuroendocrine carcinoma	ZG006 + ZG005	Recruiting
		NCT07189455 Phase III (420)	SCLC	ZG006 Topotecan	Recruiting
		NCT07231445 Phase I (100)	SCLC	ZG006 + serplulimab	Not yet recruiting
		NCT07258121 Phase I/II (400)	Solid tumor	ZG006	Not yet recruiting
EGFR × CD3	JANX008	NCT05783622 Phase I (130)	Advanced/metastatic solid tumors	JANX008	Recruiting
EGFR × CD3	EGFR-BATs	NCT04137536 Phase I (7)	Pancreatic cancer	EGFR-BATs	Active, not recruiting
EGFRvIII × CD3 × PD-L1 × 4-1BB	GNC-039	NCT04794972 Phase I (60)	Recurrent glioma Solid tumor	GNC-039	Recruiting
EGFRvIII × CD3	RO7428731	NCT05187624 Phase I (36)	Glioblastoma	RO7428731	Completed
EGFRvIII × CD3	BRiTE	NCT04903795 Phase I (18)	Glioblastoma	BRiTE	Not yet recruiting
ENPP3 × CD3	JNJ-87890387	NCT06178614 Phase I (200)	Advanced solid tumors	JNJ-87890387	Recruiting
ENPP3 × CD3	XmAb819	NCT05433142 Phase I (95)	Clear cell renal cell carcinoma	XmAb819	Recruiting
EpCAM × CD3	BA3182	NCT05808634 Phase I (168)	Advanced adenocarcinoma	BA3182	Recruiting

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TABLE 4. Ongoing Clinical Trials of Newly Developed T-Cell Engagers in Solid Tumors (cutoff date: January 15, 2026) (continued)

Target	Agent	Clinical Trial/Phase (enrollment)	Indications	Treatment Arm	Status (study ID)
EpCAM × CD3	M701	NCT05543330 Phase I/II (90)	Malignant PE NSCLC stage IV	M701 Sham comparator	Recruiting
		NCT06432296 Phase III (312)	Malignant ascites	M701 Control group (paracentesis)	Active, not recruiting
EpCAM × CD3	A-337	NCT06093698 Phase I (94)	Recurrent or metastatic solid tumors	A-337	Not yet recruiting
GPC3 × CD3	ERY974	NCT02748837 Phase I (29)	Solid tumors	ERY974	Completed
		NCT05022927 Phase I (179)	Hepatocellular carcinoma	ERY974 → ERY974 + atezolizumab + bevacizumab ERY974 + atezolizumab + bevacizumab	Active, not recruiting
GPC3 × CD3	CM350	NCT05263960 Phase I/II (248)	Advanced solid tumors	CM350	Recruiting
HER2 × CD3	Runimotamab	NCT03448042 Phase I (123)	Solid tumors	Runimotamab Trastuzumab Tocilizumab	Active, not recruiting
HER2 × CD3	HF50	NCT06822998 Phase I (10)	Advanced solid tumors	HF50	Recruiting
HER2 × CD3	VIR-5818	NCT05356741 Phase I/II (645)	Locally advanced or metastatic HER2-expressing cancers	VIR-5818 VIR-5818 + pembrolizumab	Recruiting
HER2 × CD3	HER2-BATs	NCT03272334 Phase I/II (33)	Metastatic breast cancer	HER2-BATs + pembrolizumab	Active, not recruiting
KLK2 × CD3	Pasritamig (JNJ-78278343)	NCT04898634 Phase I (216)	Prostatic neoplasms	JNJ-78278343	Recruiting
		NCT05818683 Phase I (185)	Metastatic castration-resistant prostate neoplasms, metastatic hormone-sensitive prostate cancer	JNJ-78278343 + combination agent (cetrelimab, cabazitaxel, docetaxel, apalutamide, enzalutamide, darolutamide, AAP)	Recruiting
		NCT06095089 Phase I (250)	Advanced prostate cancer	JNJ-78278343 + JNJ-87189401	Recruiting
		NCT07082920 Phase I (140)	Prostatic neoplasms	JNJ-78278343 + JNJ-95298177	Recruiting
		NCT07164443 Phase III (663)	Metastatic castration-resistant prostate neoplasms	Pasritamig + best supportive care Placebo + best supportive care	Recruiting
		NCT07225946 Phase III (800)	Metastatic castration-resistant prostate cancer	Pasritamig + docetaxel Docetaxel	Recruiting
		NCT07319871 Phase I (40)	Prostatic neoplasms	Pasritamig + JNJ-86974680	Recruiting
cMET × TROP2 × CD3 × CD28	MDX2001	NCT06239194 Phase I/IIa (115)	Advanced solid tumors	MDX2001	Recruiting
MAGE-A4/HLA-A*02:01 × CD3	CDR404	NCT06402201 Phase I (42)	Selected advanced solid tumors	CDR404	Recruiting
MAGE-A4/8 × CD3	IMA401	NCT05359445 Phase I (95)	Recurrent/refractory solid tumors	IMA401 IMA401 + pembrolizumab	Recruiting
MSLN × CD3	JNJ-79032421	NCT06255665 Phase I (35)	Advanced solid tumors	JNJ-79032421	Completed
MSLN × CD3	CT-95	NCT06756035 Phase I (70)	Advanced solid tumors	CT95	Recruiting
MSLN × CDH3 × CD3	AMG 305	NCT05800964 Phase I (37)	Advanced solid tumors	AMG 305	Active, not recruiting
MUC16 × CD3	LBL-033	NCT05779163 Phase I/II (468)	Advanced malignant tumors	LBL-033	Recruiting

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TABLE 4. Ongoing Clinical Trials of Newly Developed T-Cell Engagers in Solid Tumors (cutoff date: January 15, 2026) (continued)

Target	Agent	Clinical Trial/Phase (enrollment)	Indications	Treatment Arm	Status (study ID)
MUC16 × CD3	Ubamatamab (REGN4018)	NCT03564340 Phase I/II (890)	Recurrent ovarian cancer, recurrent MUC16+ cancers	Ubamatamab Ubamatamab + cemiplimab	Recruiting
		NCT06787612 Phase II (220)	Ovarian cancer	Ubamatamab + sarilumab Ubamatamab + bevacizumab + sarilumab Ubamatamab + cemiplimab + fianlimab + sarilumab Ubamatamab + PLD + sarilumab	Recruiting
		NCT07154290 Phase II (300)	Advanced/metastatic NSCLC	Ubamatamab + sarilumab Ubamatamab + REGN7075 + sarilumab	Not yet recruiting
$p53^{R175H}$/HLA-A*02:01 x CD3	CLSP-1025	NCT06778863 Phase I (90)	Advanced solid tumors	CLSP-1025	Recruiting (GUARDIAN-101)
PIWIL1/HLA-A*02:01 × CD3	IMC-R117C	NCT06840119 Phase I/II (600)	Selected advanced cancers	IMC-R117C IMC-R117C + chemotherapy/antiangiogenic agent Chemotherapy/antiangiogenic agent	Recruiting
PRAME × CD3	IMA402	NCT05958121 Phase I/II (145)	Recurrent/refractory solid tumors	IMA402	Recruiting
PRAME × CD3	Brenetafusp (IMC-F106C)	NCT06112314 Phase III (680)	Advanced melanoma	Brenetafusp + nivolumab Nivolumab with or without relatlimab	Recruiting (PRISM-MEL-301)
		NCT04262466 Phase I/II (727)	Advanced PRAME + solid tumors	Brenetafusp Brenetafusp + pembrolizumab Brenetafusp + chemotherapy Brenetafusp + targeted therapy Brenetafusp + multimodal therapy	Recruiting
PSMA × CD3	CC-1	NCT04104607 Phase I (86)	Castration-resistant prostatic cancer	CC-1	Recruiting
		NCT05646550 Phase I (56)	Prostate cancer recurrent	CC-1	Recruiting
PSMA × CD3	JANX007	NCT05519449 Phase I (272)	Metastatic castration-resistant prostate cancer	JANX007 JANX007 + darolutamide	Recruiting (ENGAGER-PSMA-01)
PSMA × CD3	REGN4336	NCT05125016 Phase I/II (370)	Metastatic castration-resistant prostate cancer	REGN4336 REGN4336 + cemiplimab REGN4336 + REGN5678	Recruiting
PSMA × CD3	VIR-5500 (AMX-500)	NCT05997615 Phase I (390)	Hormone-refractory prostate cancer	VIR-5500 VIR-5500 + ARSI	Recruiting
ROR1 × CD3	GNC-035	NCT05160545 Phase I (36)	Advanced/metastatic breast cancer	GNC-035	Active, not recruiting
	EMB-07	NCT05607498 Phase I (150)	Advanced/metastatic solid tumors	EMB07	Recruiting
STEAP1 × CD3	Xaluritamig (AMG509)	NCT06691984 Phase III (675)	Metastatic castration-resistant prostate cancer	Xaluritamig Active comparator (cabazitaxel/abiraterone/enzalutamide)	Recruiting
		NCT04221542 Phase I (479)	Prostate cancer	Xaluritamig (IV) Xaluritamig (SC) Xaluritamig + abiraterone/enzalutamide	Recruiting
		NCT07213674 Phase III (750)	Metastatic castration-resistant prostate cancer	Xaluritamig + abiraterone Investigator's choice (abiraterone/docetaxel/cabazitaxel)	Recruiting
		NCT06613100 Phase I (40)	Prostate cancer	Xaluritamig (neoadjuvant) Xaluritamig + GnRH antagonist	Recruiting
		NCT07140900 Phase I (60)	Metastatic hormone-sensitive prostate cancer	Xaluritamig + darolutamide Xaluritamig + abiraterone	Recruiting
		NCT06555796 Phase I (50)	Prostate cancer	Xaluritamig	Recruiting

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TABLE 4. Ongoing Clinical Trials of Newly Developed T-Cell Engagers in Solid Tumors (cutoff date: January 15, 2026) (continued)

Target	Agent	Clinical Trial/Phase (enrollment)	Indications	Treatment Arm	Status (study ID)
TMEFF2 × CD3	JNJ-70218902	NCT04397276 Phase I (82)	Metastatic castration-resistant prostate cancer	JNJ-70218902	Active, not recruiting
5T4 × CD3 x 5T4	CBA-1535	NCT07016997 Phase I (70)	Advanced solid tumors	CBA-1535 CBA-1535 + pembrolizumab	Recruiting

Abbreviations: ARSI, enzalutamide or darolutamide; ENPP3, ectonucleotide pyrophosphatase/phosphodiesterase family member 3; MAGE-A4, melanoma-associated antigen 4; NSCLC, non–small cell lung cancer; PLD, pegylated; PSMA, prostate-specific membrane antigen.

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Cell adhesion molecules are also actively being explored. CLDN18.2-directed TCEs achieved an ORR of approximately 30% in pancreatic and gastric cancers among patients with expression ≥10%, but at the cost of frequent grade ≥3 toxicity.[128,129] EpCAM targeting has been limited by normal tissue expression; however, compartmentalized delivery strategies have shown benefit. Intraperitoneal M701 significantly prolonged puncture-free survival in malignant ascites (HR, 0.40), illustrating that anatomic disease distribution can function as a key selection factor.[130] Cancer testis antigens represent another class of targets for TCE. PRAME-directed TCEs demonstrated activity exclusively in antigen-positive, HLA-A*02:01–matched tumors. Brenetafusp achieved ORRs of 11% in PRAME-positive melanoma and 0% in PRAME-negative tumors, with a marked separation in 6-month OS (95% *v* 40%).[131] An alternative strategy targets the immunosuppressive TME rather than tumor cells directly. CD33-directed TCE, AMV564, demonstrated clinical responses, including a complete response in ovarian cancer, without dose-limiting toxicity.[132] By contrast, HLA-G targeting failed to show efficacy and was associated with significant toxicity, leading to program discontinuation.[133] These results suggest that immune checkpoint–focused targeting without direct cytotoxic engagement may be insufficient for effective TCE therapy.

Novel TCE Engineering and Combination TCE Regimens

Additional approaches to further developing TCE for the clinic include novel engineering methods and combination regimens. Trispecific (1 + 1 + 1) TCE designs combine dual tumor antigen targeting or integrate costimulatory signaling domains alongside CD3 engagement, enhancing T-cell activation, persistence, and functional durability. One example is alveltamig (ZG006), a trispecific engager (DLL3xDLL3xCD3), which targets two distinct epitopes of DLL3 to enhance tumor avidity.[134] Recent phase I data showed a remarkable confirmed ORR of 91.7% in the 60-mg cohort for SCLC, suggesting that increasing binding avidity can translate into superior efficacy. Although most trispecific TCEs remain in early clinical development, they represent a promising strategy for extending TCE efficacy into solid tumors with greater heterogeneity and immune suppression.

Recent engineering strategies aim to spatially restrict T-cell activation to the TME. Protease-activatable prodrug TCEs contain cleavable peptide linkers that shield the CD3$^-$ or tumor-binding domains until exposed to tumor-associated proteases.[135] For example, TAK-186 (EGFR × CD3 probody) demonstrated reduced systemic cytokine release and improved tolerability in preclinical and early clinical testing, but was discontinued during development. Similarly, pH-dependent activation platforms exploit the acidic TME to preferentially increase CD3 or tumor antigen binding only at low pH, minimizing peripheral T-cell engagement and systemic toxicity. Gocatamig (MK-6070) uses albumin-binding domains to prolong half-life, enabling more convenient dosing while maintaining sustained exposure.[136] These conditional activation strategies represent an important evolution from constitutively active first-generation TCEs toward safer, tumor-restricted immune redirection.

Combination strategies with TCE include dual TCE, combination TCE with other immunotherapy such as ICI, and combination with conventional chemotherapy or tyrosine kinase inhibitors (TKIs). Building on the clinical efficacy of GPRC5D (talquetamab) and BCMA-targeting (teclistamab) TCEs in multiple myeloma, the MonumenTAL6 phase III study investigated talquetamab and pomalidomide or talquetamab plus teclistamab versus other standard-of-care regimens in patients with relapsed or refractory myeloma who have received an anti-CD38 antibody and lenalidomide but have not yet received a TCE.[137] Similarly, blinatumomab is being studied with standard-of-care chemotherapy regimens in acute lymphoblastic leukemia (ClinicalTrials.gov identifiers: NCT04994717, NCT03263572). A PRAME-targeted TCE, brenetafusp (IMC-F106C), is being explored in various combinations including with nivolumab in melanoma (ClinicalTrials.gov identifier: NCT06112314) or with chemotherapy or ICI in PRAME-expressing solid tumors (ClinicalTrials.gov identifier: NCT04262466). Finally, the COMBINE-EGFR-1 reported preliminary results of the combination of REGN7075, an EGFR-targeting TCE, with the ICI cemiplimab, with an ORR of 20% and a disease control rate of 80% in 20 patients with microsatellite stable colorectal cancer.[138] The study is now enrolling a cohort of patients with microsatellite stable colorectal cancer to be treated with REGN7075, cemiplimab, trifluridine-tipiracil, and bevacizumab (ClinicalTrials.gov identifier: NCT04626635).

ADCs in Development

ADC innovation is being driven by new formats (biparatopic, bispecific, dual-payload) and by replacing cytotoxics with targeted protein degraders, with several molecules already in the clinic. Biparatopic ADCs bind to two distinct epitopes on the same antigen, increasing avidity, accelerating internalization, and helping to overcome epitope-level heterogeneity; this architecture is now moving into clinical development as part of innovative formats alongside bispecific and dual-payload constructs. Bispecific ADCs can be engineered with A OR B logic (binding if either antigen is expressed, expanding the eligible population but raising off-tumor risk) or A AND B logic (requiring coexpression for higher specificity), with multiple epithelial targets under exploration.[139] Izalontamab brengitecan (iza-bren; BL-B01D1), an EGFR × HER3 bispecific topoisomerase 1-inhibitor ADC, exemplifies this strategy; in pooled phase Ia/II data in EGFR-mutant NSCLC post-TKI, it achieved a confirmed ORR of 47.4% (95% CI, 39.7% to 55.1%) and a median OS of around 24.8 months (95% CI, 18.5 to NR) and has met dual primary PFS and OS end points in a phase III trial.[140] Dual-payload ADCs incorporate two different cytotoxins on a single antibody to address payload-driven resistance. Preclinical and early translational work supports combining, for example, a microtubule inhibitor with a topoisomerase 1 inhibitor or pairing a DNA-damaging payload with a DNA-damage-response inhibitor payload, with activity and toxicity tuned by drug-to-antibody and payload ratio.[141,142] Immunostimulatory dual-payload designs, where one payload is a cytotoxin and the other is an immune agonist attached to an Fc-silent backbone, are being proposed as a way to couple direct killing with in situ immune activation while mitigating Fc-mediated off-tumor uptake.[143] Degrader-antibody conjugates (DACs) use a catalytic targeted protein degrader rather than a cytotoxic payload, maintaining the ADC architecture but changing the pharmacology from stoichiometric killing to event-driven protein loss. ORM-5029 is a first-in-human HER2-directed DAC in which a pertuzumab backbone delivers a GSPT1 (G1 to S phase transition 1) degrader (SMol006); a phase I trial in HER2-expressing solid tumors (ClinicalTrials.gov identifier: NCT05511844) is exploring dose, safety, and preliminary efficacy across HER2-altered cancers.[144] As these ADC innovations are only entering the clinic at present, combinations with ICI remain to be tested.

CHALLENGES AND POTENTIAL SOLUTIONS

Improving Safety and Managing Toxicity

Along with the potential for improved efficacy with more specifically targeted immunotherapies, there are new risks distinct from the immune-related adverse events seen with ICI. Targeted immunotherapies such as TCE and CAR T-cells may spare healthy tissues for the most part, but when there is an overlap in recognition between proteins on healthy cells and tumor antigens (OTOT toxicity), the outcome can be severe and life-threatening tissue damage via direct T-cell killing and/or cytokine release.[18] Preclinical models, especially mouse models, are crucial for initial screening for OTOT toxicities; however, differences between organisms limit the applicability of the findings from these models.[18,145] Human organs-on-chips and organoid models can be useful in more reliably identifying toxicities to healthy tissues.[146,147] Synthetic biology approaches include affinity tuning,[148] logic gating incorporating recognition of multiple antigens,[149] modifying downstream T-cell signaling pathways,[150] and inducible suicide switches.[151] Alternatively, local administration[152] and use of dasatinib[153] provide mechanisms for controlling CAR T-cell activity by limiting activity to the TME and decreasing T-cell signaling, respectively. For TCE, using conditional forms of these therapies with activation controlled by TME features such as acidic pH, matrix metalloproteinases, and elevated metabolites like adenosine or local delivery (ie, with an oncolytic virus) can limit effects on healthy tissues outside the TME.[154,155]

For TCR T-cell therapies and TCE designed to target intracellular antigens, there is potential for not only recognition of one specific antigen as with CAR T and most TCE but also multiple on-target off-tumor recognition based on the myriad combinations of human leukocyte antigen (HLA) molecules and epitopes and degeneracy of TCR recognition of antigen. TCR therapies directed against MAGE3, deemed safe initially because of being an embryonic antigen, resulted in cases of fatal neurologic and cardiac toxicity, related to recognition of different peptide sequences by the TCR.[156,157] Based on these cases with unexpected overlapping TCR recognition, further work was performed using amino acid scanning to identify critical residues in TCR recognition of HLA/epitope, which the authors propose as a more sensitive method than solely relying on screening T-cell reactivity in vitro and searching for highly similar peptide sequences.[158] Others have proposed engineering methods to increase ligand selectivity such as a CD8 to CD4 coreceptor switch (by knocking out the CD8 coreceptor and increasing expression of CD4 on TCR-modified T-cells) as a path to safer TCR T-cell therapy.[159]

A meta-analysis encompassing 12 clinical trials concluded that combination ICI/ADC regimens largely led to acceptable rates of toxicity with most common adverse events of fatigue, peripheral neuropathy, GI issues (nausea, diarrhea, decreased appetite), and rash.[160] However, other combination targeted and immunotherapy regimens have demonstrated intolerable toxicities. Hepatoxicity with the combination of vemurafenib and ipilimumab led to premature closure of clinical testing of the combination, whereas both these agents as monotherapy did not have unacceptable liver toxicity.[161] Pneumonitis, a potentially fatal immune-related adverse event associated with ICI,[5] has also been demonstrated with some ADCs, raising concerns about increased risk with the combination. Across nine clinical trials of trastuzumab deruxtecan monotherapy, the pooled incidence of pneumonitis was 15.4%.[162] Indeed, a trial of trastuzumab deruxtecan in combination with

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durvalumab and platinum chemotherapy in patients with non–small cell lung cancer found the combination regimens intolerable because of drug-related adverse effects, including fatal neutropenia and pneumonitis.[163] Protocols for surveillance and management of these overlapping toxicities are needed for early recognition and intervention of these toxicities.[164] In addition, combination regimens should be carefully studied and selected as some immunotherapies such as ipilimumab are known to have higher rates of toxicity in combination than other ICIs.[165]

Resistance Mechanisms

Resistance to TCE therapy arises through both tumor-intrinsic and tumor-extrinsic mechanisms that collectively impair immune synapse formation, T-cell activation, and effective cytotoxicity. Tumor-intrinsic escape most commonly involves loss or downregulation of the target antigen through genetic deletion, mutation, or epigenetic silencing, as well as antigenic drift and clonal evolution that generate heterogeneous expression and permit survival of antigen-negative subclones.[166,167] In parallel, tumor cells may increase resistance to killing by upregulating inhibitory ligands such as PD-L1, overexpressing antiapoptotic mediators, or disrupting interferon-γ signaling and MHC class I presentation, thereby reducing immune recognition and susceptibility to T-cell–mediated lysis.[166,168-170] Tumor-extrinsic resistance is largely driven by an immunosuppressive microenvironment enriched with regulatory T-cells, myeloid-derived suppressor cells, and cytokines such as TGF-β, IL-10, and adenosine.[168,171,172] Moreover, sustained exposure to TCEs can further induce T-cell exhaustion, marked by increased expression of inhibitory receptors including PD-1, TIGIT, TIM-3, CTLA-4, and LAG-3.[170,171] Additional pharmacologic barriers, such as antidrug antibodies and suboptimal pharmacokinetics, may reduce bioavailability and durability of response.[171] These multifactorial processes highlight the need for rational combination approaches including checkpoint blockade, costimulatory agonists, cytokine modulation, or multitargeted TCE designs to restore immune fitness and overcome resistance.

Resistance to ADC-ICI therapy arises from antigen loss or downregulation, altered internalization and trafficking that reduce effective payload delivery, and activation of bypass signaling and DNA-damage-response pathways.[173] On the immune side, impaired antigen presentation, T-cell exclusion, and microenvironment-driven suppression contribute to both primary and acquired resistance, as for TCE.[174] These mechanisms motivate next-generation strategies, including doublet ADC regimens targeting nonoverlapping antigens, bispecific antibodies or ADCs that engage two receptors simultaneously, and combinations with agents that modulate the TME or innate immunity.[175] The overarching direction is toward multidimensional biomarker models that combine antigen expression, genomics, immune signatures, and ctDNA dynamics to support rational selection, sequencing, and intensification of ADC-ICI strategies rather than simply broadening combination use.

Intra- and intertumoral heterogeneity (ITH) is a major challenge of cancer therapy, wherein features intrinsic and extrinsic to the tumor generate multiple mechanisms of resistance.[176] For example, pre-existing clones with resistance to targeted therapy may expand in response to a TKI, whereas TME elements such as myeloid cells induced by the tumor suppress T-cell responses. ITH provides a rationale for combining multiple modalities to simultaneously elude therapeutic resistance mechanisms. A meta-analysis of 12 ADC-ICI combination therapy trials demonstrated a pooled overall response rate of 58%; although this varied within individual regimens and tumor types, it compares favorably with monotherapy response rates and provides a basis for combining modalities to combat ITH.[160]

Determining Optimal Therapy Selection and Sequencing Therapies

Outside of the toxicity that can be encountered when combining multiple anticancer modalities, there are additional challenges requiring innovative solutions to improve the efficacy of cancer treatment. First, the concept of tumor heterogeneity previously discussed in terms of therapeutic resistance also poses the challenge of selection of the ideal targets. While focusing on immunotherapy rather than broadly invigorating immune responses has its benefits, tumor antigens may not be equally expressed among patients, metastatic sites, or even within the same tumor.[177-179] Shared antigens such as driver mutations (ie, Kras) across metastatic sites and patients may be most ideal for developing broadly applicable targeted immunotherapies although promise has also been shown for personalized neoantigen cancer vaccines.[179,180] Second, with multiple cancer therapies to select from, there is the challenge of prioritizing regimens with the best efficacy, sequencing therapies for the maximum benefit, and helping patients navigate trials and treatment options. Targeted and immunotherapy combinations should be rationally designed to take into account mechanisms of immune response and resistance, for example, intervening first with a targeted inhibitor to decrease an immunosuppressive TME and then using ICI to augment T-cell responses, but limiting the total exposure to both in the case of intolerable toxicity.[181] One group has developed a shift ability score to determine which therapies (chemotherapy and small-molecule inhibitors) altered the TME in a favorable direction for ICI responsiveness.[182]

An unanswered question in the field, given the novelty of targeted immunotherapy, is the ideal sequencing of TCE and cell therapy; trials are ongoing to explore different strategies. The aMMbition trial is one such example of a clinical trial exploring different sequencing strategies wherein patients with newly diagnosed multiple myeloma receive induction therapy and TCE (talquetamab) consolidation

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followed by Cilta-cel CAR T-cell therapy, or induction therapy followed by Cilta-cel and TCE (talquetamab and teclistamab) consolidation (ClinicalTrials.gov identifier: NCT06577025). It is also unknown whether resistance to one targeted therapy (ie, Kras inhibitor) confers resistance to targeted immunotherapies (ie, a TCR T-cell therapy), and the answer likely depends on the exact mechanisms of resistance. Finally, an additional challenge in navigating treatment options is reviewing molecular testing to match tumor profiles with available therapies and identifying biomarkers that are predictive of response.[183] Adding to the complexity of molecular profiling, TCR therapies and some TCE designed to target intracellular antigens are HLA-restricted and require knowledge of a patient's HLA type. Moving forward, selecting the correct combinations and sequences of therapy will involve personalized testing of the tumor and immune profile, incorporation of HLA typing, and modeling of individual's tumor with in vitro and organoid systems as well as the use of machine learning and artificial intelligence.

CONCLUSIONS AND FUTURE DIRECTIONS

Targeted immunotherapy (namely, in the form of TCE, but also with cell therapies) and combination targeted therapy/immunotherapy regimens have already demonstrated clinical efficacy in a variety of hematologic malignancies and a few solid tumor types. The clinical success of tebentafusp and tarlatamab establishes definitive proof of concept that TCEs can deliver meaningful and durable benefit in selected solid tumors. The approval of ADC-ICI combinations such as enfortumab vedotin and pembrolizumab in urothelial cancer, and many new combinations in development for breast and other tumor types, demonstrates that immunotherapy combinations can improve on ADC monotherapy response rates. However, the broader development landscape reveals that such outcomes remain limited to highly specific biological contexts. A major unresolved question is how to define and standardize actionable antigen thresholds as quantitative antigen density, intratumoral heterogeneity, and dynamic antigen modulation under therapeutic pressure critically influence efficacy yet lack validated clinical cutoffs. For TCE, the optimal balance between potency and controllability of T-cell activation remains uncertain, as next-generation strategies. Conditional activation, avidity enhancement, and half-life extension may improve efficacy but carry risks of chronic immune stimulation, T-cell exhaustion, and cumulative toxicity. The TME further complicates patient selection, with myeloid suppression, T-cell exclusion, and immune exhaustion emerging as key resistance mechanisms for both immunotherapy and combination with targeted regimens, necessitating rational combination approaches, the optimal partners and sequencing of which are still undefined. Finally, the dissociation between objective response rates and survival benefit raises the question of whether conventional RECIST-based end points adequately capture targeted immunotherapy activity in solid tumors, highlighting the need for immune-integrated end points and longitudinal biomarker assessment. Collectively, addressing these unanswered questions through biomarker-driven trial design and integrated consideration of antigen biology, molecular engineering, dosing strategy, and immune contexture will be essential for realizing the full therapeutic potential of next-generation cancer therapeutics.

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Advancing Antibody-Drug Conjugates: Current Perspectives and Future Directions

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OVERVIEW

Antibody-drug conjugates (ADCs) have rapidly emerged as one of the most transformative therapeutic agents in modern oncology. Their rational design enables selective drug delivery to tumor cells while limiting systemic exposure, resulting in meaningful clinical benefit across a wide range of malignancies. Technological advances in antibody engineering, linker stability, and payload chemistry have driven a marked expansion of approved ADCs and accelerated their transition from later treatment lines into first-line and potentially curative settings. Despite these advances, tumor heterogeneity, variable antigen expression, impaired internalization, and the emergence of intrinsic and acquired resistance mechanisms frequently limit the durability of response. In parallel, on-target off-tumor toxicities and cumulative treatment-related adverse events pose increasing concerns as ADCs are introduced earlier in the disease course and administered for longer durations. To address these limitations, extensive clinical and translational research efforts have focused on rational combination and sequencing strategies. Combinations with immune checkpoint inhibitors, targeted therapies, and monoclonal antibodies have demonstrated the potential to enhance antitumor activity, overcome resistance, and improve patient outcomes, while requiring careful management of overlapping toxicities. In parallel, sequencing strategies and emerging biomarker-driven approaches are beginning to inform optimal treatment algorithms in settings where multiple ADCs with overlapping targets or payloads are available. Finally, next-generation ADC platforms, including bispecific and dual-payload constructs, are being developed to better address tumor heterogeneity and resistance.

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INTRODUCTION

Antibody-drug conjugates (ADCs) have emerged as one of the most impactful therapeutic advances in modern oncology, fundamentally reshaping the treatment landscape across both hematologic malignancies and solid tumors. ADCs combine the targeting specificity of monoclonal antibodies with the potent cytotoxic activity of chemotherapeutic payloads, linked through chemical linkers to achieve selective delivery of highly toxic agents directly to cancer cells, while minimizing systemic exposure and off-tumor on-target toxicity.[1-3] This innovative design, conceptualized over a century ago by Paul Ehrlich as the magic bullet,[4] has achieved clinical fruition through decades of improvements in antibody engineering, linker chemistry, payload selection, and bioconjugation technologies.

The clinical development of ADCs has accelerated dramatically over the past decade, reflecting both technological advances and deepening mechanistic understanding. Following the initial US Food and Drug Administration (FDA) approval of gemtuzumab ozogamicin in 2000, the field experienced a period of relative stagnation, with early-generation ADCs limited by linker instability, suboptimal drug-to-antibody ratios (DARs), and inadequate payload potency.[5,6] However, the approval of brentuximab vedotin in 2011 and trastuzumab emtansine (T-DM1) in 2013 marked a renaissance in ADC development, demonstrating that refined molecular design could substantially improve the therapeutic index. As of early 2026, 14 ADCs have received FDA approval, and the investigational pipeline includes dozens of candidates in clinical development and hundreds of molecules undergoing evaluation.

After improving survival outcomes in later lines of therapy, ADCs are transitioning to first-line treatment and curative settings, representing a fundamental paradigm shift in their clinical positioning. As the field continues to mature, next-generation innovations, including bispecific ADCs (bsADCs), dual-payload designs, and rational combination strategies with immune checkpoint inhibitors (ICIs) and targeted therapies, promise to further expand the therapeutic potential of this drug class.

PRACTICAL APPLICATION

- Antibody-drug conjugates (ADCs) integrate the targeting precision of monoclonal antibodies with the cytotoxic potency of highly active payloads, enabling selective drug delivery and reshaping treatment paradigms across solid tumors and hematologic malignancies.
- ADC efficacy is limited by tumor heterogeneity, variable target expression, resistance mechanisms, suboptimal intracellular trafficking, and on-target off-tumor toxicities, challenges that become increasingly relevant as ADCs move into earlier and potentially curative settings.
- Rational combination strategies with immune checkpoint inhibitors, targeted agents, and monoclonal antibodies have demonstrated the potential to enhance ADC activity, overcome resistance, and improve clinical outcomes, while requiring careful management of overlapping toxicities.
- Sequencing strategies and emerging biomarker-driven approaches are critical to optimize ADC use in clinical practice, particularly in disease settings where multiple ADCs with similar payloads are available.
- Ongoing clinical development of next-generation ADCs, including bispecific and dual-payload constructs, and their integration into first-line and curative settings position ADCs as a pillar of next-generation precision oncology.

SYNERGY AND STRATEGY: COMBINING AND SEQUENCING ADCs WITH TARGETED AGENTS

ADCs, as any oncologic treatment, are characterized by intrinsic and acquired resistance mechanisms that limit their long-term benefit in many patients, necessitating innovative strategies to maximize their therapeutic potential.[3,7,8] Combination strategies have been thoroughly investigated to overcome resistance and improve the effectiveness of approved ADCs, taking into careful consideration the management of overlapping toxicities that could compromise the therapeutic index.[9,10] A multitude of phase II and III trials are currently evaluating ADCs in various combination strategies (Table 1). Moreover, sequencing strategies and translational studies are helping to define the optimal treatment algorithms in various settings.[11,12]

Combination With ICIs

Beyond their direct cytotoxic effects, ADCs possess significant immunomodulatory properties that create a rationale for combination with ICIs.[13-16] All the components of ADCs are presumably implied in their immunogenic effects. Specific payloads induce immunogenic cell death, characterized by the release of damage-associated molecular patterns and tumor neoantigens, which activate dendritic cells and enhance antigen presentation to tumor-specific T cells. Furthermore, the antibody backbone engages Fc receptors on NK cells and macrophages, triggering antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, which further amplify antigen presentation and contribute to the immunogenic reshaping of the tumor microenvironment.[13] The shift from a cold to a hot immune microenvironment induced by ADCs could be rationally complemented by immunotherapy with ICIs. Moreover, preclinical data suggest that synergistic effects could be achieved with suboptimal doses of ADC, potentially reducing toxicities.[17]

The clinical translation of ADC-ICI combination has shown promising results across multiple tumor types. Enfortumab vedotin (EV) has been approved in 2023 by the FDA in combination with pembrolizumab for patients with advanced urothelial cancer (UC) in the first-line setting, based on the marked improvement in survival demonstrated in the EV-302/KEYNOTE-A39 trial.[18] In 2025, the combination of EV and pembrolizumab in UC was also approved in the early setting as a perioperative treatment for patients with an indication to radical cystectomy and ineligible for cisplatin-based chemotherapy, based on the results of the EV-303/KEYNOTE-905 trial.[19]

In previously untreated, advanced PD-L1–positive triple-negative breast cancer (TNBC), the ASCENT-04/KEYNOTE-D19 trial demonstrated that sacituzumab govitecan (SG) plus pembrolizumab significantly improved progression-free survival (PFS) compared with standard-of-care chemotherapy plus pembrolizumab, leading to the recommendation of this first-line regimen by the NCCN guidelines.[20]

Meta-analyses of ADC-ICI combinations across solid tumors have shown that the safety profile of the combination is comparable with that of ADC or ICI monotherapy, even if the combination increases the risk of specific toxicities, such as interstitial lung disease (ILD) in patients treated with trastuzumab deruxtecan (T-DXd).[21]

Moreover, other combinations are being tested in phase II and III trials (Table 1). Datopotamab deruxtecan (Dato-DXd) in combination with durvalumab is being investigated in TNBC and non–small cell lung cancer (NSCLC). SG is being tested with pembrolizumab in NSCLC and early-stage TNBC. Sacituzumab tirumotecan in combination with pembrolizumab is being assessed in a wide range of solid tumors, including TNBC, NSCLC, and gynecologic cancers. T-DXd with pembrolizumab is being tested as a first-line treatment in different tumors. Notably, clinical benefit from ADC-ICI combinations has thus far been restricted to tumor types where single-agent PD-(L)1 blockade has already established

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TABLE 1. Phase II/III Clinical Trials With ADCs in Combination

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
ADC + IO					
TROPION-Breast03 (NCT05629585)	**Dato-DXd** + durvalumab	Trop2	TOP1i	Postneoadjuvant TNBC	III
COMPASS-TNBC (NCT06508216)	**Dato-DXd** + durvalumab			Early relapsed TNBC	Ib/II
TROPION-Breast04 (NCT06112379)	**Dato-DXd** + durvalumab			Early TNBC	III
TROPION-Breast05 (NCT06103864)	**Dato-DXd** + durvalumab			1L TNBC	III
TROPION-Lung07 (NCT05555732)	**Dato-DXd** + pembrolizumab with or without platinum			1L NSCLC	III
TROPION-Lung08 (NCT05215340)	**Dato-DXd** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
NeoCAST-2 (NCT05061550)	**Dato-DXd** + durvalumab			Neoadjuvant NSCLC	II
AVANZAR (NCT05687266)	**Dato-DXd** + durvalumab			1L NSCLC	III
EVOKE-02 (NCT05186974)	**SG** + pembrolizumab with or without platinum	Trop2	TOP1i	1L NSCLC	II
EVOKE-03 (NCT05609968)	**SG** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
ASCENT-05 (NCT05633654)	**SG** + pembrolizumab			Postneoadjuvant TNBC	III
ASCENT-04 (NCT05382286)	**SG** + pembrolizumab			1L TNBC	III
TROPHY-UO1 (NCT03547973)	**SG** + pembrolizumab or avelumab or zimberelimab			1L UC	II
EV-302/KEYNOTE-A39 (NCT04223856)	**EV** + pembrolizumab	Nectin-4	MMAE	1L UC	III
EV-103/KEYNOTE-869 (NCT03288545)	**EV** + pembrolizumab			1L UC	I/II
EV-303/KEYNOTE-905 (NCT03924895)	**EV** + pembrolizumab			Early UC	III
EV-304/KEYNOTE-B15 (NCT04700124)	**EV** + pembrolizumab			Early UC	III
TRAIN-UC-01 (NCT07241793)	**Trastuzumab rezetecan** + adebrelimab			HER2-expressing metastatic UC	II
NCT05941507	**LCB84** + anti-PD1	Trop2	MMAE	All solid tumors	I/II
IDeate-Lung03 (NCT06362252)	**I-DXd** + atezolizumab with or without carboplatin	B7-H3	TOP1i	ES-SCLC	I/II
TroFuse-033 (NCT06952504)	**Sac-TMT** + pembrolizumab	Trop2	TOP1i	1L EC pMMR	III
MK-2870-010 (NCT06312176)	**Sac-TMT** + pembrolizumab			Advanced hormone receptor–positive BC	III
MK-2870-012 (NCT06393374)	**Sac-TMT** + pembrolizumab			Early TNBC	III
TroFuse-007 (NCT06170788)	**Sac-TMT** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
MK-2870-023 (NCT06422143)	**Sac-TMT** + pembrolizumab			1L NSCLC	III
TroFuse-017 (NCT06312137)	**Sac-TMT** + pembrolizumab			Early NSCLC	III
TroFuse-011 (NCT06841354)	**Sac-TMT** + pembrolizumab			1L TNBC	III
TroFuse-036 (NCT07216703)	**Sac-TMT** + pembrolizumab			1L CC	III
InnovaTV 205 (NCT03786081)	**Tiso-V** + pembrolizumab	TF	MMAE	CC	I/II
DESTINY-Gastric05 (NCT06731478)	**T-DXd** + pembrolizumab + chemotherapy	HER2	TOP1i	1L HER2+ G/GEJC	III
DESTINY-Lung06 (NCT06899126)	**T-DXd** + pembrolizumab			1L HER2-overexpressing NSCLC	III
DESTINY-Endometrial01 (NCT06989112)	**T-DXd** + pembrolizumab			1L HER2-expressing pMMR EC	III
HERTHENA-Breast03 (NCT06797635)	**HER3-DXd** + pembrolizumab	HER3	TOP1i	Early TNBC	II
KEYMAKER-UO1 (NCT04165798)	**HER3-DXd** + pembrolizumab			1L NSCLC	II

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TABLE 1. Phase II/III Clinical Trials With ADCs in Combination (continued)

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
DV-001 (NCT05911295)	**Disitamab vedotin** + pembrolizumab	HER2	MMAE	1L HER2-expressing UC	III
RC48-C016 (NCT05302284)	**Disitamab vedotin** + toripalimab			1L HER2-expressing UC	III
NCT04609566	**Brentuximab vedotin** + pembrolizumab	CD30	MMAE	NSCLC, melanoma, HNSCC	II
Be6A Lung-02 (NCT06758401)	**Sigvotatug vedotin** + pembrolizumab	Integrin β6	MMAE	1L NSCLC TPS ≥ 50%	III
NCT07197827	**YL242** + pembrolizumab	VEGF	TOP1i	Solid tumors	I/II
BEHOLD-2 (NCT06796907)	**GSK5733584** + dostarlimab	B7-H4	TOP1i	Solid tumors	I/II
NCT03835819	**MIRV** + pembrolizumab	FRα	Microtubule inhibitor	EC	II
NCT03310957	**SGN-LIV1A** + pembrolizumab	LIV-1	MMAE	TNBC	I/II
ADC + small molecules					
HER2CLIMB-04 (NCT04539938)	**T-DXd** + tucatinib	HER2	TOP1i	HER2+ BC	II
NCT04039230	**SG** + talazoparib	Trop2	TOP1i	TNBC	I/II
TROPION-Lung14 (NCT06350097)	**Dato-DXd** + osimertinib	Trop2	TOP1i	1L EGFRm NSCLC	III
TROPION-Lung15 (NCT06417814)	**Dato-DXd** + osimertinib			EGFRm NSCLC	III
M25-287 (NCT07005102)	**Teliso-A** + osimertinib	cMET	TOP1i	1L EGFRm NSCLC	II/III
NCT07323641	**Teliso-V** + osimertinib	cMET	MMAE	EGFRm/cMET+ NSCLC	II
NCT06838273	**Iza-bren** + osimertinib	EGFRxHER3	TOP1i	1L EGFRm NSCLC	III
NCT06157892	**Disitamab vedotin** + tucatinib	HER2	MMAE		
NCT05887609	**MIRV** + olaparib	FRα	Microtubule inhibitor	PSOC	II
BLUESTAR (NCT05123482)	**AZD8205** + saruparib	B7-H4	TOP1i	Solid tumors	I/II
PETRA (NCT04644068)	**T-DXd or Dato-DXd** + saruparib	Trop2/HER2	TOP1i	Solid tumors	I/II
SEACLIFF (NCT07181161)	**AZD0516** + AZD9574	STEAP2	TOP1i	mCRPC	I/II
FONTANA (NCT05797168)	**AZD5335** + bevacizumab	FRα	TOP1i	Solid tumors	I/II
ADC + ADC					
NCT04724018	**SG + EV** with or without pembrolizumab	Trop2 Nectin-4	TOP1i MMAE	UC	I/II
TROPHY-U01 (NCT03547973)	**SG** + **EV** + zimberelimab			1L UC	II
KEYMAKER-U04 (NCT06483334)	**Sac-TMT + EV** with or without pembrolizumab	Trop2 Nectin-4	TOP1i MMAE	UC	I/II
NCT06953089	**DB-1311/BNT324 + DB-1305**	B7-H3 Trop2	TOP1i TOP1i	Solid tumors	II
ADC + mAb					
KRISTINE (NCT02131064)	**T-DM1** + pertuzumab	HER2	Microtubule inhibitor	1L HER2+ BC	III
DESTINY-Breast09 (NCT04784715)	**T-DXd** + pertuzumab	HER2	TOP1i	1L HER2+ BC	III
DESTINY-Ovarian01 (NCT06819007)	**T-DXd** + bevacizumab			1L HER2-expressing OC	III
TroFuse-021 (NCT07318558)	**Sac-TMT** + bevacizumab	Trop2	TOP1i	1L HRD-negative OC	III
InnovaTV 205 (NCT03786081)	**Tiso-V** + bevacizumab	TF	MMAE	CC	I/II
BEHOLD-2 (NCT06796907)	**GSK5733584** + bevacizumab	B7-H4	TOP1i	Solid tumors	I/II
FRAmework-01 (NCT07213804)	**LY4170156** + bevacizumab	FRα	TOP1i	PSOC	III
GLORIOSA (NCT05445778)	**MIRV** + bevacizumab	FRα	Microtubule inhibitor	PSOC	III
LIBRA (NCT07098338)	**Dato-DXd** + ramucirumab with or without rilvegostomig	Trop2	TOP1i	NSCLC	II
RAINFOL-04 (NCT07225270)	**Rina-S** + bevacizumab	FRα	TOP1i	PSOC	III
FONTANA (NCT05797168)	**AZD5335** + bevacizumab	FRα	TOP1i	Solid tumors	I/II

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TABLE 1. Phase II/III Clinical Trials With ADCs in Combination (continued)

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
ADC + bsAb					
ARTEMIDE-Gastric01 (NCT06764875)	**T-DXd** + rilvegostomig + chemotherapy	HER2	TOP1i	1L HER2+/PD-L1+ G/GEJC	III
DESTINY-BTC01 (NCT06467357)	**T-DXd** + rilvegostomig			1L HER2-expressing BTC	III
DESTINY-Endometrial01 (NCT06989112)	**T-DXd** + rilvegostomig			1L HER2-expressing pMMR EC	III
NeoCAST-2 (NCT05061550)	**Dato-DXd** + rilvegostomig	Trop2	TOP1i	Neoadjuvant NSCLC	II
TROPION-Lung10 (NCT06357533)	**Dato-DXd** + rilvegostomig			1L NSCLC	III
TROPION-Lung12 (NCT06564844)	**Dato-DXd** + rilvegostomig			Stage I high-risk NSCLC	III
TROPION-PanTumour03 (NCT05489211)	**Dato-DXd** + rilvegostomig or volrustomig			Solid tumors	II
NCT06827236	**BNT323** + BNT327	HER2	TOP1i	BC	I/II
BLUESTAR (NCT05123482)	**AZD8205** + rilvegostomig	B7-H4	TOP1i	Solid tumors	I/II
NCT06953089	**DB-1311/BNT324** + BNT327	B7-H3	TOP1i	Solid tumors	II
NCT07111520	**BNT326** + BNT327	HER3	TOP1i	NSCLC	I/II
ADC + chemotherapy					
TROPION-Urothelial03 (NCT07129993)	**Dato-DXd** + chemotherapy	Trop2	TOP1i	UC	II/III
ADC sequencing					
ALTER (NCT07151586)	**T-DXd and SG**	HER2 Trop2	TOP1i TOP1i	HER2-low TNBC	II
TRADE DXd (NCT06533826)	**T-DXd and Dato-DXd**	HER2 Trop2	TOP1i TOP1i	BC	II

NOTE. Novel ADC agents or novel combinations are highlighted in bold.
Abbreviations: 1L, first-line; ADC, antibody-drug conjugate; BC, breast cancer; BTC, biliary tract cancer; bsAb, bispecific antibody; CC, cervical cancer; cMET, cellular-metabolic equivalent; Dato-DXd, datopotamab deruxtecan; EC, endometrial cancer; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutant; ES-SCLC, extensive-stage small cell lung cancer; EV, enfortumab vedotin; FRα, folate receptor α; G/GEJC, gastric/gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HER3-DXd, patritumab deruxtecan; HNSCC, head and neck squamous cell carcinoma; HRD, homologous recombination deficiency; I-DXd, ifinatamab deruxtecan; IO, immunotherapy; Iza-bren, izalontamab brengitecan; mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; MIRV, mirvetuximab soravtansine; MMAE, monomethyl auristatin E; NSCLC, non–small cell lung cancer; OC, ovarian cancer; pMMR, mismatch repair–proficient; PSOC, platinum-sensitive ovarian cancer; Rina-S, rinatabart sesutecan; Sac-TMT, sacituzumab tirumotecan; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; Teliso-A, telisotuzumab adizutecan; Teliso-V, telisotuzumab vedotin; TF, tissue factor; Tiso-V, tisotumab vedotin; TNBC, triple-negative breast cancer; TOP1i, topoisomerase-I inhibitor; TPS, tumor proportion score; UC, urothelial cancer; VEGF, vascular endothelial growth factor.

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efficacy, whereas no meaningful benefit has been observed in tumors refractory to immune checkpoint inhibition.

Combination With Small Molecules

The combination of ADCs with tyrosine kinase inhibitors represents a mechanistically rational strategy that leverages intra- and extracellular inhibition to enhance antitumor activity across multiple tumor types.[10] In human epidermal growth factor receptor 2 (HER2)–positive breast cancer (BC), the HER2CLIMB-04 trial is evaluating the addition of tucatinib to T-DXd in pretreated patients. In *EGFR*-mutant NSCLC, the combination of Dato-DXd with osimertinib has emerged as a promising strategy to overcome resistance to single-agent anti-EGFR treatment and is being investigated in the TROPION-Lung14 (ClinicalTrials.gov identifier: NCT06350097) and TROPION-Lung15 (ClinicalTrials.gov identifier: NCT06417814) trials for first-line treatment or pretreated patients, respectively. Telisotuzumab vedotin has been combined with osimertinib in *EGFR*-mutant NSCLC with promising results, but because of high discontinuation rates related to treatment toxicities, the phase III program was withdrawn.

The combination of ADCs with poly-ADP ribose polymerase (PARP) inhibitors, represents a rational strategy with significant preclinical evidence. ADCs with a topoisomerase-I inhibitor (TOP1i) payload, such as SG and T-DXd, induce synthetic lethality when combined with PARP inhibitors as TOP1i generates single-strand DNA breaks and stabilizes TOP1-DNA covalent complexes, which require functional PARP1 for repair.[22] The BLUESTAR (ClinicalTrials.gov identifier: NCT05123482) and PETRA (ClinicalTrials.gov identifier: NCT04644068) trials are among the studies currently

TABLE 2. Clinical Trials With Antibody-Drug Conjugates in the Curative and First-Line Setting

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
TROPION-Breast03 (NCT05629585)	**Dato-DXd** + durvalumab	Trop2	TOP1i	Postneoadjuvant TNBC	III
TROPION-Breast04 (NCT06112379)	**Dato-DXd** + durvalumab			Early TNBC	III
TROPION-Breast05 (NCT06103864)	**Dato-DXd** + durvalumab			1L TNBC	III
TROPION-Breast02 (NCT05374512)	**Dato-DXd**			1L TNBC	III
TROPION-Lung07 (NCT05555732)	**Dato-DXd** + pembrolizumab with or without platinum			1L NSCLC	III
TROPION-Lung08 (NCT05215340)	**Dato-DXd** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
TROPION-Lung14 (NCT06350097)	**Dato-DXd** + osimertinib			1L EGFRm NSCLC	III
TROPION-Lung10 (NCT06357533)	**Dato-DXd** + rilvegostomig			1L NSCLC	III
TROPION-Lung12 (NCT06564844)	**Dato-DXd** + rilvegostomig			Stage I high-risk NSCLC	III
AVANZAR (NCT05687266)	**Dato-DXd** + durvalumab			1L NSCLC	III
ASCENT-05 (NCT05633654)	**SG** + pembrolizumab	Trop2	TOP1i	Postneoadjuvant TNBC	III
ASCENT-04 (NCT05382286)	**SG** + pembrolizumab			1L TNBC	III
ASCENT-03 (NCT05382299)	**SG**			1L TNBC	III
SASCIA (NCT04595565)	**SG**			Postneoadjuvant TNBC	III
EV-302/KEYNOTE-A39 (NCT04223856)	**EV** + pembrolizumab	Nectin-4	MMAE	1L UC	III
EV-103/KEYNOTE-869 (NCT03288545)	**EV** + pembrolizumab			1L UC	I/II
EV-303/KEYNOTE-905 (NCT03924895)	**EV** + pembrolizumab			Early UC	III
EV-304/KEYNOTE-B15 (NCT04700124)	**EV** + pembrolizumab			Early UC	III
KRISTINE (NCT02131064)	**T-DM1** + pertuzumab	HER2	Microtubule inhibitor	1L HER2+ BC	III
KATHERINE (NCT01772472)	**T-DM1**			Postneoadjuvant HER2+ BC	III
MARIANNE (NCT01120184)	**T-DM1** with or without pertuzumab			1L HER2+ BC	III
DESTINY-Breast05 (NCT04622319)	**T-DXd**	HER2	TOP1i	Postneoadjuvant HER2+ BC	III
DESTINY-Breast09 (NCT04784715)	**T-DXd** + pertuzumab	HER2	TOP1i	1L HER2+ BC	III
DESTINY-Breast11 (NCT05113251)	**T-DXd**			Neoadjuvant HER2+ BC	III
DESTINY-Lung04 (NCT05048797)	**T-DXd**			HER2m NSCLC	III
DESTINY-Gastric05 (NCT06731478)	**T-DXd** + pembrolizumab + chemotherapy			1L HER2+ G/GEJC	III
ARTEMIDE-Gastric01 (NCT06764875)	**T-DXd** + rilvegostomig + chemotherapy			1L HER2+/PD-L1+ G/GEJC	III
DESTINY-BTC01 (NCT06467357)	**T-DXd** + rilvegostomig			1L HER2-expressing BTC	III
DESTINY-Lung06 (NCT06899126)	**T-DXd** + pembrolizumab			1L HER2-overexpressing NSCLC	III
DESTINY-Ovarian01 (NCT06819007)	**T-DXd** + bevacizumab			1L HER2-expressing OC	III
DESTINY-Endometrial01 (NCT06989112)	**T-DXd** + pembrolizumab or rilvegostomig			1L HER2-expressing pMMR EC	III
DESTINY-Endometrial02 (NCT06989112)	**T-DXd**			Adjuvant HER2-expressing pMMR EC	III

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TABLE 2. Clinical Trials With Antibody-Drug Conjugates in the Curative and First-Line Setting (continued)

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
TroFuse-033 (NCT06952504)	**Sac-TMT** + pembrolizumab	Trop2	TOP1i	pMMR EC	III
MK-2870-012 (NCT06393374)	**Sac-TMT** + pembrolizumab			Early TNBC	III
TroFuse-007 (NCT06170788)	**Sac-TMT** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
MK-2870-023 (NCT06422143)	**Sac-TMT** + pembrolizumab			1L NSCLC	III
TroFuse-017 (NCT06312137)	**Sac-TMT** + pembrolizumab			Early NSCLC	III
TroFuse-011 (NCT06841354)	**Sac-TMT** + pembrolizumab			1L TNBC	III
TroFuse-036 (NCT07216703)	**Sac-TMT** + pembrolizumab			1L CC	III
TroFuse-021 (NCT07318558)	**Sac-TMT** + bevacizumab			1L HRD-negative OC	III
M25-287 (NCT07005102)	**Teliso-A** + osimertinib	cMET	TOP1i	1L EGFRm NSCLC	II/III
DV-001 (NCT05911295)	**Disitamab vedotin** + pembrolizumab	HER2	MMAE	1L HER2-expressing UC	III
RC48-C016 (NCT05302284)	**Disitamab vedotin** + toripalimab			1L HER2-expressing UC	III
NCT04879329	**Disitamab vedotin** + pembrolizumab			HER2-expressing UC	II
Be6A Lung-02 (NCT06758401)	**Sigvotatug vedotin** + pembrolizumab	Integrin β6	MMAE	1L NSCLC TPS ≥ 50%	III
NCT06838273	**Iza-bren** + osimertinib	EGFRxHER3	TOP1i	1L EGFRm NSCLC	III
IZABRIGHT-Breast01 (NCT06926868)	**Iza-bren**			1L TNBC	II/III
FRAmework-01 (NCT07213804)	**LY4170156** + bevacizumab	FRα	TOP1i	PSOC	III
GLORIOSA (NCT05445778)	**MIRV** + bevacizumab	FRα	Microtubule inhibitor	PSOC	III
Duravelo-2 (NCT06225596)	**BT8009 (zelenectide pevedotin)**	Nectin-4	MMAE	UC	III

NOTE. Novel ADC agents or novel combinations are highlighted in bold.
Abbreviations: 1L, first-line; ADC, antibody-drug conjugates; BC, breast cancer; BTC, biliary tract cancer; CC, cervical cancer; cMET, cellular metabolic equivalent; Dato-DXd, datopotamab deruxtecan; EC, endometrial cancer; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutant; EV, enfortumab vedotin; FRα, folate receptor α; G/GEJC, gastric/gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HRD, homologous recombination deficiency; Iza-bren, izalontamab brengitecan; MIRV, mirvetuximab soravtansine; MMAE, monomethyl auristatin E; NSCLC, non–small cell lung cancer; OC, ovarian cancer; pMMR, mismatch repair–proficient; PSOC, platinum-sensitive ovarian cancer; Sac-TMT, sacituzumab tirumotecan; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; Teliso-A, telisotuzumab adizutecan; TNBC, triple-negative breast cancer; TOP1i, topoisomerase-I inhibitor; TPS, tumor proportion score; UC, urothelial cancer.

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evaluating TOP1i-based ADCs in combination with PARP inhibitors in various tumor types.

Combination With Monoclonal Antibodies

The combination of ADCs with traditional monoclonal antibodies targeting complementary pathways offers the potential for synergistic antitumor effects. Antibody combinations can enhance receptor clustering, accelerate internalization, and improve payload delivery while maintaining antibody-dependent cellular cytotoxicity through Fc receptor engagement.[23] The FDA has approved the combination of T-DXd plus pertuzumab for the first-line treatment of patients with advanced, HER2-positive BC, based on the results of the DESTINY-Breast09 trial, which showed superior survival outcomes in comparison with the standard-of-care arm of docetaxel, trastuzumab, and pertuzumab.[24] Nonetheless, the contribution of pertuzumab to the activity of first-line T-DXd is still not clear. The addition of pertuzumab to T-DXd seemed to increase the objective response rate (ORR; 82.0% [80% CI, 73.1 to 88.8]) in comparison with T-DXd monotherapy (77.3 [80% CI, 70.0 to 83.6]) in the phase Ib/II DESTINY-Breast07 trial.[25] Nonetheless, DESTINY-Breast09 was not designed to answer this question, and data regarding the T-DXd monotherapy arm are still not available.

Currently, various ADC-bevacizumab combinations are being tested in phase III trials for gynecologic cancers, and a wide range of bispecific antibodies (bsAbs) are being tested in combination with ADCs (Table 1).

Sequencing Strategies: ADC After ADC

As multiple ADCs became available for patients with BC, determining optimal sequencing strategies has emerged as one of the most pressing clinical questions, with real-world evidence revealing substantial declines in efficacy with the use of a second sequential ADC.[26] Nonetheless, retrospective studies have been inconclusive regarding the optimal sequencing strategies. Cross-resistance between different ADCs is primarily mediated by the payload rather than the

antibody.[27-29] Cross-resistance because of loss of antigen expression, impaired internalization, or altered antibody trafficking is less frequently described.[30]

In a systematic review including more than 2,900 patients with advanced BC treated with sequential ADCs, median PFS significantly decreased with the second ADC in HER2-low tumors, where all approved ADCs include a TOP1i, but it was preserved in the HER2-positive setting, particularly when T-DXd was followed by T-DM1, which uses a different payload. Bridging traditional chemotherapy between ADCs demonstrated higher efficacy than direct sequencing of ADCs with similar payloads in some cohorts.[12]

Strategies to overcome the cross-resistance of ADCs, such as bridging two ADCs with a traditional chemotherapy regimen (the sandwich method), are still not clearly defined.[11] Translational research will be fundamental to define the optimal sequencing. Moreover, whether prior exposure to specific traditional cytotoxic agents—such as irinotecan before a TOP1i-based ADC—affects ADC activity remains unknown as no clinical data exist to guide payload selection in this context. In DESTINY-PanTumour02, T-DXd was associated with an ORR of 4% in the cohort of pancreatic tumors, by far the lowest of any cohort, possibly related to prior exposure to irinotecan.[31]

Genomic biomarkers are emerging as potential tools for guiding sequencing decisions. *PTEN* loss has been associated with de novo resistance to T-DXd but not SG,[32] whereas *RB1* alterations have been linked to superior PFS with sequential ADC therapy. These findings, although inconclusive, highlight the need for biomarker-driven patient selection to optimize sequential ADC outcomes.[33]

Ongoing prospective studies, such as TRADE-DXd (ClinicalTrials.gov identifier: NCT06533826), are designed to address these questions directly.

BC represents a paradigmatic disease model in which multiple ADCs with overlapping targets and payloads are approved, allowing us to explore the key principles of cross-resistance and sequencing in a real-world setting. These principles are likely to be applicable to other solid tumors as the ADC landscape continues to expand.

INTEGRATING ADCs INTO FIRST-LINE AND CURATIVE STRATEGIES

Treatment Positioning: Methodological Challenges

Given the efficacy observed with ADCs in pretreated patients with metastatic solid tumors, many clinical trials are now evaluating their integration into first-line and potentially curative settings (Table 2). This strategy is based on the principle that the sooner, the better and aims to ensure that a greater proportion of patients receive effective therapy, particularly in light of the attrition observed across successive lines of treatment: delaying the introduction of an effective drug may result in missed therapeutic opportunities for patients who ultimately become ineligible for subsequent systemic therapy, especially in the case of aggressive tumors.[34]

The most rigorous method to assess the impact of early frontline drug use is through an overall survival (OS)–powered trial with crossover permitted. However, such designs require larger sample sizes and are complicated by heterogeneity in postprogression treatment, including variable global access to subsequent therapies in international studies. Indeed, although clinical trials should be powered to detect improvements in patient-centric end points such as OS and/or quality of life (QoL), especially when investigating treatment positioning, this standard is infrequently met, further complicating the interpretation of trial results. In the metastatic BC setting, for example, fewer than 10% of randomized trials have used OS or QoL as the primary end point.[35] In this context, PFS2, which captures outcomes across both first- and second-line treatment, has been proposed as a potential surrogate end point when crossover is permitted.[36]

In the absence of crossover and when the investigational agent is not approved or accessible in subsequent lines of therapy, as has occurred in some international trials, the clinical question shifts from "now or later?" to "now or never?" This issue arises particularly when a first-line trial is initiated shortly after the trial evaluates the same agent in later lines, resulting in overlapping enrollment periods and the absence of protocol amendments to incorporate crossover once the agent enters routine practice in subsequent settings. With the acceleration of oncologic drug development, this challenge has become increasingly relevant. Notably, between 2013 and 2018, 17% of anticancer drugs were approved on the basis of trials that used comparators later considered suboptimal.[37]

These challenges are even more pronounced in the curative setting, where demonstrating an OS benefit requires prolonged follow-up. Shorter-term end points, such as disease-free survival (DFS), may expedite readouts but do not establish whether more patients are ultimately cured or whether effective therapy is simply delivered earlier in the disease course, unless their validity as surrogate end points for OS is rigorously demonstrated.[38,39] Moreover, access to the same investigational therapy in the metastatic setting after relapse is often inconsistent, which may further confound the assessment of long-term, patient-centered outcomes.

Urothelial Cancer and Enfortumab Vedotin

Metastatic urothelial carcinoma was the first solid tumor where an ADC, namely EV, was integrated into earlier lines of therapy. The first-line, phase III trial evaluating EV plus pembrolizumab (EV-302) was designed based on several converging observations: in the phase III EV-301 trial, EV

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improved OS in patients previously treated with platinum-based chemotherapy and ICIs, establishing its activity in later lines.[40] At the same time, approximately 30% of patients with advanced disease do not receive second-line therapy, and preclinical and early clinical data suggested biological and therapeutic synergy between EV and pembrolizumab.[41]

The EV-302 trial compared EV plus pembrolizumab with platinum-based chemotherapy in untreated, cisplatin-eligible patients with metastatic urothelial carcinoma.[18] The coprimary end points were PFS and OS. Among 886 enrolled patients, at a median follow-up of 17.2 months, the combination significantly prolonged median PFS (12.5 *v* 6.3 months; hazard ratio [HR], 0.45 [95% CI, 0.38 to 0.54]) and median OS (31.5 *v* 16.1 months; HR, 0.47 [95% CI, 0.38 to 0.58]), without detriment in QoL.[42]

Interpretation of these results, however, warrants consideration of trial design. Only approximately 30% of patients in the chemotherapy arm received maintenance avelumab, which is considered a component of contemporary standard care, and crossover to EV was not mandated; only about 25% of patients in the control arm subsequently received the drug.[41] Nevertheless, the study was powered for OS, and in the context of substantial first-to-second-line attrition, this combination should be considered for most of the patients in this setting, after the approval by regulatory authorities in the United States and Europe. Instead, among patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy, EV combined with pembrolizumab was approved on the basis of phase 1b-2 data demonstrating high response rates and durable responses.[43]

The strategy has also been extended to the perioperative setting in patients with nonmetastatic, muscle-invasive bladder cancer (MIBC). In cisplatin-ineligible patients or those declining cisplatin, the phase III KEYNOTE-905/EV-303 trial compared perioperative EV plus pembrolizumab with radical cystectomy and pelvic lymph node dissection alone.[19] After random assignment of 344 patients and a median follow-up of 25.6 months, the combination significantly improved median event-free survival (not reached *v* 15.7 months; HR, 0.40 [95% CI, 0.28 to 0.57]), median OS (not reached *v* 41.7 months; HR, 0.50 [95% CI, 0.33 to 0.74]), and pathologic complete response rates (57.1% *v* 8.6%). Grade 3 or higher adverse events (AEs) of special interest included severe skin reactions, observed in approximately 11% of patients. To our knowledge, these findings represent the first demonstration of improved perioperative outcomes beyond surgery alone in this population. In cisplatin-eligible patients, the phase III KEYNOTE-B15/EV-304 trial compared perioperative EV plus pembrolizumab with neoadjuvant cisplatin plus gemcitabine followed by radical cystectomy in 808 patients with MIBC. EV plus pembrolizumab significantly improved all survival end points as the 24-month EFS rate was 79.4% versus 66.2% (HR, 0.53 [95% CI, 0.41 to 0.70]), the 24-month OS rate was 86.9% versus 81.3% (HR, 0.65 [95% CI, 0.48 to 0.89]), and the pCR rate was 55.8% versus 32.5%.[44]

TNBC and Anti-Trop2 ADCs

In patients with metastatic TNBC, the evaluation of anti-Trop2 ADCs in the first-line setting was informed by the survival benefit of SG in patients with previously treated disease and by clinically meaningful attrition between first- and second-line therapies, which exceeds 10% overall and approaches 25%-30% in some series.[34,45,46] On this basis, SG and Dato-DXd have been investigated in patients with previously untreated metastatic TNBC, either in combination with pembrolizumab in PD-L1–positive disease or as monotherapy in patients not candidates for PD-(L)1 inhibition.

In PD-L1–positive metastatic TNBC, the phase 3 ASCENT-04 trial compared SG plus pembrolizumab with chemotherapy plus pembrolizumab.[20] Among 443 patients, the median PFS was 11.2 months for SG plus pembrolizumab and 7.8 months for chemotherapy plus pembrolizumab (HR, 0.65 [95% CI, 0.51 to 0.84]). OS data remain immature although crossover to second-line SG was permitted. Overall QoL was maintained, with reduced symptom burden and improved functioning, whereas nausea, vomiting, and diarrhea were more frequent, consistent with the known safety profile of SG.[47]

The absolute median PFS gain of 3.4 months warrants contextual interpretation.[48] The benefit appeared to be largely confined to patients with recurrent disease after a disease-free interval that exceeds 12 months, most of whom (95%) had received neoadjuvant chemotherapy without perioperative pembrolizumab, an approach that does not reflect contemporary standards. By contrast, patients with de novo metastatic TNBC derived limited apparent benefit (HR, 0.89 [95% CI, 0.59 to 1.34]).

In patients not candidates for PD-(L)1/PD-L1 blockade, ASCENT-03 and TROPION-Breast02 evaluated SG and Dato-DXd, respectively, in previously untreated metastatic TNBC. ASCENT-03 enrolled 558 patients with a treatment-free interval of >6 months, allowed crossover to SG, and used PFS as the primary end point.[49] At a median follow-up of 13.2 months, SG improved median PFS as compared with chemotherapy (9.7 *v* 6.9 months; HR, 0.62 [95% CI, 0.50 to 0.77]), with 61% of patients in the control group receiving SG at progression. TROPION-Breast02 included 644 patients irrespective of the treatment-free interval, did not mandate crossover, and specified both PFS and OS as primary end points.[50] At a median follow-up of 27.5 months, Dato-DXd improved median PFS (10.8 *v* 5.6 months; HR, 0.57 [95% CI, 0.47 to 0.69]) and OS (23.7 *v* 18.7 months; HR, 0.79 [95% CI, 0.64 to 0.98]); approximately 30% of patients in the control arm subsequently received an ADC. Toxic effects differed between agents, with neutropenia predominating with SG and mucositis and stomatitis more frequently observed with Dato-DXd.

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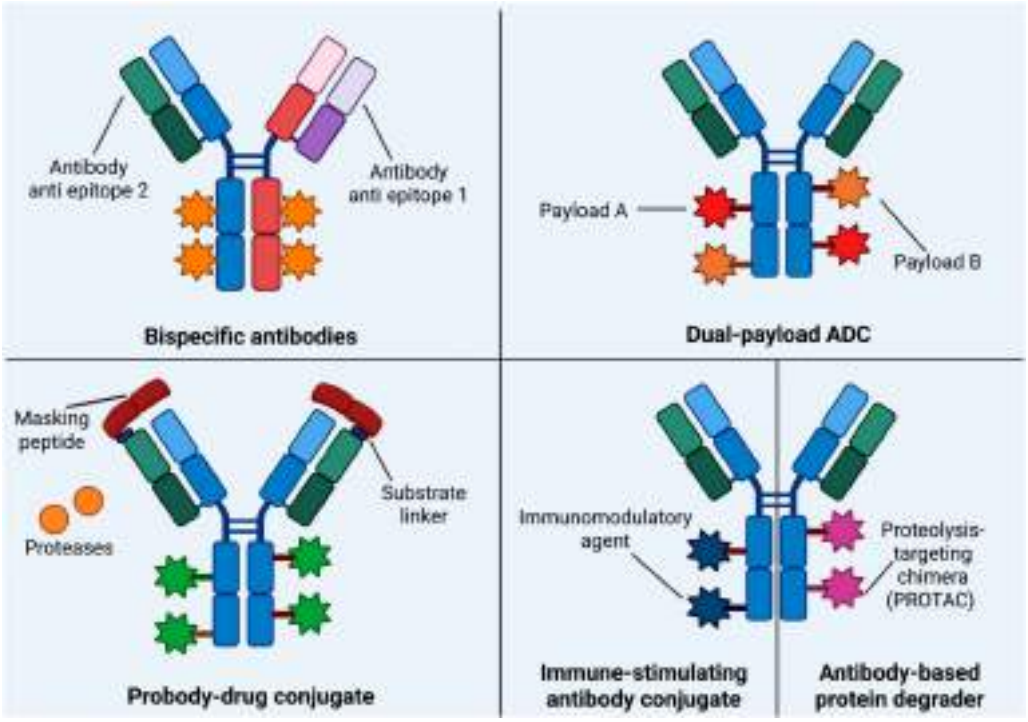

FIG 1. Next-generation antibody-drug conjugates. Created using BioRender.com/8ah0hdp. ADC, antibody-drug conjugate; PROTAC, proteolysis-targeting chimera.

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Collectively, these data support earlier integration of anti-Trop2 ADCs in metastatic TNBC. However, interpretation should account for trial design, crossover policies, access to subsequent therapies, and evolving standards of care. Selection between SG and Dato-DXd should consider treatment-free interval, toxicity profile, and dosing schedule (SG on days 1 and 8 every 3 weeks; Dato-DXd on day 1 every 3 weeks), with individualized discussion.

Anti-Trop2 ADCs are also under evaluation in early-stage TNBC, both in the neoadjuvant setting and in patients with residual disease after neoadjuvant therapy (Table 2).

HER2-Positive Breast Cancer and Anti-HER2 ADCs

T-DM1 was the first ADC approved for the treatment of solid tumors. In patients with previously treated, trastuzumab-resistant, HER2-positive BC, T-DM1 improved outcomes in both the metastatic (EMILIA and TH3RESA trials) and post-neoadjuvant early-stage settings (KATHERINE trial).[51-53] However, T-DM1 did not demonstrate superiority over taxanes plus trastuzumab in untreated metastatic disease (MARIANNE trial) or over standard neoadjuvant chemotherapy plus trastuzumab in early-stage disease (KRISTINE trial), findings that have been partly attributed to the reduced efficacy of T-DM1 in the case of HER2 heterogeneity.[54-56]

T-DXd, a next-generation ADC with a higher DAR and a bystander effect, demonstrated improved PFS and OS as compared with T-DM1 in the second-line metastatic setting, providing the rationale for evaluation in patients with untreated disease.[57] In the phase III DESTINY-Breast09 trial, 770 patients with previously untreated metastatic HER2-positive BC were randomly assigned to T-DXd plus pertuzumab or to the CLEOPATRA regimen (docetaxel, trastuzumab, and pertuzumab, followed by trastuzumab-pertuzumab maintenance), with no mandated crossover to T-DXd and PFS as the primary end point. At a median follow-up of 29.2 months, the median PFS was prolonged from 27 to 41 months (HR, 0.56 [95% CI, 0.44 to 0.71]), the longest median PFS reported to date in an unselected first-line HER2-positive metastatic population. OS data remain immature.[24]

Interpretation of these findings requires consideration of tolerability and treatment strategy. In DESTINY-Breast09, T-DXd plus pertuzumab was administered until disease progression or unacceptable toxicity, whereas the CLEOPATRA regimen transitions to chemotherapy-free trastuzumab-pertuzumab maintenance, which nearly 30% of patients receive for more than 35 months. In DESTINY-Breast09, 21% of patients discontinued T-DXd because of treatment-emergent AEs and drug-related ILD or pneumonitis occurred in 12% of patients, with two treatment-related deaths. Although no difference in time to deterioration of global QoL was observed, patient-reported nausea, vomiting, appetite loss, and constipation were more frequent with T-DXd plus pertuzumab.[94] In a disease characterized by a low first-to-second-line attrition rate (approximately 10%) and the opportunity to intensify the maintenance with palbociclib or tucatinib, the

decision to use T-DXd up front should therefore be individualized according to disease burden, central nervous system involvement, the presence of *PIK3CA* mutations, treatment-free interval in the case of recurrent disease, and patient preferences.[34,58-60]

T-DXd has also been evaluated in the postneoadjuvant setting in 1,635 patients with HER2-positive BC with residual invasive disease and node-positive disease at surgery or inoperable disease at diagnosis, in the phase III, DESTINY-Breast05 trial.[61] In this trial, at a median follow-up of 30 months, T-DXd significantly improved invasive DFS as compared with T-DM1 (HR, 0.47 [95% CI, 0.34 to 0.66]). However, drug-related ILD occurred more frequently with T-DXd (9.6% *v* 1.6%), including two fatal cases. Nevertheless, given the high baseline risk of recurrence in this selected population, these data support the intensification with T-DXd.

In the neoadjuvant setting, the phase III DESTINY-Breast11 trial compared T-DXd alone or T-DXd followed by paclitaxel, trastuzumab, and pertuzumab (T-DXd-THP), with dose-dense doxorubicin-cyclophosphamide followed by THP (ddAC-THP), in patients with high-risk HER2-positive disease.[62] Enrollment in the T-DXd–alone arm was discontinued for futility. Pathologic complete response rates (the primary end point) were 67% with T-DXd-THP, compared with 56% with ddAC-THP (absolute difference, 11% [95% CI, 4 to 8]). Although the primary end point was met, event-free survival data remain immature (HR, 0.56 [95% CI, 0.26 to 1.17]) and its interpretation is limited since only 55% of patients with residual disease received post-neoadjuvant T-DM1. Moreover, the lack of validated surrogacy between pathologic complete response and OS in this context tempers conclusions regarding long-term benefit.[39]

Collectively, anti-HER2 ADCs are reshaping both metastatic and early-stage HER2-positive BC management. However, the optimal positioning of T-DXd requires careful consideration of toxicity, sequencing, risk of attrition, and patient preferences.

NEXT-GENERATION ADCs: BISPECIFIC AND DUAL-PAYLOAD DESIGNS IN ONCOLOGY

The Need for Novel ADC Designs

Despite their remarkable clinical success across multiple tumor types in various settings, ADCs are understandably characterized by limitations that necessitate innovative designs. Overall, more than 80% of ADCs that have entered clinical trial were terminated in phase I or II, highlighting the need for innovative development strategies.[2] Current challenges include tumor heterogeneity, drug resistance, suboptimal internalization and on-target off-tumor toxicities.

Most approved ADCs rely on a single tumor-associated antigen (TAA) and deliver highly potent cytotoxic payloads, making their activity strongly dependent on homogeneous target expression and efficient intracellular trafficking.[2] In clinical practice, however, intratumoral heterogeneity, antigen downregulation, poor receptor internalization, and acquired resistance mechanisms frequently limit durability of response and premature linker cleavage enhances systemic toxicities narrowing the therapeutic index.

Moreover, the extension of clinical trials regarding ADCs into earlier treatment lines and potentially curative settings raises new requirements in terms of safety and long-term tolerability. These challenges have led to the development of next-generation ADC designs to move beyond the traditional single-payload and single-antibody compounds. Innovative strategies, including multispecific targeting to overcome heterogeneity and improve tumor selectivity, dual-payload delivery to overcome drug resistance, and alternative conjugate platforms, aim to broaden the functional scope of payloads. Collectively, these advances position ADCs as increasingly sophisticated drug systems.[3]

Bispecific ADCs

bsAbs can simultaneously engage two different TAAs or epitopes (Fig 1). This innovative design has been applied to next-generation ADCs as various bsADCs are currently under early or late-stage clinical development. Potential advantages of bsADCs include enhanced specificity through dual-antigen targeting, which reduces off-target effects in normal tissues expressing only one antigen. Furthermore, bsADCs can target compensatory signaling pathways simultaneously, such as EGFR × HER3, preventing or delaying resistance mechanisms that emerge with single-target inhibition. Preclinical studies demonstrated that bispecific constructs achieve comparable or superior efficacy to combinations of two monospecific ADCs, while simplifying manufacturing and dosing regimens.[3,63,64]

Various anti-HER2 biparatopic ADCs (ie, targeting two epitopes of the same protein) have been tested in phase I studies.[63] Biparatopic targeting induces the clustering of receptors, which are more efficiently internalized in target cells.[65] The first bsADC with published clinical data has been zanidatamab zovodotin (ZW49), a bsADC based on the bsAb zanidatamab. In a phase I trial in HER2-positive advanced tumors, the ORR was 31% with the recommended phase II dose and 67% of patients received prior HER2-targeted therapies. The most common AEs were keratitis (44%), alopecia (26%), and diarrhea (24%).[66] MEDI4276 is another anti-HER2 biparatopic ADC, which demonstrated an ORR of 9.4% in a phase I/II trial on HER2-positive breast or gastric cancers, with a median of eight prior lines of treatment. The most common AEs were nausea (59.6%), fatigue (44.7%), AST increased (42.6%), and vomiting (38.3%).[67] The biparatopic anti-HER2 ADC JSKN003 has been tested in multiple phase I trials. In platinum-resistant ovarian cancer, it demonstrated an ORR of 64.4%, reaching as high as 72.2% for HER2-expressing tumors, the most common AE was

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nausea (39.1%), and grade 1/2 ILD was observed in 8.7% of patients.[68] JSKN003 is also being tested in phase II and III trials in gastric (ClinicalTrials.gov identifier: NCT06998771), breast (ClinicalTrials.gov identifier: NCT06846437), platinum-resistant ovarian (ClinicalTrials.gov identifier: NCT06751485), and colorectal cancers (ClinicalTrials.gov identifier: NCT07384377). Neoadjuvant TQB2102, another drug in the class of biparatopic anti-HER2 ADCs, has been investigated in monotherapy in stage II to III HER2-positive BC, proving a pathologic complete response rate between 57% and 69% at various treatment schedules.[69] Various phase III trials are ongoing regarding TQB-2102. Although data are lacking, novel anti-HER2 ADCs may be considered in the post–T-DXd setting, especially in the case of agents with non–cross-resistant payloads, pending the demonstration of their efficacy in prospective clinical trials.

A biparatopic anti-METxMET ADC has been tested in MET-overexpressing tumors, but the study has been terminated early (ClinicalTrials.gov identifier: NCT04982224). An anti-FRαxFRα ADC is being tested in patients with recurrent gynecologic tumors (ClinicalTrials.gov identifier: NCT05527184).

Clinical development has also accelerated rapidly for dual TAA-targeting ADCs. Izalontamab brengitecan (BL-B01D1) is a first-in-class EGFRxHER3 bsADC linked to a TOP1i, which showed encouraging data in phase I trials. The most common grade 3/4 AEs associated with the drug were hematologic.[70] In a phase III trial in patients with nasopharyngeal cancer, it showed superior activity over standard-of-care chemotherapy.[71] Promising data were also published for patients with *EGFR*-mutant NSCLC,[72,73] UC,[74] and esophageal squamous cell carcinoma,[75] and it is currently being tested in more than 30 phase II and III trials, including first-line PD-L1–negative TNBC (ClinicalTrials.gov identifier: NCT06926868) and first-line *EGFR*-mutant NSCLC (ClinicalTrials.gov identifier: NCT06838273). Other anti-EGFR bsADCs, such as AZD9592 (ClinicalTrials.gov identifier: NCT05647122) and M1231 (ClinicalTrials.gov identifier: NCT04695847), are also being investigated.[63]

Additional candidates targeting HER2/HER3 and TROP2/HER3 combinations have shown breakthrough activity in TNBC and other challenging tumors, as well as bsADCs that simultaneously target HER2 and fast-turnover receptors, such as CD63, PRLR, and APLP2.[76]

Dual-Payload ADCs

Dual-payload ADCs incorporate two distinct therapeutic payloads on the same antibody scaffold, enabling synergistic mechanisms of action and potentially reducing resistance mechanisms because of tumor heterogeneity that limit the efficacy of single-payload ADCs (Fig 1).[77-79] By delivering two distinct payloads to the same cancer cell, these compounds can simultaneously target different cellular vulnerabilities, such as combining microtubule inhibitors with DNA-damaging agents or pairing cytotoxic drugs with immune-stimulating molecules.[80] The conjugation strategies include dual-site conjugation with traditional linear linkers or single-site conjugation with a branching linker equipped with orthogonal reaction handles.[78] Nonetheless, other than synergistic antitumor effects, dual-payload ADCs can also cause synergistic toxicities.

A HER2-targeted dual-payload ADC combining monomethyl auristatin E (MMAE) and deruxtecan achieved superior cytotoxicity against HER2-positive cells compared with T-DXd, with enhanced tumor suppression in xenograft models.[81] Similarly, a CD276/B7-H3–targeted dual-payload ADC combining a cytotoxic agent with an immunoregulating Toll-like receptor 7/8 (TLR7/8) agonist demonstrated both direct tumor cell killing and immune activation in TNBC models.[80]

KH815 is a novel dual-payload anti-Trop2 ADC platform that includes an optimized linker design that leads to the sequential delivery of triptolide (RNA polymerase-II inhibitor) and exatecan (TOP1i). The release of triptolide leads to the downregulation of the stress response protein Hsp70 and efflux pump P-gp in tumor cells, enhancing drug sensitivity, followed by gradual delivery of exatecan. The sequential release strategy, where one payload sensitizes cells before the second is released, represents an innovative approach to maximize therapeutic synergy while maintaining acceptable safety profiles.[82]

Novel ADCs

Other than dual-targeting or dual-payload ADCs, novel designs are currently being investigated in next-generation ADCs.[3]

Peptide-drug conjugates offer advantages over antibody-based platforms, including smaller size enabling superior tumor penetration, reduced immunogenicity, and simplified manufacturing.[83-85] Despite advantages in tissue penetration and cost, peptide-drug conjugates face significant limitations, such as rapid renal clearance, metabolic instability, and limited oral bioavailability.[86]

Probody-drug conjugates feature conditionally active antibodies, which, unlike traditional antibodies, could reduce on-target off-tumor toxicities (Fig 1).[3,87,88] These compounds are engineered with a masked antigen-binding site that is selectively activated by tumor-associated proteases or pH-dependent conformational changes, thereby increasing tumor specificity and reducing off-tumor toxicity.

Immune-stimulating antibody conjugates (ISACs) replace cytotoxic payloads with immunomodulatory agents that interact with pattern-recognition receptors, such as TLR7/8 agonists or stimulator of interferon genes agonists, shifting cold tumors into immunologically active microenvironments (Fig 1).[3,89-91] ISACs activate dendritic cells and promote antitumor T-cell responses while maintaining

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antibody-mediated targeting. However, clinical development has encountered challenges including systemic toxicity, cytokine release syndrome, and antidrug antibody formation.

Antibody-based protein degraders (DACs) are linked to a proteolysis-targeting chimera (PROTAC) instead of a traditional cytotoxic payload, exploiting the promising activity shown by targeted protein degradation (Fig 1).[3,92,93] PROTACs are bifunctional drugs which simultaneously bind to a protein of interest and an E3 ubiquitin ligase, thus triggering targeted degradation of oncoproteins by the ubiquitin-proteasome system. DACs are designed to target cytosolic proteins and are currently being investigated in the preclinical stage.[3] While promising, optimizing pharmacokinetics represents a significant challenge for DACs.

CONCLUSIONS

ADCs have undergone a rapid evolution from a niche therapeutic concept to a broadly applicable and clinically validated drug class across multiple tumor types. Their success reflects decades of progress in antibody engineering, linker chemistry, and payload design, which together have enabled selective delivery of highly potent cytotoxic agents and substantially improved their therapeutic index. As a result, ADCs are increasingly evaluated and adopted in earlier disease settings, including first-line and potentially curative strategies.

At the same time, the expanding clinical application of ADCs has exposed important limitations. Tumor heterogeneity, modulation of target expression, and payload-driven resistance mechanisms frequently limit the durability of response. In addition, on-target off-tumor toxicities and cumulative AEs have emerged as critical challenges, particularly as ADCs are administered for longer durations or in populations with curative intent. These considerations underscore the need for careful patient selection, longitudinal toxicity monitoring, and a deeper understanding of ADC pharmacology beyond traditional paradigms.

Combination strategies have demonstrated the potential to enhance antitumor activity and overcome resistance. Sequencing strategies, especially in disease settings where multiple ADCs with overlapping payloads are available, remain an unresolved clinical challenge, highlighting the importance of translational research and biomarker development to guide treatment decisions.

Looking ahead, next-generation ADC designs, including bispecific and dual-payload constructs, offer the opportunity to directly address key limitations of current platforms, such as antigen heterogeneity and adaptive resistance. Alongside emerging approaches such as conditionally activated ADCs and immune-stimulating compounds, these innovations signal a shift toward increasingly sophisticated ADC designs.

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Advancing Antibody-Drug Conjugates: Current Perspectives and Future Directions

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OVERVIEW

Antibody-drug conjugates (ADCs) have rapidly emerged as one of the most transformative therapeutic agents in modern oncology. Their rational design enables selective drug delivery to tumor cells while limiting systemic exposure, resulting in meaningful clinical benefit across a wide range of malignancies. Technological advances in antibody engineering, linker stability, and payload chemistry have driven a marked expansion of approved ADCs and accelerated their transition from later treatment lines into first-line and potentially curative settings. Despite these advances, tumor heterogeneity, variable antigen expression, impaired internalization, and the emergence of intrinsic and acquired resistance mechanisms frequently limit the durability of response. In parallel, on-target off-tumor toxicities and cumulative treatment-related adverse events pose increasing concerns as ADCs are introduced earlier in the disease course and administered for longer durations. To address these limitations, extensive clinical and translational research efforts have focused on rational combination and sequencing strategies. Combinations with immune checkpoint inhibitors, targeted therapies, and monoclonal antibodies have demonstrated the potential to enhance antitumor activity, overcome resistance, and improve patient outcomes, while requiring careful management of overlapping toxicities. In parallel, sequencing strategies and emerging biomarker-driven approaches are beginning to inform optimal treatment algorithms in settings where multiple ADCs with overlapping targets or payloads are available. Finally, next-generation ADC platforms, including bispecific and dual-payload constructs, are being developed to better address tumor heterogeneity and resistance.

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INTRODUCTION

Antibody-drug conjugates (ADCs) have emerged as one of the most impactful therapeutic advances in modern oncology, fundamentally reshaping the treatment landscape across both hematologic malignancies and solid tumors. ADCs combine the targeting specificity of monoclonal antibodies with the potent cytotoxic activity of chemotherapeutic payloads, linked through chemical linkers to achieve selective delivery of highly toxic agents directly to cancer cells, while minimizing systemic exposure and off-tumor on-target toxicity.[1-3] This innovative design, conceptualized over a century ago by Paul Ehrlich as the magic bullet,[4] has achieved clinical fruition through decades of improvements in antibody engineering, linker chemistry, payload selection, and bioconjugation technologies.

The clinical development of ADCs has accelerated dramatically over the past decade, reflecting both technological advances and deepening mechanistic understanding. Following the initial US Food and Drug Administration (FDA) approval of gemtuzumab ozogamicin in 2000, the field experienced a period of relative stagnation, with early-generation ADCs limited by linker instability, suboptimal drug-to-antibody ratios (DARs), and inadequate payload potency.[5,6] However, the approval of brentuximab vedotin in 2011 and trastuzumab emtansine (T-DM1) in 2013 marked a renaissance in ADC development, demonstrating that refined molecular design could substantially improve the therapeutic index. As of early 2026, 14 ADCs have received FDA approval, and the investigational pipeline includes dozens of candidates in clinical development and hundreds of molecules undergoing evaluation.

After improving survival outcomes in later lines of therapy, ADCs are transitioning to first-line treatment and curative settings, representing a fundamental paradigm shift in their clinical positioning. As the field continues to mature, next-generation innovations, including bispecific ADCs (bsADCs), dual-payload designs, and rational combination strategies with immune checkpoint inhibitors (ICIs) and targeted therapies, promise to further expand the therapeutic potential of this drug class.

PRACTICAL APPLICATION

- Antibody-drug conjugates (ADCs) integrate the targeting precision of monoclonal antibodies with the cytotoxic potency of highly active payloads, enabling selective drug delivery and reshaping treatment paradigms across solid tumors and hematologic malignancies.
- ADC efficacy is limited by tumor heterogeneity, variable target expression, resistance mechanisms, suboptimal intracellular trafficking, and on-target off-tumor toxicities, challenges that become increasingly relevant as ADCs move into earlier and potentially curative settings.
- Rational combination strategies with immune checkpoint inhibitors, targeted agents, and monoclonal antibodies have demonstrated the potential to enhance ADC activity, overcome resistance, and improve clinical outcomes, while requiring careful management of overlapping toxicities.
- Sequencing strategies and emerging biomarker-driven approaches are critical to optimize ADC use in clinical practice, particularly in disease settings where multiple ADCs with similar payloads are available.
- Ongoing clinical development of next-generation ADCs, including bispecific and dual-payload constructs, and their integration into first-line and curative settings position ADCs as a pillar of next-generation precision oncology.

SYNERGY AND STRATEGY: COMBINING AND SEQUENCING ADCs WITH TARGETED AGENTS

ADCs, as any oncologic treatment, are characterized by intrinsic and acquired resistance mechanisms that limit their long-term benefit in many patients, necessitating innovative strategies to maximize their therapeutic potential.[3,7,8] Combination strategies have been thoroughly investigated to overcome resistance and improve the effectiveness of approved ADCs, taking into careful consideration the management of overlapping toxicities that could compromise the therapeutic index.[9,10] A multitude of phase II and III trials are currently evaluating ADCs in various combination strategies (Table 1). Moreover, sequencing strategies and translational studies are helping to define the optimal treatment algorithms in various settings.[11,12]

Combination With ICIs

Beyond their direct cytotoxic effects, ADCs possess significant immunomodulatory properties that create a rationale for combination with ICIs.[13-16] All the components of ADCs are presumably implied in their immunogenic effects. Specific payloads induce immunogenic cell death, characterized by the release of damage-associated molecular patterns and tumor neoantigens, which activate dendritic cells and enhance antigen presentation to tumor-specific T cells. Furthermore, the antibody backbone engages Fc receptors on NK cells and macrophages, triggering antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, which further amplify antigen presentation and contribute to the immunogenic reshaping of the tumor microenvironment.[13] The shift from a cold to a hot immune microenvironment induced by ADCs could be rationally complemented by immunotherapy with ICIs. Moreover, preclinical data suggest that synergistic effects could be achieved with suboptimal doses of ADC, potentially reducing toxicities.[17]

The clinical translation of ADC-ICI combination has shown promising results across multiple tumor types. Enfortumab vedotin (EV) has been approved in 2023 by the FDA in combination with pembrolizumab for patients with advanced urothelial cancer (UC) in the first-line setting, based on the marked improvement in survival demonstrated in the EV-302/KEYNOTE-A39 trial.[18] In 2025, the combination of EV and pembrolizumab in UC was also approved in the early setting as a perioperative treatment for patients with an indication to radical cystectomy and ineligible for cisplatin-based chemotherapy, based on the results of the EV-303/KEYNOTE-905 trial.[19]

In previously untreated, advanced PD-L1–positive triple-negative breast cancer (TNBC), the ASCENT-04/KEYNOTE-D19 trial demonstrated that sacituzumab govitecan (SG) plus pembrolizumab significantly improved progression-free survival (PFS) compared with standard-of-care chemotherapy plus pembrolizumab, leading to the recommendation of this first-line regimen by the NCCN guidelines.[20]

Meta-analyses of ADC-ICI combinations across solid tumors have shown that the safety profile of the combination is comparable with that of ADC or ICI monotherapy, even if the combination increases the risk of specific toxicities, such as interstitial lung disease (ILD) in patients treated with trastuzumab deruxtecan (T-DXd).[21]

Moreover, other combinations are being tested in phase II and III trials (Table 1). Datopotamab deruxtecan (Dato-DXd) in combination with durvalumab is being investigated in TNBC and non–small cell lung cancer (NSCLC). SG is being tested with pembrolizumab in NSCLC and early-stage TNBC. Sacituzumab tirumotecan in combination with pembrolizumab is being assessed in a wide range of solid tumors, including TNBC, NSCLC, and gynecologic cancers. T-DXd with pembrolizumab is being tested as a first-line treatment in different tumors. Notably, clinical benefit from ADC-ICI combinations has thus far been restricted to tumor types where single-agent PD-(L)1 blockade has already established

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TABLE 1. Phase II/III Clinical Trials With ADCs in Combination

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
ADC + IO					
TROPION-Breast03 (NCT05629585)	**Dato-DXd** + durvalumab	Trop2	TOP1i	Postneoadjuvant TNBC	III
COMPASS-TNBC (NCT06508216)	**Dato-DXd** + durvalumab			Early relapsed TNBC	Ib/II
TROPION-Breast04 (NCT06112379)	**Dato-DXd** + durvalumab			Early TNBC	III
TROPION-Breast05 (NCT06103864)	**Dato-DXd** + durvalumab			1L TNBC	III
TROPION-Lung07 (NCT05555732)	**Dato-DXd** + pembrolizumab with or without platinum			1L NSCLC	III
TROPION-Lung08 (NCT05215340)	**Dato-DXd** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
NeoCAST-2 (NCT05061550)	**Dato-DXd** + durvalumab			Neoadjuvant NSCLC	II
AVANZAR (NCT05687266)	**Dato-DXd** + durvalumab			1L NSCLC	III
EVOKE-02 (NCT05186974)	**SG** + pembrolizumab with or without platinum	Trop2	TOP1i	1L NSCLC	II
EVOKE-03 (NCT05609968)	**SG** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
ASCENT-05 (NCT05633654)	**SG** + pembrolizumab			Postneoadjuvant TNBC	III
ASCENT-04 (NCT05382286)	**SG** + pembrolizumab			1L TNBC	III
TROPHY-UO1 (NCT03547973)	**SG** + pembrolizumab or avelumab or zimberelimab			1L UC	II
EV-302/KEYNOTE-A39 (NCT04223856)	**EV** + pembrolizumab	Nectin-4	MMAE	1L UC	III
EV-103/KEYNOTE-869 (NCT03288545)	**EV** + pembrolizumab			1L UC	I/II
EV-303/KEYNOTE-905 (NCT03924895)	**EV** + pembrolizumab			Early UC	III
EV-304/KEYNOTE-B15 (NCT04700124)	**EV** + pembrolizumab			Early UC	III
TRAIN-UC-01 (NCT07241793)	**Trastuzumab rezetecan** + adebrelimab			HER2-expressing metastatic UC	II
NCT05941507	**LCB84** + anti-PD1	Trop2	MMAE	All solid tumors	I/II
IDeate-Lung03 (NCT06362252)	**I-DXd** + atezolizumab with or without carboplatin	B7-H3	TOP1i	ES-SCLC	I/II
TroFuse-033 (NCT06952504)	**Sac-TMT** + pembrolizumab	Trop2	TOP1i	1L EC pMMR	III
MK-2870-010 (NCT06312176)	**Sac-TMT** + pembrolizumab			Advanced hormone receptor–positive BC	III
MK-2870-012 (NCT06393374)	**Sac-TMT** + pembrolizumab			Early TNBC	III
TroFuse-007 (NCT06170788)	**Sac-TMT** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
MK-2870-023 (NCT06422143)	**Sac-TMT** + pembrolizumab			1L NSCLC	III
TroFuse-017 (NCT06312137)	**Sac-TMT** + pembrolizumab			Early NSCLC	III
TroFuse-011 (NCT06841354)	**Sac-TMT** + pembrolizumab			1L TNBC	III
TroFuse-036 (NCT07216703)	**Sac-TMT** + pembrolizumab			1L CC	III
InnovaTV 205 (NCT03786081)	**Tiso-V** + pembrolizumab	TF	MMAE	CC	I/II
DESTINY-Gastric05 (NCT06731478)	**T-DXd** + pembrolizumab + chemotherapy	HER2	TOP1i	1L HER2+ G/GEJC	III
DESTINY-Lung06 (NCT06899126)	**T-DXd** + pembrolizumab			1L HER2-overexpressing NSCLC	III
DESTINY-Endometrial01 (NCT06989112)	**T-DXd** + pembrolizumab			1L HER2-expressing pMMR EC	III
HERTHENA-Breast03 (NCT06797635)	**HER3-DXd** + pembrolizumab	HER3	TOP1i	Early TNBC	II
KEYMAKER-UO1 (NCT04165798)	**HER3-DXd** + pembrolizumab			1L NSCLC	II

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TABLE 1. Phase II/III Clinical Trials With ADCs in Combination (continued)

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
DV-001 (NCT05911295)	**Disitamab vedotin** + pembrolizumab	HER2	MMAE	1L HER2-expressing UC	III
RC48-C016 (NCT05302284)	**Disitamab vedotin** + toripalimab			1L HER2-expressing UC	III
NCT04609566	**Brentuximab vedotin** + pembrolizumab	CD30	MMAE	NSCLC, melanoma, HNSCC	II
Be6A Lung-02 (NCT06758401)	**Sigvotatug vedotin** + pembrolizumab	Integrin β6	MMAE	1L NSCLC TPS ≥ 50%	III
NCT07197827	**YL242** + pembrolizumab	VEGF	TOP1i	Solid tumors	I/II
BEHOLD-2 (NCT06796907)	**GSK5733584** + dostarlimab	B7-H4	TOP1i	Solid tumors	I/II
NCT03835819	**MIRV** + pembrolizumab	FRα	Microtubule inhibitor	EC	II
NCT03310957	**SGN-LIV1A** + pembrolizumab	LIV-1	MMAE	TNBC	I/II
ADC + small molecules					
HER2CLIMB-04 (NCT04539938)	**T-DXd** + tucatinib	HER2	TOP1i	HER2+ BC	II
NCT04039230	**SG** + talazoparib	Trop2	TOP1i	TNBC	I/II
TROPION-Lung14 (NCT06350097)	**Dato-DXd** + osimertinib	Trop2	TOP1i	1L EGFRm NSCLC	III
TROPION-Lung15 (NCT06417814)	**Dato-DXd** + osimertinib			EGFRm NSCLC	III
M25-287 (NCT07005102)	**Teliso-A** + osimertinib	cMET	TOP1i	1L EGFRm NSCLC	II/III
NCT07323641	**Teliso-V** + osimertinib	cMET	MMAE	EGFRm/cMET+ NSCLC	II
NCT06838273	**Iza-bren** + osimertinib	EGFRxHER3	TOP1i	1L EGFRm NSCLC	III
NCT06157892	**Disitamab vedotin** + tucatinib	HER2	MMAE		
NCT05887609	**MIRV** + olaparib	FRα	Microtubule inhibitor	PSOC	II
BLUESTAR (NCT05123482)	**AZD8205** + saruparib	B7-H4	TOP1i	Solid tumors	I/II
PETRA (NCT04644068)	**T-DXd or Dato-DXd** + saruparib	Trop2/HER2	TOP1i	Solid tumors	I/II
SEACLIFF (NCT07181161)	**AZD0516** + AZD9574	STEAP2	TOP1i	mCRPC	I/II
FONTANA (NCT05797168)	**AZD5335** + bevacizumab	FRα	TOP1i	Solid tumors	I/II
ADC + ADC					
NCT04724018	**SG + EV** with or without pembrolizumab	Trop2 Nectin-4	TOP1i MMAE	UC	I/II
TROPHY-U01 (NCT03547973)	**SG** + **EV** + zimberelimab			1L UC	II
KEYMAKER-U04 (NCT06483334)	**Sac-TMT + EV** with or without pembrolizumab	Trop2 Nectin-4	TOP1i MMAE	UC	I/II
NCT06953089	**DB-1311/BNT324 + DB-1305**	B7-H3 Trop2	TOP1i TOP1i	Solid tumors	II
ADC + mAb					
KRISTINE (NCT02131064)	**T-DM1** + pertuzumab	HER2	Microtubule inhibitor	1L HER2+ BC	III
DESTINY-Breast09 (NCT04784715)	**T-DXd** + pertuzumab	HER2	TOP1i	1L HER2+ BC	III
DESTINY-Ovarian01 (NCT06819007)	**T-DXd** + bevacizumab			1L HER2-expressing OC	III
TroFuse-021 (NCT07318558)	**Sac-TMT** + bevacizumab	Trop2	TOP1i	1L HRD-negative OC	III
InnovaTV 205 (NCT03786081)	**Tiso-V** + bevacizumab	TF	MMAE	CC	I/II
BEHOLD-2 (NCT06796907)	**GSK5733584** + bevacizumab	B7-H4	TOP1i	Solid tumors	I/II
FRAmework-01 (NCT07213804)	**LY4170156** + bevacizumab	FRα	TOP1i	PSOC	III
GLORIOSA (NCT05445778)	**MIRV** + bevacizumab	FRα	Microtubule inhibitor	PSOC	III
LIBRA (NCT07098338)	**Dato-DXd** + ramucirumab with or without rilvegostomig	Trop2	TOP1i	NSCLC	II
RAINFOL-04 (NCT07225270)	**Rina-S** + bevacizumab	FRα	TOP1i	PSOC	III
FONTANA (NCT05797168)	**AZD5335** + bevacizumab	FRα	TOP1i	Solid tumors	I/II

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TABLE 1. Phase II/III Clinical Trials With ADCs in Combination (continued)

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
ADC + bsAb					
ARTEMIDE-Gastric01 (NCT06764875)	**T-DXd** + rilvegostomig + chemotherapy	HER2	TOP1i	1L HER2+/PD-L1+ G/GEJC	III
DESTINY-BTC01 (NCT06467357)	**T-DXd** + rilvegostomig			1L HER2-expressing BTC	III
DESTINY-Endometrial01 (NCT06989112)	**T-DXd** + rilvegostomig			1L HER2-expressing pMMR EC	III
NeoCAST-2 (NCT05061550)	**Dato-DXd** + rilvegostomig	Trop2	TOP1i	Neoadjuvant NSCLC	II
TROPION-Lung10 (NCT06357533)	**Dato-DXd** + rilvegostomig			1L NSCLC	III
TROPION-Lung12 (NCT06564844)	**Dato-DXd** + rilvegostomig			Stage I high-risk NSCLC	III
TROPION-PanTumour03 (NCT05489211)	**Dato-DXd** + rilvegostomig or volrustomig			Solid tumors	II
NCT06827236	**BNT323** + BNT327	HER2	TOP1i	BC	I/II
BLUESTAR (NCT05123482)	**AZD8205** + rilvegostomig	B7-H4	TOP1i	Solid tumors	I/II
NCT06953089	**DB-1311/BNT324** + BNT327	B7-H3	TOP1i	Solid tumors	II
NCT07111520	**BNT326** + BNT327	HER3	TOP1i	NSCLC	I/II
ADC + chemotherapy					
TROPION-Urothelial03 (NCT07129993)	**Dato-DXd** + chemotherapy	Trop2	TOP1i	UC	II/III
ADC sequencing					
ALTER (NCT07151586)	**T-DXd and SG**	HER2 Trop2	TOP1i TOP1i	HER2-low TNBC	II
TRADE DXd (NCT06533826)	**T-DXd and Dato-DXd**	HER2 Trop2	TOP1i TOP1i	BC	II

NOTE. Novel ADC agents or novel combinations are highlighted in bold.
Abbreviations: 1L, first-line; ADC, antibody-drug conjugate; BC, breast cancer; BTC, biliary tract cancer; bsAb, bispecific antibody; CC, cervical cancer; cMET, cellular-metabolic equivalent; Dato-DXd, datopotamab deruxtecan; EC, endometrial cancer; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutant; ES-SCLC, extensive-stage small cell lung cancer; EV, enfortumab vedotin; FRα, folate receptor α; G/GEJC, gastric/gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HER3-DXd, patritumab deruxtecan; HNSCC, head and neck squamous cell carcinoma; HRD, homologous recombination deficiency; I-DXd, ifinatamab deruxtecan; IO, immunotherapy; Iza-bren, izalontamab brengitecan; mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; MIRV, mirvetuximab soravtansine; MMAE, monomethyl auristatin E; NSCLC, non–small cell lung cancer; OC, ovarian cancer; pMMR, mismatch repair–proficient; PSOC, platinum-sensitive ovarian cancer; Rina-S, rinatabart sesutecan; Sac-TMT, sacituzumab tirumotecan; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; Teliso-A, telisotuzumab adizutecan; Teliso-V, telisotuzumab vedotin; TF, tissue factor; Tiso-V, tisotumab vedotin; TNBC, triple-negative breast cancer; TOP1i, topoisomerase-I inhibitor; TPS, tumor proportion score; UC, urothelial cancer; VEGF, vascular endothelial growth factor.

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efficacy, whereas no meaningful benefit has been observed in tumors refractory to immune checkpoint inhibition.

Combination With Small Molecules

The combination of ADCs with tyrosine kinase inhibitors represents a mechanistically rational strategy that leverages intra- and extracellular inhibition to enhance antitumor activity across multiple tumor types.[10] In human epidermal growth factor receptor 2 (HER2)–positive breast cancer (BC), the HER2CLIMB-04 trial is evaluating the addition of tucatinib to T-DXd in pretreated patients. In *EGFR*-mutant NSCLC, the combination of Dato-DXd with osimertinib has emerged as a promising strategy to overcome resistance to single-agent anti-EGFR treatment and is being investigated in the TROPION-Lung14 (ClinicalTrials.gov identifier: NCT06350097) and TROPION-Lung15 (ClinicalTrials.gov identifier: NCT06417814) trials for first-line treatment or pretreated patients, respectively. Telisotuzumab vedotin has been combined with osimertinib in *EGFR*-mutant NSCLC with promising results, but because of high discontinuation rates related to treatment toxicities, the phase III program was withdrawn.

The combination of ADCs with poly-ADP ribose polymerase (PARP) inhibitors, represents a rational strategy with significant preclinical evidence. ADCs with a topoisomerase-I inhibitor (TOP1i) payload, such as SG and T-DXd, induce synthetic lethality when combined with PARP inhibitors as TOP1i generates single-strand DNA breaks and stabilizes TOP1-DNA covalent complexes, which require functional PARP1 for repair.[22] The BLUESTAR (ClinicalTrials.gov identifier: NCT05123482) and PETRA (ClinicalTrials.gov identifier: NCT04644068) trials are among the studies currently

TABLE 2. Clinical Trials With Antibody-Drug Conjugates in the Curative and First-Line Setting

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
TROPION-Breast03 (NCT05629585)	**Dato-DXd** + durvalumab	Trop2	TOP1i	Postneoadjuvant TNBC	III
TROPION-Breast04 (NCT06112379)	**Dato-DXd** + durvalumab			Early TNBC	III
TROPION-Breast05 (NCT06103864)	**Dato-DXd** + durvalumab			1L TNBC	III
TROPION-Breast02 (NCT05374512)	**Dato-DXd**			1L TNBC	III
TROPION-Lung07 (NCT05555732)	**Dato-DXd** + pembrolizumab with or without platinum			1L NSCLC	III
TROPION-Lung08 (NCT05215340)	**Dato-DXd** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
TROPION-Lung14 (NCT06350097)	**Dato-DXd** + osimertinib			1L EGFRm NSCLC	III
TROPION-Lung10 (NCT06357533)	**Dato-DXd** + rilvegostomig			1L NSCLC	III
TROPION-Lung12 (NCT06564844)	**Dato-DXd** + rilvegostomig			Stage I high-risk NSCLC	III
AVANZAR (NCT05687266)	**Dato-DXd** + durvalumab			1L NSCLC	III
ASCENT-05 (NCT05633654)	**SG** + pembrolizumab	Trop2	TOP1i	Postneoadjuvant TNBC	III
ASCENT-04 (NCT05382286)	**SG** + pembrolizumab			1L TNBC	III
ASCENT-03 (NCT05382299)	**SG**			1L TNBC	III
SASCIA (NCT04595565)	**SG**			Postneoadjuvant TNBC	III
EV-302/KEYNOTE-A39 (NCT04223856)	**EV** + pembrolizumab	Nectin-4	MMAE	1L UC	III
EV-103/KEYNOTE-869 (NCT03288545)	**EV** + pembrolizumab			1L UC	I/II
EV-303/KEYNOTE-905 (NCT03924895)	**EV** + pembrolizumab			Early UC	III
EV-304/KEYNOTE-B15 (NCT04700124)	**EV** + pembrolizumab			Early UC	III
KRISTINE (NCT02131064)	**T-DM1** + pertuzumab	HER2	Microtubule inhibitor	1L HER2+ BC	III
KATHERINE (NCT01772472)	**T-DM1**			Postneoadjuvant HER2+ BC	III
MARIANNE (NCT01120184)	**T-DM1** with or without pertuzumab			1L HER2+ BC	III
DESTINY-Breast05 (NCT04622319)	**T-DXd**	HER2	TOP1i	Postneoadjuvant HER2+ BC	III
DESTINY-Breast09 (NCT04784715)	**T-DXd** + pertuzumab	HER2	TOP1i	1L HER2+ BC	III
DESTINY-Breast11 (NCT05113251)	**T-DXd**			Neoadjuvant HER2+ BC	III
DESTINY-Lung04 (NCT05048797)	**T-DXd**			HER2m NSCLC	III
DESTINY-Gastric05 (NCT06731478)	**T-DXd** + pembrolizumab + chemotherapy			1L HER2+ G/GEJC	III
ARTEMIDE-Gastric01 (NCT06764875)	**T-DXd** + rilvegostomig + chemotherapy			1L HER2+/PD-L1+ G/GEJC	III
DESTINY-BTC01 (NCT06467357)	**T-DXd** + rilvegostomig			1L HER2-expressing BTC	III
DESTINY-Lung06 (NCT06899126)	**T-DXd** + pembrolizumab			1L HER2-overexpressing NSCLC	III
DESTINY-Ovarian01 (NCT06819007)	**T-DXd** + bevacizumab			1L HER2-expressing OC	III
DESTINY-Endometrial01 (NCT06989112)	**T-DXd** + pembrolizumab or rilvegostomig			1L HER2-expressing pMMR EC	III
DESTINY-Endometrial02 (NCT06989112)	**T-DXd**			Adjuvant HER2-expressing pMMR EC	III

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TABLE 2. Clinical Trials With Antibody-Drug Conjugates in the Curative and First-Line Setting (continued)

Trial (NCT identifier)	Agent	Target	Payload	Setting	Phase
TroFuse-033 (NCT06952504)	**Sac-TMT** + pembrolizumab	Trop2	TOP1i	pMMR EC	III
MK-2870-012 (NCT06393374)	**Sac-TMT** + pembrolizumab			Early TNBC	III
TroFuse-007 (NCT06170788)	**Sac-TMT** + pembrolizumab			1L NSCLC TPS ≥ 50%	III
MK-2870-023 (NCT06422143)	**Sac-TMT** + pembrolizumab			1L NSCLC	III
TroFuse-017 (NCT06312137)	**Sac-TMT** + pembrolizumab			Early NSCLC	III
TroFuse-011 (NCT06841354)	**Sac-TMT** + pembrolizumab			1L TNBC	III
TroFuse-036 (NCT07216703)	**Sac-TMT** + pembrolizumab			1L CC	III
TroFuse-021 (NCT07318558)	**Sac-TMT** + bevacizumab			1L HRD-negative OC	III
M25-287 (NCT07005102)	**Teliso-A** + osimertinib	cMET	TOP1i	1L EGFRm NSCLC	II/III
DV-001 (NCT05911295)	**Disitamab vedotin** + pembrolizumab	HER2	MMAE	1L HER2-expressing UC	III
RC48-C016 (NCT05302284)	**Disitamab vedotin** + toripalimab			1L HER2-expressing UC	III
NCT04879329	**Disitamab vedotin** + pembrolizumab			HER2-expressing UC	II
Be6A Lung-02 (NCT06758401)	**Sigvotatug vedotin** + pembrolizumab	Integrin β6	MMAE	1L NSCLC TPS ≥ 50%	III
NCT06838273	**Iza-bren** + osimertinib	EGFRxHER3	TOP1i	1L EGFRm NSCLC	III
IZABRIGHT-Breast01 (NCT06926868)	**Iza-bren**			1L TNBC	II/III
FRAmework-01 (NCT07213804)	**LY4170156** + bevacizumab	FRα	TOP1i	PSOC	III
GLORIOSA (NCT05445778)	**MIRV** + bevacizumab	FRα	Microtubule inhibitor	PSOC	III
Duravelo-2 (NCT06225596)	**BT8009 (zelenectide pevedotin)**	Nectin-4	MMAE	UC	III

NOTE. Novel ADC agents or novel combinations are highlighted in bold.
Abbreviations: 1L, first-line; ADC, antibody-drug conjugates; BC, breast cancer; BTC, biliary tract cancer; CC, cervical cancer; cMET, cellular metabolic equivalent; Dato-DXd, datopotamab deruxtecan; EC, endometrial cancer; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutant; EV, enfortumab vedotin; FRα, folate receptor α; G/GEJC, gastric/gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HRD, homologous recombination deficiency; Iza-bren, izalontamab brengitecan; MIRV, mirvetuximab soravtansine; MMAE, monomethyl auristatin E; NSCLC, non–small cell lung cancer; OC, ovarian cancer; pMMR, mismatch repair–proficient; PSOC, platinum-sensitive ovarian cancer; Sac-TMT, sacituzumab tirumotecan; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; Teliso-A, telisotuzumab adizutecan; TNBC, triple-negative breast cancer; TOP1i, topoisomerase-I inhibitor; TPS, tumor proportion score; UC, urothelial cancer.

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evaluating TOP1i-based ADCs in combination with PARP inhibitors in various tumor types.

Combination With Monoclonal Antibodies

The combination of ADCs with traditional monoclonal antibodies targeting complementary pathways offers the potential for synergistic antitumor effects. Antibody combinations can enhance receptor clustering, accelerate internalization, and improve payload delivery while maintaining antibody-dependent cellular cytotoxicity through Fc receptor engagement.[23] The FDA has approved the combination of T-DXd plus pertuzumab for the first-line treatment of patients with advanced, HER2-positive BC, based on the results of the DESTINY-Breast09 trial, which showed superior survival outcomes in comparison with the standard-of-care arm of docetaxel, trastuzumab, and pertuzumab.[24] Nonetheless, the contribution of pertuzumab to the activity of first-line T-DXd is still not clear. The addition of pertuzumab to T-DXd seemed to increase the objective response rate (ORR; 82.0% [80% CI, 73.1 to 88.8]) in comparison with T-DXd monotherapy (77.3 [80% CI, 70.0 to 83.6]) in the phase Ib/II DESTINY-Breast07 trial.[25] Nonetheless, DESTINY-Breast09 was not designed to answer this question, and data regarding the T-DXd monotherapy arm are still not available.

Currently, various ADC-bevacizumab combinations are being tested in phase III trials for gynecologic cancers, and a wide range of bispecific antibodies (bsAbs) are being tested in combination with ADCs (Table 1).

Sequencing Strategies: ADC After ADC

As multiple ADCs became available for patients with BC, determining optimal sequencing strategies has emerged as one of the most pressing clinical questions, with real-world evidence revealing substantial declines in efficacy with the use of a second sequential ADC.[26] Nonetheless, retrospective studies have been inconclusive regarding the optimal sequencing strategies. Cross-resistance between different ADCs is primarily mediated by the payload rather than the

antibody.[27-29] Cross-resistance because of loss of antigen expression, impaired internalization, or altered antibody trafficking is less frequently described.[30]

In a systematic review including more than 2,900 patients with advanced BC treated with sequential ADCs, median PFS significantly decreased with the second ADC in HER2-low tumors, where all approved ADCs include a TOP1i, but it was preserved in the HER2-positive setting, particularly when T-DXd was followed by T-DM1, which uses a different payload. Bridging traditional chemotherapy between ADCs demonstrated higher efficacy than direct sequencing of ADCs with similar payloads in some cohorts.[12]

Strategies to overcome the cross-resistance of ADCs, such as bridging two ADCs with a traditional chemotherapy regimen (the sandwich method), are still not clearly defined.[11] Translational research will be fundamental to define the optimal sequencing. Moreover, whether prior exposure to specific traditional cytotoxic agents—such as irinotecan before a TOP1i-based ADC—affects ADC activity remains unknown as no clinical data exist to guide payload selection in this context. In DESTINY-PanTumour02, T-DXd was associated with an ORR of 4% in the cohort of pancreatic tumors, by far the lowest of any cohort, possibly related to prior exposure to irinotecan.[31]

Genomic biomarkers are emerging as potential tools for guiding sequencing decisions. *PTEN* loss has been associated with de novo resistance to T-DXd but not SG,[32] whereas *RB1* alterations have been linked to superior PFS with sequential ADC therapy. These findings, although inconclusive, highlight the need for biomarker-driven patient selection to optimize sequential ADC outcomes.[33]

Ongoing prospective studies, such as TRADE-DXd (ClinicalTrials.gov identifier: NCT06533826), are designed to address these questions directly.

BC represents a paradigmatic disease model in which multiple ADCs with overlapping targets and payloads are approved, allowing us to explore the key principles of cross-resistance and sequencing in a real-world setting. These principles are likely to be applicable to other solid tumors as the ADC landscape continues to expand.

INTEGRATING ADCs INTO FIRST-LINE AND CURATIVE STRATEGIES

Treatment Positioning: Methodological Challenges

Given the efficacy observed with ADCs in pretreated patients with metastatic solid tumors, many clinical trials are now evaluating their integration into first-line and potentially curative settings (Table 2). This strategy is based on the principle that the sooner, the better and aims to ensure that a greater proportion of patients receive effective therapy, particularly in light of the attrition observed across successive lines of treatment: delaying the introduction of an effective drug may result in missed therapeutic opportunities for patients who ultimately become ineligible for subsequent systemic therapy, especially in the case of aggressive tumors.[34]

The most rigorous method to assess the impact of early frontline drug use is through an overall survival (OS)–powered trial with crossover permitted. However, such designs require larger sample sizes and are complicated by heterogeneity in postprogression treatment, including variable global access to subsequent therapies in international studies. Indeed, although clinical trials should be powered to detect improvements in patient-centric end points such as OS and/or quality of life (QoL), especially when investigating treatment positioning, this standard is infrequently met, further complicating the interpretation of trial results. In the metastatic BC setting, for example, fewer than 10% of randomized trials have used OS or QoL as the primary end point.[35] In this context, PFS2, which captures outcomes across both first- and second-line treatment, has been proposed as a potential surrogate end point when crossover is permitted.[36]

In the absence of crossover and when the investigational agent is not approved or accessible in subsequent lines of therapy, as has occurred in some international trials, the clinical question shifts from "now or later?" to "now or never?" This issue arises particularly when a first-line trial is initiated shortly after the trial evaluates the same agent in later lines, resulting in overlapping enrollment periods and the absence of protocol amendments to incorporate crossover once the agent enters routine practice in subsequent settings. With the acceleration of oncologic drug development, this challenge has become increasingly relevant. Notably, between 2013 and 2018, 17% of anticancer drugs were approved on the basis of trials that used comparators later considered suboptimal.[37]

These challenges are even more pronounced in the curative setting, where demonstrating an OS benefit requires prolonged follow-up. Shorter-term end points, such as disease-free survival (DFS), may expedite readouts but do not establish whether more patients are ultimately cured or whether effective therapy is simply delivered earlier in the disease course, unless their validity as surrogate end points for OS is rigorously demonstrated.[38,39] Moreover, access to the same investigational therapy in the metastatic setting after relapse is often inconsistent, which may further confound the assessment of long-term, patient-centered outcomes.

Urothelial Cancer and Enfortumab Vedotin

Metastatic urothelial carcinoma was the first solid tumor where an ADC, namely EV, was integrated into earlier lines of therapy. The first-line, phase III trial evaluating EV plus pembrolizumab (EV-302) was designed based on several converging observations: in the phase III EV-301 trial, EV

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improved OS in patients previously treated with platinum-based chemotherapy and ICIs, establishing its activity in later lines.[40] At the same time, approximately 30% of patients with advanced disease do not receive second-line therapy, and preclinical and early clinical data suggested biological and therapeutic synergy between EV and pembrolizumab.[41]

The EV-302 trial compared EV plus pembrolizumab with platinum-based chemotherapy in untreated, cisplatin-eligible patients with metastatic urothelial carcinoma.[18] The coprimary end points were PFS and OS. Among 886 enrolled patients, at a median follow-up of 17.2 months, the combination significantly prolonged median PFS (12.5 *v* 6.3 months; hazard ratio [HR], 0.45 [95% CI, 0.38 to 0.54]) and median OS (31.5 *v* 16.1 months; HR, 0.47 [95% CI, 0.38 to 0.58]), without detriment in QoL.[42]

Interpretation of these results, however, warrants consideration of trial design. Only approximately 30% of patients in the chemotherapy arm received maintenance avelumab, which is considered a component of contemporary standard care, and crossover to EV was not mandated; only about 25% of patients in the control arm subsequently received the drug.[41] Nevertheless, the study was powered for OS, and in the context of substantial first-to-second-line attrition, this combination should be considered for most of the patients in this setting, after the approval by regulatory authorities in the United States and Europe. Instead, among patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy, EV combined with pembrolizumab was approved on the basis of phase 1b-2 data demonstrating high response rates and durable responses.[43]

The strategy has also been extended to the perioperative setting in patients with nonmetastatic, muscle-invasive bladder cancer (MIBC). In cisplatin-ineligible patients or those declining cisplatin, the phase III KEYNOTE-905/EV-303 trial compared perioperative EV plus pembrolizumab with radical cystectomy and pelvic lymph node dissection alone.[19] After random assignment of 344 patients and a median follow-up of 25.6 months, the combination significantly improved median event-free survival (not reached *v* 15.7 months; HR, 0.40 [95% CI, 0.28 to 0.57]), median OS (not reached *v* 41.7 months; HR, 0.50 [95% CI, 0.33 to 0.74]), and pathologic complete response rates (57.1% *v* 8.6%). Grade 3 or higher adverse events (AEs) of special interest included severe skin reactions, observed in approximately 11% of patients. To our knowledge, these findings represent the first demonstration of improved perioperative outcomes beyond surgery alone in this population. In cisplatin-eligible patients, the phase III KEYNOTE-B15/EV-304 trial compared perioperative EV plus pembrolizumab with neoadjuvant cisplatin plus gemcitabine followed by radical cystectomy in 808 patients with MIBC. EV plus pembrolizumab significantly improved all survival end points as the 24-month EFS rate was 79.4% versus 66.2% (HR, 0.53 [95% CI, 0.41 to 0.70]), the 24-month OS rate was 86.9% versus 81.3% (HR, 0.65 [95% CI, 0.48 to 0.89]), and the pCR rate was 55.8% versus 32.5%.[44]

TNBC and Anti-Trop2 ADCs

In patients with metastatic TNBC, the evaluation of anti-Trop2 ADCs in the first-line setting was informed by the survival benefit of SG in patients with previously treated disease and by clinically meaningful attrition between first- and second-line therapies, which exceeds 10% overall and approaches 25%-30% in some series.[34,45,46] On this basis, SG and Dato-DXd have been investigated in patients with previously untreated metastatic TNBC, either in combination with pembrolizumab in PD-L1–positive disease or as monotherapy in patients not candidates for PD-(L)1 inhibition.

In PD-L1–positive metastatic TNBC, the phase 3 ASCENT-04 trial compared SG plus pembrolizumab with chemotherapy plus pembrolizumab.[20] Among 443 patients, the median PFS was 11.2 months for SG plus pembrolizumab and 7.8 months for chemotherapy plus pembrolizumab (HR, 0.65 [95% CI, 0.51 to 0.84]). OS data remain immature although crossover to second-line SG was permitted. Overall QoL was maintained, with reduced symptom burden and improved functioning, whereas nausea, vomiting, and diarrhea were more frequent, consistent with the known safety profile of SG.[47]

The absolute median PFS gain of 3.4 months warrants contextual interpretation.[48] The benefit appeared to be largely confined to patients with recurrent disease after a disease-free interval that exceeds 12 months, most of whom (95%) had received neoadjuvant chemotherapy without perioperative pembrolizumab, an approach that does not reflect contemporary standards. By contrast, patients with de novo metastatic TNBC derived limited apparent benefit (HR, 0.89 [95% CI, 0.59 to 1.34]).

In patients not candidates for PD-(L)1/PD-L1 blockade, ASCENT-03 and TROPION-Breast02 evaluated SG and Dato-DXd, respectively, in previously untreated metastatic TNBC. ASCENT-03 enrolled 558 patients with a treatment-free interval of >6 months, allowed crossover to SG, and used PFS as the primary end point.[49] At a median follow-up of 13.2 months, SG improved median PFS as compared with chemotherapy (9.7 *v* 6.9 months; HR, 0.62 [95% CI, 0.50 to 0.77]), with 61% of patients in the control group receiving SG at progression. TROPION-Breast02 included 644 patients irrespective of the treatment-free interval, did not mandate crossover, and specified both PFS and OS as primary end points.[50] At a median follow-up of 27.5 months, Dato-DXd improved median PFS (10.8 *v* 5.6 months; HR, 0.57 [95% CI, 0.47 to 0.69]) and OS (23.7 *v* 18.7 months; HR, 0.79 [95% CI, 0.64 to 0.98]); approximately 30% of patients in the control arm subsequently received an ADC. Toxic effects differed between agents, with neutropenia predominating with SG and mucositis and stomatitis more frequently observed with Dato-DXd.

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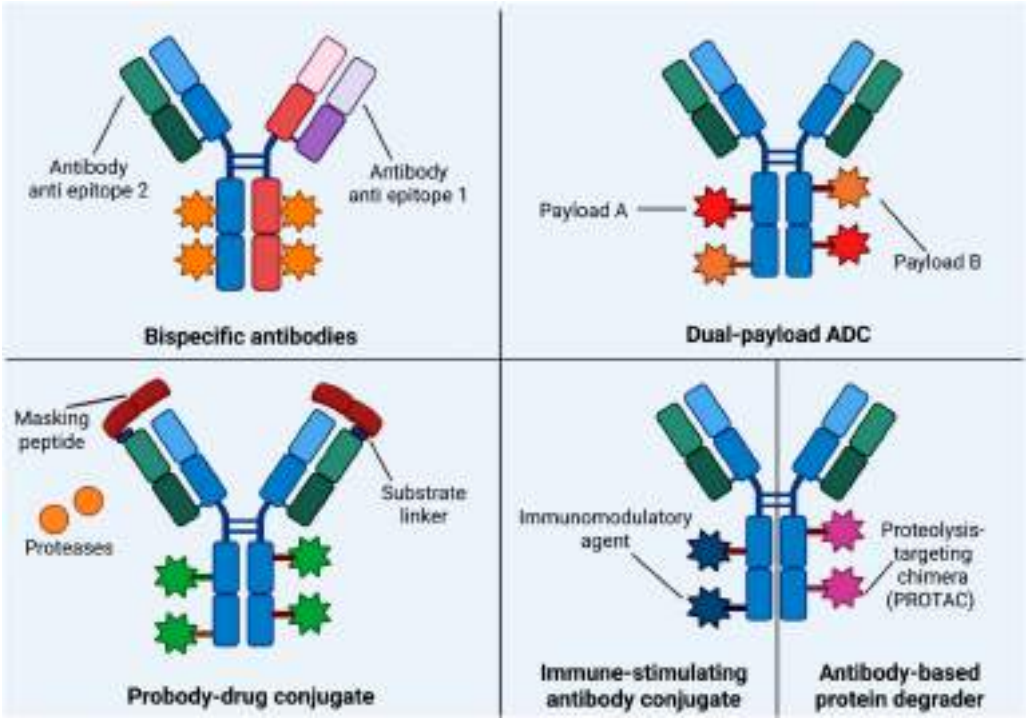

FIG 1. Next-generation antibody-drug conjugates. Created using BioRender.com/8ah0hdp. ADC, antibody-drug conjugate; PROTAC, proteolysis-targeting chimera.

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Collectively, these data support earlier integration of anti-Trop2 ADCs in metastatic TNBC. However, interpretation should account for trial design, crossover policies, access to subsequent therapies, and evolving standards of care. Selection between SG and Dato-DXd should consider treatment-free interval, toxicity profile, and dosing schedule (SG on days 1 and 8 every 3 weeks; Dato-DXd on day 1 every 3 weeks), with individualized discussion.

Anti-Trop2 ADCs are also under evaluation in early-stage TNBC, both in the neoadjuvant setting and in patients with residual disease after neoadjuvant therapy (Table 2).

HER2-Positive Breast Cancer and Anti-HER2 ADCs

T-DM1 was the first ADC approved for the treatment of solid tumors. In patients with previously treated, trastuzumab-resistant, HER2-positive BC, T-DM1 improved outcomes in both the metastatic (EMILIA and TH3RESA trials) and post-neoadjuvant early-stage settings (KATHERINE trial).[51-53] However, T-DM1 did not demonstrate superiority over taxanes plus trastuzumab in untreated metastatic disease (MARIANNE trial) or over standard neoadjuvant chemotherapy plus trastuzumab in early-stage disease (KRISTINE trial), findings that have been partly attributed to the reduced efficacy of T-DM1 in the case of HER2 heterogeneity.[54-56]

T-DXd, a next-generation ADC with a higher DAR and a bystander effect, demonstrated improved PFS and OS as compared with T-DM1 in the second-line metastatic setting, providing the rationale for evaluation in patients with untreated disease.[57] In the phase III DESTINY-Breast09 trial, 770 patients with previously untreated metastatic HER2-positive BC were randomly assigned to T-DXd plus pertuzumab or to the CLEOPATRA regimen (docetaxel, trastuzumab, and pertuzumab, followed by trastuzumab-pertuzumab maintenance), with no mandated crossover to T-DXd and PFS as the primary end point. At a median follow-up of 29.2 months, the median PFS was prolonged from 27 to 41 months (HR, 0.56 [95% CI, 0.44 to 0.71]), the longest median PFS reported to date in an unselected first-line HER2-positive metastatic population. OS data remain immature.[24]

Interpretation of these findings requires consideration of tolerability and treatment strategy. In DESTINY-Breast09, T-DXd plus pertuzumab was administered until disease progression or unacceptable toxicity, whereas the CLEOPATRA regimen transitions to chemotherapy-free trastuzumab-pertuzumab maintenance, which nearly 30% of patients receive for more than 35 months. In DESTINY-Breast09, 21% of patients discontinued T-DXd because of treatment-emergent AEs and drug-related ILD or pneumonitis occurred in 12% of patients, with two treatment-related deaths. Although no difference in time to deterioration of global QoL was observed, patient-reported nausea, vomiting, appetite loss, and constipation were more frequent with T-DXd plus pertuzumab.[94] In a disease characterized by a low first-to-second-line attrition rate (approximately 10%) and the opportunity to intensify the maintenance with palbociclib or tucatinib, the

decision to use T-DXd up front should therefore be individualized according to disease burden, central nervous system involvement, the presence of *PIK3CA* mutations, treatment-free interval in the case of recurrent disease, and patient preferences.[34,58-60]

T-DXd has also been evaluated in the postneoadjuvant setting in 1,635 patients with HER2-positive BC with residual invasive disease and node-positive disease at surgery or inoperable disease at diagnosis, in the phase III, DESTINY-Breast05 trial.[61] In this trial, at a median follow-up of 30 months, T-DXd significantly improved invasive DFS as compared with T-DM1 (HR, 0.47 [95% CI, 0.34 to 0.66]). However, drug-related ILD occurred more frequently with T-DXd (9.6% *v* 1.6%), including two fatal cases. Nevertheless, given the high baseline risk of recurrence in this selected population, these data support the intensification with T-DXd.

In the neoadjuvant setting, the phase III DESTINY-Breast11 trial compared T-DXd alone or T-DXd followed by paclitaxel, trastuzumab, and pertuzumab (T-DXd-THP), with dose-dense doxorubicin-cyclophosphamide followed by THP (ddAC-THP), in patients with high-risk HER2-positive disease.[62] Enrollment in the T-DXd–alone arm was discontinued for futility. Pathologic complete response rates (the primary end point) were 67% with T-DXd-THP, compared with 56% with ddAC-THP (absolute difference, 11% [95% CI, 4 to 8]). Although the primary end point was met, event-free survival data remain immature (HR, 0.56 [95% CI, 0.26 to 1.17]) and its interpretation is limited since only 55% of patients with residual disease received post-neoadjuvant T-DM1. Moreover, the lack of validated surrogacy between pathologic complete response and OS in this context tempers conclusions regarding long-term benefit.[39]

Collectively, anti-HER2 ADCs are reshaping both metastatic and early-stage HER2-positive BC management. However, the optimal positioning of T-DXd requires careful consideration of toxicity, sequencing, risk of attrition, and patient preferences.

NEXT-GENERATION ADCs: BISPECIFIC AND DUAL-PAYLOAD DESIGNS IN ONCOLOGY

The Need for Novel ADC Designs

Despite their remarkable clinical success across multiple tumor types in various settings, ADCs are understandably characterized by limitations that necessitate innovative designs. Overall, more than 80% of ADCs that have entered clinical trial were terminated in phase I or II, highlighting the need for innovative development strategies.[2] Current challenges include tumor heterogeneity, drug resistance, suboptimal internalization and on-target off-tumor toxicities.

Most approved ADCs rely on a single tumor-associated antigen (TAA) and deliver highly potent cytotoxic payloads, making their activity strongly dependent on homogeneous target expression and efficient intracellular trafficking.[2] In clinical practice, however, intratumoral heterogeneity, antigen downregulation, poor receptor internalization, and acquired resistance mechanisms frequently limit durability of response and premature linker cleavage enhances systemic toxicities narrowing the therapeutic index.

Moreover, the extension of clinical trials regarding ADCs into earlier treatment lines and potentially curative settings raises new requirements in terms of safety and long-term tolerability. These challenges have led to the development of next-generation ADC designs to move beyond the traditional single-payload and single-antibody compounds. Innovative strategies, including multispecific targeting to overcome heterogeneity and improve tumor selectivity, dual-payload delivery to overcome drug resistance, and alternative conjugate platforms, aim to broaden the functional scope of payloads. Collectively, these advances position ADCs as increasingly sophisticated drug systems.[3]

Bispecific ADCs

bsAbs can simultaneously engage two different TAAs or epitopes (Fig 1). This innovative design has been applied to next-generation ADCs as various bsADCs are currently under early or late-stage clinical development. Potential advantages of bsADCs include enhanced specificity through dual-antigen targeting, which reduces off-target effects in normal tissues expressing only one antigen. Furthermore, bsADCs can target compensatory signaling pathways simultaneously, such as EGFR × HER3, preventing or delaying resistance mechanisms that emerge with single-target inhibition. Preclinical studies demonstrated that bispecific constructs achieve comparable or superior efficacy to combinations of two monospecific ADCs, while simplifying manufacturing and dosing regimens.[3,63,64]

Various anti-HER2 biparatopic ADCs (ie, targeting two epitopes of the same protein) have been tested in phase I studies.[63] Biparatopic targeting induces the clustering of receptors, which are more efficiently internalized in target cells.[65] The first bsADC with published clinical data has been zanidatamab zovodotin (ZW49), a bsADC based on the bsAb zanidatamab. In a phase I trial in HER2-positive advanced tumors, the ORR was 31% with the recommended phase II dose and 67% of patients received prior HER2-targeted therapies. The most common AEs were keratitis (44%), alopecia (26%), and diarrhea (24%).[66] MEDI4276 is another anti-HER2 biparatopic ADC, which demonstrated an ORR of 9.4% in a phase I/II trial on HER2-positive breast or gastric cancers, with a median of eight prior lines of treatment. The most common AEs were nausea (59.6%), fatigue (44.7%), AST increased (42.6%), and vomiting (38.3%).[67] The biparatopic anti-HER2 ADC JSKN003 has been tested in multiple phase I trials. In platinum-resistant ovarian cancer, it demonstrated an ORR of 64.4%, reaching as high as 72.2% for HER2-expressing tumors, the most common AE was

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nausea (39.1%), and grade 1/2 ILD was observed in 8.7% of patients.[68] JSKN003 is also being tested in phase II and III trials in gastric (ClinicalTrials.gov identifier: NCT06998771), breast (ClinicalTrials.gov identifier: NCT06846437), platinum-resistant ovarian (ClinicalTrials.gov identifier: NCT06751485), and colorectal cancers (ClinicalTrials.gov identifier: NCT07384377). Neoadjuvant TQB2102, another drug in the class of biparatopic anti-HER2 ADCs, has been investigated in monotherapy in stage II to III HER2-positive BC, proving a pathologic complete response rate between 57% and 69% at various treatment schedules.[69] Various phase III trials are ongoing regarding TQB-2102. Although data are lacking, novel anti-HER2 ADCs may be considered in the post–T-DXd setting, especially in the case of agents with non–cross-resistant payloads, pending the demonstration of their efficacy in prospective clinical trials.

A biparatopic anti-METxMET ADC has been tested in MET-overexpressing tumors, but the study has been terminated early (ClinicalTrials.gov identifier: NCT04982224). An anti-FRαxFRα ADC is being tested in patients with recurrent gynecologic tumors (ClinicalTrials.gov identifier: NCT05527184).

Clinical development has also accelerated rapidly for dual TAA-targeting ADCs. Izalontamab brengitecan (BL-B01D1) is a first-in-class EGFRxHER3 bsADC linked to a TOP1i, which showed encouraging data in phase I trials. The most common grade 3/4 AEs associated with the drug were hematologic.[70] In a phase III trial in patients with nasopharyngeal cancer, it showed superior activity over standard-of-care chemotherapy.[71] Promising data were also published for patients with *EGFR*-mutant NSCLC,[72,73] UC,[74] and esophageal squamous cell carcinoma,[75] and it is currently being tested in more than 30 phase II and III trials, including first-line PD-L1–negative TNBC (ClinicalTrials.gov identifier: NCT06926868) and first-line *EGFR*-mutant NSCLC (ClinicalTrials.gov identifier: NCT06838273). Other anti-EGFR bsADCs, such as AZD9592 (ClinicalTrials.gov identifier: NCT05647122) and M1231 (ClinicalTrials.gov identifier: NCT04695847), are also being investigated.[63]

Additional candidates targeting HER2/HER3 and TROP2/HER3 combinations have shown breakthrough activity in TNBC and other challenging tumors, as well as bsADCs that simultaneously target HER2 and fast-turnover receptors, such as CD63, PRLR, and APLP2.[76]

Dual-Payload ADCs

Dual-payload ADCs incorporate two distinct therapeutic payloads on the same antibody scaffold, enabling synergistic mechanisms of action and potentially reducing resistance mechanisms because of tumor heterogeneity that limit the efficacy of single-payload ADCs (Fig 1).[77-79] By delivering two distinct payloads to the same cancer cell, these compounds can simultaneously target different cellular vulnerabilities, such as combining microtubule inhibitors with DNA-damaging agents or pairing cytotoxic drugs with immune-stimulating molecules.[80] The conjugation strategies include dual-site conjugation with traditional linear linkers or single-site conjugation with a branching linker equipped with orthogonal reaction handles.[78] Nonetheless, other than synergistic antitumor effects, dual-payload ADCs can also cause synergistic toxicities.

A HER2-targeted dual-payload ADC combining monomethyl auristatin E (MMAE) and deruxtecan achieved superior cytotoxicity against HER2-positive cells compared with T-DXd, with enhanced tumor suppression in xenograft models.[81] Similarly, a CD276/B7-H3–targeted dual-payload ADC combining a cytotoxic agent with an immunoregulating Toll-like receptor 7/8 (TLR7/8) agonist demonstrated both direct tumor cell killing and immune activation in TNBC models.[80]

KH815 is a novel dual-payload anti-Trop2 ADC platform that includes an optimized linker design that leads to the sequential delivery of triptolide (RNA polymerase-II inhibitor) and exatecan (TOP1i). The release of triptolide leads to the downregulation of the stress response protein Hsp70 and efflux pump P-gp in tumor cells, enhancing drug sensitivity, followed by gradual delivery of exatecan. The sequential release strategy, where one payload sensitizes cells before the second is released, represents an innovative approach to maximize therapeutic synergy while maintaining acceptable safety profiles.[82]

Novel ADCs

Other than dual-targeting or dual-payload ADCs, novel designs are currently being investigated in next-generation ADCs.[3]

Peptide-drug conjugates offer advantages over antibody-based platforms, including smaller size enabling superior tumor penetration, reduced immunogenicity, and simplified manufacturing.[83-85] Despite advantages in tissue penetration and cost, peptide-drug conjugates face significant limitations, such as rapid renal clearance, metabolic instability, and limited oral bioavailability.[86]

Probody-drug conjugates feature conditionally active antibodies, which, unlike traditional antibodies, could reduce on-target off-tumor toxicities (Fig 1).[3,87,88] These compounds are engineered with a masked antigen-binding site that is selectively activated by tumor-associated proteases or pH-dependent conformational changes, thereby increasing tumor specificity and reducing off-tumor toxicity.

Immune-stimulating antibody conjugates (ISACs) replace cytotoxic payloads with immunomodulatory agents that interact with pattern-recognition receptors, such as TLR7/8 agonists or stimulator of interferon genes agonists, shifting cold tumors into immunologically active microenvironments (Fig 1).[3,89-91] ISACs activate dendritic cells and promote antitumor T-cell responses while maintaining

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antibody-mediated targeting. However, clinical development has encountered challenges including systemic toxicity, cytokine release syndrome, and antidrug antibody formation.

Antibody-based protein degraders (DACs) are linked to a proteolysis-targeting chimera (PROTAC) instead of a traditional cytotoxic payload, exploiting the promising activity shown by targeted protein degradation (Fig 1).[3,92,93] PROTACs are bifunctional drugs which simultaneously bind to a protein of interest and an E3 ubiquitin ligase, thus triggering targeted degradation of oncoproteins by the ubiquitin-proteasome system. DACs are designed to target cytosolic proteins and are currently being investigated in the preclinical stage.[3] While promising, optimizing pharmacokinetics represents a significant challenge for DACs.

CONCLUSIONS

ADCs have undergone a rapid evolution from a niche therapeutic concept to a broadly applicable and clinically validated drug class across multiple tumor types. Their success reflects decades of progress in antibody engineering, linker chemistry, and payload design, which together have enabled selective delivery of highly potent cytotoxic agents and substantially improved their therapeutic index. As a result, ADCs are increasingly evaluated and adopted in earlier disease settings, including first-line and potentially curative strategies.

At the same time, the expanding clinical application of ADCs has exposed important limitations. Tumor heterogeneity, modulation of target expression, and payload-driven resistance mechanisms frequently limit the durability of response. In addition, on-target off-tumor toxicities and cumulative AEs have emerged as critical challenges, particularly as ADCs are administered for longer durations or in populations with curative intent. These considerations underscore the need for careful patient selection, longitudinal toxicity monitoring, and a deeper understanding of ADC pharmacology beyond traditional paradigms.

Combination strategies have demonstrated the potential to enhance antitumor activity and overcome resistance. Sequencing strategies, especially in disease settings where multiple ADCs with overlapping payloads are available, remain an unresolved clinical challenge, highlighting the importance of translational research and biomarker development to guide treatment decisions.

Looking ahead, next-generation ADC designs, including bispecific and dual-payload constructs, offer the opportunity to directly address key limitations of current platforms, such as antigen heterogeneity and adaptive resistance. Alongside emerging approaches such as conditionally activated ADCs and immune-stimulating compounds, these innovations signal a shift toward increasingly sophisticated ADC designs.

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Immunotherapy in Localized Colorectal Cancer: Current Practice and Future Directions

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OVERVIEW

Immune checkpoint inhibitors (ICIs) have fundamentally transformed the treatment landscape for localized colorectal cancer (CRC), particularly for the mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) subgroups. This review evaluates the current clinical evidence and evolving paradigms of immunotherapy in early-stage CRC. In localized MSI-H colon and rectal cancers, neoadjuvant immunotherapy has demonstrated unprecedented efficacy, yielding near-universal major pathologic responses and high rates of pathologic complete responses. For MSI-H rectal cancer, these deep and sustained clinical complete responses have established nonoperative management as a viable, organ-preserving standard of care for highly selected patients undergoing rigorous multidisciplinary surveillance. Despite these rapid advancements, critical questions remain regarding optimal regimen selection, treatment duration, and the integration of circulating tumor DNA (ctDNA) for molecular residual disease monitoring. Although ctDNA is a promising dynamic biomarker, it currently cannot replace definitive pathologic assessment outside of clinical trials. Furthermore, extending the benefits of immunotherapy to the majority of patients with microsatellite-stable (MSS) CRC represents a significant unmet clinical need. Current evidence for ICIs in localized MSS disease remains limited, although investigational combination strategies incorporating radiation, chemotherapy, and novel immune modulators are yielding hypothesis-generating signals. Future progress hinges on precision de-escalation protocols and biomarker-driven, response-adapted trial designs to validate surrogate end points and optimize patient outcomes across all localized CRC subtypes.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have reshaped colorectal cancer (CRC) care, but their impact has been most transformative in the biologically distinct subgroup of mismatch repair-deficient (dMMR) or microsatellite instability high (MSI-H) tumors. In contrast to microsatellite stable (MSS), MSI CRCs are characterized by multiple frameshift mutations resulting in high mutational burden,[1-4] providing the biologic and clinical rationale for their evaluation in earlier-stage settings.

Mismatch repair deficiency is present in 15%-20% of stage II to III CRC.[2] Historically, management of localized CRC has relied on surgery with risk-adapted chemotherapy or multimodality therapy for rectal cancer. However, early-phase neoadjuvant studies have reported unprecedented rates of major pathologic response and pathologic complete response (pCR) following short-course immunotherapy in resectable MSI colon and rectal cancers.[3-5] In rectal cancer, these responses have enabled organ-preserving strategies in selected patients,[6] and recent studies have also raised critical questions regarding the optimal approach (monotherapy ICI *v* doublet ICI), duration, and timing (whether to be given before or after surgery of ICI therapy).[7,8] Simultaneously, extending immunotherapy benefit to MSS CRC, where responses remain limited, remains a major unmet need.[9,10] In this review, we examine the current evidence for immunotherapy in localized CRC, focusing on MSI colon and rectal cancer, perioperative strategies, nonoperative management, and evolving approaches in MSS disease.

IMMUNOTHERAPY IN THE TREATMENT OF LOCALIZED MSI COLORECTAL CANCER

Rationale for Immunotherapy in MSI CRC in the Neoadjuvant Versus Adjuvant Setting

Neoadjuvant immunotherapy offers distinct immunologic advantages in MSI CRC. With the primary tumor in situ, sustained antigen exposure promotes expansion of tumor-specific $CD8^+$ T-cell clones and the establishment of systemic immune memory, a process often referred to as immune priming.[11] By contrast, adjuvant immunotherapy is

PRACTICAL APPLICATIONS

- Microsatellite instability-high (MSI-H) colorectal cancer (CRC) is uniquely immunogenic. High tumor mutational burden and an inflamed tumor microenvironment render these tumors highly responsive to PD-1–based immune checkpoint blockade.
- Universal mismatch repair testing is essential in all newly diagnosed localized CRCs. Identification of MSI status should occur early because it directly influences therapeutic strategy and eligibility for immunotherapy-based approaches.
- Neoadjuvant immunotherapy produces unprecedented pathologic response rates in localized MSI colon cancer. Major pathologic response rates approach 95%-100%, with pathologic complete responses (pCRs) in approximately two thirds of patients in early-phase trials.
- Organ preservation is emerging as a viable strategy in MSI rectal cancer. Sustained clinical complete responses after PD-1 blockade have enabled nonoperative management in selected patients under rigorous multidisciplinary surveillance.
- The optimal integration of immunotherapy remains undefined. Key questions include regimen selection (single-agent vs dual checkpoint blockade), treatment duration, timing relative to surgery, and the role of perioperative versus neoadjuvant-only strategies.
- Circulating tumor DNA is a promising but imperfect biomarker. ctDNA may refine risk stratification and guide adjuvant decision making but currently cannot replace pathologic assessment or justify omission of surgery outside clinical trials.
- Microsatellite-stable (MSS) disease remains a major unmet need. Immunotherapy alone has limited activity in localized MSS CRC, and combination strategies with chemotherapy, radiation, or novel immune modulators remain investigational.
- Future progress will depend on biomarker-driven, response-adapted strategies. Validation of pCR and molecular residual disease as surrogate end points may enable rational de-escalation and precision perioperative immunotherapy approaches.

administered in an antigen-depleted environment following tumor resection. Although this strategy may target micrometastatic disease, it may not generate the same magnitude of immune activation achieved when the intact tumor serves as a continuous source of neoantigen. A proposed management algorithm for locally advanced MSI CRC, developed in concordance with National Comprehensive Cancer Network (NCCN) guidelines and reflecting the authors' current opinion, is shown in Figure 1, where dashed boxes indicate areas where evidence continues to evolve.

Neoadjuvant Immunotherapy in Localized MSI Colorectal Cancer

Multiple studies now suggest that neoadjuvant immune checkpoint inhibition has produced deep responses in resectable MSI-H colon cancer. In the NICHE study, 4 weeks of neoadjuvant nivolumab plus ipilimumab produced pathologic responses in 100% of MSI-H tumors, with major pathologic response (MPR) in 97% and pCR in 69%.[5] NICHE-2 further confirmed these findings in a larger cohort of stage II to III MSI-H colon cancer. Following two doses of nivolumab and one dose of ipilimumab, 98% of patients achieved MPR and approximately two-thirds achieved pCR, with no recurrences reported at a median follow-up of over 3 years.[4] Grade 3 to 4 immune-related adverse events occurred in approximately 4% of patients, supporting the feasibility and safety of this strategy.

Similarly, the randomized phase Ib NEOSHOT trial[12] demonstrated high response rates with dual PD-1/Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4) checkpoint blockade (sintilimab plus IBI310), achieving MPR in 95% and pCR in 68% with the majority also having adjuvant ICI of 3 months of IBI310-sintilimab ± adjuvant chemotherapy versus surgery and adjuvant chemotherapy for cT4 or N+ resectable cancers.

Complementing this, single-agent PD-1 blockade has also demonstrated substantial activity. NEOPRISM-CRC evaluated neoadjuvant pembrolizumab administered for nine weeks in high-risk stage II to III MSI-H CRC (stratified by tumor mutational burden (TMB) as an exploratory biomarker, although this ended up not being a clinically useful stratification factor). Single-agent immunotherapy achieved pCRs observed in 59%, confirming that monotherapy may be sufficient for selected patients.[13] Ludford et al reported that 6 months of preoperative pembrolizumab across localized MSI-H solid tumors achieved MPR in 93% and pCR in 79% of CRCs, with durable disease control and no early recurrences observed.[3] Key studies of neoadjuvant immunotherapy in localized dMMR/MSI-H CRC are summarized in Table 1.

Perioperative Immunotherapy in Localized MSI Colorectal Cancer

Trials such as NICHE-2,[4] NICHE-3,[15] RESET-C,[16] NEOPRISM-CRC,[13] and NEOSHOT 3 (ClinicalTrials.gov identifier: NCT05890742) evaluate short-course neoadjuvant immune checkpoint blockade followed by surgery with no planned postoperative immunotherapy, leveraging immune priming in the presence of intact tumor antigen. By contrast,

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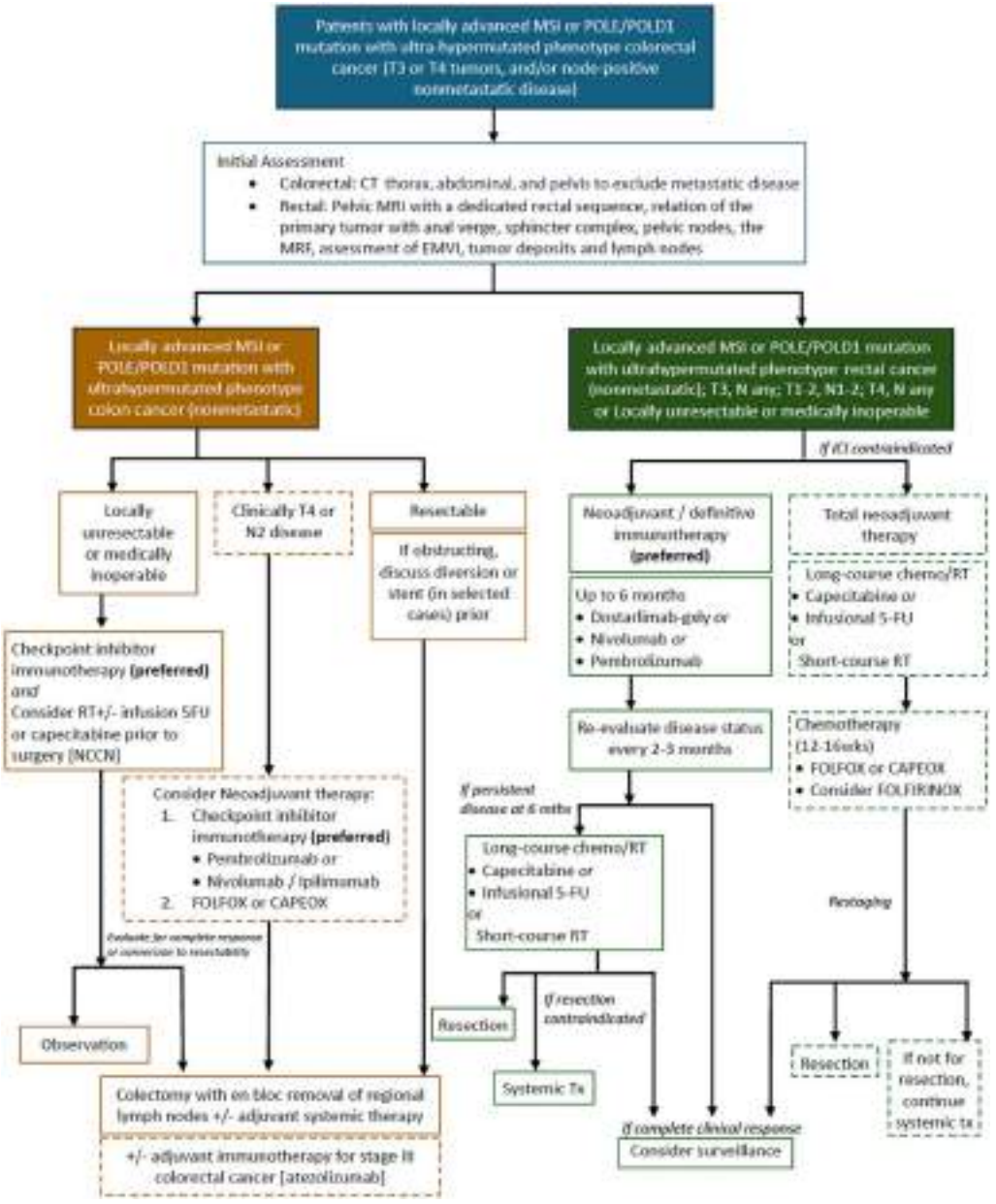

FIG 1. Management of locally advanced MSI colorectal cancer. Developed in concordance with NCCN guidelines. Dashed boxes highlight immunotherapy decision points, including opportunities for de-escalation and emerging areas where evidence continues to evolve. CAPOX, capecitabine and oxaliplatin; CT, computed tomography; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, oxaliplatin; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; RT, radiation therapy.

perioperative trials including PICC,[19] IMHOTEP,[24] and AZUR-2 (ClinicalTrials.gov identifier: NCT05855200) incorporate immunotherapy both before and after surgery, aiming to combine neoadjuvant immune activation with postoperative eradication of molecular residual disease. These approaches address distinct biologic questions, and relapse-free survival (RFS) and overall survival (OS) should not be compared with outcomes from a neoadjuvant only immunotherapy trial.

The PICC trial[19] evaluated neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, followed by surgery and in the majority, postoperative immunotherapy in locally advanced MSI-H CRC. In the MSI-H cohort, neoadjuvant PD-1–based therapy achieved MPR rates of 88% and pCR rates of 65% with 2-year event-free survival at 100% at a median follow-up of 15 months.[19] Building on this concept, IMHOTEP[24] is investigating perioperative ICI in localized MSI-H in a tumor agnostic setting. Similarly, AZUR-2 is an ongoing global phase III, open-label, randomized trial evaluating perioperative dostarlimab monotherapy (3 months neoadjuvant and 9 months adjuvant) versus standard-of-care surgery and adjuvant doublet chemotherapy with

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TABLE 1. Neoadjuvant Immunotherapy in Localized dMMR/MSI-H CRC

Study	Phase/Type	Design Terminology	No.	Disease Setting	Intervention	ICI Target	cCR (%)	pCR (%)	MPR (%)	Key Notes
NICHE final analysis[14]	Prospective	WOT; SAS (pMMR randomized)	62	Colon cancer (dMMR/pMMR), I-III	Ipilimumab + nivolumab (±celecoxib) → surgery	PD-1 + CTLA-4	NA	68 (dMMR)	97 (dMMR)	Confirms reproducibility of near-universal response in dMMR colon cancer
NICHE-2[4]	Prospective	WOT; SAS	115	Colon cancer (dMMR), II-III	Nivolumab + ipilimumab → surgery	PD-1 + CTLA-4	NA	68	95	Largest neoadjuvant ICI data set; excellent surgical feasibility and early disease control
NICHE-3[15]	Prospective	WOT; SAS	59	Colon cancer (dMMR), I-III	Nivolumab + relatlimab → surgery	PD-1 + LAG-3	NA	68	92	Alternative checkpoint pairing; shorter follow-up but strong pathologic efficacy
RESET-C[16]	Prospective	WOT; SAS	85	Colon cancer (dMMR), I-II	Pembrolizumab → surgery	PD-1	NA	44	57	Demonstrates meaningful pCR even in earlier-stage dMMR disease
NEOPRISM-CRC[13]	Prospective	WOT; SAS	32	CRC (dMMR/MSI-H), II-III	Pembrolizumab → surgery	PD-1	NA	59	NR	High pCR rate; short follow-up; translationally enriched
Cercek et al[6] (dostarlimab)	Prospective	SAS; NOM	117	dMMR tumors (rectal and non-rectal), I-III	Dostarlimab (6 months) ± NOM	PD-1	100 (rectal)	NA	NA	Landmark demonstration of organ preservation via NOM in dMMR rectal cancer
VOLTAGE-A[17]	Prospective	SAS	44	Rectal cancer (mixed MSS/MSI-H), II-III	CRT → nivolumab	PD-1	NA	60 (MSI-H)	NA	Included for MSI-H rectal signal; supports post-CRT ICI responsiveness
NEST-1[18]	Prospective	WOT; SAS	12	CRC (dMMR and pMMR), I-III	Botensilimab + balstilimab → surgery	PD-1 + CTLA-4	NR	Reported	NR	ctDNA dynamics correlated with response; low severe toxicity
Ludford et al[3]	Prospective	SAS; NOM	35	MSI-H/dMMR solid tumors (incl CRC)	Pembrolizumab ± surgery/NOM	PD-1	Endoscopic cCR	pCR (subset)	NR	Demonstrates feasibility of response-adapted NOM across MSI-H tumors
PICC[19]	Randomized	WOT; SAS (randomized)	34	CRC (dMMR/MSI-H), II-III	Toripalimab ± celecoxib → surgery	PD-1	NA	88 (combo)	94	Celecoxib arm associated with higher pCR; exploratory signal
Li et al[20] (2025)	Prospective	WOT; SAS	22	Locally advanced CRC (MSI-H/POLE)	PD-1 blockade ± CAPOX → surgery	PD-1	9	70	NR	Downstaging enabled avoidance of multivisceral resection
Chen et al (2023)[21]	Prospective	SAS; NOM	17	Rectal cancer (dMMR/MSI-H), II-III	Sintilimab → surgery or NOM	PD-1	NR	18	NR	Mixed surgical and NOM approach; small cohort
NEOCAP[22]	Prospective	WOT; SAS; NOM-enabled	52	CRC (dMMR/MSI-H), I-III	Camrelizumab + apatinib → surgery/NOM	PD-1	54	61	NR	Combination strategy with higher toxicity; NOM explored
Xiao et al (2023)[23]	Real-world	SAS; NOM	73	CRC (dMMR/MSI-H), II-III	Anti–PD-1 ± CRT → surgery or NOM	PD-1	23	57	NR	Real-world evidence supporting both surgery and NOM pathways

Abbreviations: CAPOX, capecitabine and oxaliplatin; cCR, complete clinical response; CRC, colorectal cancer; ctDNA, circulating tumor DNA; CTLA-4, Cytotoxic T-Lymphocyte-Associated protein 4; dMMR, mismatch repair-deficient; ICI, immune checkpoint inhibitor; LAG-3, lymphocyte-activation gene 3; MPR, major pathologic response; MSI-H, microsatellite instability-high; MSS, microsatellite-stable; NOM, nonoperative management; pCR, pathologic complete response; pMMR, mismatch repair proficient; SAS, single-arm study; WOT, window of opportunity.

T4N0 or stage III MSI-H colon cancer, with event-free survival as the primary end point (ClinicalTrials.gov identifier: NCT05855200). Perioperative immunotherapy in localized MSI CRC is rapidly evolving into two distinct strategies: neoadjuvant only priming versus perioperative MRD eradication. As such, efficacy outcomes should be interpreted within, not across, these trial designs.

Adjuvant Immunotherapy in Localized MSI Colorectal Cancer

If an early stage MSI-H CRC undergoes up-front resection, then adjuvant therapy decisions are guided by pathologic TNM stage and risk features. In stage II MSI-H colon cancer, fluoropyrimidine-only chemotherapy confers little incremental benefit, while in stage III disease, oxaliplatin-based chemotherapy, as established by the MOSAIC trial, demonstrated improved disease-free survival (DFS) and OS with adjuvant 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) compared with fluorouracil alone.[25] The IDEA trial refined this approach by showing that shorter-duration oxaliplatin-based therapy may be sufficient for selected low-risk stage III patients.[26]

Unlike the neoadjuvant setting, where MPR and pCR may well serve as early surrogate end points for RFS and OS, the key question in adjuvant therapy is prevention of recurrence. In the phase III ATOMIC trial,[8] adding one year of atezolizumab to 6 months of adjuvant modified 5-fluorouracil, leucovorin, oxaliplatin-6 (mFOLFOX6) in resected stage III MSI-H colon cancer significantly improved DFS. At a median follow-up of 37.2 months, 3-year DFS was 86.4% versus 76.6% with chemotherapy alone (hazard ratio, 0.50 [95% CI, 0.35 to 0.72]; $P < .0001$). Grade ≥3 treatment-related adverse events occurred in 71.7% of patients receiving atezolizumab plus mFOLFOX6 compared with 62.1% with mFOLFOX6 alone.[8] Given that patients may have already had surgical resection before seeing a medical oncologist, mFOLFOX6 plus atezolizumab is now the standard of care for these patients. However, as the RFS from the ATOMIC trial is inferior to the aforementioned neoadjuvant ICI trials, it is likely that adjuvant immunotherapy is most likely to be beneficial in patients with residual lymph node disease or tumor deposits, extramural venous invasion, perineural invasion, or resection margin 1 which may mean the higher likelihood of being circulating tumor DNA (ctDNA) positive. A key caveat is that neoadjuvant trials enroll by clinical stage (preoperative imaging), whereas adjuvant studies like ATOMIC enroll by postresection pathologic stage (TNM) so the populations (and baseline recurrence risk) are not directly comparable. An overview of neoadjuvant and adjuvant treatment strategies in early-stage dMMR CRC is shown in Table 2.

Neoadjuvant Immunotherapy in Localized MSI Rectal Cancer

Standard of care for locally advanced rectal cancer (LARC) has historically consisted of trimodality therapy of systemic chemotherapy, (chemo)radiation, and total mesorectal excision (TME). Total neoadjuvant therapy (TNT) is now widely adopted to improve systemic control and organ preservation opportunities.[27,28] However, there are significant toxicities and morbidity with this strategy.

In the landmark phase II study by Cercek et al[6], 6 months of neoadjuvant dostarlimab for stage II to III MSI rectal cancer produced a 100% clinical complete response (cCR) at initial reporting, allowing patients to omit chemoradiation (CRT) and surgery. In MSI-H rectal cancer, the key practical issue is therefore not whether radiation potentiates immunotherapy, but how confidently we can identify true complete responders and select patients for nonoperative management without compromising cure. Whether such outcomes are reproducible outside highly selected single-institution cohorts remains an open question. The AZUR-1 multicenter, global trial of neoadjuvant dostarlimab in MSI-H rectal cancer has completed accrual and results are awaited to evaluate this strategy in a larger, multi-institutional fashion.[29]

Technical and Clinical Considerations in Neoadjuvant Immunotherapy for dMMR Localized CRC

Accurate determination of MMR and/or MSI status is critical and should be made available as early as possible. Universal testing with immunohistochemistry (IHC) and/or MSI polymerase chain reaction (PCR) should be performed before treatment initiation.[2,30] Although next-generation sequencing (NGS)–based assays (targeted panels or comprehensive genomic profiling) may offer greater analytic robustness for MSI/MMR classification and can reduce the risk of false-negative results occasionally seen with PCR- or IHC-based approaches (eg, low tumor cellularity, suboptimal fixation, equivocal IHC staining, or atypical patterns of MMR loss), NGS is often constrained by cost, access, and longer turnaround times. In many systems, these assays have materially different turnaround times: MMR IHC can be available within approximately 48-72 hours, standalone MSI-PCR typically within approximately 3-5 days, whereas NGS-based MSI assessment from multigene panels often returns later (eg, approximately 10-15 working days for tissue panels), with ctDNA-based panels generally requiring ≥7 days and may be less reliable in early-stage disease when tumor fraction is low.

A pragmatic workflow in many health systems is therefore a tiered strategy: rapid up-front IHC (with or without MSI PCR) to enable timely treatment decisions, coupled with reflex NGS in cases with discordant, equivocal, or clinically incongruent results, or when broader profiling is already planned. Extended genomic profiling, including TMB, is not required as standard of care and has not been shown to meaningfully refine treatment selection in MSI-H CRC.[1] Accurate patient selection is essential when adopting a neoadjuvant immunotherapy strategy. High-quality radiologic staging with contrast-enhanced computed tomography (CT) for colon cancers, and magnetic resonance imaging (MRI) scans for

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TABLE 2. Overview of Neoadjuvant/Adjuvant Therapies in Early-Stage dMMR CRC

Study	Phase/Type	Design Terminology	N	Disease Setting	Intervention	ICI Target	cCR (%)	pCR (%)	MPR (%)	Key Notes
NICHE[5]	Prospective	WOT; SAS	40	Colon cancer (dMMR/pMMR), I-III	Ipilimumab + nivolumab → surgery	PD-1 + CTLA-4	NA	60 (dMMR)	95 (dMMR)	Established neoadjuvant ICI as biologically superior to chemotherapy in dMMR
NICHE final analysis[14]	Prospective	WOT; SAS	62	Colon cancer (dMMR/pMMR), I-III	Ipilimumab + nivolumab → surgery	PD-1 + CTLA-4	NA	69 (dMMR)	97 (dMMR)	Reinforces consistency and depth of pathologic response
NICHE-2[4]	Prospective	WOT; SAS	115	Colon cancer (dMMR), II-III	Nivolumab + ipilimumab → surgery	PD-1 + CTLA-4	NA	68	95	Benchmark neoadjuvant data set for dMMR colon cancer
NICHE-3[15]	Prospective	WOT; SAS	59	Colon cancer (dMMR), II–III	Nivolumab + relatlimab → surgery	PD-1 + LAG-3	NA	68	92	Confirms robustness across checkpoint combinations
ATOMIC[8]	Randomized	Adjuvant RCT	712	Colon cancer (dMMR), stage III	mFOLFOX6 ± atezolizumab (12 months)	PD-L1	NA	NA	NA	Demonstrates DFS benefit of adjuvant ICI; no pathologic end points
FOxTROT[27]	Randomized	Neoadjuvant chemo RCT	1,053	Colon cancer (II-III; incl dMMR subgroup)	Neoadjuvant FOLFOX *v* up-front surgery	None	NA	NA	NA	Highlights limited chemosensitivity of dMMR tumors, supporting ICI-first strategies

Abbreviations: cCR, complete clinical response; CTLA-4, Cytotoxic T-Lymphocyte-Associated protein 4; DFS, disease-free survival; dMMR, mismatch repair-deficient; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; ICI, immune checkpoint inhibitor; LAG-3, Lymphocyte-Activation Gene 3; mFOLFOX6, modified 5-fluorouracil, leucovorin, oxaliplatin-6; MPR, major pathologic response; NA, not applicable; NR, not reported; pCR, pathologic complete response; pMMR, mismatch repair proficient; RCT, randomized control trial; SAS, single-arm study; WOT, window of opportunity.

rectal cancers are essential. Fluorodeoxyglucose-positron emission tomography has limited value in localized CRC and is not routinely recommended.

Conventional tumor regression grading systems were developed for chemotherapy and radiotherapy, and they may not fully capture immune-mediated responses.[31] Careful histopathologic assessment of the resection specimen after neoadjuvant immunotherapy is essential. Evaluation should not be limited to the primary tumor bed but also include all resected lymph nodes with attention to nodal regression, fibrosis, and immune-related changes.[32] This is important both to confirm the pretreatment stage, given the high rates of tumor and nodal downstaging seen with neoadjuvant immunotherapy guiding postoperative risk stratification and adjuvant treatment decisions.

The optimal timing of surgery following the last cycle of neoadjuvant immunotherapy remains an area of active investigation. Evidence from neoadjuvant immunotherapy studies across solid tumors suggests that immune-mediated tumor regression may continue after treatment cessation, raising the possibility that longer intervals between immunotherapy and surgery could increase rates of MPR and pCR.[33] This is in sharp contrast to a shorter timing of surgery after neoadjuvant chemotherapy (NAC) and to an extent longer after long-course chemoradiotherapy.

Role of ctDNA and Multidisciplinary Decision Making

ctDNA is emerging as both a dynamic response biomarker during neoadjuvant therapy and a tool for minimal/molecular residual disease (MRD) detection after surgery. In NICHE-2, on-treatment ctDNA clearance/decline was associated with deeper pathologic responses, and all evaluable patients were MRD-negative at approximately 3 weeks postoperatively. Early prospective data suggest that ctDNA may also be predictive of benefit from adjuvant single-agent immunotherapy in MSI-H disease. In a prospective, investigator-initiated phase II study presented by Janjigian,[34] ctDNA-guided adjuvant PD-1 blockade was evaluated in resected early-stage MSI-H solid tumors. Among ctDNA-positive patients treated with 6 months of pembrolizumab, 85% (11/13) achieved ctDNA clearance, with median RFS not reached and a 2-year OS of 92% (median follow-up of 32 months). By contrast, ctDNA-positive patients who did not receive immunotherapy experienced rapid recurrence (median RFS 0.8 months; 100% recurrence), while ctDNA-negative patients observed.[34]

Despite this promise, ctDNA has important limitations to determine response or guide nonoperative management. In addition, some postoperative ctDNA-negative patients still relapse, highlighting sensitivity constraints both in tumor informed and tumor agnostic assays. Therefore, ctDNA cannot substitute for pathologic assessment or independently justify omission of surgery or adjuvant therapy outside a clinical trial.

Future Directions for Immunotherapy in MSI Localized CRC

An important next step is aligning clinical trial design with the regulatory and payer environment. In MSI-H CRC, neoadjuvant immune checkpoint blockade consistently achieves high rates of MPR and pCR. However, long-term end points such as DFS and RFS remain the standard for regulatory approval and guideline incorporation. A key priority is therefore determining whether pCR can be validated as a reliable surrogate for durable clinical benefit in this biologically distinct subgroup and whether posttreatment ctDNA clearance can serve as an early marker of long-term efficacy, enabling more timely evaluation of therapeutic strategies without prolonged follow-up.

Equally important is defining the evidentiary threshold for routine clinical adoption. The reproducibility and magnitude of benefit observed across multiple neoadjuvant studies raise the question of whether additional confirmatory phase III trials are required for all patients or whether future randomized studies should focus on refining treatment duration, regimen selection, timing of surgery, and risk-adapted escalation or de-escalation strategies. Addressing these questions will be critical to moving neoadjuvant immunotherapy from proof of efficacy to standardized implementation in clinical practice.

NONOPERATIVE MANAGEMENT AFTER NEOADJUVANT IMMUNOTHERAPY IN MSI LOCALIZED COLORECTAL CANCER

Neoadjuvant immune checkpoint inhibition has introduced a realistic organ-preservation paradigm in localized MSI-H CRC, driven by high rates of deep tumor regression. However, the feasibility of a watch-and-wait (W&W) strategy differs fundamentally between rectal and colon primaries. In the rectum, response assessment can be repeated with endoscopy and high-resolution MRI, enabling structured surveillance. In the proximal colon, limitations in local assessment and nodal evaluation make confirmation of complete response more challenging. This section summarizes current evidence for nonoperative management in MSI-H rectal cancer, the evolving role of ctDNA, and the barriers to extending organ preservation to colon cancer.

Nonoperative Management of MSI Rectal Cancer

As previously reported, Cercek et al[6] reported a 100% cCR rate in patients treated with 6 months of dostarlimab, a PD-1 inhibitor. Long-term follow-up and expansion cohorts have consistently reproduced these findings, with durable responses observed without the requirement for CRT or TME. The success of the W&W strategy in this cohort relies heavily on a rigorous surveillance protocol that is anatomically feasible in the rectum but difficult to replicate elsewhere. The standard surveillance algorithm, which is also listed in national guidelines, typically includes:

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- Digital rectal examination and flexible sigmoidoscopy: Performed every 3-4 months for the first 2 years and then every 6 months.
- High-resolution MRI: Performed every 3-6 months to assess for mural thickening or mesorectal nodal status for a total of 3 years.
- CT imaging: Performed every 6-12 months for 5 years to assess distant metastatic disease.

Treatment Decisions

Patients achieving cCR (no palpable or visible tumor and negative MRI) may proceed to observation if this aligns with the patients' goals of care. Those with residual disease would theoretically undergo TME, although to date, near-universal cCR rates in exclusive MSI-H cohorts have made salvage surgery rare. This approach spares patients the significant morbidity of TME, including low anterior resection syndrome and permanent stoma formation, establishing neoadjuvant PD-1 blockade followed by W&W as a preferred standard of care for eligible patients with MSI-H rectal cancer.

Role of ctDNA in Rectal Cancer Surveillance

Although endoscopic and radiographic assessments are the cornerstones of W&W, ctDNA is under active investigation as a molecular adjunct to predict response and monitor for recurrence. In the metastatic and adjuvant settings, ctDNA clearance is a strong predictor of favorable outcomes.[35] The utility of ctDNA in the neoadjuvant W&W setting is more nuanced. Data suggest that while sustained ctDNA negativity correlates well with low recurrence risk, the sensitivity of current assays for detecting minimal residual disease (MRD) in the absence of distant metastases remains a limitation. For instance, in cohorts treated with TNT, ctDNA clearance does not always perfectly align with pCR, and a negative ctDNA result does not definitively rule out microscopic locoregional disease.[36] Consequently, although ctDNA is a valuable complementary tool, particularly for detecting distant failure, it currently cannot replace endoscopic and MRI surveillance for confirming local control in the rectum.

Colon Cancer: The Challenge of Surveillance and Organ Preservation

The success of W&W in the rectum has prompted interest in similar strategies for MSI-H colon cancer. High pCR and MPR rates after neoadjuvant immunotherapy in MSI-H colon cancer have prompted interest in W&W strategies, but adoption remains limited. Although rectal W&W pathways provide a clear template, the optimal surveillance strategy after neoadjuvant immunotherapy, particularly for colon primaries and in patients managed nonoperatively, remains undefined. A pragmatic approach is to anchor follow-up intensity to the best-estimated pretreatment clinical stage: where the primary tumor has been resected after neoadjuvant immunotherapy, clinicians may reasonably adhere to standard postoperative (adjuvant) surveillance schedules aligned to that baseline risk. The key barriers are anatomic and technical rather than biologic:

- Endoscopic limitations: Unlike the rectum, the proximal colon is difficult to access for quick, frequent checks. Assessing a healed tumor bed in the thin-walled cecum carries higher procedural risks and technical challenges than in the rectum.
- Radiographic blind spots: Cross-sectional imaging (CT/MRI) is less sensitive for detecting microscopic residual disease in the colon wall or adjacent mesentery compared with rectal MRI.
- Nodal uncertainty: Although MSI tumors have a lower rate of nodal metastases, the inability to surgically sample lymph nodes leave a theoretical risk of occult nodal disease that simple observation cannot address.

Future Directions

Biomarker Refinement

Although MSI remains the gatekeeper for immunotherapy eligibility, it is an imperfect predictor of response depth. Approximately 5%-10% of MSI patients exhibit primary resistance to PD-1 blockade. Future efforts must integrate predictive biomarkers to identify this subset before the initiation of treatment.

- TMB: TMB has emerged as a critical stratifier. Data from the NEOPRISM-CRC trial[13] suggest that TMB-high tumors may achieve pCR with shorter courses of therapy compared with TMB-intermediate tumors, which may require dual checkpoint blockade (anti-CTLA-4/anti-PD-1) to overcome lower immunogenicity.
- Lynch syndrome status: Distinguishing between sporadic MSI and Lynch syndrome-associated cancers is vital. The risk of metachronous primaries in patients with Lynch syndrome adds a layer of complexity to organ preservation strategies, potentially favoring segmental resection over active surveillance even in the setting of a complete clinical response, unless rigorous, lifelong pan-colonic surveillance can be guaranteed.[37]

High-Sensitivity ctDNA Assays

The current reliance on radiographic imaging is insufficient for the nonoperative management of colon cancer. The future lies in ultrasensitive, tumor-informed ctDNA assays capable of detecting MRD at levels below the threshold of current commercial tests. Validating a molecular CR, defined by sustained ctDNA clearance in the context of endoscopic normality, is the primary hurdle to extending organ preservation to the proximal colon. Upcoming trials are exploring dynamic escalation strategies, where patients with persistent ctDNA positivity after an initial course of neoadjuvant immunotherapy are triaged to surgery or intensified combination therapy (eg, adding lymphocyte-activation gene 3

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[LAG-3] or TIM-3 inhibitors), while those with early and sustained clearance might be candidates for de-escalation trials.

De-Escalation and Novel Combinations

With pCR rates approaching 70%-100%, the focus is shifting from efficacy to de-escalation. The NICHE-2 trial demonstrated that major pathologic responses could be achieved with as little as 4 weeks of treatment. Investigational approaches are now evaluating minimal-duration therapy (eg, single-dose ipilimumab/nivolumab) to limit toxicity while maintaining efficacy. Conversely, for the minority of nonresponders, novel checkpoints such as LAG-3 (relatlimab) are showing promise in overcoming resistance to standard PD-1 blockade. A risk-adapted algorithm where the intensity and duration of immunotherapy—and the extent of surgery (or lack thereof) are modulated by real-time molecular response assessment would allow for a precision neoadjuvant approach.

LOCALIZED MSS COLON CANCER

ICIs have transformed outcomes in MSI CRC, but most CRCs are microsatellite stable (MSS/mismatch repair proficient [pMMR]), where benefit from PD-1/PD-L1–directed therapy remains limited—particularly in localized disease.[9,38] This likely reflects the lower neoantigen load and an immune-excluded tumor microenvironment enriched with suppressive populations such as regulatory T cells and myeloid-derived suppressor cells.[10,39] Previous studies have demonstrated limited benefits with ICI alone or in combination with chemotherapy in MSS CRC.[9,38,40] However, newer generation agents may have greater efficacy in this population, prompting the need to re-evaluate this topic.[41,42]

Many studies have shown that outcomes for patients with MSS CRC are significantly worse than MSI-H patients, even with localized disease[43] and even with adjuvant chemotherapy.[26] Given the impressive outcomes observed in MSI-H cancers treated with immunotherapy, there is a need to determine how immunotherapy could augment the treatment of localized MSS CRC. Here, we review the state of evidence for ICI in localized MSS colon and rectal cancer. Current standard therapies and clinical trial data for localized MSS CRC are summarized in Table 3.

Current Standard Therapy

Standard therapy for localized MSS colon cancer consists of up-front surgery followed by adjuvant chemotherapy based on pathologic TNM stage and other high-risk features.[62] In resected high-risk stage II (especially T4N0) and stage III disease, adjuvant chemotherapy is routinely recommended. However, the 3-year DFS of the highest-risk stage III (T4 and/or N2) patients is still only 64.4%, even with 6 months of adjuvant chemotherapy, highlighting a population of patients with a need for improved therapies.[26]

There is a limited role for NAC in operable colon cancer and the patients most likely to derive meaningful benefit are those with truly high-risk radiologic features, particularly cT4a/b tumors (and/or threatened-margin disease), where downstaging and earlier systemic control may be most relevant. The FOxTROT Collaborative Group evaluated a 6-week course of NAC FOLFOX and 18 weeks of adjuvant FOLFOX and noted a small but significant decrease in 3-year recurrence rate compared with adjuvant-only FOLFOX (16.9% NAC *v* 21.5% control).[27] Rate of pCR with NAC was 4% and at least some regression in 62% compared with 18% with any regression in the control (up-front surgery) arm. In OPTICAL, a perioperative approach using 3 months of preoperative mFOLFOX6/capecitabine and oxaliplatin (CAPOX) versus up-front surgery was similarly tested in locally advanced colon cancer, providing an additional randomized evidence base supporting NAC feasibility and potential DFS benefit in appropriately selected high-risk patients.[63] Broad adoption of NAC has been cautioned by the inability to focus this strategy on only high-risk patients. Further, more adjuvant chemotherapy was given in the NAC group than control, affecting the comparison of recurrence rate, and FOxTROT was not powered to detect differences in overall recurrence or survival.

Colon Cancer and ICI

Several studies have sought to improve outcomes through the use of neoadjuvant ICI in localized MSS colon or CRC. Single-agent ICI with 1 month of nivolumab demonstrated few major pathologic responses (MPR, 15.7%, 3/19 patients) and pCR (5.2%, 1/19 patients) in the NICOLE trial.[44] Among the patients with colon cancer treated in the BASKET II trial of combined 3 months of FOLFOX with sintilimab (anti-PD1) and bevacizumab (anti-vascular endothelial growth factor) for patients with T4 disease, a pCR rate of 20.6% (7/34) and MPR of 64.7% (22/34) was found.[45] When ipilimumab (anti-CTLA4) was added to nivolumab in the pMMR subset of the NICHE trial, MPR rates was observed to be 19.4% (6/31).[64] Strikingly, the botensilimab (Fc-enhanced anti-CTLA-4 antibody) monotherapy arm of the UNICORN trial showed no effect on MPR (0%) or pCR (0%), whereas combining it with balstilimab (anti-PD-1) led to 36% of patients with MPR and 29% with pCR.[42] Of note, these studies used different ICI regimens and timing between receiving ICI and surgery. Results from the NEST trial suggested that longer duration between neoadjuvant botensilimab/balstilimab and surgery improved pCR to 40% (6/15) and MPR to 47% (7/15).[41]

Which Immune Checkpoint to Target: PD-1, PD-L1, or CTLA4?

Neoadjuvant anti–PD-1 monotherapy appears to have only a small effect on improving pathologic outcomes in MSS colon cancer. However, the addition of CTLA4, particularly second-generation CTLA4 antibodies, to anti–PD-1 demonstrates an improvement in pCR and MPR,[42,64] although longer-time data are needed.

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TABLE 3. Overview of Localized MSS CRC Trials

Study Name	Type	N	Disease Setting	Intervention	ICI Target	cCR (%)[a]	pCR (%)[a]	MPR (%)[a]	DFS-3 (%)
Colon									
Current standard therapy									
IDEA (3 months)[26]	RCT	12,881	Stage III colon cancer	Surgery → FOLFOX/CAPOX × 3 months	None	—	—	—	83.1
IDEA (6 months)	RCT	12,881	Stage III colon cancer	Surgery → FOLFOX/CAPOX × 6 months	None	—	—	—	83.3
FOxTROT[27] (neoadjuvant)	RCT	1,052	Colon cancer (cT3-T4)	FOLFOX → surgery → chemotherapy	None	—	0.0	—	
FOxTROT (control)	RCT	1,052	Colon cancer (cT3-T4)	Surgery → chemotherapy	None	—	—	—	
Trials									
NICOLE[44]	SAS	22	Colon cancer (cT3-T4)	Nivolumab → surgery	PD-1	—	5.3	15.8	
NICHE-2[4]	SAS	31	Colon cancer (cT3-T4)	Ipilimumab + nivolumab → surgery	PD-1/CTLA-4	—	—	19.4	
BASKETII[45]	SAS	38	pMMR CRC (T4NxM0)	mFOLFOX6 + bevacizumab + sintilimab → surgery	PD-1	—	20.6	64.7	
NEST1[41]	SAS[6]	9	pMMR CRC	Botensilimab + balstilimab → surgery	PD-1/CTLA-4	—	11.1	66.7	
NEST2[41]	SAS	15	pMMR CRC	Botensilimab + balstilimab → surgery	PD-1/CTLA-4	40.0	—	46.7	
UNICORN BOT alone[42]	WOT	14	Colon cancer (cT3-4, N0-2)	Botensilimab alone	PD-1	—	0.0	0.0	
UNICORN BOT/BAL[42]	WOT	14	Colon cancer (cT3-4, N0-2)	Botensilimab + balstilimab	PD-1/CTLA-4	—	29.0	36.0	
Rectal									
Current standard therapy									
PRODIGE-23[46,47] (control)	RCT	230	LARC	CRT → surgery → chemotherapy	None	—	12.0	—	69.0
PRODIGE-23[46,47] (neoadjuvant)	RCT	231	LARC	mFOLFIRINOX → CRT → surgery → chemotherapy	None	—	28.0	—	76.0
OPRA[48] (INCT-CRT)	RCT	158	LARC	Chemotherapy → CRT → NOM/surgery	None	—	—	—	76.0
OPRA[48] (CRT-CNCT)	RCT[10]	166	LARC	CRT → chemotherapy → NOM/surgery	None	—	—	—	76.0
Trials									
neoFOLCAB[49]	SAS	29	pMMR LARC	mFOLFOXIRI + bevacizumab + camrelizumab → surgery	PD-1	34.5	35.5	—	
Zhou et al (Control)[50]	RCT	12	pMMR LARC	XELOX alone	None	—	0.0	8.3	
Zhou et al (ICI)[50]	RCT	13	pMMR LARC	XELOX + cadonilimab	PD-1/CTLA-4	—	15.4	46.2	
FIRM[51]	SAS	30	pMMR LARC	FOLFOX + serplulimab → surgery	PD-1	—	42.9	67.9	
PKUCH04[52]	SAS	25	pMMR LARC	Camrelizumab + CAPOX → CRT → CAPOX	PD-1	19.0	33.3	33.3	
POLAR-STAR (control)[53]	RCT	49	LARC	CRT → surgery	None	—	14.0	40.0	

(continued on following page)

TABLE 3. Overview of Localized MSS CRC Trials (continued)

Study Name	Type	N	Disease Setting	Intervention	ICI Target	cCR (%)[a]	pCR (%)[a]	MPR (%)[a]	DFS-3 (%)
POLAR-STAR (concurrent ICI)[53]	RCT	54	LARC	CRT + tislelizumab → surgery	PD-1	—	31.0	59.0	
POLAR-STAR (sequential ICI)[53]	RCT	48	LARC	CRT → tislelizumab → surgery	PD-1	—	35.0	56.0	
Xiao et al (control)[54]	RCT	67	pMMR LARC	CRT → surgery	None	3.0	28.6	—	
Xiao et al (ICI)[54]	RCT	67	pMMR LARC	CRT + sintilimab → surgery	PD-1	16.4	36.8	—	
NRG-GI002 (Control)[55]	RCT	95	pMMR LARC	FOLFOX → CRT → surgery	None	13.6	29.4	—	
NRG-GI002 (ICI)[55]	RCT	90	pMMR LARC	FOLFOX → CRT + pembrolizumab → surgery	PD-1	13.9	31.9	—	
Lin et al (Tislelizumab)[56]	SAS	29	pMMR LARC	CRT + tislelizumab → CAPOX + tislelizumab → surgery	PD-1	—	34.8	—	
STELLAR II (control)[57]	RCT	48	pMMR LARC	SCRT → chemotherapy → surgery	None	26.1	17.1	—	
STELLAR II (ICI)[57]	RCT	52	pMMR LARC	SCRT → chemotherapy + sintilimab → surgery	PD-1	50.0	48.5	—	
SPRING-01 (Control)[58]	RCT[38]	49	LARC	SCRT → CAPOX → surgery	None	32.7	32.7	46.9	
SPRING-01 (ICI)[58]	RCT	49	LARC	SCRT → CAPOX + sintilimab → surgery	PD-1	61.2	59.2	73.5	
TORCH (Control)[59]	RCT	59	pMMR LARC	SCRT → CAPOX → surgery	None	35.6	50.0	—	
TORCH (ICI)[59]	RCT	62	pMMR LARC	SCRT → CAPOX + toripalimab → surgery	PD-1	43.5	50.0	—	
UNION (control)[60]	RCT	118	pMMR LARC	SCRT or CRT → CAPOX → surgery	None	—	15.3	—	
UNION (ICI)[60]	RCT	113	pMMR LARC	SCRT or CRT → CAPOX + camrelizumab → surgery	PD-1	—	39.8	—	
VOLTAGE-D[61]	SAS	25	pMMR LARC	CRT → nivolumab + ipilimumab → surgery	PD-1/CTLA-4	—	44.0	—	

Abbreviations: CAPOX, capecitabine and oxaliplatin; cCR, complete clinical response; CRC, colorectal cancer; CRT, chemoradiation therapy; CTLA-4, Cytotoxic T-Lymphocyte-Associated protein 4; DFS-3, 3-year disease-free survival; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; ICI, immune checkpoint inhibitor; LARC, locally advanced rectal cancer; mFOLFIRINOX, modified 5-fluorouracil, leucovorin, irinotecan, oxaliplatin; mFOLFOX6, modified 5-fluorouracil, leucovorin, oxaliplatin-6; mFOLFOXIRI, modified 5-fluorouracil, leucovorin, irinotecan, oxaliplatin; MPR, major pathologic response; MSS, microsatellite stable; NOM, nonoperative management; pCR, pathologic complete response; pMMR, mismatch repair proficient; RCT, randomized control trial; RT, radiation therapy; SAS, single-arm study; SCRT, short-course radiation therapy; WOT, window-of-opportunity trial; XELOX, capecitabine, oxaliplatin.

[a]In pMMR or MSS population.

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Prognostic Factors

Although most studies have not evaluated the effect of PD-L1 status in response to ICI in pMMR colon cancer, there is evidence for effect of immune activation in resected tumors. In the NICHE and NICOLE trials, higher levels of immune infiltration ($CD3^+$ and $CD8^+$ T cells and higher Immunoscore) correlated with responses to ICI.[41,64] However, it is not clear whether there are inherent differences in the tumors before therapy that correlate with response or predict long-term benefit. Additional studies are needed to evaluate the optimal ICI agent and timing of delivery and the impact on recurrence and OS.

LOCALIZED MSS RECTAL CANCER

Current Standard Therapy

Standard of care for pMMR LARC consists of trimodality therapy using chemotherapy, radiation, and surgery. TNT for patients with LARC have improved rates of local recurrence, metastases-free survival, and OS compared to prior standard regimens and are the standard therapy for patients with LARC. In PRODIGE-23, when FOLFIRINOX was used, 28% (59/212) of patients achieved pCR with TNT compared with 12% (26/215) in the control arm of neoadjuvant CRT alone, as well as improved DFS and OS.[46,48] The OPRA trial evaluated TNT with each induction chemotherapy followed by CRT (INCT-CRT) and CRT followed by chemotherapy (CRT-CNCT) but also permitted W&W for patients who achieved nCR or cCR. With both TNT strategies, 74% (225/304) of patients were offered W&W. However, accounting for regrowth, the TME-free survival was 39%-54%. Notably, DFS-5 and OS-5 were similar between these TNT arms which relied on FOLFOX/CAPOX and PRODIGE-23.[48] Despite these improvements, the majority of patients do require surgery, and the outcomes are worse than are observed for MSI cancers, again questioning whether ICI can improve outcomes.

Rectal Cancer and ICI

A growing number of studies have evaluated immune checkpoint blockade for LARC, either alone or as a potentiator of the radiation effect. The potential immunostimulatory effects of radiation through the release of antigen and chemoattractant molecules have been theorized to be a prime opportunity for the addition of ICI.[65-67] The primary end points for these trials have been pCR or cCR rates, and long-term patient outcomes have not read out. However, we know there is a strong correlation between pCR and DFS/OS from other prior studies.[47]

A series of trials combined anti–PD-1 antibodies at the same time as CRT either as the sole neoadjuvant treatment or as part of TNT. The NECTAR and POLAR-STAR (experimental arm A) trials evaluated CRT + tislelizumab in patients primarily with pMMR LARC and found pCR rates of 40% and 34%, respectively.[53,68] Several trials have demonstrated similar rates of pCR with the addition of ICI to CRT.[54,69,70] TNT + ICI trials have also demonstrated slightly improved pCR/cCR rates compared with historical controls of standard therapy (pCR/cCR 31.9%-43.5% for TNT + ICI *v* 29.4% in NRG-GI002 and 28% in PRODIGE-23),[46,55] although most of these are single-arm trials and those that randomized with and without ICI have not consistently demonstrated a benefit. Thus, this treatment strategy with the addition of ICI to CRT remains hypothesis generating, rather than routine care.

Other groups have started with (chemo)radiation followed by immunotherapy with the rationale that ICI could help boost the immunostimulatory effects initiated by radiation treatment. Interestingly, the CRT-CNCT arm of the OPRA demonstrated a statistically significant higher TME-free survival compared with INCT-CRT,[48] which could similarly be interpreted to reflect this immunologic impact of upfront radiation, but it is thought more likely that reassessment was occurring too early after CRT for the INCT-CRT arm, and the full effects of the CRT was not being appreciated for those individuals. Trials that employed a TNT-like strategy with CRT followed by ICI monotherapy (CRT-CNICI) found similar rates of pCR between 30% and 36% compared with approximately 15% in CRT alone.[14,53,71-73] TNT with short-course radiation therapy (SCRT) followed by chemotherapy + ICI has also been studied in several trials. Rates of pCR ranged from 33.3% to 59.2% suggesting sequencing radiation therapy before ICI could improve pCR rates, but again there is controversy over whether this is the effect of the systemic therapy or time from radiation to assessment. Additionally, while intriguing, the pCR rates for CRT-CNICI approaches are not that different from standard TNT with chemotherapy, suggesting that the ICI approach is not meaningfully improving current treatment standards.

Three trials used multiagent chemotherapy with ICI: neoFOLCAB, a study by Zhou et al, and the FIRM trial. NeoFOLCAB evaluated modified 5-fluorouracil, leucovorin, irinotecan, oxaliplatin + camrelizumab (anti–PD-1) + bevacizumab followed by surgery or W&W in lower risk (cT2-3, N0-1) rectal cancer and achieved a cCR rate of 34.5% (10/29).[49] The trial by Zhou et al[50] demonstrated improvement in pCR with the addition of a novel PD-1-CTLA4 bispecific antibody to perioperative CAPOX (pCR 15.4 bispecific/CAPOX *v* 0% in CAPOX). However, the pCR rate was low compared with trials employing radiation ± ICI. Most recently, the FIRM trial observed that neoadjuvant FOLFOX with serplulimab (anti–PD-1) led to a pCR 42.9% and MPR rate of 67.9%, which was even greater in a post hoc analysis of high rectal cancers (pCR 71.4%, MPR 85.7%).[51]

Which Immune Checkpoint to Target: PD-1, PD-L1, or CTLA4?

Most ICI rectal cancer trials have used anti-PD1 antibodies alone, with chemotherapy, and/or with radiation. In other

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solid tumor ICI trials, few differences have been seen blocking PD-1 versus PD-L1. Consistent with current NCCN guidelines, there appears to be no difference in pCR rates between antibodies targeting PD-1 versus PD-L1 (pCR range 30%-40% *v* 25%-46%), although there are significantly fewer studies with anti–PD-L1 antibodies. In metastatic CRC, the comparison of KEYNOTE-177 and the recently presented results of the COMMIT trial suggest that targeting PD-1 is more effective than PD-L1 targeting,[74,75] even when considering chemoimmunotherapy. The effect of multipathway ICI blockade is also being studied. Combining PD-1 and CTLA4 inhibition with CRT in pMMR LARC further improved pCR to 44% (compared with 30% with nivolumab monotherapy) in the VOLTAGE trial.[61] Trials with PD-1/CTLA4 bispecific antibodies are underway and may reveal additional benefit.[50,76]

Prognostic Factors

Although data are limited, similar to the studies of ICI and MSS colon cancer, $CD8^+$ T-cell L1 in the pre-CRT sample correlated with response to ICI in MSS LARC.[73,77] Insights from the NICHE study suggest that a meaningful minority (26%) of pMMR tumors can mount a pathologic response to short-course dual checkpoint blockage. These responders are enriched for an immune-primed phenotype with higher baseline proliferation signatures/TCF1 and increased KI-67 $CD8^+$ T cells

Future Directions for ICI in MSS Localized Colorectal Cancer

In MSS colon cancer, current evidence for immune checkpoint inhibition is limited and largely confined to small neoadjuvant studies. Combination strategies, particularly dual PD-1/CTLA-4 blockade and next-generation CTLA-4 antibodies, have demonstrated higher pathologic response rates than PD-1 monotherapy and appear more promising than chemotherapy alone in early-phase cohorts. Targeting other immunoregulatory molecules, like TIGIT, are further emerging, such as was seen in the NEOTERIC trial.[78] However, these approaches remain investigational, and no randomized data have established a survival benefit. Future trials must determine whether immunotherapy can meaningfully reduce recurrence risk beyond optimized oxaliplatin-based chemotherapy and identify which MSS patients, if any, derive durable benefit.

In MSS LARC, the most consistent signals have emerged when ICI is combined with radiation or CRT, supporting the hypothesis that radiation-induced antigen release may partially overcome immune exclusion. The role of ICI without radiation is less clear, particularly in patients with low-risk disease who would have qualified for the PROSPECT trial.[79] In the limited studies, pCR rates are much lower with ICI + chemotherapy compared with ICI + radiation, except for the recently presented FIRM trial. The correct chemotherapy regimen for the TNT approach has been evaluated with the recently complete JANUS study, and this will inform future study for how to improve upon TNT.[80] Given the higher rates of pCR and cCR seen after ICI, the role of nonoperative management becomes a question. Recurrence rates and long-term patient outcomes are needed to better evaluate this strategy as well as the optimal ICI-neoadjuvant regimen. At this time, a clear role for ICI has not been established for LARC, although the opportunities suggested by early data remain worth further study.

CONCLUSION

Immunotherapy is rapidly redefining curative-intent treatment for localized MSI CRC. Across multiple neoadjuvant studies, short-course PD-1–based therapy, alone or as dual checkpoint inhibitor, has delivered consistently high major pathologic response and pCR rates, with encouraging early recurrence outcomes. In rectal cancer, these deep responses have enabled nonoperative management in highly selected patients supported by intensive multidisciplinary surveillance; in colon cancer, organ preservation remains constrained by limitations in local and nodal assessment.

The next phase of the field is implementation science and precision de-escalation: defining the minimum effective regimen and duration, clarifying the role of perioperative strategies, and determining whether pCR and ctDNA dynamics can be validated as surrogate end points for durable benefit. By contrast, MSS/pMMR disease remains largely resistant to checkpoint blockade in the localized setting. Early signals with combinations (radiation, chemotherapy, and next-generation immune modulators) are hypothesis-generating, and future progress will require biomarker-driven, response-adapted trials with long-term outcomes to justify practice change.

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Emerging and Established Targets in Colorectal Cancer: Translating Biology Into Therapeutics

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OVERVIEW

Alterations in the mitogen-activated protein kinase (MAPK) pathway play a central role in colorectal cancer (CRC) tumor biology, therapeutic response, and resistance. *RAS* oncogenic mutations are present in up to 35% of CRC; they represent constitutively active molecular switches that impair GTP hydrolysis and promote ligand-independent signaling. The development of allele-specific KRAS G12C inhibitors exploits a cryptic pocket to trap the protein in its inactive (OFF) conformation. In metastatic CRC, where EGFR feedback loop limits monotherapy efficacy, combinations of KRAS G12C inhibitors with EGFR blockade and chemotherapy have demonstrated meaningful activity. Parallel efforts allowed the development of RAS(ON) inhibitors that sterically block the interaction with downstream effectors. Co-occurring genomic alterations, MAPK pathway reactivation, and pharmacologic limitations drive primary and acquired resistance. *BRAF V600* mutations drive approximately 10% of CRCs; first-generation, type I BRAF inhibitors require combination with upstream EGFR, downstream MEK/ERK blockade to overcome adaptive feedback reactivation. Emerging strategies include paradox breaking RAF inhibitors, type II pan-RAS inhibitors, and immunotherapy combinations, particularly relevant for the immune-activated phenotype of BRAF-mutant microsatellite stable tumors. Beyond *RAS* and *RAF*, novel therapeutic avenues (such as antibody-drug conjugates, bispecific antibodies, DNA damage response inhibitors, and tumor microenvironment modulating agents) are reshaping precision oncology in CRC. Integrating multiomics profiling with dynamic biomarkers may enable durable activity and personalized treatment strategies.

MITOGEN-ACTIVATED PROTEIN KINASE SIGNALING PATHWAY

The RAS/RAF/MEK/ERK signaling pathway (Fig 1) is physiologically crucial for regulation of vital cell functions, including proliferation, differentiation, mitosis, and apoptosis. The conventional pathway is initiated by the binding of extracellular ligands (first messenger) to their corresponding transmembrane receptor tyrosine kinase (RTK), triggering their dimerization (signal transduction) and autophosphorylation. This allows for the recruitment of Src homology 2 domain-containing phosphatase 2 (SHP2), tyrosine-protein kinase Src, the adaptor protein growth factor receptor-bound protein 2 (Grb2), and subsequently of son of sevenless 1 (SOS1) to act as a guanine nucleotide exchange factor (GEF) that catalyzes the exchange of GDP for GTP on RAS, thereby converting RAS from its inactive (OFF) GDP-bound state to its active (ON) GTP-bound state. Activated RAS-GTP recruits RAF kinases to the plasma membrane via direct binding, promoting RAF dimerization and conformational activation, followed by phosphorylation of MEK1/2 and downstream ERK1/2. Activated ERK translocates to the nucleus, where it regulates transcription factor activity and gene expression. Activated ERK mediates multiple negative feedback loops that suppress upstream signaling. RAS has intrinsically slow GTPase activity, but its hydrolysis function is markedly accelerated by GTPase-activating proteins (GAPs), such as neurofibromin 1 (NF-1), leading to protein resynthesis half-life of 23 hours.[1,2]

Colorectal cancer is a classical mitogen-activated protein kinase (MAPK)–driven malignancy, with aberrant activity across the cascade present in 55%-60% of tumors via gain-of-function mutations, loss of negative regulators, and upstream receptor overactivation. The result is constitutive ERK signaling, independent of ligand binding.

Notably, activating mutations in *KRAS*/*NRAS* and *BRAF* V600E are almost invariably mutually exclusive in colorectal cancer (CRC), reflecting their functional redundancy as dominant drivers of MAPK pathway activation. Either alteration alone is sufficient to sustain constitutive ERK signaling; combined activation does not confer additional selective advantage and may be negatively selected because

PRACTICAL APPLICATIONS

- Genomic profiling is crucial in metastatic colorectal cancer (CRC) management: *RAS* and *BRAF* alterations govern prognosis and eligibility for targeted therapies.
- The expanding landscape of RAS directed therapies, including RAS(OFF) and RAS(ON) inhibitors, will enable a broader range of actionable *KRAS* and *NRAS* allele-specific mutations.
- *For BRAF V600E*-mutant CRC, combination regimens of BRAF and EGFR inhibitors are now established therapeutic options. Paradox breaking RAF and ERK inhibitors may soon expand beyond V600-mutant allele.
- The growing pipeline of antibody-drug conjugates targeting human epidermal growth factor receptor 2, CEACAM5, CLDN18.2, and other antigens may soon offer novel treatment strategies for mCRC
- Integration of ctDNA dynamics, immune signatures, and replication stress biomarkers will allow real-time treatment adaptation, personalized, and durable therapeutic strategies across CRC subtypes.

of excessive pathway output.[3] Beyond the MAPK canonical pathway, because of its direct coupling to RAS, evolutionary conservation, and central role in controlling proliferation, RAS functions as a signaling hub for alternative effector pathways, such as PI3K–AKT–mTOR (critical for cell survival) and RalGDS (for invasion and metastasis), determined by effector availability, subcellular localization, feedback regulation, and co-occurring genomic alterations.[4,5]

RAS

The *RAS* family of proto-oncogenes *KRAS* (chromosome 12p12.1), *HRAS* (11p15.5), and *NRAS* (1p13.2) encode their respective small GTP-binding hydrolases KRAS (Kirsten RAS), HRAS (Harvey RAS), and NRAS (Neuroblastoma RAS) that function as molecular binary switches. The three RAS proteins share approximately 85% sequence homology, leading to near-identical catalytic domains.

Although *NRAS* and *HRAS* mutations are relatively infrequent (5% and <1%, respectively), *KRAS* alterations are among the most common driver alterations in CRC (30%–35%).[3] *RAS* somatic alterations (predominantly missense point mutations) typically arise in codons 12, 13, 61, 117, and 146 (Table 1). These hotspot mutations can inhibit GTP hydrolysis and/or prevent GAP binding, locking RAS in the GTP-bound active state, always on, regardless of extracellular stimuli.[6,7]

The prognostic value of *RAS* alterations in CRC remains controversial. *RAS* mutations have been associated with an increased risk of recurrence and death,[8,9] particularly in the presence of specific variant alleles (eg, G12C, G12V).[10–12] However, when controlled for stage, laterality, and treatment, *RAS* status was not found to be independently linked with worse survival outcomes.[13]

KRAS status is highly concordant between primary tumor and metastatic sites because of its early emergence during carcinogenesis, supporting the use of either tumor samples for KRAS testing.[14,15] Opposite to its prognostic value, RAS mutations represent an established negative predictive biomarker for anti-EGFR therapy (cetuximab, panitumumab) because of futile upstream blockade while downstream RAS' aberrant functionality becomes ligand independent.[16,17] Therefore, the development of intracellular blockade strategies with direct inhibition of RAS became crucial,[18,19] shifting RAS testing from negative predictor of anti-EGFR benefit toward a central role as a companion diagnostic for RAS-directed treatments.

Direct RAS Inhibitors

Early attempts at direct RAS inhibition largely failed because of the absence of stable allosteric pockets on RAS, the essential role of wild-type RAS in normal tissues, and compensatory prenylation mechanisms that bypassed pharmacologic blockade.[20] Furthermore, in light of RAS' ubiquitous expression, toxicity was of major concern.[5] Efforts then switched toward the development of mutant allele-selective RAS inhibitors. KRAS G12C replaces glycine with cysteine, which has a reactive thiol (–SH), one of the most nucleophilic side-chain groups in proteins, allowing for electrophilic warheads in small molecules to form covalent bonds. The discovery of a cryptic allosteric pocket adjacent to Switch II (S-PII)—present only in the GDP-bound conformation of KRAS G12C—enabled the development of RAS(OFF) inhibitors that covalently bind this site and trap KRAS in its inactive state.[21]

KRAS G12C(OFF) Inhibitors

Oncogenic *KRAS* G12C mutations occur in approximately 4% of patients with CRC and has been associated with poorer prognosis compared with other *KRAS* mutations and to *KRAS* wild-type tumors.[22–24] *KRAS* G12C covalent inhibitors were initially developed in non–small cell lung cancer (NSCLC), where the mutation is more prevalent (40% of RAS-mutant NSCLC)[25] and single-agent activity is observed.[26,27] However, the colonic epithelium is physiologically EGFR-driven and retains strong RTK feedback circuits,[28,29] justifying the limited single-agent activity of KRAS G12C inhibitors as observed with sotorasib (overall response rate [ORR] of 9.7%)[30] and adagrasib (ORR, 19%)[31] monotherapy—and providing the rationale for combination strategies (Table 2).

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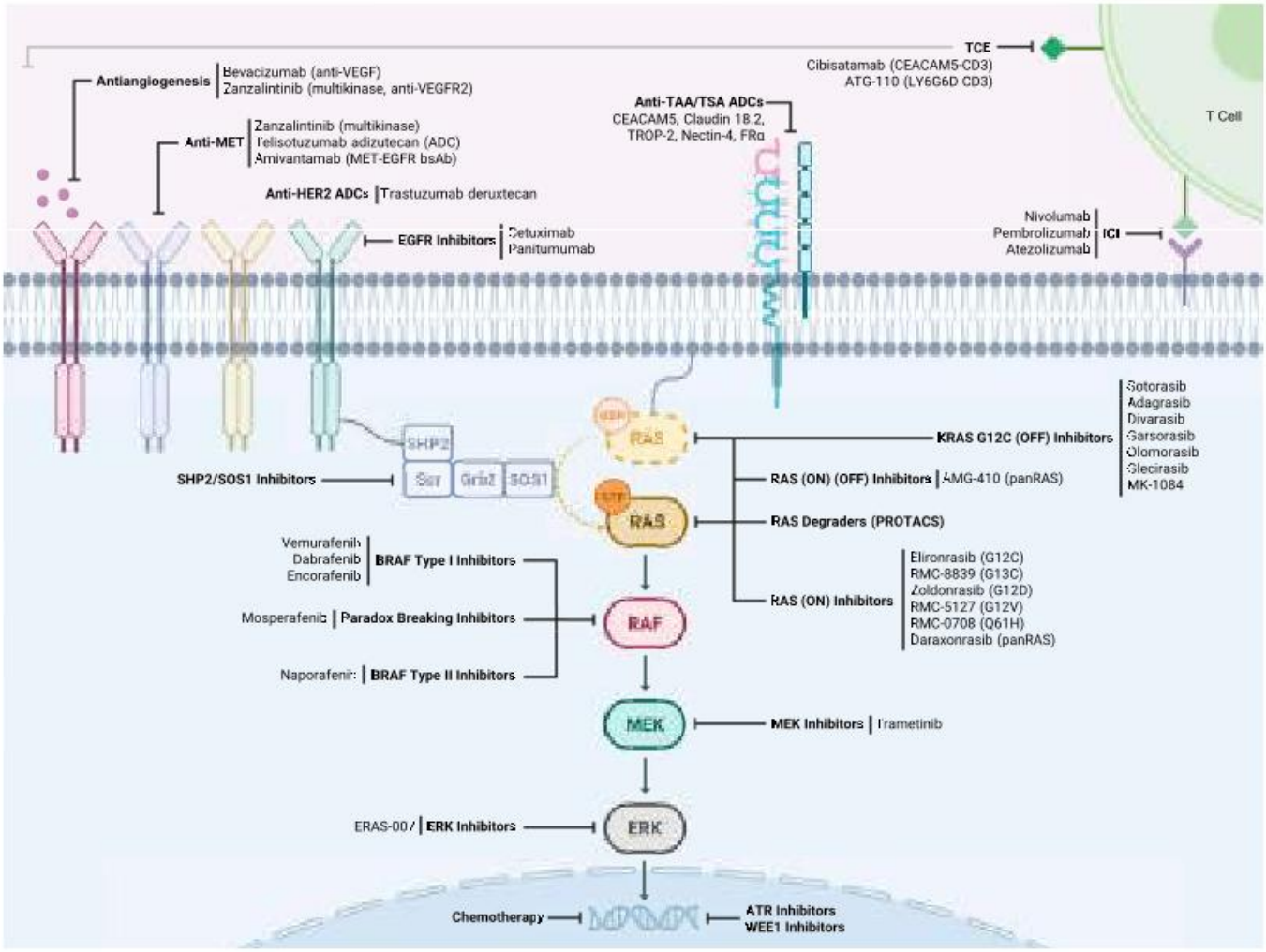

FIG 1. Overview of current and emerging therapeutic strategies for metastatic colorectal cancer, both in monotherapy and combinations. ADC, antibody-drug conjugate; ATR, ataxia telangiectasia and Rad3-related; bsAb, bispecific antibody; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FRα, folate receptor alpha; GDP, guanosine diphosphate; GRB2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; MEK, mitogen-activated ERK kinase; PROTAC, proteolysis targeting chimera; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma small GTPase protein; SHP2, Src homology 2 domain-containing phosphatase 2; SOS1, son of sevenless; TAA, tumor-associated antigens; TCE, T-cell engager; TROP-2, trophoblast cell surface antigen 2; TSA, tumor-specific antigens; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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The logical next step was to then combine KRAS G12C allele-specific inhibitors with EGFR antagonists. The US Food and Drug Administration (FDA) granted accelerated approval in 2024 for the combination of adagrasib and cetuximab for previously treated *KRAS* G12C-mutated metastatic CRC (mCRC) based on the phase I/II KRYSTAL-1 trial. The addition of an anti-EGFR antibody increased both ORR (46%) and mPFS (6.9 months). Expected class-effect adverse events (AEs) were observed including rash, nausea, and diarrhea; 27.7% were grade ≥3 with 29.8% of patients requiring a dose reduction but not drug discontinuation.[31,32]

The pivotal phase III CodeBreaK300 trial explored the combination of sotorasib and panitumumab in patients with KRAS G12C-mutated chemorefractory mCRC. Dual blockade showed an ORR of 26.4%, a median duration of response (mDOR) of 10.1 months, and significantly prolonged progression-free survival (PFS) versus standard-of-care trifluridine-tipiracil or regorafenib (5.6 *v* 2 months; hazard ratio, 0.48 [95% CI, 0.30 to 0.78]; $P = .005$), leading to FDA approval for the combination.[33] The majority of patients receiving sotorasib-panitumumab perceived an improvement in their quality of life compared with those receiving standard-of-care therapy.[34] The safety profile was similar to that one reported for KRYSTAL-1 (with the addition of hypomagnesemia), although up to 45.3% of patients were reported to experience grade ≥3 treatment-related AE (TRAE).

Other G12C inhibitors have been combined with cetuximab for patients with chemorefractory mCRC in phase I/II trials: divarasib demonstrated an ORR of 62.5%, with a mDOR of

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TABLE 1. Overview of RAS Mutations Nomenclature in CRC

			Mutational Hotspots (CRC)							
Exon	aa Length	Functional Domain	Position (gene)	aa Encoded by WT gene	Mut	aa (DNA) Change	HGVS	Hydrolysis Rate[a] (×10-5sec-1)	Affected Motif	Functional Consequence
2	1-37	Encode part of G-domain (catalytic): P-loop (aa 10-16; for phosphate-binding and GTP stabilization) + switch I (aa 30-37)	Codon 12	Glycine (Gly, G): GGT	G12A	Glycine (GGT) > alanine (GCT)	c.35G>C (p.Gly12Ala)	Extremely low (1.3)	P-Loop	Diminished hydrolysis > impaired capacity to convert its on signal (GTP) back into an off signal (GDP)
					G12C	Glycine (GGT) > cysteine (TGT)	c.34G>T (p.Gly12Cys)	Intermediate (49)		
					G12D	Glycine (GGT) > aspartic acid (GAT)	c.35G>A (p.Gly12Asp)	Intermediate (19)		
					G12R	Glycine (GGT) > arginine (CGT)	c.34G>C (p.Gly12Arg)	Extremely low (1.8)		
					G12S	Glycine (GGT) > serine (AGT)	c.34G>A (p.Gly12Ser)	Low		
					G12V	Glycine (GGT) > valine (GTT)	c.35G>T(p.Gly12Val)	Low (4.2)		
			Codon 13	Glycine (Gly, G): GGC	G13D	Glycine (GGC) > aspartic acid (GAC)	c.38G>A(p.Gly13Asp)	Low (9.6)		
3	38-104	Encode part of G-domain (catalytic): Switch I (minor portion; aa 38-40, for engagement with downstream effectors) + Switch II (aa 58-72, for hydrolysis coordination)	Codon 59	Alanine (Ala, A): GCA	A59T	Alanine (GCA) > threonine (ACA)	c.175G>A (p.Ala59Thr)	Low	Switch II	Diminished hydrolysis > impaired capacity to convert its on signal (GTP) back into an off signal (GDP)
			Codon 61	Glutamine (Gln, Q): CAA	Q61H	Glutamine (CAA) > histidine (CAT)	c.183A>T (p.Gln61His)	Extremely low (1.3)		
					Q61K	Glutamine (CAA) > lysine (AAA)	c.181C>A (p.Gln61Lys)	Extremely low		
					Q61L	Glutamine (CAA) > leucine (CTA)	c.182A>T (p.Gln61Leu)	Extremely low (0.8)		
					Q61R	Glutamine (CAA) > arginine (CGA)	c.182A>G(p.Gln61Arg)	Extremely low		
4	105-188/189	Encode part of G-domain (catalytic; guanine binding pockets) + HVR domain (contains CAAX motif, for protein attachment to the cell membrane)	Codon 117	Lysine (Lys, K): AAG	K117N	Lysine (AAG) > asparagine (AAT)	c.351G>C (p.Lys117Asn)	Nearly preserved (~wt), but rapid intrinsic nucleotide exchange (protein remains GTP-bound)	Guanine binding pockets	Loss of ability to hold onto GDP > new GTP molecule built
			Codon 146	Alanine (Ala, A): GCT	A146T	Alanine (GCT) > threonine (ACT)	c.436G>A (p.Ala146Thr)			
					A146V	Alanine (GCT) > valine (GTT)	c.437C>T (p.Ala146Val)			
					A146P	Alanine (GCT) > proline (CCT)	c.436G>C (p.Ala146Pro)			

NOTE. The human RAS gene family (KRAS, NRAS, and HRAS) generally contain four coding exons but can vary slightly because of alternative splicing and noncoding regions. Exon 1 is not herein included, as it primarily functions as the control segment (5′ untranslated region). All herein mutations are single-nucleotide (missense) variants and are relevant to CRC.

Abbreviations: aa, amino acid; CRC, colorectal cancer; HGVS, human genome variation society nomenclature; HVR, hypervariable region; Mut, mutation; WT, wild type.

[a]For reference: RAS wild-type intrinsic hydrolysis rate = 68 $\times 10^{-5}$sec^{-1}.

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TABLE 2. KRAS G12C Inhibitors in Combination for the Treatment of *KRAS* G12C-Mutant mCRC

Variable	Sotorasib		Adagrasib	Divarasib	Garsorasib	Calderasib		Olomorasib	Glecirasib
Developer	Amgen (AMG-510; Lumakras)		Mirati/BMS (Krazati)	Genentech/Roche (GDC-6036)	Inventisbio (D-1553)	Merck (MK-1084)		Eli Lilly (LY3537982)	Jacobio (JAB-21822)
Current status	FDA approved (January 2025), in combination with panitumumab (CodeBreaK-300), with CDx		FDA approved (June 2024), in combination with cetuximab (KRYSTAL-1)	Phase Ib	Phase II	Phase I (KANDLELIT-001)		Phase I (LOXO-RAS-20001)	Phase III (China-only)
MoA[a]	First gen, IC50 100 nM		First gen, IC50 0.1-1 nM	Second gen, IC50 <0.01 nM	Second gen, IC50 18 nM	Second gen; IC50 0.01-10 nM		Second gen; IC50 3.35 nM	Second gen; IC50 1.6 nM
Patient selection	Chemorefractory		Chemorefractory	Chemorefractory; prior KRAS G12Ci allowed (17%)	Chemorefractory	Chemorefractory	Chemorefractory and chemo-naïve	Chemorefractory	Chemorefractory
G12C testing	Prospective (central) therascreen KRAS RGQ PCR Kit (QIAGEN GmbH) on tissue		Tissue (local); 83% concordance on prospective (central) ctDNA	Central blood or local tissue/blood	Tissue/blood (unknown if centrally confirmed)	NA	NA	NA	NA
Prior anti-EGFR	No protocol exclusion of prior anti-EGFR		3% prior anti-EGFR	NA	NA	NA	NA	NA	NA
Regimen	960 mg OD + panitumumab (CodeBreaK-300)[34]	960 mg OD + FOLFIRI + panitumumab (CodeBreaK-101)[41]	600 mg BD + cetuximab (KRYSTAL-1)[31]	400 mg OD + cetuximab[35]	600 mg BD + cetuximab[36]	Dose escalation + cetuximab[37]	Dose escalation + cetuximab + FOLFOX[37]	Dose escalation ± cetuximab[38]	800 mg + cetuximab[39]
ORR	30.2% (18.3-44.3)	57.5% (40.9-73)	46% (28-66)	62.5% (40.6-81.2)	51.7%	50% (32-68)	14% (2-43)	42% (39-93)	50%
mDoR	4.4mo (1.9-6)	6.6mo	7.6mo (5.7-NE)	6.9mo (5.5-12.3)	NA	NA	NA	7.6mo (6.0-12.2)	5.1mo (13.1-NE)
mPFS	5.6mo (HR 0.48; p 0.005)	8.2mo (7-10.8)	6.9mo (5.4-8.1)	8.1mo (5.5-12.3)	7.6mo	NA	NA	7.5mo (6.6-8.8)	6.9mo (5.4-6.9)

[a]All KRAS G12Ci within this table are covalent and irreversible GDP-binders, orally available and highly selective (with the exception of sotorasib, which can also inhibit HRAS G12C).
Abbreviations: BD, twice per day; FDA, US Food and Drug Administration; FOLFIRI, folinic acid, fluorouracil and irinotecan chemotherapy; G12Ci, G12C inhibitor; gen, generation; HR, hazard ratio; IC50, half maximal inhibitory concentration; mDOR, median duration of response; NA, not available; NE, nonestimable; OD, once per day.

6.9 months, mPFS of 8.1 months, and comparable toxicity.[35] The combination of cetuximab with garsorasib led to an ORR of 51.7% and mPFS of 7.6 months, with all grade ≥3 TRAE being attributed to cetuximab and only 6.9% of patients requiring a dose reduction of garsorasib because of transaminitis.[36] Similar ORR was reported for the combination with MK-1084 in the KANDLELIT-001 trial (arm 5).[37] Olomorasib achieved an ORR of 42%, mDOR of 7.6 months, with 24% of grade ≥3 TRAEs, 2% of patients requiring dose reduction of olomorasib, and 22% warranted temporary hold.[38] The Chinese trial of glecirasib reported a distinct safety profile (anemia, hyperbilirubinemia, hypertriglyceridemia), and the results suggest that the combination might outperform monotherapy in terms of ORR—22.7% reported for the single-agent cohort and 50% for glecirasib-cetuximab doublet (no direct comparison); the phase III study is ongoing.[39]

The addition of chemotherapy to the doublet was pursued to provide genotype-independent cytotoxic pressure and address the biological heterogeneity characteristic of mCRC. The CodeBreaK101 (Subprotocol H) phase Ib trial assessed the combination of KRAS G12C inhibitor (sotorasib) with an anti-EGFR antibody (panitumumab) and chemotherapy (folinic acid, fluorouracil and irinotecan chemotherapy [FOLFIRI]). Within the chemorefractory population, the triplet strategy moderately improved ORR (57.5%) in comparison with rates observed with doublet therapy, although mDOR and mPFS were comparable (6.6 and 8.2 months, respectively), while the frequency of grade ≥3 events rose to 50%.[40,41] The same therapeutic strategy was explored in the chemotherapy-naïve cohort of CodeBreaK101, for which a similar rate of TRAEs was observed, along with an encouraging ORR of 75%.[42] Conversely, the triplet MK-1084, cetuximab and modified fluorouracil, leucovorin, and oxaliplatin-6 in the first/second-line metastatic setting of KANDLELIT-001 (arm 6, n = 20) demonstrated an ORR of 14%.[37] The phase III CodeBreaK301 of sotorasib, panitumumab, and FOLFIRI versus FOLFIRI ± bevacizumab in the first-line setting is ongoing.[43]

The FDA approval of sotorasib-panitumumab relies on the companion diagnostic test (CDx) QIAGEN Therascreen KRAS RGQ PCR Kit (on tissue) for the detection of the KRAS G12C mutation—although its status may be determined using other FDA-approved or Clinical Laboratory Improvement Amendments–validated assays, including comprehensive genomic profiling platforms, as indicated by the approval of adagrasib-cetuximab. Notwithstanding, not all trials mandated central mutational confirmation and were heterogeneous regarding its detection on tissue and/or plasma; mutational concordance has been reported to range between 83% and 95%.[32,35,44] Only a limited number of patients with prior exposure to anti-EGFR therapy have been enrolled in KRAS G12C inhibitor trials so far (eg, only one patient reported by KRYSTAL-1). Of note, the emergence of subclonal RAS mutations in plasma upon anti-EGFR therapy in originally RAS wild-type CRC is well established.[45] Because trial exclusion criteria are not always explicit, careful consideration should be given to differentiate tumors with up-front clonal mutation from acquired subclonal mutational status.

Some studies performed dynamic biomarker analyses. A 95% KRAS G12C allele clearance upon treatment was observed in 55% of cases with adagrasib monotherapy and in 88% with cetuximab combination.[31] All patients treated with single-agent divarasib who achieved a partial response had a variant allele frequency (VAF) of <1%[46]; 77.3% of patients who received divarasib-cetuximab had a VAF of <0.5% at cycle 3.[35] Whether ctDNA clearance is predictive of response and/or survival remains to be established.

Resistance to KRAS G12C Inhibition

Several unique or coexisting mechanisms are involved in resistance to KRAS G12C inhibition.[47] Primary resistance because of concomitant gene alterations at baseline was described in CodeBreaK101: 84% of patients presented with co-occurring alterations in *APC*, 74% in *TP53*, 33% in *SMAD4*, 28% in *PIK3CA*, 26% in *EGFR* (mostly amplifications), 19% in *BRAF* (amplifications or class II/III missense mutations), and 14% in *ARID1A*.[44] Similarly, KRYSTAL-1 reported 12%-14% of alterations in *PIK3CA*, 68% *TP53* mutations, and 3%-4% *EGFR* amplifications.[31] *TP53* and *PIK3CA* mutations are frequent in CRC and have been previously reported as able to interfere with KRAS inhibition,[48,49] although this was not observed in limited exploratory analyses with adagrasib.[50]

Acquired resistance to KRAS G12C inhibition is primarily linked to upstream reactivation of EGFR,[51] including its amplification, *MEK1/2* mutations, and secondary *KRAS*/*NRAS*/*HRAS* mutations/copy number gain.[5,32,35] For instance, cfDNA analyses of 58 CRC patients with progressive disease on single-agent KRAS G12C inhibitor revealed a second hit on *KRAS* for 62% of samples, while 69% of patients had at least one newly acquired RAS/MAPK pathway aberration.[52] Furthermore, a signaling shift toward the physiologically redundant PI3K pathway has been described following combined G12C-EGFR inhibition.,[32,47,53] as well as the emergence of subclonal heterogeneity via acquired non-MAPK alterations at low variant allele frequencies.[47]

Pharmacoproperties must also be considered. Dose intensity matters; subtherapeutic doses, in addition to being less efficacious (eg, sotorasib-panitumumab ORR 26.4% for 960 mg *v* 5.7% for 240 mg),[51] might facilitate resistance via partial inhibition rather than complete dependency collapse, expansion of preexisting resistant subclones, or acquisition of secondary mutations that confer reduced drug binding or pathway bypass.[29] Furthermore, dose stability prevents resistance; intermittent target suppression creates pharmacologic windows during which oncogenic signaling can recover

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despite covalent binding. Therefore, although combination strategies are essential, KRAS G12C inhibitor dose interruptions due to chemotherapy may lead to suboptimal dosing and, consequently, resistance. This, in the presence of AEs unrelated to KRAS G12C inhibitors, efforts in maintaining their concentration stability should be considered.

Other RAS(OFF) Inhibitors

RAS(OFF) direct inhibitors for the other major *RAS* mutations are still in development. The structural challenge is the lack of a suitably positioned nucleophile (ie, Cys12) and accessibility that allows for covalent irreversible binding. Furthermore, the majority of mutations within codons 12 and 13 retain at least some degree of intrinsic GTPase activity (G12C maintains similar rates as to wild-type RAS), whereas codon 61 mutations retain minimal hydrolysis rate—both intrinsic and GAP-assisted, for which the off-state-trapping mechanism of covalent G12C inhibition might not be broadly applicable.[54,55]

Promising alternatives might evolve from preclinical work in G12S. The serine hydroxyl (−OH) in G12S is weakly nucleophilic compared to a thiol (−SH) in G12C. However, preclinical suppression of oncogenic signaling in KRAS G12S-mutated cell cultures was achieved by chemical acylation of the noncatalytic serine and consequent covalent engagement of S-IIP.[56,57]

RAS(ON) Inhibitors

The Revolution Medicines' platform is currently developing RAS(ON) inhibitors that do not rely mandatorily on covalency to account for non–cysteine-dependent mutations. These bind through conformational recognition and protein–protein interface stabilization by scaffolding of a tricomplex involving RAS-GTP, cyclophilin A (intracellular chaperone protein), and the drug, which sterically block the interaction with downstream effectors. Daraxonrasib (RMC-6236) is a first-in-class, RAS^{MULTI}(ON) inhibitor designed to inhibit active, GTP-bound KRAS/NRAS/HRAS, including the major relevant alleles (G12D, G12V, G12A, G12S, G13D, Q61X).[58] It is currently being tested in monotherapy (ClinicalTrials.gov identifier: NCT05379985) and in combination with standard-of-care chemotherapy or other investigational agents, including other RAS(ON) inhibitors (ClinicalTrials.gov identifiers: NCT06445062, NCT06128551). RMC-5127 (G12V) and RMC-0708 (Q61H), both allele-specific noncovalent agents due to the targeted non-nucleophilic residues (valine and histidine, respectively), are in the pipeline for clinical testing. Zoldonrasib (RMC-9805), an allele-specific G12D(ON) inhibitor that, despite being a tricomplex agent, also relies on covalency for bonding with Asp-12, has recently received FDA Breakthrough Therapy Status for metastatic NSCLC,[59] based on the phase I/Ib trial (ClinicalTrials.gov identifier: NCT06040541) that also enrolled patients with mCRC.

Perspectives for Targeting RAS

The modest durability of responses and the multiple resistance mechanisms under treatment-selective pressure justify the need to explore novel therapeutic alternatives. In terms of direct RAS-targeting, noncovalent inhibitors that bind both active (ON) and inactive (OFF) states are in preclinical development, either via a P110 allosteric pocket (KAL-21404358)[60] or the formation of a salt bridge with Asp12 (TH-Z835), both unique to *KRAS* G12D.[61] Furthermore, JAB-22000 is being explored as the payload for JAB-BX600, a first-in-class EGFR-KRAS G12D antibody-drug conjugate. Additionally, PROteolysis TArgeting Chimeras that induce proteasomal degradation of oncogenic RAS through recruitment of E3 ubiquitin ligases (ClinicalTrials.gov identifier: NCT07023731) are in development.

Given the extensive feedback regulation within the MAPK pathway, coinhibition of upstream and downstream signaling nodes has emerged as a logical approach to suppress adaptive pathway reactivation beyond EGFR inhibition. Src homology region two domain-containing phosphatase-2 (SHP2) and SOS1 inhibitors offer a means to broadly dampen RAS nucleotide exchange and signaling flux across wild-type and mutant RAS pools.[62]

A summary (nonexhaustive) of broad novel RAS-targeting strategies currently being developed for the treatment of CRC is presented in Figure 1. These include immunomodulatory strategies, such as immune checkpoint inhibitors (ICI), vaccines (ClinicalTrials.gov identifiers: NCT04853017, NCT06411691, NCT04117087), oncolytic viruses (ClinicalTrials.gov identifier: NCT01274624), multispecific antibodies, and adoptive and engager-based T-cell approaches (ClinicalTrials.gov identifier: NCT06218914).[63]

BRAF

Somatic genomic alterations in the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) are found in approximately 10% of colorectal cancers[64] and are categorized into three functional classes based on their requirement for RAF dimerization and RAS activation.[65] Class I *BRAF* mutations (BRAFm) encompass those affecting the V600 residue (exon 15) upon substitution of its valine, functioning as RAS-independent monomers. In turn, class II (non-V600, such as K601, L597; *BRAF* fusions) act as RAS-independent homodimers, with intermediate-high kinase activity, while class III (non-V600; eg, D594, G466) are RAS- and dimer-dependent with impaired kinase activity.[66]

BRAF V600 Inhibitors

Class I BRAFm, the most common and clinically significant alterations of the *BRAF* gene, are the only mutations selectively inhibited by currently available—all type I—BRAF inhibitors (vemurafenib, dabrafenib, encorafenib).[65,67] The most frequent *BRAF* mutation V600E is associated with old

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age, female sex, CMS1 subtype (including MSI-high and hypermethylated tumors), and right-sided tumors. Patients with mCRC harboring this mutation exhibit significantly shorter overall survival and worse response to conventional chemotherapy regimens.[68-73]

The V600 mutations introduce a negative charge that mimics phosphorylation and physically push the αc-helix into the "IN" (active) position, stabilize the DFG-IN conformation, which dismisses the need for BRAF to instinctively dimerize, resulting in a constitutively active monomer. Type I BRAF inhibitors are ATP-competitive antagonists; they bind the ATP pocket in this active conformation and effectively inhibit monomeric BRAF V600E, thereby suppressing downstream MAPK signaling.[74,75]

Early attempts at BRAF inhibitors in monotherapy showed disappointing results because of the rapid development of an adaptive feedback reactivation toward compensatory EGFR-mediated MAPK signaling.[67,76,77]

Consecutive approaches combined type I BRAF inhibitors with EGFR or MEK inhibitors (±chemotherapy), which led to improved response rates and survival outcomes.[78-81] The phase III clinical trial BEACON CRC demonstrated superior efficacy of encorafenib + cetuximab over conventional chemotherapy -while delaying quality-of-life decline, leading to FDA approval in patients with chemo-refractory mCRC.[82,83] The doublet was subsequently explored in the first-line setting within the BREAKWATER trial; combining encorafenib plus cetuximab with fluorouracil-based chemotherapy in previously untreated patients led to an improved response rate and nearly doubled median PFS as well as OS, granting recent FDA approval.[84]

To address reactivation of ERK signaling, the HERKULES-3 phase Ib/II trial recruited patients with mCRC BRAF V600E for treatment with ERAS-007, a novel, potent ERK inhibitor, in combination with encorafenib and cetuximab (EC). Preliminary efficacy data showed an ORR of 40%.[85] Additional strategies incorporating type I BRAF inhibitors in mCRC are presented in Table 3.

Paired ctDNA genomic profiling analyses from the BEACON CRC trial provided preliminary insights into acquired resistance to combinations with BRAF inhibitors.[92] Expectedly, the majority of acquired alterations pertained to the MAPK pathway, followed by *MET* or *ALK* fusions, and were predominately subclonal. Furthermore, SRC kinases have been reported to be activated in BRAFm V600E CRC following therapeutic inhibition of BRAF and EGFR, suggesting that SRC may represent a potential resistance mechanism independent of MAPK signaling.[93,94] Moreover, the analyses provided evidence of a stimulatory effect on T cells by BRAF inhibition thereby supporting the rationale for combining BRAF-targeted treatment with immunotherapy.

For patients with BRAFm V600E and high microsatellite instability (MSI-H) tumors, ICI are currently the preferred first-line treatment option in clinical practice, supported by the findings of the KEYNOTE-177 and CheckMate-8HW trials.[95,96] However, the SEAMARK trial (ClinicalTrials.gov identifier: NCT05217446) is currently evaluating the combination of pembrolizumab with or without encorafenib and cetuximab in the first-line setting.

Contrasting with BRAF wild-type microsatellite stable (MSS) CRC—established cold tumors with limited sensitivity to ICI—BRAFm MSS CRC represents an immunologically distinct subpopulation, enriched for the immune-activated CMS1 signature, PD-L1 expression, and CD8-T cell infiltration.[97] Notably, all patients with BRAFm V600E (n = 3) MSS mCRC included in the randomized METIMMOX trial achieved a complete response after receiving short-course oxaliplatin-based chemotherapy, alternating with nivolumab in the first-line setting.[98] In a phase II trial, mCRC patients with MSS and BRAFm V600E, the combination of PD-1, BRAF, and MEK inhibition showed a promising ORR of 25% and DCR of 75%,[89] whereas a phase I/II study combining encorafenib, cetuximab, and nivolumab demonstrated an ORR of 50% and DCR of 96%. Transcriptomic analysis revealed that non-responding tumors exhibited a higher complement activation signature, whereas an increased interferon-γ—supporting the notion of immune activation—was observed among responders.[86] A randomized phase II trial evaluating encorafenib and cetuximab with or without nivolumab for patients with previously treated MSS, BRAF V600E metastatic mCRC is ongoing.

Perspectives for Targeting RAF

Despite the successful combination of BRAF type I inhibitors and anti-EGFR agents to bypass the adaptive feedback reactivation, the combination is not light on toxicity. Next-generation paradox-breaking BRAF inhibitors emerge as novel therapeutic alternative engineered to intrinsically avoid paradoxical MAPK hyperactivation by interfering with the RAF dimer interface. Mosperafenib (RG6344, RO7276389), with activity against BRAF WT, BRAF V600, RAF1, and brain penetrant, was well tolerated by previously treated patients with mCRC BRAFm V600E, with no reports of squamous cell carcinoma or keratoacanthoma, typical of type I BRAF inhibitors paradoxical activity in normal cells. The ORR was 14.8%-25%, with incremental benefit of mPFS in patients not previously exposed to a BRAFi (mPFS 7.3 months).[99]

Importantly, while non-negligible progress has been made for V600-driven disease, *BRAF* alterations beyond V600 remain treatment orphan. Class II BRAF mutants evade suppression by type I inhibitors because of their reliance on obligate dimer-based signaling; blockade of one protomer of a dimer leads to a conformational shift that, paradoxically, activates the partner protomer. Meanwhile, class III BRAFm have low/absent kinase activity, therefore, type I BRAF inhibitors bind weakly (or not at all), while RAS remains highly

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TABLE 3. Strategies Incorporating Type I BRAF Inhibitors in mCRC[86-88,90,91]

Trial	Phase	Setting	Sample	Treatment	ORR	mPFS, Months	mOS, Months
BREAKWATER Elez et al[84]	III	First-line, MSS	637	Encorafenib + cetuximab + mFOLFOX6	65.7%	12.8	30.3
				Encorafenib + cetuximab	45.6%	6.8	19.5
				Chemotherapy	37.4%	7.1	15.1
BREAKWATER, Cohort 3 Kopetz et al[87]	III	First-line, MSS	147	Encorafenib + cetuximab + FOLFIRI	64.4%	NE	NE
				FOLFIRI ± bevacizumab	39.2%	NE	NE
BEACON CRC Kopetz et al[83]	III	Metastatic, previously treated	665	Encorafenib + binimetinib + cetuximab	26%	4.3	9
				Encorafenib + cetuximab	20%	4.2	8.4
				Cetuximab + chemotherapy	2%	1.5	5.4
ANCHOR CRC Van Cutsem et al[88]	II	Metastatic, previously treated	95	Encorafenib + binimetinib + cetuximab	47.8%	5.8	18.3
IMPROVEMENT Wang et al[81]	II	Advanced/metastatic	21	Cetuximab + vemurafenib + FOLFIRI	81%	9.7	15.4
TAPUR Klute et al[80]	II	Metastatic, previously treated	30	Cobimetinib + vemurafenib	30%	3.6	9
Tian et al[89]	II	Metastatic	37	Dabrafenib + trametinib + spartalizumab	24.3%	4.3	13.6
Yaeger et al[78]	II	Metastatic, previously treated	15	Vemurafenib + panitumumab	13%	3.2	7.6
SWOG1406 Kopetz et al[90]	II	Metastatic	106	Vemurafenib + cetuximab + irinotecan	17%	4.2	9.6
				Cetuximab + irinotecan	4%	2	5.9
SWOG-2107 Morris et al[86]	I/II	Metastatic, MSS, previously treated	26	Encorafenib + cetuximab + nivolumab	46%	7.4	22
Corcoran et al[77]	I	Metastatic	142	Dabrafenib + panitumumab	10%	3.5	13.2
				Trametinib + panitumumab	0%	2.6	8.2
				Dabrafenib + trametinib + panitumumab	21%	4.2	9.1
van Geel et al[91]	Ib	Metastatic, previously treated	54	Encorafenib + cetuximab + alpelisib	17.9%	4.2	NE
				Encorafenib + cetuximab	19.2%	3.7	NE
Hong et al[79]	Ib	Metastatic, previously treated	19	Vemurafenib + cetuximab + irinotecan	35%	7.7	NE

Abbreviations: FOLFIRI, folinic acid, fluorouracil and irinotecan chemotherapy; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin-6; mOS, median overall survival; mPFS, median progression-free survival; MSS, microsatellite stability; NE, nonestimable; ORR, overall response rate.

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active and CRAF continues signaling.[100,101] Novel BRAF-targeting agents are currently in development to hopefully address the lack of targeting alternatives across RAF alterations. Naporafenib (LHX254), a type II pan-RAF inhibitor, designed to inhibit both monomeric and dimeric forms of BRAF and CRAF (while sparing ARAF) by inducing the DFG-out conformation, thereby creating an irregular surface that cannot support the dimerization interface, is currently under investigation.[102]

BEYOND RAS AND RAF

The therapeutic landscape of colorectal cancer (CRC) has evolved substantially with the identification of key molecular subsets, including mismatch repair deficiency and microsatellite instability (dMMR/MSI-H), POLE mutations, tumor molecular burden-high, RAS and BRAF alterations, and human epidermal growth factor receptor 2 (HER2) amplification.[103-108] These discoveries have enabled precision therapies and ICIs for molecularly defined patient populations. However, most CRC, particularly MSS tumors, remain resistant to immunotherapy and lack durable targeted treatment options because of tumor heterogeneity, adaptive resistance mechanisms, and complex tumor microenvironment (TME) interactions that limit traditional driver-based approaches. Advances in comprehensive molecular profiling, spatial biology, and immune characterization are revealing new vulnerabilities beyond canonical RAS and RAF signaling, enabling therapeutic strategies including antibody-drug conjugate (ADC), bispecific and multispecific antibodies, DNA damage response (DDR) targeting, next-generation immunotherapies, TME-directed approaches, cellular therapies, and epigenetic modulation.

Early clinical success with HER2-directed antibody-based combinations was demonstrated in the phase II MOUNTAINEER trial, which established trastuzumab plus tucatinib, a highly selective HER2 tyrosine kinase inhibitor, as an effective regimen in chemotherapy-refractory, HER2-positive, RAS wild-type metastatic CRC.[109] Building on this foundation, HER2-directed antibody-drug conjugates have further expanded therapeutic options in CRC, including for more heavily pretreated populations and selected patients previously treated with HER2-directed therapy. HER2-directed ADCs, particularly trastuzumab deruxtecan, have demonstrated clinically meaningful activity in HER2+ metastatic CRC, establishing proof of concept for this strategy in CRC.[110,111] ADCs exploit tumor-related antigen expression for selective cytotoxic payload delivery. Optimization of linker chemistry, drug-to-antibody (DAR), and topoisomerase I-based payloads has enhanced efficacy in biologically heterogeneous CRC, with topoisomerase I inhibitors providing bystander killing and reduced susceptibility to P-glycoprotein–mediated efflux.[110–113] Building on the proof of concept established by HER2-directed ADCs, multiple additional antigen classes are being explored in CRC. These include adhesion molecules (CEACAM5, CDH17), tight junction proteins (claudins 1, 2, 18.2), growth factor receptors (HER3, MET, EGFR), immune-related targets (B7-H3, PD-L1), development and stem cell markers (LGR5, ROR1), and others such as tissue factor, TROP-2, mesothelin, nectin-4, ADAM-9, Ca 19-9, guanylyl cyclase C, folate receptor alpha, PTK7, and TM4SF1. Emerging evidence suggests that certain ADCs may also modulate antitumor immunity via immunogenic cell death and STING pathway activation, providing rational combinations with ICIs[114,115]; however, resistance remains multifactorial, involving antigen heterogeneity, impaired internalization, altered lysosomal processing, drug efflux, and microenvironmental barriers such as hypoxia and macrophage sequestration.[115,116]

Angiogenesis-targeted therapies remain foundational in metastatic CRC, with VEGF inhibition improving outcomes even in refractory disease as demonstrated in SUNLIGHT and FRESCO/FRESCO-2 trials.[117–122] Building on this backbone, combinations of VEGF pathway inhibition with ICIs have been explored to sensitize MSS tumors to immunotherapy. However, in contrast to the positive results of STELLAR-303 evaluating zanzalintinib plus atezolizumab, prior strategies combining PD-1 blockade with anti-VEGF antibodies such as bevacizumab (ATEZOTRIBE), VEGF pathway-targeted multikinase inhibitors including lenvatinib (LEAP-017) and regorafenib-based combinations with ipilimumab and nivolumab (RIN) have been largely negative.[120,123–125] Similarly, efforts to convert immunologically cold MSS tumors into inflamed, ICI-responsive phenotypes through chemotherapy, radiotherapy, or other targeted combinations have generally failed which suggests that effective immunotherapy sensitization in MSS CRC likely requires more precise modulation of the TME and biomarker-guided patient selection.[126]

Bispecific and multispecific antibody platforms aim to overcome pathway redundancy and antigen heterogeneity through coordinated targeting. Tumor-intrinsic constructs such as EGFR-MET and VEGF-DLL4 bispecific antibodies have demonstrated early signals of activity in metastatic CRC, with efficacy influenced by tumor sidedness and prior therapy exposure.[127–129] In parallel, T-cell engaging bispecific antibodies are being developed to promote T-cell recruitment and activation within tumors. For example, cibisatamab, which targets carcinoembryonic antigen (CEA) and CD3, is being evaluated in combination with ICIs in early-phase studies.[130] Additional bispecific platforms pair PD-1 blockade with complementary immune or tumor microenvironment pathways such as CTLA-4, VEGF, and transforming growth factor (TGF)-β, integrating checkpoint inhibition with modulation of angiogenesis and stromal immune suppression.[131] In addition, strategies incorporating fibroblast activation protein–α (FAP)-targeted 4-1BB agonists represent a next-generation approach to costimulatory immunotherapy to deliver potent T-cell and NK cell activation to the TME.[132] Next-generation ICIs, including Fc-engineered and conditionally activated or masked CTLA-4 antibodies designed to enhance intratumoral regulatory T-cell depletion through augmented Fc-mediated effector function while improving tumor-specific immune response and reducing systemic toxicity, have demonstrated encouraging efficacy with manageable safety profiles.[133–135] Consistent with this strategy, botensilimab combined with the anti–PD-1 antibody balstilimab produced clinical activity in the phase I C-800-01 study in heavily pretreated MSS mCRC, with an ORR of 17%, a DCR of 61%, and a 12-month OS rate of 60%. Clinical benefit was largely confined to patients without active liver metastases, underscoring the immunosuppressive role of the liver microenvironment and placing liver metastasis status as a potential predictor of immunotherapy benefit.[135,136]

Beyond CTLA-4, combination strategies are exploring additional checkpoint targets, including LAG-3, TIGIT, and TIM-3, alongside PD-1/PD-L1 inhibitors to restore exhausted T-cell function and overcome adaptive resistance, although clinical activity in MSS CRC remains modest.[137–139]

Beyond checkpoint blockade, cellular therapies such as chimeric antigen receptor T-cell therapy (CAR-T) cells represent a promising but challenging strategy in CRC. Their efficacy has historically been constrained by antigen heterogeneity and the immunosuppressive TME. More recently, early studies targeting CEA and GUCY2C have demonstrated feasibility, manageable toxicity, and preliminary antitumor activity. Additional antigen-directed approaches, including EpCAM, HER2, and TAG-72-targeted CAR-T strategies, are under investigation, although concerns regarding on-target, off-tumor toxicity and limited trafficking in solid tumors remain.[140,141]

Emerging approaches increasingly focus on TME-directed targets that can relieve local immune suppression, enhance

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immune cell trafficking into tumor nests, and restore effector function. These include CCR8-mediated regulatory T-cell activity, TGF-β–driven stromal fibrosis, adenosine-mediated metabolic suppression, CSF1R-dependent macrophage polarization, and CXCR1/2-driven myeloid recruitment. Innate immune activation via STING agonists and macrophage checkpoint inhibition through CD47 blockade aim to enhance antigen presentation and promote adaptive immune priming.[142-145]

Beyond TME roles, a growing body of evidence supports that many CRCs exhibit chronic replication stress driven by oncogenic signaling and defective checkpoint control, creating therapeutic vulnerability to DDR inhibition. Although PARP inhibitors have shown limited activity in unselected CRC, ATR, and WEE1 inhibitors have demonstrated signals of benefit in molecular selected subsets, such as TP-53 mutant and replication stress-high tumors.[146] Finally, epigenetic dysregulation also contributes to immune evasion in MSS CRC by altering antigen presentation, interferon signaling, and endogenous retroviral expression. Epigenetic therapies, including DNMT and HDAC inhibitors, can induce viral mimicry states that increase tumor immunogenicity, representing an orthogonal approach to sensitize tumors to ICIs through modulation of tumor-intrinsic immune signaling.[147]

Next generation of precision oncology in CRC will increasingly rely on integrated, multidimensional biomarker strategies that capture tumor-intrinsic features, TME contexture, and dynamic evolution under therapy. By combining spatial and molecular profiling with AI-driven interpretation, clinicians may soon be able to personalize treatment selection, anticipate resistance, and adapt therapy in real time, ultimately expanding the benefits of immunotherapy and targeted interventions to a broader CRC population.[148,149]

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

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Emerging and Established Targets in Colorectal Cancer: Translating Biology Into Therapeutics

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OVERVIEW

Alterations in the mitogen-activated protein kinase (MAPK) pathway play a central role in colorectal cancer (CRC) tumor biology, therapeutic response, and resistance. *RAS* oncogenic mutations are present in up to 35% of CRC; they represent constitutively active molecular switches that impair GTP hydrolysis and promote ligand-independent signaling. The development of allele-specific KRAS G12C inhibitors exploits a cryptic pocket to trap the protein in its inactive (OFF) conformation. In metastatic CRC, where EGFR feedback loop limits monotherapy efficacy, combinations of KRAS G12C inhibitors with EGFR blockade and chemotherapy have demonstrated meaningful activity. Parallel efforts allowed the development of RAS(ON) inhibitors that sterically block the interaction with downstream effectors. Co-occurring genomic alterations, MAPK pathway reactivation, and pharmacologic limitations drive primary and acquired resistance. *BRAF V600* mutations drive approximately 10% of CRCs; first-generation, type I BRAF inhibitors require combination with upstream EGFR, downstream MEK/ERK blockade to overcome adaptive feedback reactivation. Emerging strategies include paradox breaking RAF inhibitors, type II pan-RAS inhibitors, and immunotherapy combinations, particularly relevant for the immune-activated phenotype of BRAF-mutant microsatellite stable tumors. Beyond *RAS* and *RAF*, novel therapeutic avenues (such as antibody-drug conjugates, bispecific antibodies, DNA damage response inhibitors, and tumor microenvironment modulating agents) are reshaping precision oncology in CRC. Integrating multiomics profiling with dynamic biomarkers may enable durable activity and personalized treatment strategies.

MITOGEN-ACTIVATED PROTEIN KINASE SIGNALING PATHWAY

The RAS/RAF/MEK/ERK signaling pathway (Fig 1) is physiologically crucial for regulation of vital cell functions, including proliferation, differentiation, mitosis, and apoptosis. The conventional pathway is initiated by the binding of extracellular ligands (first messenger) to their corresponding transmembrane receptor tyrosine kinase (RTK), triggering their dimerization (signal transduction) and autophosphorylation. This allows for the recruitment of Src homology 2 domain-containing phosphatase 2 (SHP2), tyrosine-protein kinase Src, the adaptor protein growth factor receptor-bound protein 2 (Grb2), and subsequently of son of sevenless 1 (SOS1) to act as a guanine nucleotide exchange factor (GEF) that catalyzes the exchange of GDP for GTP on RAS, thereby converting RAS from its inactive (OFF) GDP-bound state to its active (ON) GTP-bound state. Activated RAS-GTP recruits RAF kinases to the plasma membrane via direct binding, promoting RAF dimerization and conformational activation, followed by phosphorylation of MEK1/2 and downstream ERK1/2. Activated ERK translocates to the nucleus, where it regulates transcription factor activity and gene expression. Activated ERK mediates multiple negative feedback loops that suppress upstream signaling. RAS has intrinsically slow GTPase activity, but its hydrolysis function is markedly accelerated by GTPase-activating proteins (GAPs), such as neurofibromin 1 (NF-1), leading to protein resynthesis half-life of 23 hours.[1,2]

Colorectal cancer is a classical mitogen-activated protein kinase (MAPK)–driven malignancy, with aberrant activity across the cascade present in 55%-60% of tumors via gain-of-function mutations, loss of negative regulators, and upstream receptor overactivation. The result is constitutive ERK signaling, independent of ligand binding.

Notably, activating mutations in *KRAS*/*NRAS* and *BRAF* V600E are almost invariably mutually exclusive in colorectal cancer (CRC), reflecting their functional redundancy as dominant drivers of MAPK pathway activation. Either alteration alone is sufficient to sustain constitutive ERK signaling; combined activation does not confer additional selective advantage and may be negatively selected because

PRACTICAL APPLICATIONS

- Genomic profiling is crucial in metastatic colorectal cancer (CRC) management: *RAS* and *BRAF* alterations govern prognosis and eligibility for targeted therapies.
- The expanding landscape of RAS directed therapies, including RAS(OFF) and RAS(ON) inhibitors, will enable a broader range of actionable *KRAS* and *NRAS* allele-specific mutations.
- *For BRAF V600E*-mutant CRC, combination regimens of BRAF and EGFR inhibitors are now established therapeutic options. Paradox breaking RAF and ERK inhibitors may soon expand beyond V600-mutant allele.
- The growing pipeline of antibody-drug conjugates targeting human epidermal growth factor receptor 2, CEACAM5, CLDN18.2, and other antigens may soon offer novel treatment strategies for mCRC
- Integration of ctDNA dynamics, immune signatures, and replication stress biomarkers will allow real-time treatment adaptation, personalized, and durable therapeutic strategies across CRC subtypes.

of excessive pathway output.[3] Beyond the MAPK canonical pathway, because of its direct coupling to RAS, evolutionary conservation, and central role in controlling proliferation, RAS functions as a signaling hub for alternative effector pathways, such as PI3K–AKT–mTOR (critical for cell survival) and RalGDS (for invasion and metastasis), determined by effector availability, subcellular localization, feedback regulation, and co-occurring genomic alterations.[4,5]

RAS

The *RAS* family of proto-oncogenes *KRAS* (chromosome 12p12.1), *HRAS* (11p15.5), and *NRAS* (1p13.2) encode their respective small GTP-binding hydrolases KRAS (Kirsten RAS), HRAS (Harvey RAS), and NRAS (Neuroblastoma RAS) that function as molecular binary switches. The three RAS proteins share approximately 85% sequence homology, leading to near-identical catalytic domains.

Although *NRAS* and *HRAS* mutations are relatively infrequent (5% and <1%, respectively), *KRAS* alterations are among the most common driver alterations in CRC (30%–35%).[3] *RAS* somatic alterations (predominantly missense point mutations) typically arise in codons 12, 13, 61, 117, and 146 (Table 1). These hotspot mutations can inhibit GTP hydrolysis and/or prevent GAP binding, locking RAS in the GTP-bound active state, always on, regardless of extracellular stimuli.[6,7]

The prognostic value of *RAS* alterations in CRC remains controversial. *RAS* mutations have been associated with an increased risk of recurrence and death,[8,9] particularly in the presence of specific variant alleles (eg, G12C, G12V).[10–12] However, when controlled for stage, laterality, and treatment, *RAS* status was not found to be independently linked with worse survival outcomes.[13]

KRAS status is highly concordant between primary tumor and metastatic sites because of its early emergence during carcinogenesis, supporting the use of either tumor samples for KRAS testing.[14,15] Opposite to its prognostic value, RAS mutations represent an established negative predictive biomarker for anti-EGFR therapy (cetuximab, panitumumab) because of futile upstream blockade while downstream RAS' aberrant functionality becomes ligand independent.[16,17] Therefore, the development of intracellular blockade strategies with direct inhibition of RAS became crucial,[18,19] shifting RAS testing from negative predictor of anti-EGFR benefit toward a central role as a companion diagnostic for RAS-directed treatments.

Direct RAS Inhibitors

Early attempts at direct RAS inhibition largely failed because of the absence of stable allosteric pockets on RAS, the essential role of wild-type RAS in normal tissues, and compensatory prenylation mechanisms that bypassed pharmacologic blockade.[20] Furthermore, in light of RAS' ubiquitous expression, toxicity was of major concern.[5] Efforts then switched toward the development of mutant allele-selective RAS inhibitors. KRAS G12C replaces glycine with cysteine, which has a reactive thiol (–SH), one of the most nucleophilic side-chain groups in proteins, allowing for electrophilic warheads in small molecules to form covalent bonds. The discovery of a cryptic allosteric pocket adjacent to Switch II (S-PII)—present only in the GDP-bound conformation of KRAS G12C—enabled the development of RAS(OFF) inhibitors that covalently bind this site and trap KRAS in its inactive state.[21]

KRAS G12C(OFF) Inhibitors

Oncogenic *KRAS* G12C mutations occur in approximately 4% of patients with CRC and has been associated with poorer prognosis compared with other *KRAS* mutations and to *KRAS* wild-type tumors.[22–24] *KRAS* G12C covalent inhibitors were initially developed in non–small cell lung cancer (NSCLC), where the mutation is more prevalent (40% of RAS-mutant NSCLC)[25] and single-agent activity is observed.[26,27] However, the colonic epithelium is physiologically EGFR-driven and retains strong RTK feedback circuits,[28,29] justifying the limited single-agent activity of KRAS G12C inhibitors as observed with sotorasib (overall response rate [ORR] of 9.7%)[30] and adagrasib (ORR, 19%)[31] monotherapy—and providing the rationale for combination strategies (Table 2).

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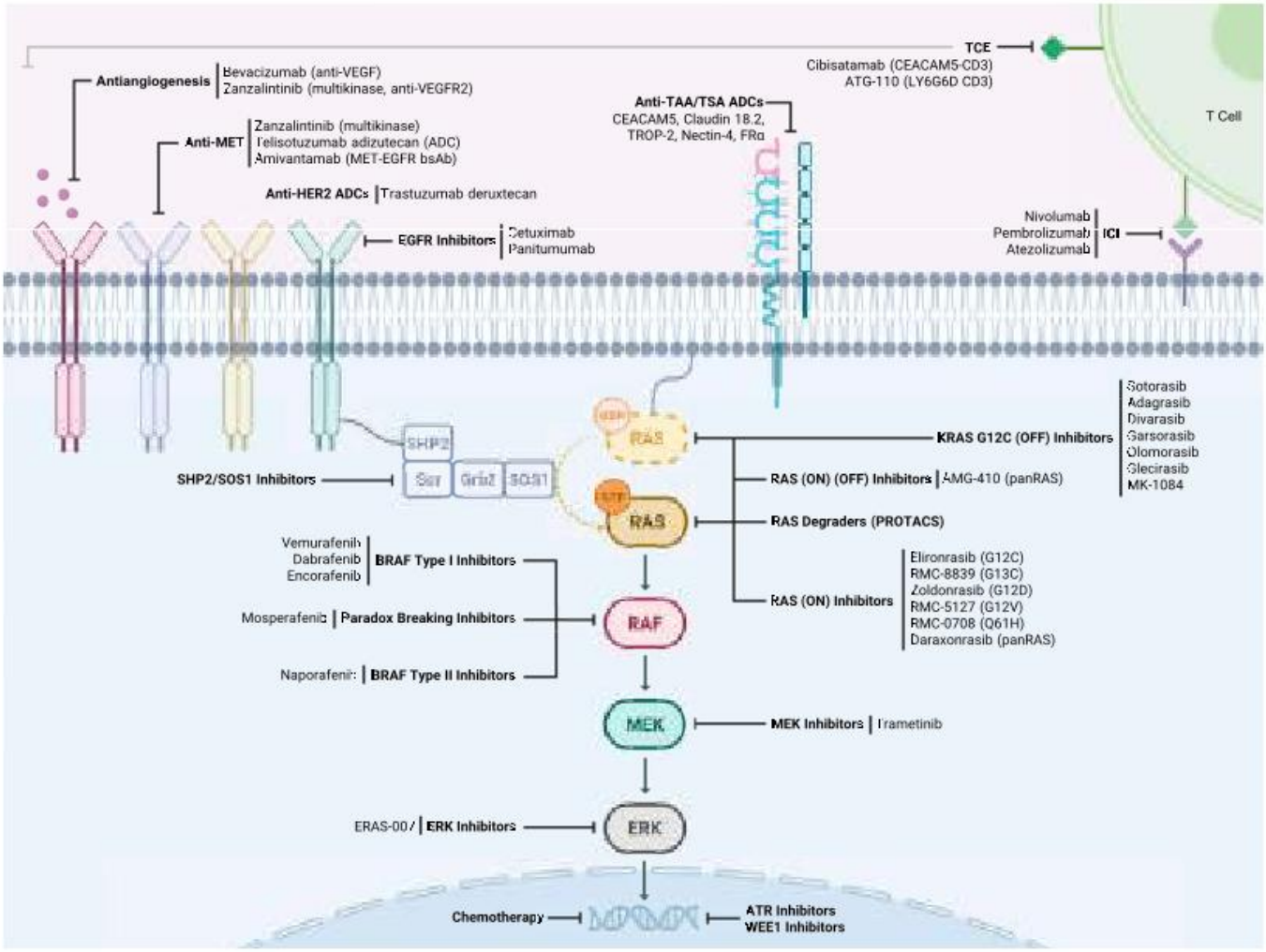

FIG 1. Overview of current and emerging therapeutic strategies for metastatic colorectal cancer, both in monotherapy and combinations. ADC, antibody-drug conjugate; ATR, ataxia telangiectasia and Rad3-related; bsAb, bispecific antibody; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FRα, folate receptor alpha; GDP, guanosine diphosphate; GRB2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; MEK, mitogen-activated ERK kinase; PROTAC, proteolysis targeting chimera; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma small GTPase protein; SHP2, Src homology 2 domain-containing phosphatase 2; SOS1, son of sevenless; TAA, tumor-associated antigens; TCE, T-cell engager; TROP-2, trophoblast cell surface antigen 2; TSA, tumor-specific antigens; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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The logical next step was to then combine KRAS G12C allele-specific inhibitors with EGFR antagonists. The US Food and Drug Administration (FDA) granted accelerated approval in 2024 for the combination of adagrasib and cetuximab for previously treated *KRAS* G12C-mutated metastatic CRC (mCRC) based on the phase I/II KRYSTAL-1 trial. The addition of an anti-EGFR antibody increased both ORR (46%) and mPFS (6.9 months). Expected class-effect adverse events (AEs) were observed including rash, nausea, and diarrhea; 27.7% were grade ≥3 with 29.8% of patients requiring a dose reduction but not drug discontinuation.[31,32]

The pivotal phase III CodeBreaK300 trial explored the combination of sotorasib and panitumumab in patients with KRAS G12C-mutated chemorefractory mCRC. Dual blockade showed an ORR of 26.4%, a median duration of response (mDOR) of 10.1 months, and significantly prolonged progression-free survival (PFS) versus standard-of-care trifluridine-tipiracil or regorafenib (5.6 *v* 2 months; hazard ratio, 0.48 [95% CI, 0.30 to 0.78]; $P = .005$), leading to FDA approval for the combination.[33] The majority of patients receiving sotorasib-panitumumab perceived an improvement in their quality of life compared with those receiving standard-of-care therapy.[34] The safety profile was similar to that one reported for KRYSTAL-1 (with the addition of hypomagnesemia), although up to 45.3% of patients were reported to experience grade ≥3 treatment-related AE (TRAE).

Other G12C inhibitors have been combined with cetuximab for patients with chemorefractory mCRC in phase I/II trials: divarasib demonstrated an ORR of 62.5%, with a mDOR of

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TABLE 1. Overview of RAS Mutations Nomenclature in CRC

			Mutational Hotspots (CRC)							
Exon	aa Length	Functional Domain	Position (gene)	aa Encoded by WT gene	Mut	aa (DNA) Change	HGVS	Hydrolysis Rate[a] (×10-5sec-1)	Affected Motif	Functional Consequence
2	1-37	Encode part of G-domain (catalytic): P-loop (aa 10-16; for phosphate-binding and GTP stabilization) + switch I (aa 30-37)	Codon 12	Glycine (Gly, G): GGT	G12A	Glycine (GGT) > alanine (GCT)	c.35G>C (p.Gly12Ala)	Extremely low (1.3)	P-Loop	Diminished hydrolysis > impaired capacity to convert its on signal (GTP) back into an off signal (GDP)
					G12C	Glycine (GGT) > cysteine (TGT)	c.34G>T (p.Gly12Cys)	Intermediate (49)		
					G12D	Glycine (GGT) > aspartic acid (GAT)	c.35G>A (p.Gly12Asp)	Intermediate (19)		
					G12R	Glycine (GGT) > arginine (CGT)	c.34G>C (p.Gly12Arg)	Extremely low (1.8)		
					G12S	Glycine (GGT) > serine (AGT)	c.34G>A (p.Gly12Ser)	Low		
					G12V	Glycine (GGT) > valine (GTT)	c.35G>T(p.Gly12Val)	Low (4.2)		
			Codon 13	Glycine (Gly, G): GGC	G13D	Glycine (GGC) > aspartic acid (GAC)	c.38G>A(p.Gly13Asp)	Low (9.6)		
3	38-104	Encode part of G-domain (catalytic): Switch I (minor portion; aa 38-40, for engagement with downstream effectors) + Switch II (aa 58-72, for hydrolysis coordination)	Codon 59	Alanine (Ala, A): GCA	A59T	Alanine (GCA) > threonine (ACA)	c.175G>A (p.Ala59Thr)	Low	Switch II	Diminished hydrolysis > impaired capacity to convert its on signal (GTP) back into an off signal (GDP)
			Codon 61	Glutamine (Gln, Q): CAA	Q61H	Glutamine (CAA) > histidine (CAT)	c.183A>T (p.Gln61His)	Extremely low (1.3)		
					Q61K	Glutamine (CAA) > lysine (AAA)	c.181C>A (p.Gln61Lys)	Extremely low		
					Q61L	Glutamine (CAA) > leucine (CTA)	c.182A>T (p.Gln61Leu)	Extremely low (0.8)		
					Q61R	Glutamine (CAA) > arginine (CGA)	c.182A>G(p.Gln61Arg)	Extremely low		
4	105-188/189	Encode part of G-domain (catalytic; guanine binding pockets) + HVR domain (contains CAAX motif, for protein attachment to the cell membrane)	Codon 117	Lysine (Lys, K): AAG	K117N	Lysine (AAG) > asparagine (AAT)	c.351G>C (p.Lys117Asn)	Nearly preserved (~wt), but rapid intrinsic nucleotide exchange (protein remains GTP-bound)	Guanine binding pockets	Loss of ability to hold onto GDP > new GTP molecule built
			Codon 146	Alanine (Ala, A): GCT	A146T	Alanine (GCT) > threonine (ACT)	c.436G>A (p.Ala146Thr)			
					A146V	Alanine (GCT) > valine (GTT)	c.437C>T (p.Ala146Val)			
					A146P	Alanine (GCT) > proline (CCT)	c.436G>C (p.Ala146Pro)			

NOTE. The human RAS gene family (KRAS, NRAS, and HRAS) generally contain four coding exons but can vary slightly because of alternative splicing and noncoding regions. Exon 1 is not herein included, as it primarily functions as the control segment (5′ untranslated region). All herein mutations are single-nucleotide (missense) variants and are relevant to CRC.

Abbreviations: aa, amino acid; CRC, colorectal cancer; HGVS, human genome variation society nomenclature; HVR, hypervariable region; Mut, mutation; WT, wild type.

[a]For reference: RAS wild-type intrinsic hydrolysis rate = 68 $\times 10^{-5}$sec^{-1}.

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TABLE 2. KRAS G12C Inhibitors in Combination for the Treatment of *KRAS* G12C-Mutant mCRC

Variable	Sotorasib		Adagrasib	Divarasib	Garsorasib	Calderasib		Olomorasib	Glecirasib
Developer	Amgen (AMG-510; Lumakras)		Mirati/BMS (Krazati)	Genentech/Roche (GDC-6036)	Inventisbio (D-1553)	Merck (MK-1084)		Eli Lilly (LY3537982)	Jacobio (JAB-21822)
Current status	FDA approved (January 2025), in combination with panitumumab (CodeBreaK-300), with CDx		FDA approved (June 2024), in combination with cetuximab (KRYSTAL-1)	Phase Ib	Phase II	Phase I (KANDLELIT-001)		Phase I (LOXO-RAS-20001)	Phase III (China-only)
MoA[a]	First gen, IC50 100 nM		First gen, IC50 0.1-1 nM	Second gen, IC50 <0.01 nM	Second gen, IC50 18 nM	Second gen; IC50 0.01-10 nM		Second gen; IC50 3.35 nM	Second gen; IC50 1.6 nM
Patient selection	Chemorefractory		Chemorefractory	Chemorefractory; prior KRAS G12Ci allowed (17%)	Chemorefractory	Chemorefractory	Chemorefractory and chemo-naïve	Chemorefractory	Chemorefractory
G12C testing	Prospective (central) therascreen KRAS RGQ PCR Kit (QIAGEN GmbH) on tissue		Tissue (local); 83% concordance on prospective (central) ctDNA	Central blood or local tissue/blood	Tissue/blood (unknown if centrally confirmed)	NA	NA	NA	NA
Prior anti-EGFR	No protocol exclusion of prior anti-EGFR		3% prior anti-EGFR	NA	NA	NA	NA	NA	NA
Regimen	960 mg OD + panitumumab (CodeBreaK-300)[34]	960 mg OD + FOLFIRI + panitumumab (CodeBreaK-101)[41]	600 mg BD + cetuximab (KRYSTAL-1)[31]	400 mg OD + cetuximab[35]	600 mg BD + cetuximab[36]	Dose escalation + cetuximab[37]	Dose escalation + cetuximab + FOLFOX[37]	Dose escalation ± cetuximab[38]	800 mg + cetuximab[39]
ORR	30.2% (18.3-44.3)	57.5% (40.9-73)	46% (28-66)	62.5% (40.6-81.2)	51.7%	50% (32-68)	14% (2-43)	42% (39-93)	50%
mDoR	4.4mo (1.9-6)	6.6mo	7.6mo (5.7-NE)	6.9mo (5.5-12.3)	NA	NA	NA	7.6mo (6.0-12.2)	5.1mo (13.1-NE)
mPFS	5.6mo (HR 0.48; p 0.005)	8.2mo (7-10.8)	6.9mo (5.4-8.1)	8.1mo (5.5-12.3)	7.6mo	NA	NA	7.5mo (6.6-8.8)	6.9mo (5.4-6.9)

[a]All KRAS G12Ci within this table are covalent and irreversible GDP-binders, orally available and highly selective (with the exception of sotorasib, which can also inhibit HRAS G12C).
Abbreviations: BD, twice per day; FDA, US Food and Drug Administration; FOLFIRI, folinic acid, fluorouracil and irinotecan chemotherapy; G12Ci, G12C inhibitor; gen, generation; HR, hazard ratio; IC50, half maximal inhibitory concentration; mDOR, median duration of response; NA, not available; NE, nonestimable; OD, once per day.

6.9 months, mPFS of 8.1 months, and comparable toxicity.[35] The combination of cetuximab with garsorasib led to an ORR of 51.7% and mPFS of 7.6 months, with all grade ≥3 TRAE being attributed to cetuximab and only 6.9% of patients requiring a dose reduction of garsorasib because of transaminitis.[36] Similar ORR was reported for the combination with MK-1084 in the KANDLELIT-001 trial (arm 5).[37] Olomorasib achieved an ORR of 42%, mDOR of 7.6 months, with 24% of grade ≥3 TRAEs, 2% of patients requiring dose reduction of olomorasib, and 22% warranted temporary hold.[38] The Chinese trial of glecirasib reported a distinct safety profile (anemia, hyperbilirubinemia, hypertriglyceridemia), and the results suggest that the combination might outperform monotherapy in terms of ORR—22.7% reported for the single-agent cohort and 50% for glecirasib-cetuximab doublet (no direct comparison); the phase III study is ongoing.[39]

The addition of chemotherapy to the doublet was pursued to provide genotype-independent cytotoxic pressure and address the biological heterogeneity characteristic of mCRC. The CodeBreaK101 (Subprotocol H) phase Ib trial assessed the combination of KRAS G12C inhibitor (sotorasib) with an anti-EGFR antibody (panitumumab) and chemotherapy (folinic acid, fluorouracil and irinotecan chemotherapy [FOLFIRI]). Within the chemorefractory population, the triplet strategy moderately improved ORR (57.5%) in comparison with rates observed with doublet therapy, although mDOR and mPFS were comparable (6.6 and 8.2 months, respectively), while the frequency of grade ≥3 events rose to 50%.[40,41] The same therapeutic strategy was explored in the chemotherapy-naïve cohort of CodeBreaK101, for which a similar rate of TRAEs was observed, along with an encouraging ORR of 75%.[42] Conversely, the triplet MK-1084, cetuximab and modified fluorouracil, leucovorin, and oxaliplatin-6 in the first/second-line metastatic setting of KANDLELIT-001 (arm 6, n = 20) demonstrated an ORR of 14%.[37] The phase III CodeBreaK301 of sotorasib, panitumumab, and FOLFIRI versus FOLFIRI ± bevacizumab in the first-line setting is ongoing.[43]

The FDA approval of sotorasib-panitumumab relies on the companion diagnostic test (CDx) QIAGEN Therascreen KRAS RGQ PCR Kit (on tissue) for the detection of the KRAS G12C mutation—although its status may be determined using other FDA-approved or Clinical Laboratory Improvement Amendments–validated assays, including comprehensive genomic profiling platforms, as indicated by the approval of adagrasib-cetuximab. Notwithstanding, not all trials mandated central mutational confirmation and were heterogeneous regarding its detection on tissue and/or plasma; mutational concordance has been reported to range between 83% and 95%.[32,35,44] Only a limited number of patients with prior exposure to anti-EGFR therapy have been enrolled in KRAS G12C inhibitor trials so far (eg, only one patient reported by KRYSTAL-1). Of note, the emergence of subclonal RAS mutations in plasma upon anti-EGFR therapy in originally RAS wild-type CRC is well established.[45] Because trial exclusion criteria are not always explicit, careful consideration should be given to differentiate tumors with up-front clonal mutation from acquired subclonal mutational status.

Some studies performed dynamic biomarker analyses. A 95% KRAS G12C allele clearance upon treatment was observed in 55% of cases with adagrasib monotherapy and in 88% with cetuximab combination.[31] All patients treated with single-agent divarasib who achieved a partial response had a variant allele frequency (VAF) of <1%[46]; 77.3% of patients who received divarasib-cetuximab had a VAF of <0.5% at cycle 3.[35] Whether ctDNA clearance is predictive of response and/or survival remains to be established.

Resistance to KRAS G12C Inhibition

Several unique or coexisting mechanisms are involved in resistance to KRAS G12C inhibition.[47] Primary resistance because of concomitant gene alterations at baseline was described in CodeBreaK101: 84% of patients presented with co-occurring alterations in *APC*, 74% in *TP53*, 33% in *SMAD4*, 28% in *PIK3CA*, 26% in *EGFR* (mostly amplifications), 19% in *BRAF* (amplifications or class II/III missense mutations), and 14% in *ARID1A*.[44] Similarly, KRYSTAL-1 reported 12%-14% of alterations in *PIK3CA*, 68% *TP53* mutations, and 3%-4% *EGFR* amplifications.[31] *TP53* and *PIK3CA* mutations are frequent in CRC and have been previously reported as able to interfere with KRAS inhibition,[48,49] although this was not observed in limited exploratory analyses with adagrasib.[50]

Acquired resistance to KRAS G12C inhibition is primarily linked to upstream reactivation of EGFR,[51] including its amplification, *MEK1/2* mutations, and secondary *KRAS*/*NRAS*/*HRAS* mutations/copy number gain.[5,32,35] For instance, cfDNA analyses of 58 CRC patients with progressive disease on single-agent KRAS G12C inhibitor revealed a second hit on *KRAS* for 62% of samples, while 69% of patients had at least one newly acquired RAS/MAPK pathway aberration.[52] Furthermore, a signaling shift toward the physiologically redundant PI3K pathway has been described following combined G12C-EGFR inhibition.,[32,47,53] as well as the emergence of subclonal heterogeneity via acquired non-MAPK alterations at low variant allele frequencies.[47]

Pharmacoproperties must also be considered. Dose intensity matters; subtherapeutic doses, in addition to being less efficacious (eg, sotorasib-panitumumab ORR 26.4% for 960 mg *v* 5.7% for 240 mg),[51] might facilitate resistance via partial inhibition rather than complete dependency collapse, expansion of preexisting resistant subclones, or acquisition of secondary mutations that confer reduced drug binding or pathway bypass.[29] Furthermore, dose stability prevents resistance; intermittent target suppression creates pharmacologic windows during which oncogenic signaling can recover

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despite covalent binding. Therefore, although combination strategies are essential, KRAS G12C inhibitor dose interruptions due to chemotherapy may lead to suboptimal dosing and, consequently, resistance. This, in the presence of AEs unrelated to KRAS G12C inhibitors, efforts in maintaining their concentration stability should be considered.

Other RAS(OFF) Inhibitors

RAS(OFF) direct inhibitors for the other major *RAS* mutations are still in development. The structural challenge is the lack of a suitably positioned nucleophile (ie, Cys12) and accessibility that allows for covalent irreversible binding. Furthermore, the majority of mutations within codons 12 and 13 retain at least some degree of intrinsic GTPase activity (G12C maintains similar rates as to wild-type RAS), whereas codon 61 mutations retain minimal hydrolysis rate—both intrinsic and GAP-assisted, for which the off-state-trapping mechanism of covalent G12C inhibition might not be broadly applicable.[54,55]

Promising alternatives might evolve from preclinical work in G12S. The serine hydroxyl (−OH) in G12S is weakly nucleophilic compared to a thiol (−SH) in G12C. However, preclinical suppression of oncogenic signaling in KRAS G12S-mutated cell cultures was achieved by chemical acylation of the noncatalytic serine and consequent covalent engagement of S-IIP.[56,57]

RAS(ON) Inhibitors

The Revolution Medicines' platform is currently developing RAS(ON) inhibitors that do not rely mandatorily on covalency to account for non–cysteine-dependent mutations. These bind through conformational recognition and protein–protein interface stabilization by scaffolding of a tricomplex involving RAS-GTP, cyclophilin A (intracellular chaperone protein), and the drug, which sterically block the interaction with downstream effectors. Daraxonrasib (RMC-6236) is a first-in-class, RAS^{MULTI}(ON) inhibitor designed to inhibit active, GTP-bound KRAS/NRAS/HRAS, including the major relevant alleles (G12D, G12V, G12A, G12S, G13D, Q61X).[58] It is currently being tested in monotherapy (ClinicalTrials.gov identifier: NCT05379985) and in combination with standard-of-care chemotherapy or other investigational agents, including other RAS(ON) inhibitors (ClinicalTrials.gov identifiers: NCT06445062, NCT06128551). RMC-5127 (G12V) and RMC-0708 (Q61H), both allele-specific noncovalent agents due to the targeted non-nucleophilic residues (valine and histidine, respectively), are in the pipeline for clinical testing. Zoldonrasib (RMC-9805), an allele-specific G12D(ON) inhibitor that, despite being a tricomplex agent, also relies on covalency for bonding with Asp-12, has recently received FDA Breakthrough Therapy Status for metastatic NSCLC,[59] based on the phase I/Ib trial (ClinicalTrials.gov identifier: NCT06040541) that also enrolled patients with mCRC.

Perspectives for Targeting RAS

The modest durability of responses and the multiple resistance mechanisms under treatment-selective pressure justify the need to explore novel therapeutic alternatives. In terms of direct RAS-targeting, noncovalent inhibitors that bind both active (ON) and inactive (OFF) states are in preclinical development, either via a P110 allosteric pocket (KAL-21404358)[60] or the formation of a salt bridge with Asp12 (TH-Z835), both unique to *KRAS* G12D.[61] Furthermore, JAB-22000 is being explored as the payload for JAB-BX600, a first-in-class EGFR-KRAS G12D antibody-drug conjugate. Additionally, PROteolysis TArgeting Chimeras that induce proteasomal degradation of oncogenic RAS through recruitment of E3 ubiquitin ligases (ClinicalTrials.gov identifier: NCT07023731) are in development.

Given the extensive feedback regulation within the MAPK pathway, coinhibition of upstream and downstream signaling nodes has emerged as a logical approach to suppress adaptive pathway reactivation beyond EGFR inhibition. Src homology region two domain-containing phosphatase-2 (SHP2) and SOS1 inhibitors offer a means to broadly dampen RAS nucleotide exchange and signaling flux across wild-type and mutant RAS pools.[62]

A summary (nonexhaustive) of broad novel RAS-targeting strategies currently being developed for the treatment of CRC is presented in Figure 1. These include immunomodulatory strategies, such as immune checkpoint inhibitors (ICI), vaccines (ClinicalTrials.gov identifiers: NCT04853017, NCT06411691, NCT04117087), oncolytic viruses (ClinicalTrials.gov identifier: NCT01274624), multispecific antibodies, and adoptive and engager-based T-cell approaches (ClinicalTrials.gov identifier: NCT06218914).[63]

BRAF

Somatic genomic alterations in the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) are found in approximately 10% of colorectal cancers[64] and are categorized into three functional classes based on their requirement for RAF dimerization and RAS activation.[65] Class I *BRAF* mutations (BRAFm) encompass those affecting the V600 residue (exon 15) upon substitution of its valine, functioning as RAS-independent monomers. In turn, class II (non-V600, such as K601, L597; *BRAF* fusions) act as RAS-independent homodimers, with intermediate-high kinase activity, while class III (non-V600; eg, D594, G466) are RAS- and dimer-dependent with impaired kinase activity.[66]

BRAF V600 Inhibitors

Class I BRAFm, the most common and clinically significant alterations of the *BRAF* gene, are the only mutations selectively inhibited by currently available—all type I—BRAF inhibitors (vemurafenib, dabrafenib, encorafenib).[65,67] The most frequent *BRAF* mutation V600E is associated with old

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age, female sex, CMS1 subtype (including MSI-high and hypermethylated tumors), and right-sided tumors. Patients with mCRC harboring this mutation exhibit significantly shorter overall survival and worse response to conventional chemotherapy regimens.[68-73]

The V600 mutations introduce a negative charge that mimics phosphorylation and physically push the αc-helix into the "IN" (active) position, stabilize the DFG-IN conformation, which dismisses the need for BRAF to instinctively dimerize, resulting in a constitutively active monomer. Type I BRAF inhibitors are ATP-competitive antagonists; they bind the ATP pocket in this active conformation and effectively inhibit monomeric BRAF V600E, thereby suppressing downstream MAPK signaling.[74,75]

Early attempts at BRAF inhibitors in monotherapy showed disappointing results because of the rapid development of an adaptive feedback reactivation toward compensatory EGFR-mediated MAPK signaling.[67,76,77]

Consecutive approaches combined type I BRAF inhibitors with EGFR or MEK inhibitors (±chemotherapy), which led to improved response rates and survival outcomes.[78-81] The phase III clinical trial BEACON CRC demonstrated superior efficacy of encorafenib + cetuximab over conventional chemotherapy -while delaying quality-of-life decline, leading to FDA approval in patients with chemo-refractory mCRC.[82,83] The doublet was subsequently explored in the first-line setting within the BREAKWATER trial; combining encorafenib plus cetuximab with fluorouracil-based chemotherapy in previously untreated patients led to an improved response rate and nearly doubled median PFS as well as OS, granting recent FDA approval.[84]

To address reactivation of ERK signaling, the HERKULES-3 phase Ib/II trial recruited patients with mCRC BRAF V600E for treatment with ERAS-007, a novel, potent ERK inhibitor, in combination with encorafenib and cetuximab (EC). Preliminary efficacy data showed an ORR of 40%.[85] Additional strategies incorporating type I BRAF inhibitors in mCRC are presented in Table 3.

Paired ctDNA genomic profiling analyses from the BEACON CRC trial provided preliminary insights into acquired resistance to combinations with BRAF inhibitors.[92] Expectedly, the majority of acquired alterations pertained to the MAPK pathway, followed by *MET* or *ALK* fusions, and were predominately subclonal. Furthermore, SRC kinases have been reported to be activated in BRAFm V600E CRC following therapeutic inhibition of BRAF and EGFR, suggesting that SRC may represent a potential resistance mechanism independent of MAPK signaling.[93,94] Moreover, the analyses provided evidence of a stimulatory effect on T cells by BRAF inhibition thereby supporting the rationale for combining BRAF-targeted treatment with immunotherapy.

For patients with BRAFm V600E and high microsatellite instability (MSI-H) tumors, ICI are currently the preferred first-line treatment option in clinical practice, supported by the findings of the KEYNOTE-177 and CheckMate-8HW trials.[95,96] However, the SEAMARK trial (ClinicalTrials.gov identifier: NCT05217446) is currently evaluating the combination of pembrolizumab with or without encorafenib and cetuximab in the first-line setting.

Contrasting with BRAF wild-type microsatellite stable (MSS) CRC—established cold tumors with limited sensitivity to ICI—BRAFm MSS CRC represents an immunologically distinct subpopulation, enriched for the immune-activated CMS1 signature, PD-L1 expression, and CD8-T cell infiltration.[97] Notably, all patients with BRAFm V600E (n = 3) MSS mCRC included in the randomized METIMMOX trial achieved a complete response after receiving short-course oxaliplatin-based chemotherapy, alternating with nivolumab in the first-line setting.[98] In a phase II trial, mCRC patients with MSS and BRAFm V600E, the combination of PD-1, BRAF, and MEK inhibition showed a promising ORR of 25% and DCR of 75%,[89] whereas a phase I/II study combining encorafenib, cetuximab, and nivolumab demonstrated an ORR of 50% and DCR of 96%. Transcriptomic analysis revealed that non-responding tumors exhibited a higher complement activation signature, whereas an increased interferon-γ—supporting the notion of immune activation—was observed among responders.[86] A randomized phase II trial evaluating encorafenib and cetuximab with or without nivolumab for patients with previously treated MSS, BRAF V600E metastatic mCRC is ongoing.

Perspectives for Targeting RAF

Despite the successful combination of BRAF type I inhibitors and anti-EGFR agents to bypass the adaptive feedback reactivation, the combination is not light on toxicity. Next-generation paradox-breaking BRAF inhibitors emerge as novel therapeutic alternative engineered to intrinsically avoid paradoxical MAPK hyperactivation by interfering with the RAF dimer interface. Mosperafenib (RG6344, RO7276389), with activity against BRAF WT, BRAF V600, RAF1, and brain penetrant, was well tolerated by previously treated patients with mCRC BRAFm V600E, with no reports of squamous cell carcinoma or keratoacanthoma, typical of type I BRAF inhibitors paradoxical activity in normal cells. The ORR was 14.8%-25%, with incremental benefit of mPFS in patients not previously exposed to a BRAFi (mPFS 7.3 months).[99]

Importantly, while non-negligible progress has been made for V600-driven disease, *BRAF* alterations beyond V600 remain treatment orphan. Class II BRAF mutants evade suppression by type I inhibitors because of their reliance on obligate dimer-based signaling; blockade of one protomer of a dimer leads to a conformational shift that, paradoxically, activates the partner protomer. Meanwhile, class III BRAFm have low/absent kinase activity, therefore, type I BRAF inhibitors bind weakly (or not at all), while RAS remains highly

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TABLE 3. Strategies Incorporating Type I BRAF Inhibitors in mCRC[86-88,90,91]

Trial	Phase	Setting	Sample	Treatment	ORR	mPFS, Months	mOS, Months
BREAKWATER Elez et al[84]	III	First-line, MSS	637	Encorafenib + cetuximab + mFOLFOX6	65.7%	12.8	30.3
				Encorafenib + cetuximab	45.6%	6.8	19.5
				Chemotherapy	37.4%	7.1	15.1
BREAKWATER, Cohort 3 Kopetz et al[87]	III	First-line, MSS	147	Encorafenib + cetuximab + FOLFIRI	64.4%	NE	NE
				FOLFIRI ± bevacizumab	39.2%	NE	NE
BEACON CRC Kopetz et al[83]	III	Metastatic, previously treated	665	Encorafenib + binimetinib + cetuximab	26%	4.3	9
				Encorafenib + cetuximab	20%	4.2	8.4
				Cetuximab + chemotherapy	2%	1.5	5.4
ANCHOR CRC Van Cutsem et al[88]	II	Metastatic, previously treated	95	Encorafenib + binimetinib + cetuximab	47.8%	5.8	18.3
IMPROVEMENT Wang et al[81]	II	Advanced/metastatic	21	Cetuximab + vemurafenib + FOLFIRI	81%	9.7	15.4
TAPUR Klute et al[80]	II	Metastatic, previously treated	30	Cobimetinib + vemurafenib	30%	3.6	9
Tian et al[89]	II	Metastatic	37	Dabrafenib + trametinib + spartalizumab	24.3%	4.3	13.6
Yaeger et al[78]	II	Metastatic, previously treated	15	Vemurafenib + panitumumab	13%	3.2	7.6
SWOG1406 Kopetz et al[90]	II	Metastatic	106	Vemurafenib + cetuximab + irinotecan	17%	4.2	9.6
				Cetuximab + irinotecan	4%	2	5.9
SWOG-2107 Morris et al[86]	I/II	Metastatic, MSS, previously treated	26	Encorafenib + cetuximab + nivolumab	46%	7.4	22
Corcoran et al[77]	I	Metastatic	142	Dabrafenib + panitumumab	10%	3.5	13.2
				Trametinib + panitumumab	0%	2.6	8.2
				Dabrafenib + trametinib + panitumumab	21%	4.2	9.1
van Geel et al[91]	Ib	Metastatic, previously treated	54	Encorafenib + cetuximab + alpelisib	17.9%	4.2	NE
				Encorafenib + cetuximab	19.2%	3.7	NE
Hong et al[79]	Ib	Metastatic, previously treated	19	Vemurafenib + cetuximab + irinotecan	35%	7.7	NE

Abbreviations: FOLFIRI, folinic acid, fluorouracil and irinotecan chemotherapy; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin-6; mOS, median overall survival; mPFS, median progression-free survival; MSS, microsatellite stability; NE, nonestimable; ORR, overall response rate.

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active and CRAF continues signaling.[100,101] Novel BRAF-targeting agents are currently in development to hopefully address the lack of targeting alternatives across RAF alterations. Naporafenib (LHX254), a type II pan-RAF inhibitor, designed to inhibit both monomeric and dimeric forms of BRAF and CRAF (while sparing ARAF) by inducing the DFG-out conformation, thereby creating an irregular surface that cannot support the dimerization interface, is currently under investigation.[102]

BEYOND RAS AND RAF

The therapeutic landscape of colorectal cancer (CRC) has evolved substantially with the identification of key molecular subsets, including mismatch repair deficiency and microsatellite instability (dMMR/MSI-H), POLE mutations, tumor molecular burden-high, RAS and BRAF alterations, and human epidermal growth factor receptor 2 (HER2) amplification.[103-108] These discoveries have enabled precision therapies and ICIs for molecularly defined patient populations. However, most CRC, particularly MSS tumors, remain resistant to immunotherapy and lack durable targeted treatment options because of tumor heterogeneity, adaptive resistance mechanisms, and complex tumor microenvironment (TME) interactions that limit traditional driver-based approaches. Advances in comprehensive molecular profiling, spatial biology, and immune characterization are revealing new vulnerabilities beyond canonical RAS and RAF signaling, enabling therapeutic strategies including antibody-drug conjugate (ADC), bispecific and multispecific antibodies, DNA damage response (DDR) targeting, next-generation immunotherapies, TME-directed approaches, cellular therapies, and epigenetic modulation.

Early clinical success with HER2-directed antibody-based combinations was demonstrated in the phase II MOUNTAINEER trial, which established trastuzumab plus tucatinib, a highly selective HER2 tyrosine kinase inhibitor, as an effective regimen in chemotherapy-refractory, HER2-positive, RAS wild-type metastatic CRC.[109] Building on this foundation, HER2-directed antibody-drug conjugates have further expanded therapeutic options in CRC, including for more heavily pretreated populations and selected patients previously treated with HER2-directed therapy. HER2-directed ADCs, particularly trastuzumab deruxtecan, have demonstrated clinically meaningful activity in HER2+ metastatic CRC, establishing proof of concept for this strategy in CRC.[110,111] ADCs exploit tumor-related antigen expression for selective cytotoxic payload delivery. Optimization of linker chemistry, drug-to-antibody (DAR), and topoisomerase I-based payloads has enhanced efficacy in biologically heterogeneous CRC, with topoisomerase I inhibitors providing bystander killing and reduced susceptibility to P-glycoprotein–mediated efflux.[110–113] Building on the proof of concept established by HER2-directed ADCs, multiple additional antigen classes are being explored in CRC. These include adhesion molecules (CEACAM5, CDH17), tight junction proteins (claudins 1, 2, 18.2), growth factor receptors (HER3, MET, EGFR), immune-related targets (B7-H3, PD-L1), development and stem cell markers (LGR5, ROR1), and others such as tissue factor, TROP-2, mesothelin, nectin-4, ADAM-9, Ca 19-9, guanylyl cyclase C, folate receptor alpha, PTK7, and TM4SF1. Emerging evidence suggests that certain ADCs may also modulate antitumor immunity via immunogenic cell death and STING pathway activation, providing rational combinations with ICIs[114,115]; however, resistance remains multifactorial, involving antigen heterogeneity, impaired internalization, altered lysosomal processing, drug efflux, and microenvironmental barriers such as hypoxia and macrophage sequestration.[115,116]

Angiogenesis-targeted therapies remain foundational in metastatic CRC, with VEGF inhibition improving outcomes even in refractory disease as demonstrated in SUNLIGHT and FRESCO/FRESCO-2 trials.[117–122] Building on this backbone, combinations of VEGF pathway inhibition with ICIs have been explored to sensitize MSS tumors to immunotherapy. However, in contrast to the positive results of STELLAR-303 evaluating zanzalintinib plus atezolizumab, prior strategies combining PD-1 blockade with anti-VEGF antibodies such as bevacizumab (ATEZOTRIBE), VEGF pathway-targeted multikinase inhibitors including lenvatinib (LEAP-017) and regorafenib-based combinations with ipilimumab and nivolumab (RIN) have been largely negative.[120,123–125] Similarly, efforts to convert immunologically cold MSS tumors into inflamed, ICI-responsive phenotypes through chemotherapy, radiotherapy, or other targeted combinations have generally failed which suggests that effective immunotherapy sensitization in MSS CRC likely requires more precise modulation of the TME and biomarker-guided patient selection.[126]

Bispecific and multispecific antibody platforms aim to overcome pathway redundancy and antigen heterogeneity through coordinated targeting. Tumor-intrinsic constructs such as EGFR-MET and VEGF-DLL4 bispecific antibodies have demonstrated early signals of activity in metastatic CRC, with efficacy influenced by tumor sidedness and prior therapy exposure.[127–129] In parallel, T-cell engaging bispecific antibodies are being developed to promote T-cell recruitment and activation within tumors. For example, cibisatamab, which targets carcinoembryonic antigen (CEA) and CD3, is being evaluated in combination with ICIs in early-phase studies.[130] Additional bispecific platforms pair PD-1 blockade with complementary immune or tumor microenvironment pathways such as CTLA-4, VEGF, and transforming growth factor (TGF)-β, integrating checkpoint inhibition with modulation of angiogenesis and stromal immune suppression.[131] In addition, strategies incorporating fibroblast activation protein–α (FAP)-targeted 4-1BB agonists represent a next-generation approach to costimulatory immunotherapy to deliver potent T-cell and NK cell activation to the TME.[132] Next-generation ICIs, including Fc-engineered and conditionally activated or masked CTLA-4 antibodies designed to enhance intratumoral regulatory T-cell depletion through augmented Fc-mediated effector function while improving tumor-specific immune response and reducing systemic toxicity, have demonstrated encouraging efficacy with manageable safety profiles.[133–135] Consistent with this strategy, botensilimab combined with the anti–PD-1 antibody balstilimab produced clinical activity in the phase I C-800-01 study in heavily pretreated MSS mCRC, with an ORR of 17%, a DCR of 61%, and a 12-month OS rate of 60%. Clinical benefit was largely confined to patients without active liver metastases, underscoring the immunosuppressive role of the liver microenvironment and placing liver metastasis status as a potential predictor of immunotherapy benefit.[135,136]

Beyond CTLA-4, combination strategies are exploring additional checkpoint targets, including LAG-3, TIGIT, and TIM-3, alongside PD-1/PD-L1 inhibitors to restore exhausted T-cell function and overcome adaptive resistance, although clinical activity in MSS CRC remains modest.[137–139]

Beyond checkpoint blockade, cellular therapies such as chimeric antigen receptor T-cell therapy (CAR-T) cells represent a promising but challenging strategy in CRC. Their efficacy has historically been constrained by antigen heterogeneity and the immunosuppressive TME. More recently, early studies targeting CEA and GUCY2C have demonstrated feasibility, manageable toxicity, and preliminary antitumor activity. Additional antigen-directed approaches, including EpCAM, HER2, and TAG-72-targeted CAR-T strategies, are under investigation, although concerns regarding on-target, off-tumor toxicity and limited trafficking in solid tumors remain.[140,141]

Emerging approaches increasingly focus on TME-directed targets that can relieve local immune suppression, enhance

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immune cell trafficking into tumor nests, and restore effector function. These include CCR8-mediated regulatory T-cell activity, TGF-β–driven stromal fibrosis, adenosine-mediated metabolic suppression, CSF1R-dependent macrophage polarization, and CXCR1/2-driven myeloid recruitment. Innate immune activation via STING agonists and macrophage checkpoint inhibition through CD47 blockade aim to enhance antigen presentation and promote adaptive immune priming.[142-145]

Beyond TME roles, a growing body of evidence supports that many CRCs exhibit chronic replication stress driven by oncogenic signaling and defective checkpoint control, creating therapeutic vulnerability to DDR inhibition. Although PARP inhibitors have shown limited activity in unselected CRC, ATR, and WEE1 inhibitors have demonstrated signals of benefit in molecular selected subsets, such as TP-53 mutant and replication stress-high tumors.[146] Finally, epigenetic dysregulation also contributes to immune evasion in MSS CRC by altering antigen presentation, interferon signaling, and endogenous retroviral expression. Epigenetic therapies, including DNMT and HDAC inhibitors, can induce viral mimicry states that increase tumor immunogenicity, representing an orthogonal approach to sensitize tumors to ICIs through modulation of tumor-intrinsic immune signaling.[147]

Next generation of precision oncology in CRC will increasingly rely on integrated, multidimensional biomarker strategies that capture tumor-intrinsic features, TME contexture, and dynamic evolution under therapy. By combining spatial and molecular profiling with AI-driven interpretation, clinicians may soon be able to personalize treatment selection, anticipate resistance, and adapt therapy in real time, ultimately expanding the benefits of immunotherapy and targeted interventions to a broader CRC population.[148,149]

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

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Promising New Platforms and Targets in the Management of Gastroesophageal Cancers

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OVERVIEW

Gastric and gastroesophageal junction cancers remain a major global cause of cancer-related mortality. Despite incremental advances in surgery and systemic therapy, durable survival gains have been limited, underscoring persistent unmet medical needs. However, the treatment paradigm has undergone a rapid transformation, driven by the integration of immunotherapy in curative-intent systemic treatment and the expansion of biomarker-guided systemic therapies. In the perioperative setting, immune checkpoint inhibitors combined with optimized cytotoxic chemotherapy have demonstrated encouraging efficacy, with recent phase III trials contributing to the establishment of combination of immunotherapy and chemotherapy as an emerging therapeutic platform. In advanced disease, precision oncology frameworks continue to expand beyond traditional biomarkers. Established targets such as human epidermal growth factor receptor 2 are now complemented by newly validated markers including claudin18.2, whereas additional actionable alterations—such as MET and TROP2—are actively under clinical investigation. These developments are redefining treatment algorithms and introducing new sequencing considerations, particularly in the context of tumor heterogeneity and biomarker coexpression. Concurrent advances in molecular diagnostics and next-generation sequencing are also facilitating the comprehensive identification of therapeutically relevant alterations. This review outlines the evolving therapeutic landscape of gastric and gastroesophageal junction cancers, spanning perioperative immunotherapy, newly validated molecular targets, and next-generation drug development platforms. By integrating biomarker-driven strategies with innovative modalities, such as antibody-drug conjugates, bispecific antibodies, chimeric antigen receptor-T-cell therapy, and vaccines, we highlight how precision therapeutics are reshaping treatment paradigms across resectable and advanced disease.

INTRODUCTION

Gastric cancer (GC) and gastroesophageal junction cancer (GEJC) rank fifth in cancer-related mortality worldwide and remain a major global health challenge.[1,2] Although their incidence and primary tumor locations vary by region, treatment paradigms are increasingly unified around precision medicine approaches that match therapeutic strategies with tumor biology, rather than geography. This biomarker-driven framework has fundamentally transformed both resectable and advanced disease management over the past 5 years.

In the curative-intent setting, perioperative chemotherapy combined with immune checkpoint inhibition has emerged as a new standard of care following the landmark MATTERHORN trial, which demonstrated the survival benefits of combined durvalumab plus fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy.[3,4] This success contrasts with the negative result[5] obtained in the adjuvant-only setting, highlighting the importance of treatment timing and strategy. Concurrently, biomarker-selected perioperative approaches targeting human epidermal growth factor receptor 2 (HER2) and mismatch repair-deficient disease have shown exceptional pathologic response rates, suggesting that precision medicine is likely to increasingly guide curative treatment selection.

In advanced disease, molecular characterization now guides the selection of first-line treatment (Table 1). Standard biomarker testing includes mismatch repair status, PD-L1 expression, HER2, and claudin 18.2 (CLDN18.2) using immunohistochemistry (IHC), HER2 amplification confirmation by in situ hybridization (ISH), and microsatellite instability using the polymerase chain reaction or next-generation sequencing (NGS). Up to 40% of patients demonstrate coexpression of PD-L1 with HER2 or CLDN18.2,[6,7] necessitating thoughtful treatment combinations and sequencing. Beyond

PRACTICAL APPLICATIONS

- Perioperative chemoimmunotherapy is emerging as a new treatment platform for resectable gastric and gastroesophageal junction cancers, highlighting the importance of integrating immune checkpoint inhibitors with optimized chemotherapy backbones in curative-intent strategies.
- Biomarker-guided treatment selection is increasingly central to clinical practice, with established targets such as human epidermal growth factor receptor 2 and newly validated markers including claudin18.2 defining distinct therapeutic subsets in advanced disease.
- Emerging therapeutic platforms, including antibody-drug conjugates, bispecific antibodies, chimeric antigen receptor-T therapies, and cancer vaccines, may expand treatment options beyond currently established targets and reshape future treatment strategies.

these established targets, antibody-drug conjugates (ADCs), bispecific antibodies, bispecific T-cell engagers (BiTEs), chimeric antigen receptor (CAR)-T cells, and cancer vaccines represent emerging platforms that leverage tumor-specific antigens to deliver spatially restricted cytotoxicity (Fig 1).

This review examines GC/GEJC therapeutics through a biomarker-driven lens, organizing treatment strategies by molecular profile: immunotherapy-responsive diseases (PD-L1-positive, MSI-H), HER2-positive diseases, and CLDN18.2-positive diseases, as well as emerging targets beyond established biomarkers. For each biomarker category, we address both resectable and advanced disease settings, platform technologies applicable to each target, and future directions for integrating these approaches into clinical practice.

IMMUNOTHERAPY-RESPONSIVE DISEASE

PD-L1–Positive and MSI-High Advanced Disease

Immune checkpoint inhibition has become the cornerstone of first-line treatment for patients with PD-L1–positive GC/GEJC. Three phase III trials have established anti–PD-1 antibodies combined with chemotherapy as the standard of care for patients with a PD-L1 combined positive score (CPS) of ≥1. CheckMate-649 demonstrated that nivolumab plus chemotherapy improved outcomes, with a median progression-free survival (PFS) of 7.5 months compared with 6.9 months and an overall survival (OS) of 13.8 months compared with 11.4 months.[8] Similar benefits have been demonstrated in subsequent studies of combination chemotherapy with pembrolizumab (KEYNOTE-859) and tislelizumab (RATIONALE-305).[9,10]

The magnitude of the benefits was found to be correlated with the PD-L1 expression level. In CheckMate-649, patients with CPS <1 showed few benefits in terms of OS (hazard ratio [HR], 0.93), in contrast to those with CPS ≥10 (HR, 0.67).[8] Accordingly, immunotherapy recommendations are guided by PD-L1 expression, with the NCCN, ASCO, ESMO, and JGCA guidelines supporting the addition of immunotherapy to systemic chemotherapy for patients with CPS ≥1.

In patients with MSI-high advanced GC/GEJC, immunotherapy alone can be highly effective. The phase II NO LIMIT study demonstrated that nivolumab plus low-dose ipilimumab produced robust and durable responses in this molecular subset,[11] establishing dual checkpoint inhibition as a chemotherapy-free option for this population.

Other chemoimmunotherapy combinations have yielded negative results including LEAP-015 (lenvatinib plus pembrolizumab with chemotherapy) and STAR-221 (anti-TIGIT antibody plus anti–PD-1 with chemotherapy).[12,13] The development of immunotherapy approaches is ongoing, including the phase II trial (ClinicalTrials.gov identifier: NCT06256328) of ONO-4578 (EP4 antagonist) combined with nivolumab and chemotherapy, with early data meeting the primary end point of PFS.

The success of checkpoint inhibition in advanced disease has prompted extensive investigations in the curative-intent setting, where immune priming in the context of intact tumor antigen presentation and lower disease burden offers theoretical advantages.

Perioperative Immunotherapy

Treatment strategies for resectable GC/GEJC have historically differed by region. While D2 lymphadenectomy followed by adjuvant chemotherapy (typically S-1 or capecitabine/oxaliplatin [CAPOX]) has been standard in East Asia,[14-17] Western practice adopted perioperative chemotherapy, most commonly FLOT.[18,19] Recent Asian trials validated the perioperative approach in selected high-risk populations. The PRODIGY study demonstrated that neoadjuvant docetaxel/oxaliplatin/S-1 followed by surgery and adjuvant S-1 improved PFS compared with up-front surgery (HR, 0.70, $P = .023$), with the greatest benefits in clinical T4 disease.[20] Similarly, RESOLVE showed that perioperative SOX improved the 3-year disease-free survival compared with adjuvant CAPOX (HR, 0.79, $P = .034$) in T4a node–positive or T4b disease.[21] These results demonstrated that perioperative chemotherapy benefits patients with high tumor burden at diagnosis although optimal patient selection criteria remain debated and regional practice patterns continue to evolve.

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TABLE 1. Targeted Therapies in Gastric and Gastroesophageal Junction Cancer

Target	Prevalence	Biomarker Definition	Setting	Approved Therapy	Key Trial(s)	Clinical Outcome
PD-L1	CPS ≥1: approximately 40%-50% CPS ≥10: approximately 20%-30%		Advanced 1L	Nivolumab + chemotherapy Pembrolizumab + chemotherapy Tislelizumab + chemotherapy	CheckMate-649 KEYNOTE-859 RATIONALE-305	mOS 13.8 *v* 11.4 months (nivo) Benefit correlates with CPS
MSI-H/ dMMR	Approximately 5% of advanced Approximately 10% perioperative		Advanced 1L Perioperative	Nivolumab + ipilimumab (chemotherapy-free)	NO LIMIT NEONIPIGA	High ORR/durability pCR 50%-60% (perioperative)
HER2	15%-20%	IHC 3+ or IHC 2+/ ISH+	Advanced 1L	Trastuzumab + chemotherapy Pembrolizumab + trastuzumab + chemotherapy (if PD-L1 CPS ≥1)	ToGA KEYNOTE-811	mOS 13.8 *v* 11.1 months (ToGA) mOS 20.1 *v* 15.7 months (K-811)
			Advanced 1L	Zanidatamab + chemotherapy Zanidatamab + tislelizumab + chemotherapy	HERIZON-GEA-01	Doublet: Superior PFS *v* T + chemotherapy Triplet: Superior PFS and OS *v* T + chemotherapy
			Advanced 2L	Trastuzumab deruxtecan (T-DXd)	DESTINY-Gastric04	Superior to RAM + PTX HR 0.74 for PFS
			Perioperative	Investigational	PHERFLOT	pCR 48.4% (FLOT + T + P)
CLDN18.2	Approximately 30%-40%	≥75% IHC 2+/3+ (43-14A)	Advanced 1L (HER2-negative)	Zolbetuximab + chemotherapy	SPOTLIGHT GLOW	mOS benefit approximately 3 months Consistent across chemotherapy platforms
FGFR2	Amplification approximately 5% Overexpression 15%-20%		Advanced	None (trials terminated)	FORTITUDE-101/ 102	Failed despite phase II promise

Abbreviations: CPS, combined positive score; dMMR, mismatch repair-deficient; FGFR2, fibroblast growth factor receptor 2; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; IO, immunotherapy; ISH, in situ hybridization; mOS, median overall survival; MSI-H, microsatellite instability-high; ORR, objective response rate; P, pembrolizumab; pCR, pathologic complete response; PFS, progression-free survival; PTX, paclitaxel; RAM, ramucirumab; T, trastuzumab; TPC, treatment of physician's choice.

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Representative studies on the application of immunotherapy in the perioperative setting are described in Table 2. Despite the efficacy of checkpoint inhibitors in advanced disease, the adjuvant-only strategy has failed. The ATTRACTION-5 trial demonstrated no survival benefits from the addition of nivolumab to adjuvant chemotherapy after D2 gastrectomy in patients with pathologic stage III disease.[5] This failure likely reflects that adjuvant therapy addresses only micrometastatic disease after removing the primary tumor and its antigenic reservoir, thereby limiting opportunities for immune priming. Furthermore, surgery itself induces immunosuppression through wound healing responses and systemic inflammation. By contrast, neoadjuvant approaches leverage the intact tumor architecture and antigen presentation to generate robust T-cell responses before resection, whereas perioperative strategies maintain immune activation through both preoperative priming and postoperative boosting.

Multiple phase II perioperative immunotherapy trials have demonstrated improved pathologic response rates. Asian studies using doublet chemotherapy backbones (S-1 plus oxaliplatin [SOX]/CAPOX) plus checkpoint inhibitors reported pathologic complete response (pCR) rates of 22%-29% versus 7%-8% with chemotherapy alone,[29,30,32,33] with NEOSUMMIT-01 showing encouraging 3-year event-free survival (EFS; 74.7% *v* 56.2%) and OS (81.3% *v* 72.2%).[29,30] The DANTE study using FLOT plus atezolizumab achieved pCR rates of approximately 23% versus 14%.[31] These consistent signals established proof of concept for perioperative checkpoint inhibition across chemotherapy platforms.

However, two global phase III trials have produced divergent results that critically inform the therapeutic strategy. The KEYNOTE-585 trial randomly assigned patients with clinical T3+ or node-positive disease to receive perioperative chemotherapy (80% received fluoropyrimidine/cisplatin doublets; 20% received FLOT) with or without pembrolizumab. Despite substantial improvements in pCR (12.9% *v* 2.0%), the study was deemed a statistical failure, narrowly missing its primary end point of EFS (median EFS of 44.4 *v* 25.7 months, $P = .0198$ *v* the prespecified threshold

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TABLE 2. Key Clinical Trials of Perioperative Strategies in Resectable Gastric and Gastroesophageal Junction Cancers

Study Name/Identifier (ref)	Phase	Disease Setting	No.	Experimental Regimen	Control Regimen	Primary End Point	Pathologic Response/ Outcomes	Recurrence and Survival Outcomes	Safety and Tolerability
Unselected population/adjuvant approach with immunotherapy									
ATTRACTION-5/ NCT03006705 [5]	III	pStage IIIA-C, resected	755	Surgery → CAPOX or S-1 + nivolumab	Surgery → CAPOX or S-1 + placebo	Relapse-free survival	—	3-year RFS rates; 68.4% (95% CI, 63.0 to 73.2) in nivolumab *v* 65.3% (59.9 to 70.2) in placebo (HR, 0.90, *P* = .44) HR for OS; 0.88 (0.66 to 1.17)	Grade 3/4 AE; 62% *v* 56% (mainly neutrophil count decreased) m/c AE; decreased appetite, nausea, diarrhea
Unselected population/perioperative approach with immunotherapy									
MATTERHORN/ NCT04592913 [3]	III	Primary ≥T2 or N+, resectable	948	2 cycles of NAT (FLOT D1, 15 + durvalumab D1) → surgery →2 cycles of AT (FLOT D1, 15 + durvalumab D1) → durvalumab maintenance (N = 474)	2 cycles of NAT (FLOT D1, 15 + placebo D1) → surgery → 2 cycles of AT (FLOT D1, 15 + placebo D1) → placebo maintenance (N = 474)	Event-free survival	19.2% (95% CI, 15.7 to 23.0) in durvalumab *v* 7.2% (5.0 to 9.9) in placebo	EFS: NR (95% CI, 40.74 to NR) *v* 32.8 months (27.86 to NR); HR, 0.71 (95% CI, 0.58 to 0.86) OS: NR *v* 47.2 months (45.1 to NR); *P* = .03	Grade 3/4 AE: 71.6% *v* 71.2% (mainly neutropenia) m/c AE: Diarrhea (62.3% *v* 57.6%), nausea (50.7% *v* 50.5%)
KEYNOTE-585/ NCT03221426 [22,23]	III	Primary ≥T3 or N+, resectable	Main (n = 804)	3 cycles of NAT (XP or FP + pembrolizumab) → surgery → 3 cycles of AT (XP or FP + pembrolizumab) → pembrolizumab maintenance (N = 402)	3 cycles of NAT (XP or FP + placebo) → surgery → 3 cycles of AT (XP or FP + placebo) → placebo maintenance (N = 402)	Event-free survival, pathologic complete response, overall survival	12.9% (95% CI, 9.8 to 16.6) in pembrolizumab *v* 2.0% (0.9 to 3.9) in placebo	EFS: 44.4 months (95% CI, 33.0 to 69.8) *v* 25.7 months (20.8 to 36.5); HR 0.81 (95% CI, 0.67 to 0.98); *P* = .0198 ($P_{threshold}$ = .07 [24-27,37]) OS: 71.8 months (52.5 to NR) *v* 55.7 (41.7 to NR) months (HR, 0.86 [95% CI, 0.71 to 1.06])	Grade 3/4 AE: 78% *v* 74% (mainly neutropenia) m/c AE: Nausea (60% *v* 64%), anemia (42% *v* 40%)
			FLOT (n = 203)	4 cycles of NAT (FLOT+ pembrolizumab) → surgery →4 cycles of AT (FLOT + pembrolizumab) → pembrolizumab maintenance (N = 100)	4 cycles of NAT (FLOT+ placebo) → surgery →4 cycles of AT (FLOT + placebo) → placebo maintenance (N = 103)		Main + FLOT group; 13.0% (10.2 to 16.3) in pembrolizumab *v* 2.4% (1.3 to 4.2) in placebo	Main + FLOT group EFS: 47.0 months (36.2 to NR) *v* 26.9 months (22.1 to 34.7); HR, 0.80 (0.67 to 0.95) OS: NR (59.2 to NR) *v* 55.7 (42.8 to NR); HR 0.86 (0.71 to 1.03)	

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TABLE 2. Key Clinical Trials of Perioperative Strategies in Resectable Gastric and Gastroesophageal Junction Cancers (continued)

Study Name/Identifier (ref)	Phase	Disease Setting	No.	Experimental Regimen	Control Regimen	Primary End Point	Pathologic Response/ Outcomes	Recurrence and Survival Outcomes	Safety and Tolerability
NEOSUMMIT-01/ NCT04250948 [29,30]	II	Primary ≥T3 and N+, resectable	108	3 cycles of NAT (SOX or CAPOX + toripalimab)→ surgery→ 5 cycles of AT (SOX or CAPOX + toripalimab) → toripalimab monotherapy for 6 months (N = 54)	3 cycles of NAT (SOX or CAPOX) → surgery→ 5 cycles of AT (SOX or CAPOX; N = 54)	Pathologic complete response or near-complete response rate	pCR rate; 22.2% *v* 7.4% MPR rate; 44.4% *v* 20.4%	3-year EFS: 74.7% (95% CI, 63.6 to 87.7) *v* 56.2% (43.3 to 73.0); HR 0.52 (0.27 to 1.00), *P* = .047 3-year OS: 81.3% (71.4 to 92.4) *v* 72.2% (61.2 to 85.2); HR, 0.45 (0.21 to 0.95), *P* = .031	Grade 3/4 AE; 35.2% *v* 29.6% (mainly thrombocytopenia, leukopenia)
DANTE/ NCT03421288 [31]	II/III	Primary ≥T2 or N+, resectable	295 (phase II)	4 cycles of NAT (FLOT + atezolizumab 840 mg once every 2 weeks) → surgery → 4 cycles of AT (FLOT + atezolizumab 840 mg once every 2 weeks) → 8 cycles of atezolizumab 1200 mg once every 3 weeks monotherapy (N = 146)	4 cycles of NAT (FLOT) → surgery → 4 cycles of AT (FLOT; N = 149)	Progression-free survival/ disease-free survival for phase II → event-free survival for phase III	pCR rate; 23% *v* 14% MPR rate; 49% *v* 38%	Not reported	m/c AE; diarrhea, nausea, alopecia
PERSIST/ NCT04982939 [32,33]	II	Primary ≥T2 or N+, resectable	264	3 cycles of NAT (SOX + sintilimab) → surgery → 5 cycles of AT (SOX + sintilimab) → sintilimab maintenance for up to 1 year (N = 131)	3 cycles of NAT (SOX) → surgery → 5 cycles of AT (SOX; N = 133)	Pathologic complete response	pCR rate; 29.3% *v* 8.3% MPR rate; 69.5% *v* 43.8%	Not reported	Grade 3/4 AE; 14.5% *v* 8.3%
Unselected population/perioperative approach with immunotherapy and antiangiogenic agents									
DRAGON-IV/ NCT04208347 [28]	III	Primary ≥T3 or N+, resectable	360	3 cycles of NAT (SOX + camrelizumab + rivoceranib) → surgery → 3 cycles of AT (SOX + camrelizumab + rivoceranib) → rivoceranib/ camrelizumab maintenance	3 cycles of NAT (SOX) → surgery → 3 cycles of AT (SOX) → S-1 for 1year	Pathologic complete response rate Event-free survival	pCR rate; 16.7% (95% CI, 11.5 to 22.9) in rivo/cam *v* 4.4% (1.9 to 8.6) in SOX MPR rate; 51.1% (43.6 to 58.6) *v* 37.8% (30.7 to 45.3)	Not reported (ongoing)	Grade 3/4 AE; 34% *v* 17% (mainly WBC count decreased)

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TABLE 2. Key Clinical Trials of Perioperative Strategies in Resectable Gastric and Gastroesophageal Junction Cancers (continued)

Study Name/Identifier (ref)	Phase	Disease Setting	No.	Experimental Regimen	Control Regimen	Primary End Point	Pathologic Response/ Outcomes	Recurrence and Survival Outcomes	Safety and Tolerability
EPOC2001/ NCT04745988 [27]	II	Primary ≥T2 or N+, resectable	32	12 weeks of NAT (4 cycles of FLOT once every 2 weeks + 3 cycles of pembrolizumab once every 3 weeks + lenvatinib 8 mg once daily) → surgery → 12 weeks of AT (4 cycles of FLOT once every 2 weeks + 3 cycles of pembrolizumab once every 3 weeks + lenvatinib 8 mg once daily) → pembrolizumab maintenance for 11 cycles	—	Major pathologic response rate	pCR rate; 22% (95% CI, 9 to 40) MPR rate; 47% (80% CI, 34 to 60)	Not reported	Grade 3/4 AE; AST/ALT increased (28%), platelet count decreased (19%)
HER2-positive population/perioperative approach with HER2-targeted agents									
RTOG-1010/ NCT01196390 [34]	III	Primary ≥T2 or N+, esophageal adenocarcinoma, HER2 IHC 3+ or IHC 2+/ISH	203	Concurrent chemoradiation with paclitaxel/carboplatin + trastuzumab once per week → surgery → 13 cycles of trastuzumab 6 mg/kg every 3 weeks	Concurrent chemoradiation with paclitaxel/carboplatin once per week → surgery	Disease-free survival	Not reported	DFS: 19.6 months (13.5 to 26.2) *v* 14.2 months (10.5 to 23.0): HR, 0.99 (0.71 to 1.39); *P* = .97 OS; 38.5 months (26.2 to 70.4) *v* 38.9 months (29.0 to 64.5); HR, 1.04 (0.71 to 1.50); *P* = .85	Grade 3/4 AE; 43% *v* 54% (mainly hematologic)
HER2-positive population/perioperative approach with immunotherapy and HER2-targeted agents									
NCT04661150 [35]	II	Primary ≥T3 or N+, resectable, HER2 IHC 3+ or IHC 2+/ISH +	42	3 cycles of NAT (CAPOX + atezolizumab + trastuzumab) → surgery → 5 cycles of AT (CAPOX + atezolizumab + trastuzumab; N = 21)	3 cycles of NAT (CAPOX + trastuzumab) → surgery → 5 cycles of AT (CAPOX + trastuzumab; N = 21)	Pathologic complete response rate	Pathologic CR rate: 38.1% (95% CI, 18.1 to 61.6) *v* 14% (3.0 to 36.3) Major pathologic response: 42.9% (21.8 to 66.0) *v* 19.0% (5.4 to 41.9) Objective response rate: 28.6% (11.3 to 52.2) *v* 33.3% (14.6 to 57.0)	EFS/OS; not reached	Grade 3/4 AE; 57% *v* 67% (mainly weight decreased and neutrophil count decrease)

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TABLE 2. Key Clinical Trials of Perioperative Strategies in Resectable Gastric and Gastroesophageal Junction Cancers (continued)

Study Name/Identifier (ref)	Phase	Disease Setting	No.	Experimental Regimen	Control Regimen	Primary End Point	Pathologic Response/ Outcomes	Recurrence and Survival Outcomes	Safety and Tolerability
NEOSUMMIT-02/ ChicT-R2200058732 [25]	II	Primary ≥T3 or N+, resectable, HER2 IHC 3+ or IHC 2+/ ISH +	22	4 cycles of NAT (SOX + sintilimab + trastuzumab once every 3 weeks) → surgery → 4 cycles of AT (SOX + sintilimab + trastuzumab once every 3 weeks)	—	Major pathologic response	Pathologic CR rate: 55% (95% CI, 32 to 76) MPR rate; 60%	EFS/OS: not reached 2-year EFS rate: 73% (95% CI, 46 to 100) 2-year OS rate: 96% (95% CI, 87 to 100)	Grade 3 AE: 27% m/c AE: nausea (64%), neutropenia (64%), thrombocytopenia (64%)
NCT03950271 [26]	II	Primary ≥T4 or N+, resectable, HER2 IHC 3+ or IHC 2+/ ISH +	25	4 cycles of NAT (CAPOX + camrelizumab + trastuzumab once every 3 weeks) → surgery → 4 cycles of AT (CAPOX)	—	Pathologic complete response rate	21.7% (95% CI, 7.5 to 43.7)	EFS/OS: not reached 3-year EFS: 75.0% (95% CI, 59.4 to 94.7) 3-year OS: 78.5% (95% CI, 63 to 3 = 97.3)	Grade 3 AE: 36% m/c AE: nausea (84%), fatigue (84%)
PHERFLOT/ NCT05504720 [36]	II	Primary ≥T2 or N+, esophageal adenocarcinoma, HER2 IHC 3+ or IHC 2+/ISH +	31	9 weeks of NAT (3 cycles of pembrolizumab/ trastuzumab +4 cycles of FLOT) → surgery → 9 weeks of AT (3 cycles of pembrolizumab/ trastuzumab + 4 cycles of FLOT) → 11 cycles of pembrolizumab/ trastuzumab maintenance		Pathologic complete response rate	Pathologic CR rate: 48.4% (30.2 to 66.9) MPR rate: 67.7% (48.6 to 83.3)	Not reported	Grade 3/4 AE: 48.4% (m/c; diarrhea)
MSI-H or dMMR population/perioperative approach with immunotherapy									
NEONIPIGA/ NCT04006262 [37]	II	Primary ≥T2 or N+, resectable, dMMR or MSI-H	32	12 weeks of NAT (nivolumab 240 mg once every 2 weeks + ipilimumab 1 mg/kg once every 6 weeks) → surgery → 9 cycles of AT (nivolumab 480 mg once every 4 weeks)	—	Pathologic complete response rate	58.6% (90% CI, 41.8 to 74.1)	30 patients (97%) were alive and free of recurrence/ progression	Grade 3/4 AE; 19% m/c AE; pruritus, hyperthyroidism, fatigue, diarrhea
INFINITY/ NCT04817826 [38]	II	Primary ≥T2 or N+, resectable, dMMR or MSI-H (EBV-negative)	36 (cohort 1; n = 18, cohort 2; n = 18)	Cohort 1: 12 weeks of NAT (single-dose tremelimumab + durvalumab once every 3 weeks) → surgery Cohort 2: 12 weeks of NAT (single-dose tremelimumab + durvalumab once every 3 weeks) → if cCR, No operative management and if no cCR, surgery		Cohort 1: pCR rate Cohort 2: cCR rate at 2 years	Cohort 1: pCR rate 60%, MPR rate 80% Cohort 2: cCR rate 76%	Cohort 1: PFS/OS not reached, 2-year OS 73.3% Cohort 2: PFS/OS not reached, 1-year OS 100%	Cohort 1: grade 3/4 AE, 17% Cohort 2: grade 3/4 AE, 17%

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TABLE 2. Key Clinical Trials of Perioperative Strategies in Resectable Gastric and Gastroesophageal Junction Cancers (continued)

Study Name/Identifier (ref)	Phase	Disease Setting	No.	Experimental Regimen	Control Regimen	Primary End Point	Pathologic Response/ Outcomes	Recurrence and Survival Outcomes	Safety and Tolerability
NICE/NCT04744649 [24]	II	Primary ≥T2 and N+/primary ≥T3 and any N, resectable (cohort A—PD-L1 CPS ≥5; cohort B—EBV-positive; cohort C; MSI-H or dMMR)	22 for cohort C (dMMR or MSI-H)	4 cycles of NAT (CAPOX + toripalimab once every 3 weeks) → surgery → 4 cycles of AT (CAPOX + toripalimab once every 3 weeks)	—	Major pathologic response rate	pCR rate; 80% MPR rate; 93.3%	EFS/OS: not reached 1-year OS rate: 93.8%	Grade 3/4 AE: 37.5% m/c AE: ALT/AST elevation (56.3%), neutropenia (43.8%)
Biomarker-selected population/adjuvant approach with immunotherapy									
NCT05769725	II	pStage IIIC, resected, MSI-H or TMB-H (≥10 mutations/Mb) or PD-L1 CPS ≥5	70	Surgery → docetaxel/S-1 + serplulimab (HLX10)	Surgery → docetaxel/S-1	Disease-free survival	Ongoing	Ongoing	Ongoing
NCT06036745	II	pStage IIIB-C, resected, MSI-H or TMB-H (≥10 mutations/Mb) or PD-L1 CPS ≥5	20	Surgery → SOX + pembrolizumab	—	3-year disease-free survival rate	Ongoing	Ongoing	Ongoing

Abbreviations: AE, adverse event; AT, adjuvant treatment; CAPOX, capecitabine/oxaliplatin; cCR, clinical complete response; CPS, combined positive score; CR, complete response; dMMR, deficient mismatch repair; EFS, event-free survival; FLOT, docetaxel/oxaliplatin/5-FU regimen; FP, 5-FU/cisplatin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; m/c, most common; Mb, megabases; MPR, major pathologic response; MSI-H, microsatellite instability-high; NAT, neoadjuvant treatment; NR, not reached; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; Ref, reference; RFS, relapse-free survival; SOX, S-1/oxaliplatin; TMB-H, tumor mutational burden-high; XP, capecitabine/cisplatin.

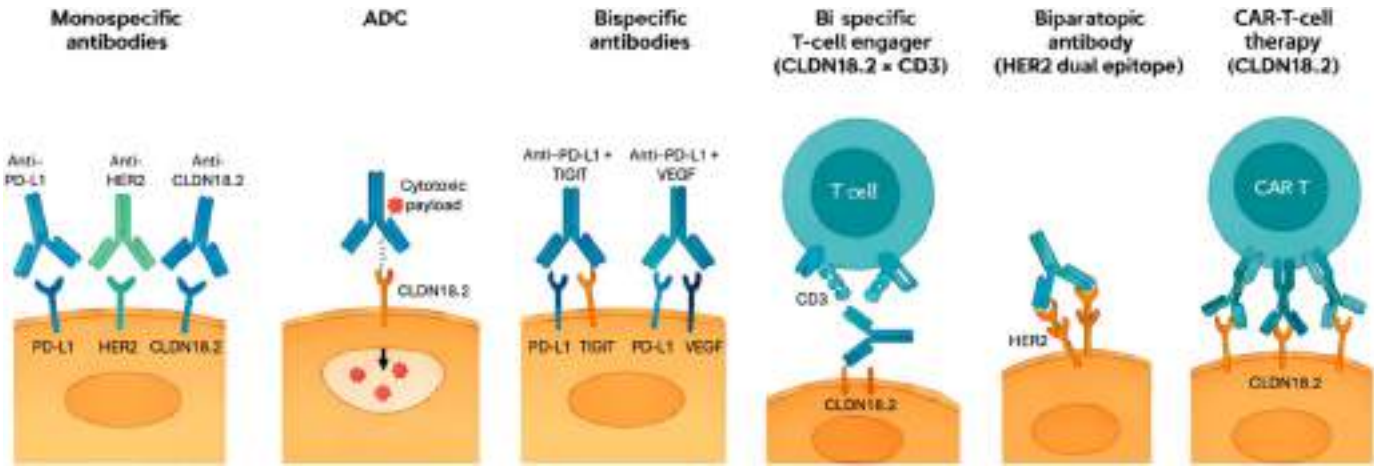

FIG 1. Immunotherapy and targeted therapy approaches in gastroesophageal cancer. ADC, antibody-drug conjugate; CAR, chimeric antigen receptor; HER2, human epidermal growth factor receptor 2.

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P = .0178). Similarly, OS showed no statistically significant benefit (HR, 0.86 [95% CI, 0.71 to 1.06]).[22,23,39] This disconnect between the pathologic response and survival outcomes demonstrates that pCR alone does not guarantee clinical benefits and suggests that doublet chemotherapy backbones may provide insufficient cytotoxic activity to optimize immunotherapy synergy.

In stark contrast, the MATTERHORN study demonstrated definitive survival benefits using three-drug FLOT chemotherapy. The study enrolled PD-L1 all-comers with clinical T2+ or node-positive disease, randomly assigning them to perioperative FLOT with or without durvalumab. pCR rates were 19.2% versus 7.2%, respectively. Critically, the median EFS was not reached in the durvalumab arm versus 32.8 months with placebo (HR, 0.71, P < .001), and the final analysis demonstrated a statistically significant improvement in the OS (HR, 0.78, P = .021).[3,4] Grade 3/4 adverse events were similar between the arms (71%-72%), predominantly reflecting FLOT-related neutropenia rather than immunotherapy toxicity. Based on these results, perioperative FLOT plus durvalumab obtained regulatory approval and established a new standard of care for resectable GC/GEJC.

The divergent outcomes between the KEYNOTE-585 and MATTERHORN studies indicate that the quality of the chemotherapy backbone critically determines the success of perioperative immunotherapy. The superior tumor cytoreduction of FLOT likely creates more favorable conditions for immune activation through enhanced immunogenic cell death, greater tumor antigen release, and more effective debulking before surgery. Despite the encouraging pCR rates, the failure of KEYNOTE-585 emphasizes that survival end points in curative-intent disease require both effective immune priming and adequate chemotherapy partner activity. With that, the optimal chemotherapy backbone and optimal clinical staging for this perioperative chemo-immunotherapy approach should be explored further.

Biomarker-selected perioperative strategies demonstrate exceptional promise and may enable treatment personalization beyond the FLOT-durvalumab platform. MSI-high or dMMR populations consistently achieve high pCR rates with immunotherapy,[24,37,38] raising questions about whether cytotoxic chemotherapy is necessary in these profoundly immunotherapy-sensitive tumors. Some trials have explored nonoperative management in MSI-high patients, achieving a clinical complete response. HER2-positive disease represents another opportunity for precision perioperative therapy. Trials combining trastuzumab, pembrolizumab, and chemotherapy achieved pCR rates of 22%-55%,[25,26,35] demonstrating that dual pathway blockade (immune plus HER2-directed) produces favorable outcomes despite using doublet rather than triplet chemotherapy backbones. This suggests that biomarker-driven targeting may allow chemotherapy de-escalation while preserving its efficacy. Antiangiogenic combinations targeting the immunosuppressive tumor vasculature are also under investigation.[27,28]

The emerging treatment paradigm emphasizes both platform optimization and precision patient selection. The MATTERHORN study establishes perioperative FLOT plus durvalumab as a standard treatment for PD-L1 all-comers in resectable GC/GEJC. However, critical questions remain regarding its applicability to Asian populations, where MATTERHORN enrolled fewer patients than KEYNOTE-585 and established practice patterns differ. The integration of molecular profiling to guide perioperative regimen selection represents the next frontier in which matching treatment intensity to tumor biology through chemotherapy de-escalation in MSI-high disease or targeted therapy intensification in HER2-positive disease could move beyond current one-size-fits-all approaches.

HER2-POSITIVE DISEASE

HER2 amplification occurs in 15%-20% of GC/GEJC, with HER2 positivity defined as IHC 3+ or IHC 2+ with ISH

amplification. HER2-positive tumors are more common toward the gastroesophageal junction and frequently demonstrate PD-L1 coexpression,[40] creating opportunities for dual pathway targeting.

In addition to traditional HER2-positive tumors, oncogenic HER2 activation through somatic *ERBB2* gene mutations has recently emerged as a target for HER2-targeted therapy. However, HER2 mutations alone do not reflect HER2 overexpression,[41] and HER2 mutations are not yet considered an established standard target for GC/GEJC. Further exploration is needed on HER2-targeted therapy for HER2-mutated GC/GEJC.

First-Line Therapy in Advanced Disease

The role of HER2 as a therapeutic target in GC/GEJC was established by the ToGA trial, which demonstrated that adding trastuzumab to chemotherapy improved outcomes compared with chemotherapy alone (median OS of 13.8 months *v* 11.1 months), establishing this combination as a standard of care for HER2-positive advanced disease.[42] The KEYNOTE-811 study further advanced this paradigm, demonstrating that adding pembrolizumab to trastuzumab plus chemotherapy improved outcomes in patients with PD-L1 CPS ≥1, becoming the preferred first-line strategy for this biomarker-defined population.[43]

Most recently, zanidatamab, a bispecific antibody targeting two distinct HER2 epitopes, showed promising results in the phase III HERIZON-GEA-01 trial. This three-arm study randomly assigned patients to trastuzumab plus chemotherapy, zanidatamab plus chemotherapy, or zanidatamab plus tislelizumab plus chemotherapy. Zanidatamab plus chemotherapy demonstrated superior PFS versus trastuzumab plus chemotherapy, whereas the triplet combination proved to be superior in terms of both the PFS and OS compared with trastuzumab plus chemotherapy.[44] These results suggest that enhanced HER2 engagement through biparatopic binding and the addition of checkpoint inhibition may further improve outcomes beyond the current standards.

Second-Line Therapy and the HER2 Heterogeneity Challenge

Initially, HER2-directed therapy faced multiple setbacks in the second-line setting. Trials of trastuzumab beyond progression (T-ACT), trastuzumab emtansine (GATSBY), and lapatinib (TyTAN) all failed to demonstrate benefits,[45-47] likely reflecting the fundamental differences between breast and gastric HER2 biology. GC/GEJC exhibits marked intratumoral and interlesional HER2 heterogeneity, with mixed HER2-positive and HER2-negative clones within individual tumors.[48,49] Furthermore, temporal heterogeneity poses additional challenges: approximately 30%-60% of patients lose HER2 expression after progression to trastuzumab-based first-line therapy.[45-49] This antigen loss occurs through clonal selection under therapeutic pressure, leaving HER2-negative clones to predominate at relapse.

Trastuzumab deruxtecan (T-DXd), an ADC with a significant bystander effect, overcomes these heterogeneity barriers. Unlike naked antibodies that require uniform high-level HER2 expression, T-DXd couples trastuzumab to a highly membrane-permeable topoisomerase inhibitor payload (deruxtecan). After antigen binding and internalization, linker cleavage releases the cytotoxic payload, which diffuses beyond the directly targeted cell to kill neighboring HER2-low or HER2-negative cells—the bystander effect. This mechanism potentially induces immunogenic cell death, further amplifying antitumor activity.

DESTINY-Gastric01 and DESTINY-Gastric02 studies have demonstrated T-DXd efficacy in previously treated HER2-positive GC/GEJC in Asian and Western populations, respectively.[50,51] DESTINY-Gastric04 definitively established the superiority of T-DXd over ramucirumab plus paclitaxel in the second-line setting (median OS not reported at the time of approval versus historical controls), making T-DXd standard second-line therapy for HER2-positive metastatic GC/GEJC.[52]

However, critical biomarker questions remain, despite the clinical success of T-DXd. Digital pathology and machine learning approaches now quantify HER2 optical density and the spatial proximity of HER2-positive to HER2-negative cells, with combined metrics predicting T-DXd benefit beyond simple IHC scoring.[53] Predictors of ADC efficacy extend beyond antigen expression: higher immune infiltrate, particularly $CD8^+$ T cells, correlates with improved outcomes, supporting the hypothesis that ADC-induced immunogenic cell death contributes mechanistically to efficacy.[54] Conversely, genomic alterations including PIK3CA mutations and oncogene coamplifications modestly attenuate responses, suggesting that pathway interactions influence ADC activity.

Given the high frequency of HER2 antigen loss post-trastuzumab (30%-60%), repeat biopsy is strongly recommended before initiating second-line therapy in GC/GEJC. This practice, distinct from breast cancer, in which the HER2 status remains more stable, reflects the unique biology of gastric HER2 heterogeneity and enables appropriate patient selection for HER2-directed therapies.

Exploratory phase II data suggest potential activity in HER2-low disease (IHC 1+/2+ ISH-negative), with an overall response rate (ORR) of 26.3%,[55] although the degree to which the bystander killing effect truly overcomes spatial heterogeneity compared with simply lowering expression thresholds remains to be fully characterized. Randomized trials are needed to define the role of T-DXd in HER2-low GC/GEJC.

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Platform evolution for HER2-directed ADCs includes biparatopic constructs targeting two HER2 epitopes, potentially expanding patient populations or bypassing resistance mechanisms. However, biparatopic binding does not guarantee improved function unless both epitopes meaningfully enhance internalization or stability. Critical development questions include defining optimal biomarker cut points distinct from diagnostic thresholds, characterizing antigen stability across treatment lines, harmonizing IHC methodologies across trials, and integrating spatial and genomic biomarkers for patient selection.

Perioperative HER2-Targeted Therapy

In the perioperative setting, HER2-directed approaches show promise but require further investigation. The RTOG-1010 trial demonstrated no benefits from adding trastuzumab to chemoradiotherapy in resectable esophageal adenocarcinoma.[34] However, combining a dual pathway blockade with chemotherapy has shown exceptional promise. The phase II PHERFLOT trial reported a pCR rate of 48.4% with FLOT plus trastuzumab and pembrolizumab,[36] whereas Asian studies combining HER2-directed therapy, checkpoint inhibition, and chemotherapy achieved pCR rates of 22%-55% despite using doublet chemotherapy backbones.[25,26,35] These results suggest that HER2-positive disease may enable chemotherapy de-escalation in the perioperative setting when combined with dual immune and HER2 pathway blockade although randomized trials are needed to establish optimal regimens and confirm survival benefit.

CLDN18.2-POSITIVE DISEASE

CLDN18.2 is a tight junction protein with restricted expression in the normal gastric mucosa that persists in GC/GEJC. In normal gastric epithelium, CLDN18.2 localizes to tight junctions with apical-basal polarity sequestering it from the extracellular space. Malignant transformation disrupts this polarity, exposing CLDN18.2 on the cell surface and making it accessible to therapeutic targeting. This lineage-restricted expression limits on-target/off-tumor toxicity, primarily to the gastric mucosa, creating a favorable therapeutic window. However, its expression is heterogeneous, with only 39% of CLDN18.2-positive cases showing uniform expression across all tumor cores, with 25% discordance between primary and metastatic sites.[6,56] This heterogeneity has important implications for biomarker assessment and the selection of therapeutic platforms.

Established Therapy: Zolbetuximab

Two phase III trials established zolbetuximab, a monoclonal antibody targeting CLDN18.2, as the standard first-line therapy for CLDN18.2-positive, HER2-negative advanced GC/GEJC. CLDN18.2 positivity was defined as moderate-to-strong staining in ≥75% of tumor cells when using the 43-14A antibody clone. The SPOTLIGHT trial demonstrated that the first-line modified fluoropyrimidine, leucovorin, and oxaliplatin regimen (mFOLFOX) plus zolbetuximab improved both PFS and OS versus mFOLFOX alone.[57] GLOW similarly demonstrated benefit using the CAPOX chemotherapy backbone.[58] The consistency of benefit across chemotherapy platforms established zolbetuximab as a validated therapeutic approach for this molecular subset.

Common adverse events of zolbetuximab include nausea, vomiting, and decreased appetite, likely reflecting the on-target, off-tumor effects of CLDN18.2 expression in normal gastric mucosa, causing antibody-mediated gastritis. These toxicities can be managed using aggressive prophylactic antiemetics, proton pump inhibitors, and infusion rate modifications.[57,58] Recently, expert consensus guidelines have started to provide standardized approaches for the prevention and management of zolbetuximab toxicity.

Future development focuses on combining CLDN18.2-targeted agents with immunotherapy to leverage potential synergies. The phase II ILUSTRO trial demonstrated the tolerability and efficacy of zolbetuximab combinations with checkpoint inhibitor, with an exceptional approximate 2-year median PFS for patients who were double biomarker (PD-L1/CLDN 18.2)–positive.[59] The ongoing phase III LUCERNA study will evaluate first-line chemotherapy plus pembrolizumab with or without zolbetuximab in patients who are HER2-negative and CLDN18.2-positive, with PD-L1 CPS ≥1,[60] addressing whether dual pathway targeting further improves outcomes in biomarker-selected populations.

Platform Development in CLDN18.2-Positive Disease

The lineage-restricted expression of CLDN18.2, as well as its cell-surface accessibility after malignant transformation, and validation as a therapeutic target make it an ideal antigen for emerging platform technologies. Multiple therapeutic modalities now target CLDN18.2, each leveraging distinct mechanisms to overcome the challenges inherent to this disease.

Antibody-Drug Conjugates

CLDN18.2-directed ADCs aim to address the limitations of heterogeneity observed with naked antibodies. While zolbetuximab requires ≥75% expression for regulatory-approved use, ADCs with membrane-permeable payloads theoretically overcome regional heterogeneity through bystander killing of lower-expressing or negative cells. Early clinical data support this concept. Multiple CLDN18.2-ADCs have been developed although they differ in their critical design features. The 19202 antibody clone binds to CLDN18.2 more specifically than 43-14A (which also recognizes CLDN18.1), potentially enabling more selective targeting. CMG901 demonstrated proof-of-concept efficacy in pretreated CLDN18.2-positive GC/GEJC with manageable toxicity although the optimal IHC assay, antibody clone selection, and expression cut points remain under investigation.[61]

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The heterogeneity challenge persists despite the theoretical bystander advantages. Only 39% of the CLDN18.2-positive cases showed uniform expression, and 25% demonstrated primary metastatic discordance. Whether the ADC bystander effect truly overcomes spatial heterogeneity compared with simply lowering the expression thresholds required for a response remains incompletely characterized. The harmonization of IHC methodologies, validation of optimal antibody clones for patient selection, and determination of expression cut points that predict ADC benefit (likely distinct from the 75% threshold established for zolbetuximab) represent critical development priorities.

Bispecific T-Cell Engagers

Bispecific T-cell engagers (BiTEs) are engineered immunotherapeutic molecules designed to direct the host's immune system against tumor by bridging T cells and their targets, triggering potent cytotoxic response.[62] CLDN18.2-directed BiTEs physically bridge CD3 on T cells and CLDN18.2 on tumor cells, creating a cytolytic synapse that drives major histocompatibility complex (MHC)–independent T-cell activation and tumor killing. This approach bypasses the requirements for antigen presentation or costimulation, enabling T-cell–mediated cytotoxicity even in tumors with defective antigen processing machinery. The demonstrated immune sensitivity of the GC/GEJC suggests that the tumor microenvironment can support T-cell activation and sustain antitumor activity when appropriately engaged.

ASP2138, a CLDN18.2-CD3 BiTE, continues in phase I/Ib development with preliminary efficacy, showing an ORR of 62.5% when combined with pembrolizumab and infusional fluorouracil, leucovorin, and oxaliplatin, now advancing to a registration phase III randomized global study.[63] These early results provide proof of concept for CLDN18.2-directed T-cell engagement. However, dose-limiting toxicities require careful characterization. Cytokine release syndrome (CRS) represents the primary concern with BiTEs, reflecting systemic T-cell activation. In addition, CLDN18.2 expression in normal gastric mucosa creates a risk for on-target/off-tumor gastritis, potentially more severe than observed with naked antibodies given the potent cytotoxicity induced by BiTE-activated T cells. Optimal combination strategies, dose optimization, prophylactic approaches for CRS management, and patient selection criteria will determine whether BiTEs can be safely integrated with standard-of-care regimens.

CAR-T Cells

CARs are synthetic receptors that allow T cells to recognize tumor-associated antigens in an MHC-independent manner. CAR-T-cell therapy is a type of immunotherapy that uses T cells engineered to express CARs with tumor specificity.[64] CT041-ST-01 represents a landmark achievement: the first randomized CAR-T trial demonstrating survival benefits outside of hematologic malignancies. This phase II study compared satri-cel (CT041, a CLDN18.2-directed CAR-T) versus physician's choice in previously treated CLDN18.2-positive GC/GEJC, meeting its primary end point of statistically significant improvement in the PFS and validating CLDN18.2 as a targetable antigen for cellular therapy.[65]

However, translating this proof of concept into a broader clinical impact requires addressing its fundamental limitations. While CAR-T cells successfully trafficked to tumors, persistence was limited and decreased with successive infusions. This contrasts markedly with hematologic malignancies where durable CAR-T-cell persistence measured in years drives long-term remissions. In solid tumors, antigens exhibit spatial heterogeneity and dynamic expression, dense stroma creates physical barriers to CAR-T trafficking and penetration, and the immunosuppressive tumor microenvironment impairs CAR-T-cell function and survival. Treatment also requires at least 2 weeks of hospitalization per infusion cycle, creating substantial logistical and economic burdens.

Realizing potential of CAR-T cells in GC/GEJC requires overcoming persistence limitations through tumor microenvironment reprogramming strategies: checkpoint inhibitor combinations to reverse T-cell exhaustion, targeting immunosuppressive myeloid populations, engineering armored CAR-T cells with cytokine secretion capabilities, or metabolic interventions. Novel in vivo CAR-T technologies using lentiviral or lipid nanoparticle delivery systems to directly transduce CAR constructs in vivo[66] may streamline manufacturing and reduce costs. While the CT041 trial provides critical proof that CAR-T cells can achieve clinical benefits in GC/GEJC, the challenge remains to enhance their durability to match the transformative outcomes seen in hematologic malignancies.

CLINICAL APPLICATIONS OF ESTABLISHED BIOMARKERS

Established biomarkers discussed earlier are recognized to coexist rather than being not mutually exclusive. Recent molecular profiling studies have demonstrated that PD-L1 expression, HER2, dMMR, and CLDN18.2 expression frequently overlap within individual tumors although the degree of overlap varies across cohorts.[56,67] While certain biomarker-defined subgroups remain relatively distinct, clinically relevant coexpression—such as PD-L1 positivity alongside other targetable alterations—is observed in a meaningful proportion of patients.

This overlap introduces complexity in treatment selection, particularly in the first-line setting where multiple biomarker-driven therapies may be applicable. Therapeutic prioritization should consider the relative strength of predictive biomarkers, expected magnitude of benefit, disease burden, and clinical trajectory.[68] For example, tumors with high PD-L1 expression (PD-L1 CPS above 10) may preferentially benefit from immunotherapy, whereas other

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biomarker-defined populations may derive greater benefit from targeted approaches.

Given the absence of prospective data to guide treatment sequencing in biomarker-overlapping populations, a pragmatic and individualized approach is warranted. Future studies specifically addressing biomarker coexpression and optimal therapeutic prioritization will be critical to refine precision treatment strategies in this setting. Other opportunities are to develop combination strategies using coexpressing biomarkers.

BEYOND ESTABLISHED BIOMARKERS

Emerging Molecular Targets

Comprehensive molecular profiling has identified additional targetable alterations in GC/GEJC, including cell surface proteins (CEACAM5, CEACAM6, cadherin 17), receptor tyrosine kinase amplifications (fibroblast growth factor receptor 2 [FGFR2], c-MET, EGFR), and oncogenic mutations (KRAS).[69,70] While these targets occur at lower frequency than HER2, PD-L1, or CLDN18.2, they represent potential therapeutic opportunities, particularly for patients without established biomarkers. Importantly, early development patterns suggest that ADCs and bispecific antibodies may succeed where traditional monoclonal antibodies have failed, reflecting improved drug delivery and enhanced potency.

FGFR2

FGFR2 functions as a receptor tyrosine kinase, undergoes amplification in approximately 5% and overexpression in 15%-20% of GC/GEJC, and is associated with poor prognosis.[71] Bemarituzumab, an anti-FGFR2 monoclonal antibody, showed initial promise in the phase II FIGHT trial (median PFS 9.5 *v* 7.4 months; median OS 19.2 *v* 13.5 months), with enhanced benefit in patients demonstrating FGFR2 staining in >10% of tumor cells.[72] This 10% cut point informed patient selection for the FORTITUDE phase III program.

However, FORTITUDE-101, which randomly assigned patients to mFOLFOX with or without bemarituzumab, met its primary OS end point at interim analysis but showed attenuation of treatment effect on subsequent analysis.[73] FORTITUDE-102, evaluating mFOLFOX and nivolumab with or without bemarituzumab, was stopped early for inadequate efficacy.[74] Several factors may explain these disappointing results: (1) the 10% expression cut point may inadequately delineate truly FGFR2-dependent tumors, (2) substantial intratumoral heterogeneity exists similar to HER2 and CLDN18.2, and (3) relatively small sample sizes might have limited statistical power. Ongoing efforts focus on clarifying FGFR2 amplification rates using NGS and determining concordance between amplification and overexpression. FGFR2-targeted ADCs such as SIM0686 and BG-C137 are currently in phase I evaluation (ClinicalTrials.gov identifiers: NCT07050459, NCT06625593), potentially offering advantages through payload delivery that bypasses the limitations observed with naked antibodies.

c-MET

c-MET shares several characteristics with FGFR2: receptor tyrosine kinase function, amplification in approximately 5% and overexpression in 15%-20% of GC/GEJC, and association with poor prognosis.[75] Traditional c-MET–directed antibodies faced similar challenges, with both the METGastric and RILOMET trials yielding negative results.[76,77]

However, ADCs have demonstrated renewed promise. A phase I trial of ABBV-400 (telisotuzumab vedotin), a c-MET–targeted ADC, demonstrated a 28% response rate in patient with refractory GC/GEJC, leading to an ongoing randomized phase II trial (ClinicalTrials.gov identifier: NCT06628310).[78] Bispecific antibodies also show potential. GC/GEJC frequently coexpresses EGFR and c-MET, creating rationale for dual targeting. Amivantamab, an EGFR/c-MET bispecific antibody, demonstrated a 38% response rate in this population in a phase II trial,[79] suggesting that simultaneous pathway blockade may overcome single-target resistance mechanisms.

Trophoblast Cell Surface Antigen 2

Trophoblast cell surface antigen 2 (TROP2) demonstrates overexpression in approximately 35% of GC/GEJC. TROP2 signaling is associated with increased tumor growth, metastatic spread, and drug resistance.[80] A phase II study of MK-2870, a TROP2-directed ADC using a belotecan-derivative topoisomerase I inhibitor payload, demonstrated a 22% response rate in refractory GC/GEJC.[81] A randomized phase III trial comparing MK-2870 versus investigator's choice in refractory GC/GEJC is ongoing (ClinicalTrials.gov identifier: NCT06356311),[82] potentially establishing a new treatment option for patients exhausting standard therapies.

Clinical Implementation

Comprehensive NGS should be considered for all patients with advanced GC/GEJC to identify actionable alterations beyond routine biomarkers. While novel targets including FGFR2 and c-MET have faced setbacks with traditional antibody approaches, ADCs and bispecific antibodies hold substantial potential to transform treatment. The field must balance pursuit of frontline indications by addressing the substantial unmet need in second-line and beyond settings, where the standard of care has remained largely unchanged for over a decade outside of HER2-positive disease.

EVOLVING PLATFORM TECHNOLOGIES

Bispecific Antibodies Beyond CLDN18.2

Dual-targeting bispecifics use complementary mechanisms to enhance their efficacy beyond single-agent approaches.

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Rilvegostomig, a PD-1/TIGIT bispecific antibody, combines PD-1 blockade with TIGIT inhibition, targeting checkpoints expressed on exhausted T cells and natural killer cells. In GEMINI-Gastric Substudy 2, first-line rilvegostomig plus chemotherapy in HER2-negative locally advanced/metastatic gastroesophageal adenocarcinoma achieved an ORR of 52.5% and a disease control rate of 100%.[83] This compound is advancing in combination with chemotherapy and HER2- or CLDN18.2-directed ADCs in first-line biomarker-positive disease.

PD-1/PD-L1-VEGF bispecifics combine immune checkpoint blockade with antiangiogenic effects, addressing both T-cell exhaustion and the immunosuppressive vascular microenvironment. Angiogenesis is a well-validated target in GC/GEJC with ramucirumab established in second-line therapy. Pumitamig, an anti–VEGF/PD-L1 bispecific, will be evaluated against nivolumab plus chemotherapy in first-line advanced gastroesophageal adenocarcinoma (GEA) (ROSETTA Gastric-204 trial).[84] Taken together, these approaches reflect efforts to overcome single-pathway resistance through the simultaneous engagement of complementary mechanisms.

Cancer Vaccines

Cancer vaccines prime antitumor immune responses by delivering antigens to activate T cells, with both $CD8^+$ cytotoxic and $CD4^+$ helper cells contributing to their efficacy. Platforms vary in antigen selection (shared tumor-associated antigens versus personalized neoantigens) and delivery systems (mRNA, viral vectors, peptide-based).

Vaccines are unlikely to work as monotherapy in established diseases. Their promise lies in generating long-lived T-cell responses that improve tail-of-the-curve survival in curative-intent settings. In low tumor burden contexts such as perioperative or adjuvant therapy, vaccines may prevent metastasis through sustained immune surveillance. Proof of concept exists in other malignancies: personalized mRNA vaccines plus PD-1 inhibition improved recurrence-free survival in melanoma, whereas vaccine combinations showed encouraging survival in pancreatic cancer.[85,86]

GC/GEJC offers two complementary approaches. Personalized neoantigen vaccines leverage tumor-specific mutations but require expensive sequencing and face heterogeneity challenges. Shared tumor-associated antigen vaccines target commonly expressed proteins, thereby avoiding sequencing costs. HER-Vaxx, which targets three B-cell epitopes on the HER2 extracellular domain, demonstrated significantly improved survival when added to chemotherapy versus chemotherapy alone (ORR 0.60 favoring vaccine) in HER2-positive GEA, establishing proof of concept for shared antigen vaccination outside the setting of standard HER2-directed therapies.[87]

The perioperative setting represents the most promising context for vaccine therapy, where immune surveillance needs only to eliminate micrometastatic disease rather than debulking established tumors. VISTA evaluates a fixed-epitope vaccine perioperatively in patients with HLA-selected esophageal adenocarcinoma.[88] Success in this setting could establish vaccines as low-toxicity adjuvant therapy improving cure rates for patients with resectable GC/GEJC.

CONCLUSION

The treatment landscape for GC/GEJC is rapidly evolving through the integration of perioperative immunotherapy and the expansion of biomarker-guided therapies. Perioperative FLOT plus durvalumab has demonstrated survival benefit in the landmark MATTERHORN trial, establishing a new standard of care for resectable disease. Biomarker-selected perioperative strategies in HER2-positive and MSI-high disease demonstrate exceptional response rates, suggesting that precision medicine will increasingly enable treatment personalization beyond current approaches.

In advanced disease, precision oncology is evolving beyond established biomarkers with the expansion of actionable targets. Following HER2, CLDN18.2-targeted therapy now represents a standard biomarker-defined treatment subset, whereas additional targets such as FGFR2, c-MET, and TROP2 are under active clinical investigation. Importantly, up to 40% of patients have demonstrated coexpression of PD-L1 with HER2 or CLDN18.2, necessitating thoughtful treatment sequencing and combination strategies. Spatial, temporal, and treatment-induced heterogeneity complicate biomarker assessment, making repeat biopsy at progression increasingly essential—particularly for HER2 and CLDN18.2 where antigen dynamics significantly affect therapeutic decisions.

Emerging platforms including ADCs, bispecific antibodies, CAR-T therapies, and cancer vaccines are poised to expand the therapeutic possibilities beyond the current biomarker landscape. ADCs demonstrate renewed promise where traditional antibodies have failed, overcoming heterogeneity through the bystander effect and payload delivery. CLDN18.2-directed BiTEs and CAR-T cells provide proof of concept for cellular immunotherapies in solid tumors although the persistence limitations must be addressed. Cancer vaccines show potential in perioperative settings where immune surveillance can eliminate minimal residual disease.

Future progress will depend on integrating these modalities into biomarker-based treatment algorithms, refining combination strategies, addressing the substantial unmet need in second-line and beyond settings, and advancing trial designs capable of addressing tissue heterogeneity through spatial and genomic biomarker integration. Collectively, these developments herald a shift toward increasingly personalized treatment across all disease stages, matching therapeutic intensity to tumor biology.

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Neoadjuvant Systemic Therapy in Kidney and Bladder Cancer: Current Evidence and Emerging Paradigms

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OVERVIEW

Neoadjuvant systemic therapy has emerged as a strategy to improve outcomes in high-risk localized genitourinary malignancies. In bladder cancer, neoadjuvant cisplatin-based chemotherapy with or without immunotherapy is standard of care, with pathologic complete response (pCR) serving as a validated surrogate for survival after chemotherapy and a promising potential surrogate for survival after other neoadjuvant treatments like immunotherapy. Enfortumab vedotin and immune checkpoint inhibitors have expanded treatment options, with ongoing studies evaluating novel adjuvant approaches tailored to patients' postoperative circulating tumor DNA. In renal cell carcinoma (RCC), the field is nascent, no approved neoadjuvant regimens exist, and treatment outside clinical trials is not recommended. Early trials of tyrosine kinase inhibitor monotherapy showed limited pathologic responses, while immune checkpoint inhibitor-based combinations have demonstrated feasibility, safety, and the capacity to induce pathologic responses including pCR. Critical gaps remain in both diseases. In RCC, standardized pathologic response criteria are lacking, and surrogacy between pathologic end points and long-term outcomes has not been established. In bladder cancer, optimal post-pCR management and integration of novel agents require further study. Emerging technologies, particularly artificial intelligence (AI)–driven digital pathology, offer potential to enhance diagnosis, refine prognostic stratification, and predict treatment response, although prospective validation across diverse populations is needed. This chapter examines neoadjuvant therapy and pathologic response assessment in RCC and bladder cancer, explores pathologic biomarker development including AI applications, and highlights future directions to optimize therapeutic sequencing and outcomes.

INTRODUCTION

The treatment paradigm for localized genitourinary malignancies has undergone significant evolution over the past decade, with neoadjuvant systemic therapy emerging as a compelling strategy to improve outcomes for patients with high-risk disease. Although surgery remains the cornerstone of curative-intent treatment for both renal cell carcinoma (RCC) and urothelial carcinoma of the bladder, the integration of effective systemic agents in the preoperative setting offers several potential advantages: early treatment of micrometastatic disease, in vivo assessment of tumor sensitivity, and the opportunity to leverage pathologic response as a meaningful clinical end point.

In bladder cancer, neoadjuvant cisplatin-based chemotherapy has long been established as a standard of care, with pathologic complete response (pCR) serving as a validated surrogate for long-term survival. The advent of immune checkpoint inhibitors and antibody-drug conjugates (ADCs) has expanded the therapeutic landscape, prompting renewed investigation into optimal neoadjuvant regimens and the clinical implications of achieving pCR for postsurgical management decisions. By contrast, neoadjuvant therapy in RCC represents a more nascent field. However, the remarkable efficacy of immune checkpoint inhibitor combinations, vascular endothelial growth factor (VEGF)–targeted agents, and hypoxia inducible factor (HIF)-2α inhibitors in the metastatic setting has catalyzed exploration of these agents preoperatively.

Critical questions remain in both diseases, although at different stages of maturity. In bladder cancer, the integration of immunotherapy into the neoadjuvant space has prompted re-evaluation of the significance of pathologic response and whether pCR achieved with novel agents carries the same prognostic weight as that observed with chemotherapy. Furthermore, the optimal postoperative management of patients who achieve a pCR remains an area of active investigation. In RCC, the field is at an earlier stage: There is currently no approved neoadjuvant regimen, no standardized methodology for pathologic response assessment or minimal residual disease evaluation, and no established surrogacy of pathologic end points with long-term outcomes. These gaps represent both challenges and opportunities for advancing the field.

PRACTICAL APPLICATIONS

- In renal cell carcinoma (RCC), neoadjuvant therapy remains investigational; treatment outside clinical trials is not recommended given the absence of approved regimens and lack of validated pathologic end points.
- Neoadjuvant cisplatin-based chemotherapy remains standard of care for cisplatin-eligible patients with muscle-invasive bladder cancer, with enfortumab vedotin plus pembrolizumab as an excellent option for cisplatin-ineligible patients.
- Pathologic complete response after chemotherapy is a validated surrogate for survival in bladder cancer; development and validation of standardized pathologic response criteria with outcome surrogacy is a critical need in RCC.
- Randomized trials comparing neoadjuvant versus adjuvant strategies are needed in RCC to define optimal perioperative therapeutic sequencing.
- Artificial intelligence–driven digital pathology shows promise for enhancing diagnosis, prognosis, and treatment response prediction but requires prospective validation in diverse populations.

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Emerging technologies, particularly artificial intelligence (AI)–driven pathologic analysis, offer the potential to address some of these unmet needs. AI-enabled tools that integrate morphologic features with molecular and spatial data may enhance our ability to predict outcomes, detect minimal residual disease, and inform adjuvant treatment strategies across genitourinary cancers. This chapter examines the current state of neoadjuvant therapy and pathologic response assessment in RCC and bladder cancer, explores the frontier of pathologic biomarker development, and highlights future directions to advance the field.

NEOADJUVANT TREATMENT AND PATHOLOGIC RESPONSES IN RCC

Current Landscape of Neoadjuvant Therapy in RCC

Neoadjuvant systemic therapy is not currently a standard of care for localized or locally advanced RCC. There are no approved neoadjuvant regimens, and treatment outside of clinical trials is not recommended.[1] However, the compelling rationale for perioperative systemic therapy, combined with transformative advances in the metastatic setting, has spurred significant clinical investigation in this space (Table 1).

The importance of timing in the delivery of immunotherapy has been underscored by data from other solid tumors, most notably melanoma. The phase II SWOG S1801 trial compared neoadjuvant-adjuvant pembrolizumab (three cycles before surgery followed by adjuvant therapy) to adjuvant pembrolizumab alone for resectable stage III/IV melanoma.[2] With a median follow-up of 14 months, the neoadjuvant-adjuvant approach demonstrated a 23% improvement in event-free survival (EFS; 2-year EFS 72% *v* 49%), providing early evidence that initiating immunotherapy with the tumor in situ may confer superior outcomes. Updated 3-year follow-up data confirmed the durability of benefit, with the neoadjuvant-adjuvant approach demonstrating continued superiority in EFS (hazard ratio [HR], 0.59 [95% CI, 0.40 to 0.86]).[3] The phase III NADINA trial subsequently confirmed these findings, randomly assigning patients with resectable stage III melanoma to two cycles of neoadjuvant ipilimumab-nivolumab followed by response-driven adjuvant therapy versus surgery followed by adjuvant nivolumab.[4] The neoadjuvant approach demonstrated a 12-month EFS of 83.7% compared with 57.2% in the adjuvant arm (HR, 0.32), with 59% of patients achieving a major pathologic response (MPR) and thereby avoiding adjuvant therapy altogether. Updated 2-year data confirmed the durability of benefit, with HR, 0.40.[5] These studies provide a biologic and clinical framework supporting further investigation of neoadjuvant immunotherapy in RCC.

Historical Experience With Neoadjuvant Tyrosine Kinase Inhibitor Monotherapy

Early exploration of neoadjuvant therapy in RCC focused on VEGF receptor tyrosine kinase inhibitors (TKIs), leveraging the established efficacy of these agents in the metastatic setting.[6] Multiple phase II trials evaluated neoadjuvant TKI monotherapy, including axitinib, pazopanib, sunitinib, and sorafenib (Table 1).[7-10] Treatment durations ranged from 8 to 16 weeks, with sample sizes typically between 18 and 40 patients. Primary and secondary end points varied, with radiographic objective response rate (ORR) as the most common efficacy measure.

Across these trials, imaging-based partial response rates assessed by RECIST criteria ranged from approximately 6% to 46%, with the majority of patients demonstrating stable disease. Median tumor diameter reductions were modest, typically 10%-30%. Pathologic response was infrequently evaluated, and when assessed, pCR was exceedingly rare. In a retrospective series of 168 patients receiving various neoadjuvant TKIs, the overall partial response rate was only 6% with no complete responses.[11] These early trials established that neoadjuvant therapy was feasible and reasonably well-tolerated, with potential to facilitate nephron-sparing surgery in select patients by reducing tumor size and complexity.

However, significant limitations constrain interpretation of these data. Studies were small, single-arm, and nonrandomized. There was no standardized methodology for

TABLE 1. Neoadjuvant Systemic Therapy Trials in RCC

Trial	Phase	Drug	No.	Eligibility	Treatment Duration	Primary End Point	ORR	EFS/DFS
TKI monotherapy								
Cowey et al	2	Sorafenib	30	cT2-T4 or TanyN + M0/M1	4-8 weeks	Safety/feasibility	7%	NR
Karam et al	2	Axitinib	24	cT2-T3bN0M0 ccRCC	12 weeks	ORR	46%	NR
Rini et al	2	Pazopanib	25	cT1-T3aN0M0	8-16 weeks	Renal parenchyma preservation	36%	NR
Silberstein et al	2	Sunitinib	12	Imperative NSS indication, ccRCC	8 weeks	Feasibility	29%	NR
Bilen et al	2	Cabozantinib	17	cT2-T4N0-1M0 ccRCC	12 weeks	ORR	35%	1-year DFS 82%
IO monotherapy/combinations								
Gorin et al	1	Nivolumab	17	High-risk nonmetastatic ccRCC	3 doses	Safety	0%	NR
PROSPER RCC	3	Nivolumab	819	cT2-T4 or TanyN + M0	1 neoadjuvant + 9 adjuvant doses	RFS	NR	No difference (HR, 0.97)
NESCIO (arm A)	2	Nivolumab	14	cT1b-T3aN0M0 or TanyN1M0, grade 3 to 4 ccRCC	6 weeks	Pathologic response	pRR 7%	Immature
NESCIO (arm B)	2	Ipilimumab + nivolumab	14	cT1b-T3aN0M0 or TanyN1M0, grade 3 to 4 ccRCC	6 weeks	Pathologic response	pRR 14%	Immature
NESCIO (arm C)	2	Relatlimab + nivolumab	14	cT1b-T3aN0M0 or TanyN1M0, grade 3 to 4 ccRCC	6 weeks	Pathologic response	pRR 14%	Immature
IO-TKI combinations								
NEOAVAX	2	Avelumab + axitinib	40	cT1b-T4N0-1M0, grade 3 to 4, high-risk ccRCC	12 weeks	ORR	30%	68% DF at 23.5 months
Karam et al	2	Sitravatinib + nivolumab	17	cT3-T4 or TanyN + M0 ccRCC	8 weeks	ORR	12%	24-month DFS: 88%
Huang et al	2	Toripalimab + axitinib	20	cT2-T3N0-1M0 ccRCC	12 weeks	ORR	45% (pCR 21%)	NR
Bilen et al	2	Lenvatinib + pembrolizumab	15	cT3-T4 or TanyN + M0 ccRCC	12 weeks	ORR	20%	NR

Abbreviations: ccRCC, clear cell renal cell carcinoma; DF, disease-free; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; IO, immunotherapy; mo, months; NR, not reported; NSS, nephron-sparing surgery; ORR, objective response rate; pCR, pathologic complete response; pRR, pathologic response rate; RFS, recurrence-free survival; TKI, tyrosine kinase inhibitor.

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pathologic response assessment, pathologic end points were not routinely evaluated, and long-term outcomes such as recurrence-free (RFS) and overall survival (OS) were not systematically reported. Additionally, these studies had limited representation of patients with nodal involvement, with several key trials excluding these patients altogether or including only a small minority. Furthermore, these studies were conducted exclusively in US populations, which may limit external generalizability. Collectively, these trials highlighted the limited efficacy of TKI monotherapy in inducing significant tumor regression, particularly pathologic responses, and underscored the need for novel therapeutic strategies.

Notably, a recent phase II trial of neoadjuvant cabozantinib demonstrated that TKI therapy can modulate the tumor immune microenvironment, with correlative analyses revealing activation of $CD8^+$ T cells, depletion of immunosuppressive myeloid populations, and induction of immune niches harboring TCF1+ stem-like $CD8^+$ T cells.[12] This provides mechanistic rationale for combining neoadjuvant TKIs with immune checkpoint inhibitors.

Neoadjuvant Immunotherapy Trials

The approval of immune checkpoint inhibitors as first-line therapy for metastatic RCC prompted investigation in the neoadjuvant setting (Table 1).[13] Gorin et al[14] reported results from a phase I trial evaluating three doses of neoadjuvant nivolumab in 17 patients with high-risk nonmetastatic clear cell RCC. All patients completed neoadjuvant therapy and proceeded to nephrectomy without surgical delay. Although all patients had radiologically stable disease, one patient (6.7%) demonstrated features of an immune-related pathologic response. The study confirmed that neoadjuvant nivolumab was safe and did not compromise surgical outcomes, although the limited pathologic activity raised questions about efficacy.

PROSPER (ECOG-ACRIN EA8143) was the first phase III trial of neoadjuvant immunotherapy in RCC.[15] This open-label study enrolled 819 patients with high-risk RCC (clinical ≥T2 or T any N+) planned for nephrectomy. Patients were randomly assigned to perioperative nivolumab (one dose before surgery followed by nine adjuvant doses) versus surgery alone. There was no difference in RFS between arms (HR, 0.97 [95% CI, 0.74 to 1.28]), and the study was stopped early for futility.

Several considerations limit interpretation of the PROSPER results. The trial was not designed with the intent of primary tumor reduction; rather, the hypothesis centered on immune priming before surgery and eradication of micrometastatic disease. Pathologic response was not reported as an end point, precluding assessment of whether neoadjuvant nivolumab induced meaningful changes in the primary tumor. Furthermore, it remains unclear whether the limited duration of neoadjuvant treatment was sufficient to generate a robust antitumor immune response. The trial also included both clear cell and non-clear cell histologies. Despite these limitations, PROSPER established the feasibility and safety of perioperative immunotherapy in RCC and set the stage for subsequent trials.

The NESCIO trial directly addressed the question of whether short-course neoadjuvant immunotherapy could induce pathologic responses in RCC.[16] This randomized, noncomparative phase II trial enrolled 42 patients with intermediate- to high-risk resectable clear cell RCC, including grade 3 to 4 tumors or sarcomatoid/rhabdoid differentiation, who were randomly assigned 1:1:1 to receive two cycles (6 weeks) of nivolumab monotherapy, ipilimumab-nivolumab, or relatlimab-nivolumab, followed by nephrectomy at week 7. Notably, the study population was enriched for locally advanced disease, with approximately 99% of patients having T3-T4 tumors and approximately 25% having lymph node involvement. Pathologic response was assessed using International Neoadjuvant Melanoma Consortium (INMC) criteria and defined as ≤50% viable tumor. Interim results demonstrated pathologic response rates of 7.1% with nivolumab monotherapy, 14.3% with ipilimumab-nivolumab, and 14.3% with relatlimab-nivolumab; the combination arms met predefined efficacy thresholds while nivolumab monotherapy did not.[16] RFS data remain immature; however, all patients who achieved a pathologic response were alive and disease-free at the data cutoff. The NESCIO trial provides important proof-of-concept that short-course neoadjuvant immunotherapy can induce pathologic responses in RCC, although mature survival data are needed to define the clinical significance of these findings.

Neoadjuvant Immunotherapy Plus TKI Combination Trials

The remarkable efficacy of immunotherapy combined with TKIs in metastatic RCC, now established as first-line standard of care, has provided compelling rationale for investigating these regimens in the neoadjuvant setting. The NEOAVAX trial evaluated avelumab plus axitinib for 12 weeks in 40 patients with high-risk nonmetastatic clear cell RCC (including grade 3 to 4 tumors).[17,18] By RECIST criteria, 30% achieved partial response with a median tumor downsizing of 20%; notably, no patients experienced disease progression during neoadjuvant therapy. An exploratory analysis presented at ASCO Annual Meeting 2025 applied INMC pathologic response criteria to surgical specimens: no patient achieved pCR, but three (7.5%) had MPR (≤10% viable tumor) and 12 (30%) had partial pathologic response.[19] Intriguingly, pathologic response was not associated with radiologic response, underscoring the complexity of treatment effect assessment in RCC. Patients with MPR had numerically superior disease-free survival (DFS) and demonstrated distinct tumor microenvironment changes, including $CD8^+CD39^+$ T-cell infiltration.

Karam et al[20] evaluated neoadjuvant sitravatinib, a spectrum-selective TKI targeting TAM receptors (TYRO3, AXL, MERTK) and VEGFR, in combination with nivolumab in patients with locally advanced clear cell RCC in a phase II study. The ORR was modest at 11.8% with median primary tumor shrinkage of 13.5%, and the primary end point was not met. However, the combination demonstrated a favorable safety profile with no grade 4/5 treatment-related adverse events and an encouraging 24-month DFS of 88%. Importantly, correlative tissue analyses demonstrated changes in the tumor microenvironment resulting in an immunologically active tumor by the time of surgery, including upregulation of interferon-gamma response pathways.

Huang et al[21] evaluated toripalimab plus axitinib for 12 weeks in 20 patients with locally advanced clear cell RCC (T2-T3N0-1M0). This combination demonstrated the highest pCR rate in any neoadjuvant RCC trial to date: four of 19 patients undergoing surgery (21%) achieved pCR, with an ORR of 45% and tumor shrinkage in 95% of patients. Patients achieving pCR remained recurrence free at study completion, though sample size limited interpretation of this finding.

More recently, Bilen et al[22] reported results from a phase II study of perioperative lenvatinib plus pembrolizumab in patients with locally advanced nonmetastatic clear cell RCC. Patients received four cycles of combination therapy followed by surgery and 13 cycles of adjuvant pembrolizumab. Among 15 evaluable patients, the ORR was 20% (all partial responses) with 80% achieving stable disease; no patients progressed on neoadjuvant therapy. The median primary tumor reduction was 21% (range, 3%-37%). The combination demonstrated excellent surgical feasibility: 93% of patients proceeded to surgery without delay, and no intraoperative or drug-related postoperative complications were observed. At the time of analysis, two patients had experienced disease recurrence.

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Collectively, these immunotherapy-TKI trials demonstrate several consistent findings: (1) combination therapy produces more substantial tumor downsizing than immunotherapy alone; (2) disease progression during neoadjuvant therapy is rare; (3) surgical feasibility is preserved; and (4) pathologic responses, including pCR, can occur. The observation that patients achieving pCR in the Huang study remained recurrence-free, while similar trends were seen in NEOAVAX for major pathologic responders, suggests pathologic response may have prognostic value, although validation in larger cohorts is essential.

Defining Pathologic Response in RCC

The central tenets of pathologic response assessment in the neoadjuvant setting require that any proposed framework be (1) standardized across institutions and pathologists, (2) reproducible with low interobserver variability, and (3) correlated with meaningful patient outcomes such as DFS and OS. Without these elements, pathologic response cannot serve as a reliable surrogate end point for clinical trials or a basis for therapeutic decision-making.

In melanoma, the INMC established standardized criteria for pathologic response assessment based on the percentage of viable residual tumor: pCR (0% viable tumor), near-complete response (near-pCR, ≤10% viable tumor), partial response (pPR, >10%-50% viable tumor), and nonresponse (pNR, > 50% viable tumor).[23,24] MPR, encompassing pCR and near-pCR (≤10% viable tumor), has been strongly associated with EFS in neoadjuvant melanoma trials. In the OpACIN, OpACIN-neo, and PRADO studies, patients achieving pathologic response demonstrated a 3-year RFS of 95% compared with 37% for nonresponders.[4,25,26] This robust correlation has enabled response-directed adjuvant therapy strategies, wherein patients achieving MPR may safely forgo additional systemic treatment.

Whether similar thresholds apply to RCC remains uncertain. The International Neoadjuvant Kidney Cancer Consortium (INKC) has recently proposed a pathologic response framework adapted specifically for RCC, suggesting classifications analogous to the melanoma experience but acknowledging the unique histopathologic features of kidney cancer including tumor necrosis patterns, regressive changes, and immunotherapy-related effects.[27] Retrospective data suggest that immunotherapy-based therapy can induce pathologic responses in kidney cancer: Panian et al[28] reported that among 52 patients with advanced RCC who received immunotherapy before cytoreductive nephrectomy, 44% experienced pathologic downstaging and 13% achieved pCR. Notably, the heterogeneous patterns of response observed with immunotherapy in RCC, including variable degrees of tumor necrosis, fibrosis, inflammatory infiltration, and residual viable tumor, may not map directly onto the melanoma framework. The NEOAVAX and NESCIO trials applied INMC criteria to RCC, providing early feasibility data, but prospective validation in larger cohorts with long-term follow-up will be essential to establish the clinical utility of pathologic response in RCC.

Neoadjuvant Versus Adjuvant Approaches

The optimal timing of perioperative systemic therapy remains an area of active investigation.[1,29] In the adjuvant setting, pembrolizumab has level 1 evidence demonstrating DFS and OS benefit in KEYNOTE-564, though other single-agent adjuvant immunotherapy trials (CheckMate-914, IMmotion010, PROSPER) were negative.[15,30-32] More recently, the RAMPART trial demonstrated that adjuvant durvalumab plus tremelimumab improved 3-year DFS compared with active monitoring (81% *v* 73%; HR, 0.65), with benefit driven primarily by the high-risk population (HR, 0.52); however, the combination was associated with substantial toxicity, with 40% of patients experiencing grade 3 adverse events compared with 8% in the monitoring arm.[33] Preliminary results from LITESPARK-022 showed that adding the HIF-2α inhibitor belzutifan to adjuvant pembrolizumab significantly improved DFS compared with pembrolizumab alone, representing the first combination to demonstrate superiority over adjuvant pembrolizumab monotherapy. Neoadjuvant therapy offers potential advantages including enhanced immune response with tumor in situ, in vivo assessment of treatment sensitivity, and the opportunity to de-escalate adjuvant therapy in patients achieving deep pathologic responses. However, neoadjuvant approaches carry risks of treatment-related toxicity causing surgical delay, disease progression during treatment, and overtreatment of patients curable by surgery alone. Both strategies face challenges in patient selection, and critically, the lack of established surrogacy between pathologic end points and long-term outcomes in RCC limits the ability to use pathologic response to guide adjuvant therapy decisions.

NEOADJUVANT TREATMENT AND PATHOLOGIC RESPONSES IN BLADDER CANCER

Evolving Data on Neoadjuvant Treatments

Perioperative therapy for muscle-invasive bladder cancer (MIBC) is evolving rapidly (Fig 1). Cisplatin-based combination chemotherapy remains the established standard for neoadjuvant treatment in MIBC, with pCR rates of 27.5%-42% compared with up to 15% with radical cystectomy alone (Tables 2 and 3).[34,36,39] The National Comprehensive Cancer Network (NCCN) recommends three to six cycles of dose-dense MVAC (ddMVAC) with growth factor support as a preferred neoadjuvant regimen, with four cycles of gemcitabine and cisplatin (GC) as an alternative.[40] Comparative data from the VESPER trial demonstrated superior outcomes with ddMVAC versus GC in the neoadjuvant setting. Among 437 patients receiving neoadjuvant chemotherapy, 5-year OS was significantly higher at 66% versus 57%, as was 3-year progression-free survival at 66% versus 56%, although at the expense of significantly greater toxicity.[36,41] The pCR rate was numerically higher for neoadjuvant ddMVAC

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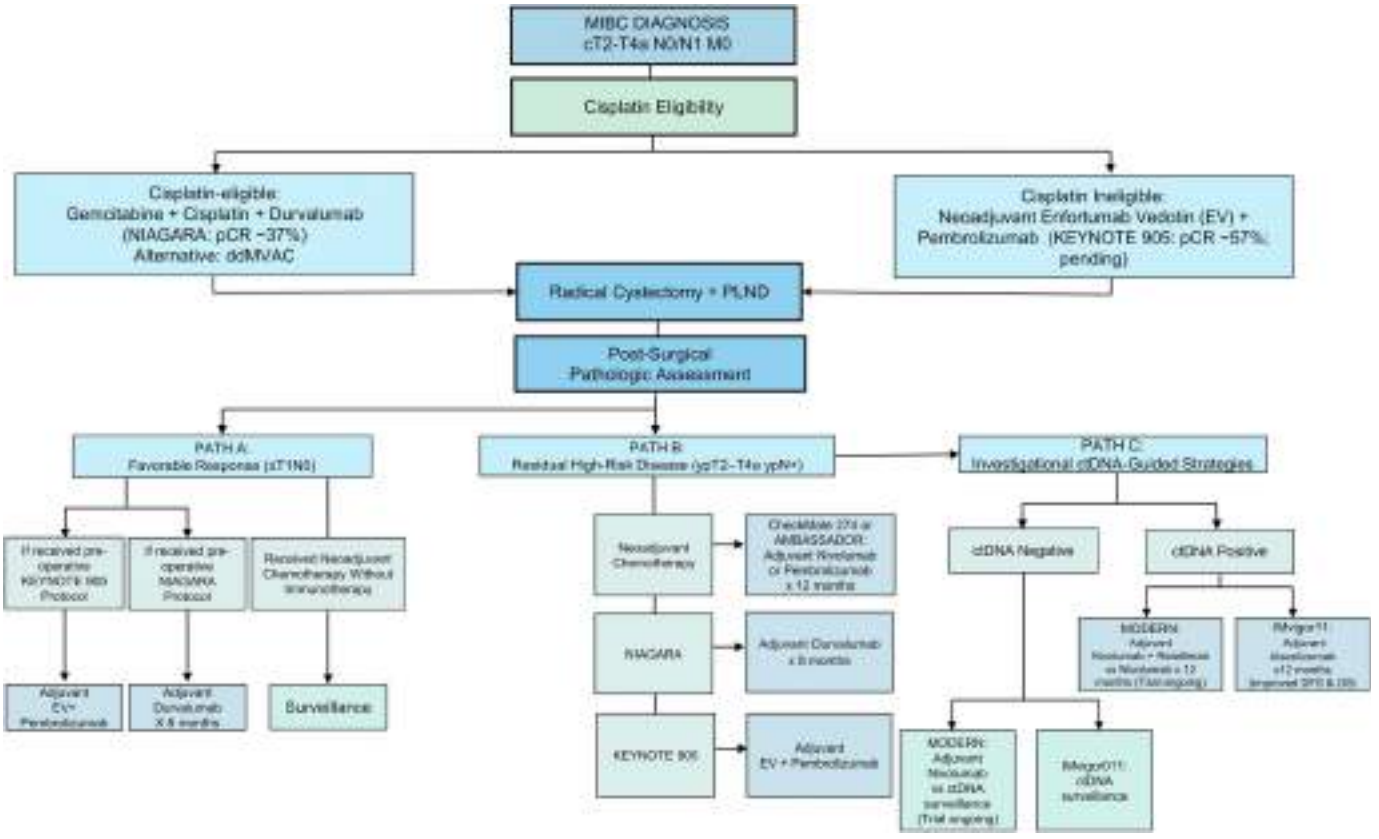

FIG 1. Perioperative management algorithm for muscle-invasive bladder cancer integrating platinum eligibility, neoadjuvant immunochemotherapy, and emerging ctDNA-guided strategies. ctDNA, circulating tumor DNA; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, cisplatin; EV, enfortumab vedotin; IO, immunotherapy; pCR, pathologic complete response; PLND, pelvic lymph node dissection.

compared with GC (42% *v* 36%).[42] Interpretation of these findings is limited because the overall trial was negative for its primary end point and prescribed more ddMVAC than prior trials.[43,44]

For cisplatin-eligible patients, chemo-immunotherapy combinations represent the most significant recent advance. The NIAGARA trial evaluated perioperative durvalumab (a PD-L1 inhibitor) before and after radical cystectomy plus neoadjuvant gemcitabine-cisplatin.[34] Addition of durvalumab resulted in 24-month EFS of 67.8% versus 59.8% without durvalumab (HR, 0.68 [95% CI, 0.56 to 0.82]) and improved OS (82.2% *v* 75.2%; HR, 0.75 [95% CI, 0.59 to 0.93]). The chemo-immunotherapy combination achieved pCR rate of 37.3% versus 27.5% with chemotherapy alone. Based on these results, NCCN now lists gemcitabine-cisplatin-durvalumab before cystectomy, followed by adjuvant durvalumab, as a category 1 preferred regimen.[40]

For cisplatin-ineligible patients, the standard of care for perioperative therapy is now enfortumab vedotin and pembrolizumab (EVP). The landmark KEYNOTE-905/EV-303 trial included 344 patients with MIBC who were ineligible for or declined cisplatin.[35] With a median follow-up of 25.6 months, EVP significantly improved EFS (HR, 0.40), OS (HR, 0.50), and pCR rate (57.1% *v* 8.6%). Median EFS for patients with pCR to EVP was not reached, compared with 26.1 months for patients without pCR. Grade ≥3 treatment-related adverse events occurred in 71.3% of patients assigned to EVP versus 45.9% in the control arm.

KEYNOTE-B15/EV-304 is an ongoing randomized phase III trial comparing perioperative EVP to neoadjuvant gemcitabine plus cisplatin for cisplatin-eligible patients. Per press release, the trial demonstrated statistically significant improvements in event-free and OS, and may raise questions regarding the future of neoadjuvant cisplatin-based chemotherapy.[45,46] For cisplatin-ineligible patients, EV plus dual immune checkpoint inhibition will be investigated in the ongoing phase III VOLGA trial.[47]

Early data suggest promise for other perioperative ADC combinations. Disitimab vedotin (DV) is a human epidermal growth factor receptor 2 (HER2)–directed ADC. When combined with gemcitabine in a phase II trial of 26 patients with HER2-expressing MIBC, 59% experienced pCR.[48] In the phase II RC48-C017 trial, neoadjuvant DV plus toripalimab achieved pCR rate of 63.6%, with pCR in 84.6% of cases with 3+ HER2.[49] In phase II neoadjuvant trials, the TROP-2 targeted ADC sacituzumab govitecan (SG) achieved pCR rates of 36.4% and 44.4% as monotherapy and in combination with pembrolizumab, respectively.[50,51]

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TABLE 2. Phase III Neoadjuvant Trials in Muscle-Invasive Bladder Cancer

Trial	Study Population	Treatment Regimen	No. (evaluable)	pCR % (95% CI)	<pT2N0% (95% CI)	Reference
NIAGARA	Cisplatin-eligible MIBC (cT2–T4aN0/1M0)	Durvalumab + Gem/Cis → RC → durvalumab	533	37.3 (33.2 to 41.6)	—	Powles et al (2024)[34]
		Gem/Cis → RC	530	27.5 (23.8 to 31.6)	—	
EV-303/KEYNOTE-905	Cisplatin-ineligible MIBC (cT2-T4aN0/1M0)	EVP → RC →EVP	Approximately 218	57.1	—	Vulsteke et al (2025)[35]
		RC alone	Approximately 218	8.6	—	
VESPER	Cisplatin eligible Nonmetastatic MIBC (cT2-T4aN0M0)	dd-MVAC (neoadjuvant)	218	42	77%	Pfister et al (2022)[36]
		Gem/Cis (neoadjuvant)	219	36	63	

Abbreviations: dd-MVAC, dose-dense methotrexate, vinblastine, doxorubicin, cisplatin; EVP, enfortumab vedotin plus pembrolizumab; Gem/Cis, gemcitabine/cisplatin; MIBC, muscle-invasive bladder cancer; pCR, pathologic complete response; RC, radical cystectomy.

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Neoadjuvant checkpoint inhibitor monotherapy has shown mixed results. The phase II PURE-01 study demonstrated 37% pCR rate with preoperative pembrolizumab.[37,52] The ABACUS trial reported 31% pCR rate with two cycles of atezolizumab.[38,53] However, checkpoint inhibitor monotherapy for cisplatin-ineligible patients appears unlikely to supplant existing standards like perioperative EVP.

Prognostic Implications of Pathologic Response

pCR, defined as ypT0N0, represents a favorable outcome.[39,54] Achieving pCR after neoadjuvant chemotherapy is associated with a 55% improvement in survival and 81% lower risk of recurrence.[54] As a result, pCR in MIBC has been used as a primary end point in phase II trials.[38,55] Notably, the phase III NIAGARA trial and several ongoing phase III trials employed pCR as a coprimary end point alongside EFS.[34,46,47,56] However, the US Food and Drug Administration has not formally accepted pCR as a validated standalone primary end point in registrational studies for MIBC. The excellent prognosis associated with pCR has motivated investigation into whether patients with clinical complete response (cCR) can safely undergo bladder sparing approaches, to improve patient quality of life and better align with patient goals.[57-60] However, as many as one in four patients with cCR may harbor occult residual muscle-invasive disease.[61] Ongoing efforts suggest that bladder magnetic resonance imaging and cell-free DNA may improve concordance between cCR and pCR.[62]

Patients with residual muscle-invasive disease at cystectomy are at a high risk of recurrence, warranting adjuvant therapy.[54,63-65] If cisplatin-based neoadjuvant chemotherapy was given without immunotherapy and residual disease is ypT2-T4a and/or ypN+, nivolumab or pembrolizumab may be considered.[40,64-66] Adjuvant nivolumab or pembrolizumab may also be considered for patients with high-risk residual disease who are cisplatin-ineligible. If no neoadjuvant therapy was given with pT3-T4a and/or pN+ disease, adjuvant cisplatin-based chemotherapy is preferred.[40,64,65,67]

Postsurgery Approaches in the Context of pCR

For patients achieving pCR following neoadjuvant cisplatin-based chemotherapy without immunotherapy, surveillance without additional systemic therapy is standard.[40] By

TABLE 3. Phase II Signal-Seeking Neoadjuvant Trials in Muscle-Invasive Bladder Cancer

Trial	Study Population	Treatment Regimen	No.	pCR % (95% CI)	<pT2N0% (95% CI)	Reference
SAKK 06/17	Operable MIBC (cT2–T4aN0-1)	Durvalumab + Gem/Cis → RC → durvalumab	57	32.7 (20.3 to 47.1)	60.5 (36.2 to 78.1)	Cathomas et al (2023)[87]
BLASST-1	MIBC (cT2-4aN0-1M0)	Nivolumab + Gem/Cis	41	49	65.8	Gupta et al (2020)[88]
PURE-01	MIBC (cT2-4aN0M0)	Pembrolizumab (monotherapy)	114	36.8	—	Necchi et al (2020)[37]
ABACUS	Cisplatin-ineligible MIBC	Atezolizumab (monotherapy)	95	31 (21 to 41)	39	Powles et al (2019)[38]
Atezolizumab + Gem/Cis	MIBC (cT2–T4aN0M0)	Atezolizumab + Gem/Cis	39	44	69 (55 to 79)	Funt et al (2022)[89]
Pembrolizumab + Gemcitabine (GU14-188)	Cisplatin-ineligible MIBC	Pembrolizumab + Gemcitabine	—	45.2	51.6	Kaimakliotis et al (2020)[90]
Nivolumab ± Ipilimumab	Cisplatin-ineligible MIBC	Nivolumab (C1) vs Nivo/Ipi (C2)	30	C1: 13%; C2: 7%	C1: 26%; C2: 20%	Guercio et al (2022)[91]

Abbreviations: C1, cohort; C2, cohort 2; Gem/Cis, gemcitabine/cisplatin; MIBC, muscle-invasive bladder cancer; pCR, pathologic complete response; RC, radical cystectomy.

contrast, when perioperative durvalumab with gemcitabine-cisplatin is administered preoperatively, standard practice entails resuming durvalumab postoperatively irrespective of pathologic response.[34] Similarly, when EVP is administered preoperatively, standard practice incorporates postoperative resumption of EVP independent of pathologic response.[35] No published studies have definitively delineated the relative contributions of preoperative versus postoperative components of these perioperative sandwich regimens.

Nevertheless, pCR maintains robust prognostic value for patients receiving perioperative sandwich therapy. In NIAGARA's durvalumab-containing arm, patients achieving pCR demonstrated 2-year EFS of 92.1% compared with 53% among patients without pCR.[68] Exploratory subgroup analysis indicated that addition of perioperative durvalumab may improve outcomes even among patients achieving pCR. However, whether the observed benefit derives from the preoperative component, postoperative component, or both remains unknown.

Circulating Tumor DNA in Adjuvant Treatment Selection

Circulating tumor DNA (ctDNA) after cystectomy has emerged as a highly prognostic biomarker.[69-71] Multiple studies demonstrate that ctDNA positivity identifies patients at substantially elevated risk of recurrence and death, whereas persistent ctDNA negativity correlates with favorable outcomes.[66,71-73]

The IMvigor011 trial prospectively validated ctDNA-guided adjuvant therapy in patients at a high risk of recurrence.[72] Among 761 enrolled patients, 250 who tested ctDNA-positive were randomly assigned to atezolizumab versus placebo. Atezolizumab significantly improved DFS (median 9.9 *v* 4.8 months, HR, 0.64) and OS (median 32.8 *v* 21.1 months, HR, 0.59). Among 357 patients with persistently negative ctDNA during one year of postcystectomy surveillance, DFS was 95% at 1 year and 88% at 2 years, suggesting potential for serial ctDNA monitoring to identify patients who may safely forgo adjuvant therapy.[72] However, 39 of the 357 persistently negative patients (11%) did experience disease recurrence or death, and IMvigor011 did not randomly assign patients with persistently negative ctDNA to adjuvant immunotherapy versus placebo. The ongoing trial MODERN (ClinicalTrials.gov identifier: NCT05987241) will be pivotal in defining optimal care for ctDNA-negative patients, randomly assigning patients with negative baseline ctDNA to either adjuvant nivolumab versus serial ctDNA monitoring without adjuvant therapy.

Notably, most published postoperative ctDNA studies in MIBC excluded patients with pCR, as enrollment was restricted to patients with residual muscle-invasive disease and/or node-positive disease.[66,71,72] Consequently, the prognosis of patients with both pCR plus negative ctDNA remains incompletely characterized.

Implementation of the IMvigor011 surveillance approach carries an important caveat: no patients received immune checkpoint blockade before cystectomy.[72] The trial enrolled only patients who received neoadjuvant chemotherapy without immunotherapy (52%) or no neoadjuvant therapy (48%). Therefore, IMvigor011 results may not generalize to patients receiving sandwich immunotherapy-containing regimens such as EVP or gemcitabine-cisplatin-durvalumab and do not establish whether patients achieving negative ctDNA status with these regimens can safely forgo the adjuvant component.[34,35]

Notably, the ctDNA analyses of IMvigor011, IMvigor010, CheckMate 274, and NIAGARA all employed the Signatera ctDNA assay, which uses a personalized gene panel informed by whole-exome sequencing.[66,71,72,74] Alternative methodologies, including tumor-uninformed approaches and strategies informed by whole-genome sequencing, are under investigation. Both tumor-informed and tumor-agnostic approaches have demonstrated promise for clinical application.[75,76]

EMERGING PATHOLOGIC BIOMARKERS IN RCC AND BLADDER CANCER

The integration of AI with digital pathology has emerged as a transformative approach to biomarker development in genitourinary oncology. By extracting high-dimensional features from routine hematoxylin and eosin (H&E)-stained whole-slide images, AI-based models offer the potential to enhance diagnostic accuracy, refine prognostic stratification, predict treatment response, and ultimately guide therapeutic decision making.

AI-Powered Pathology for Diagnosis and Prognosis

The application of AI to digital pathology in genitourinary oncology remains an emerging field, with most studies representing early-phase development and retrospective validation rather than prospective clinical implementation. Nonetheless, accumulating evidence suggests potential utility across several domains. Expert pathologic evaluation remains the gold standard for diagnosis in bladder cancer and RCC. AI has emerged as a promising complementary technology to enhance consistency in tumor morphology and microenvironment analysis across both malignancies and provide data to inform individual prognosis.

In bladder cancer, diagnostic models have achieved accuracy comparable with expert uropathologists.[77] Computational pathology has also enabled identification of morphologic features, including nuclear area, shape irregularity, and papillary architecture, that correlate with molecular subtypes, potentially enabling molecular classification from routine H&E slides without transcriptomic profiling.[78]

Beyond diagnosis, AI models have demonstrated prognostic value across the disease spectrum. In non–muscle-invasive

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bladder cancer (NMIBC), predicting response to intravesical bacillus Calmette-Guérin (BCG) therapy has significant implications for treatment selection and cystectomy timing. Lotan et al developed AI-based histologic assays using transurethral resection specimens from 944 patients stratified by risk categories for recurrence, progression, and BCG-unresponsive disease.[79] In validation, high-risk patients demonstrated inferior outcomes across all end points, with the AI assays providing predictive information beyond conventional clinicopathologic factors. Additional work demonstrated that deep learning models combining histopathology images with clinical data predict RFS with greater accuracy than models relying solely on clinical variables.[80]

For MIBC, Zheng et al[77] developed a prognostic model using whole-slide images from The Cancer Genome Atlas (TCGA) and validated it in an independent cohort, demonstrating that AI-derived risk scores could stratify patients into groups with significantly different OS independent of conventional clinicopathologic variables. AI models have also demonstrated capacity to predict occult lymph node metastasis from primary tumor analysis. Harmon et al[81] showed that deep learning models evaluating cystectomy specimens achieved an AUC of 0.807 when combined with clinical variables, outperforming clinicopathologic models alone.

In RCC, AI applications span subtype classification, nuclear grading, molecular prediction, and survival prognostication. A comprehensive systematic review of digital pathology and AI in RCC analyzed 26 studies encompassing data from multiple institutional cohorts and found that deep learning models achieved AUCs exceeding 0.93 for histologic subtype classification (distinguishing clear cell, papillary, and chromophobe RCC), 0.89-0.96 for nuclear grading in clear cell RCC, and 0.70-0.89 for predicting molecular aberrations including BAP1 and PBRM1 mutations.[82] For survival prediction, Chen et al[83] developed a deep learning model using 1,752 whole-slide images from multiple centers including TCGA (n = 530), Shanghai General Hospital, and Clinical Proteomic Tumor Analysis Consortium cohorts. The model achieved an AUC of 0.784 for predicting 5-year survival status in the TCGA cohort, with external validation confirming performance (AUC 0.774 in the General cohort, 0.702 in CPTAC). While the resulting competing-risk nomogram distinguished patients with high survival risk, these findings require validation in geographically diverse populations.

Additional work has explored multimodal AI models integrating clinical features, computed tomography imaging, and histopathologic whole-slide images.[84] Zang et al reported that a multimodal predictive recurrence score developed from 1,648 patients in China and TCGA database outperformed established clinical tools including the Leibovich score, University of California Los Angeles Integrated Staging System score, and KEYNOTE-564 risk classification in internal and external validation cohorts. The model reclassified a substantial proportion of patients across risk categories, suggesting potential utility in refining adjuvant therapy decisions. However, as a retrospective study primarily derived from a single country, generalizability to Western populations and different health care settings remains uncertain, and prospective validation is needed.

Predicting Response to Neoadjuvant Therapy

The ability to predict pathologic response before neoadjuvant therapy initiation represents a critical unmet need. In MIBC, approximately 35% of patients achieve pCR to neoadjuvant chemotherapy, and pCR is strongly associated with long-term survival, with 5-year OS rates approaching 90%.[85] Bai et al[85] developed a Graph-based Multimodal Late Fusion deep learning framework integrating histopathology and cell type data from H&E images with RNA sequencing-derived gene expression profiles using data from SWOG S1314. The multimodal approach outperformed unimodal models in predicting neoadjuvant chemotherapy response and identified key gene signatures that drive predictive power. Earlier work demonstrated that machine learning models using nuclear morphology and tissue architecture features from biopsy specimens could achieve 65%-73% accuracy in predicting response.[86]

Surrogacy and Integration Into Clinical Practice

Despite these advances, several challenges remain before AI-derived biomarkers can be routinely integrated into clinical practice. Most studies to date are retrospective in design, with potential for selection bias and inadequate control of confounders. Many models have been developed and validated primarily within single geographic regions, raising questions about generalizability across diverse patient populations, health care systems, and laboratory practices. Technical variability in slide preparation, staining protocols, and scanning equipment may limit reproducibility when models are applied to external data sets. Furthermore, the lack of standardized reporting frameworks makes cross-study comparisons difficult.

Prospective validation in independent, geographically diverse cohorts with long-term follow-up is essential to establish whether AI-derived biomarkers provide surrogacy for meaningful clinical outcomes such as OS. Standardization of assays and analytical pipelines across institutions will be critical for clinical implementation. Additionally, the integration of multiple biomarker modalities, histopathologic features, molecular alterations, and radiologic imaging may provide complementary information that enhances predictive accuracy beyond any single approach, although this adds complexity to validation and implementation.

For AI pathology tools to transition from research to clinical practice, interpretability remains important, clinicians and pathologists benefit from understanding which features drive model predictions. As these technologies mature and undergo rigorous prospective validation, they hold potential to augment the management of localized genitourinary

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cancers by enabling more precise risk stratification and personalized treatment strategies.

CONCLUSIONS

Neoadjuvant systemic therapy represents a rapidly evolving treatment paradigm in genitourinary oncology, with distinct levels of maturity across disease states. In bladder cancer, cisplatin-based neoadjuvant chemotherapy is well-established, with EVP as an excellent option for patients who are cisplatin-ineligible. pCR remains an important favorable prognostic marker, although further investigation is required to determine whether adjuvant treatment de-escalation is safe for patients with pCR following preoperative EVP or gemcitabine-cisplatin-durvalumab. Integration of additional prognostic and predictive biomarkers, particularly ctDNA and AI tools, may ultimately enable identification of patients for whom omission of adjuvant therapy represents a safe strategy to reduce toxicity and financial burdens. As perioperative options for MIBC expand, shared decision making will be essential to align care with individual patient goals and preferences.

In RCC, the field remains nascent, there are no approved neoadjuvant regimens, and treatment outside of clinical trials is not recommended. However, the biologic rationale for perioperative therapy is compelling, supported by data from melanoma demonstrating superior outcomes with neoadjuvant-adjuvant approaches compared with adjuvant therapy alone. Early-phase trials of neoadjuvant immunotherapy and immunotherapy plus TKI combinations in RCC have established feasibility and safety while demonstrating that pathologic responses, including complete responses, can occur.

A critical gap limiting progress in RCC is the lack of standardized, validated pathologic response criteria with established surrogacy for long-term outcomes. Although the melanoma experience with INMC criteria provides a framework, whether similar thresholds apply to kidney cancer remains uncertain. Prospective validation of pathologic end points in larger cohorts with mature survival data is essential to enable response-directed adjuvant therapy strategies.

To address these knowledge gaps, participation in clinical trials should be encouraged. Future directions should prioritize (1) randomized trials comparing neoadjuvant with adjuvant approaches in RCC; (2) in RCC, development and validation of standardized pathologic response criteria with demonstrated surrogacy for survival; (3) in bladder cancer, continued refinement of neoadjuvant regimens incorporating novel agents and determination of optimal post-treatment management based on pathologic response and markers of minimal residual disease; (4) integration of predictive AI-tools; and (5) identification of optimal treatment combinations and duration across both diseases. As systemic therapies continue to improve, the opportunity to leverage neoadjuvant strategies for enhanced tumor control and personalized management will become increasingly relevant across genitourinary malignancies.

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How to Optimize Treatment for Patients With Poor-Risk Testicular Cancer

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OVERVIEW

Male germ cell tumors, of which testicular is the most common, are rare but generally highly curable malignancies. Cure rates in the metastatic setting are among the highest for any solid tumor, although outcomes in the poor-risk subgroup remain suboptimal. Although most men are cured, risk prognostication tools have identified poor-risk patients with inferior outcomes leading to significant mortality in this predominantly young patient population. To optimize survival in this group, proper therapy selection throughout the treatment course of poor-risk patients is vital to maximize survival opportunities. Established first-line therapies are available requiring expertise in their selection and toxicity management. Surgical evaluation remains vital for poor-risk patients to address unique disease characteristics seen in this population including multifocal residual disease, extensive mediastinal disease, and brain metastases. Salvage systemic therapies have been developed with several options of conventional and high-dose chemotherapy, requiring expertise in patient selection and treatment delivery. This review discusses the treatment landscape of poor-risk patients, systemic therapy selection, surgical evaluation of patients, treatment of brain metastases, and contemporary management strategies of pertinent clinical scenarios highlighting the multidisciplinary approach needed to optimize cure rates in this group.

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INTRODUCTION

Germ cell tumors (GCTs) are relatively rare malignancies accounting for approximately 1% of male cancers, with testicular cancer representing the most common primary site.[1] Most patients with distant metastatic disease can be cured because of the extraordinary success of combination chemotherapy developed over decades of collaborative basic and clinical research.[2] Despite these advances, mortality from metastatic GCTs remains a substantial clinical and societal burden and is associated with the greatest average number of years of life lost among adult malignancies. Through international collaborations identifying essential prognostic features, patients at the highest risk of poor prognosis have been identified.[3] Although poor-risk patients have had major improvements in outcomes because of randomized trials optimizing their treatment strategy, outcomes remain suboptimal and approximately a third of poor-risk patients will die of their disease. The management of poor-risk GCT requires collaborative efforts between medical oncologists, surgeons, and referral to high-volume tertiary centers with expertise in this complex population.

FIRST-LINE TREATMENT APPROACHES

Overview of Standard Therapy

Risk Stratification

Current risk stratification guidelines for advanced GCTs use the International Germ Cell Cancer Collaborative Group (IGCCCG) classification first published in 1997.[3] Poor-risk patients are defined as nonseminoma histology either having a mediastinal primary tumor site, nonpulmonary visceral metastasis, or the following tumor maker levels: alpha-fetoprotein (AFP) >10,000 ng/mL, human chorionic gonadotropin (hCG) >50,000 mIU/mL, and lactate dehydrogenase (LDH) >10× upper limit of normal. Results from the IGCCCG Update Consortium examining a contemporary cohort of patients receiving frontline cisplatin-etoposide–based combination chemotherapy demonstrated improvements in outcomes for poor-risk patients compared with historical data, with 5-year progression-free survival (PFS) of 54% versus 41% and overall survival (OS) of 67% versus 48%, respectively.[4] Adverse clinical features carrying the most significant risk of negative prognosis include nonpulmonary

PRACTICAL APPLICATIONS

- Patients with poor-risk germ cell tumor require comprehensive evaluation for proper treatment selection based on disease site, extent of disease, and comorbidities.
- The standard-of-care first-line therapy is four cycles of a cisplatin-based triple drug regimen; selected regimens have unique toxicity profiles and inform proper patient selection.
- Careful evaluation postchemotherapy of residual masses and tumor markers is required as surgery remains an integral component of cure for many poor-risk patients.
- Salvage systemic therapy includes conventional or high-dose chemotherapy regiments with patient selection based on established prognostic factors and disease characteristics.
- Brain metastases, while rare, are more common in poor-risk patients with increased morbidity and mortality, and treatment requires multidisciplinary evaluation with both local and systemic therapies used depending on clinical context.

visceral metastases, mediastinal primary site, increasing age, and brain metastases.[4,5]

BEP or VIP × 4 as Standard of Care

Four cycles of combination cisplatin-based chemotherapy, either bleomycin plus etoposide plus cisplatin (BEP) or VP-16 (etoposide) plus ifosfamide plus cisplatin (VIP), is the standard of care for poor-risk GCTs in the first-line setting (Table 1). An intergroup trial examining BEP versus VIP × 4 demonstrated comparable results in poor-risk GCTs, with modestly higher hematologic and other toxicity in the VIP arm.[7] These regimens are expected to cure 50%-60% of poor-risk patients as first-line therapy.[7-9,11] Therapy, given in 3-week cycles, should be maintained on schedule at full doses for optimal efficacy. Granulocyte-colony stimulating factor (G-CSF) support is used to maintain treatment dose and schedule during cycles. Various factors may lead a clinician to choose BEP versus VIP as first-line therapy (Table 2). Bleomycin should be avoided in patients with extensive pulmonary metastases, age >50 years, intrinsic pulmonary disease, and those with significant renal impairment.

Tumor Marker Decline

Poor-risk patients presenting with markedly elevated serum hCG levels (>50,000 mIU/mL) pose distinct clinical challenges. In the setting of frontline combination chemotherapy, these hCG levels are expected to decrease 1 logarithmic unit per cycle during the first two cycles. Unfavorable decline is a poor prognostic marker.[12,13] Subsequently, the rate of decline slows for unknown reasons; however, care should be made not to alter or switch curative-intent therapy on the basis of reduction in the rate of hCG decline without a confirmed rise. In a retrospective analysis of 41 patients presenting with hCG >50,000 mIU/mL, <10% had normalized their hCG at the start of the fourth and final cycle; however, 22 of 41 (53%) remained continuously disease-free after frontline chemotherapy. Fifteen of 31 (48%) patients with elevated hCG >1 month after completion of chemotherapy eventually normalized their hCG and remained continuously disease free. For patients with declining but detectable hCG at completion of chemotherapy, it is recommended to monitor weekly but without initiation of salvage therapies unless there is a confirmed rise in tumor markers or radiographic progression.

Treatment Intensification

Attempts to improve up-front combination therapy through cisplatin dose intensification,[6,14] incorporation of frontline high-dose chemotherapy,[8,9] and addition of multiagent chemotherapy regimens[10,15,16] have not improved OS in randomized trials compared with BEP or VIP × 4. Response adaptive intensification in unfavorable tumor marker decline significantly improved PFS in the GETUG-13 trial, its primary end point, although OS was nonsignificant.[17] More recently, the TIP (paclitaxel, ifosfamide, and cisplatin) regimen compared with BEP in intermediate-risk and poor-risk patients did not improve outcomes.[18] Accelerated BEP given in 2-week cycles versus standard BEP cycles is actively enrolling in a randomized phase III trial (ClinicalTrials.gov identifier: NCT02582697). The standard of care remains BEP or VIP × 4.

Special Treatment Considerations

High Burden of Disease and Induction Therapy

At times, poor-risk patients present with extensive high-volume disease requiring treatment initiation before orchiectomy or biopsy. Patients with a testicular mass and elevated tumor markers (AFP or hCG) do not require biopsy before treatment if extensive amount of disease is threatening end-organ function and in the appropriate clinical context. A course 0 is considered for patients with threatened end-organ function who require treatment for disease stabilization in the acute setting before definitive curative intent therapy and consists of standard dose etoposide and cisplatin in a 3-5-day regimen. Patients with extensive metastatic choriocarcinoma may have bleeding with the initiation of chemotherapy, such as pulmonary hemorrhage requiring invasive ventilator support or bleeding of brain metastases (Fig 1).

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TABLE 1. First-Line Chemotherapy in Poor-Risk GCT

Regimen	Outcomes	Trial
BEP × 4 *v* VIP × 4	5-year PFS, 49% *v* 56%[a] 5-year OS, 57% *v* 62%[a]	Nichols, et al[6] Hinton, et al[7]
BEP × 4 *v* BEP × 2 + HDCT × 2	1-year durable CR, 46% *v* 48%[a] 2-year OS, 69% *v* 67%[a]	Motzer, et al[8]
BEP × 4 *v* VIP × 1 + HD-VIP × 3	2-year PFS, 45% *v* 58%[a] 2-year OS, 66% *v* 73%[a]	Daugaard, et al[9]
BEP × 4 *v* BEP × 1 + dose dense regimen[b]	5-year PFS, 47% *v* 59% 5-year OS, 61% *v* 71%[a]	Fizazi, et al[10]

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; CR, complete response; GCT, germ cell tumor; HDCT, high-dose chemotherapy; HD-VIP, high-dose VIP; OS, overall survival; PFS, progression-free survival; VIP, etoposide, ifosfamide, and cisplatin.
[a]Not statistically significant.
[b]In patients with unfavorable tumor marker decline.

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Primary Mediastinal Nonseminomatous GCTs

Patients with primary mediastinal nonseminomatous GCT (PMNSGCT) have poor-risk disease regardless of other disease criteria, and multimodality treatment is required. Owing to anatomic boundaries in the mediastinum, postchemotherapy resection after frontline chemotherapy carries a risk of serious pulmonary toxicities. In a large retrospective series of 221 PMNSGCT postchemotherapy resections, bleomycin (BEP) exposure was associated with higher rates of severe pulmonary complications including acute respiratory failure and prolonged ventilator requirements.[19] Another smaller series did not observe significantly increased rates of pulmonary toxicities in this population after BEP, possibly because patients were monitored closely with pulmonary function tests and bleomycin was either dropped or switched to ifosfamide (eg, VIP) when a significant decline in diffusion capacity of carbon monoxide occurred. Nevertheless, because of these concerns, some institutions prefer VIP × 4.[20]

TABLE 2. Selection of First-Line Chemotherapy in Poor-Risk GCT

Chemotherapy Regimen	Clinical Features Favoring Selection
VIP × 4	Significant renal impairment unable to tolerate bleomycin[a] Extensive pulmonary metastases PMNSGCT Age >50 years
BEP × 4	All other patients
Induction course EP × 1 followed by 4 cycles of triple drug regimen	Extensive metastatic disease with end-organ function risk Choriocarcinoma syndrome with risk of pulmonary hemorrhage

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; GCT, germ cell tumor; hCG, human chorionic gonadotropin; VIP, etoposide, ifosfamide, and cisplatin; PMNSGCT, primary mediastinal nonseminomatous germ cell tumor.
[a]Cisplatin and ifosfamide also carry a risk of nephrotoxicity and should be used with caution in kidney dysfunction.

Toxicity Management

Poor-risk patients require four cycles of triple-drug regimen and thus have greater toxicity with subsequent cycles. Cumulative bleomycin exposure can lead to pulmonary toxicity and pulmonary fibrosis, and care should be taken during treatment cycles for monitoring of pulmonary status and identification of emerging bleomycin toxicity (new nonproductive cough, shortness of breath, basilar rales, inspiratory lag, or decreasing pulmonary function tests).[7] Patients in whom bleomycin is discontinued for toxicity still require four courses of triple drug regimen, and VIP should be substituted for subsequent cycles. VIP comparably has higher rates of myelosuppression and renal toxicity.

Surveillance After Frontline Therapy

At the completion of frontline chemotherapy, patients with poor-risk disease require thoughtful analysis of their chemotherapy response and subsequent steps. Patients may have down-trending but not normalized tumor markers after chemotherapy completion and require close (at times weekly) monitoring until either normalization or subsequent rise signaling relapse. Sanctuary sites in the remaining testis or brain should be evaluated for tumor marker rise in the setting of stable or minimal radiographic disease. During the first year of follow-up, poor-risk patients at our centers generally undergo clinical evaluation every 6-8 weeks, including history, physical examination, and serum tumor marker measurement, including AFP and hCG, with imaging every 3 months.[21]

POSTCHEMOTHERAPY ASSESSMENT

Postchemotherapy Imaging

Postchemotherapy radiologic imaging of all known sites of metastases is required for all patients to identify any residual disease. Currently, there is no imaging technique that reliably differentiates patients with residual disease from those with necrosis/fibrosis or teratoma after chemotherapy.

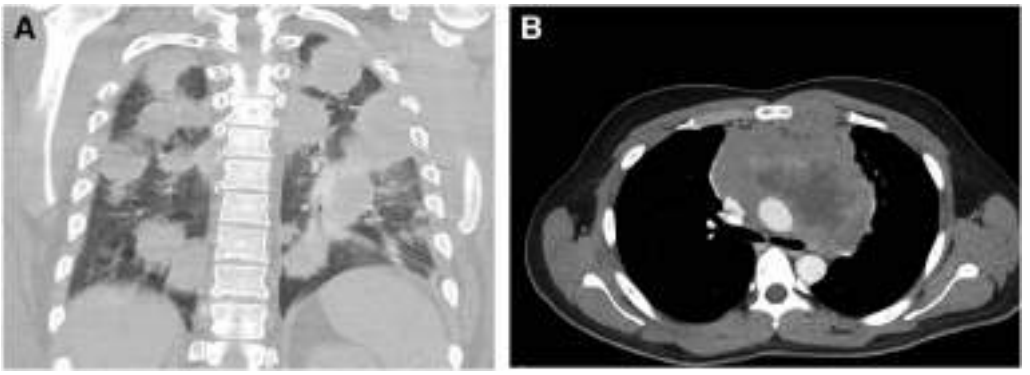

FIG 1. (A) Advanced pulmonary disease in the setting of choriocarcinoma syndrome with highly elevated hCG at risk of pulmonary toxicity with BEP and pulmonary hemorrhage. The patient received VIP × 4 and remains with no evidence of disease. (B) PMNSGCT presenting with large mediastinal mass. The patient received VIP × 4 and subsequent mediastinal mass resection. BEP, bleomycin, etoposide, and cisplatin; hCG, human chorionic gonadotropin; PMNSGCT, primary mediastinal nonseminomatous germ cell tumor; VIP, etoposide, ifosfamide, and cisplatin.

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Computed tomography (CT) remains the most commonly used imaging tool in these patients, although magnetic resonance imaging (MRI) is increasing in popularity to limit radiation exposure. 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) is not indicated in the management of patients with nonseminoma and in patients with residual masses <3 cm in seminoma after chemotherapy.

Residual Masses

Postchemotherapy Management of Residual Masses

At PC-RPLND, the histologic composition of resected masses is necrosis in 40%-50%, teratoma in 35%-40%, and viable carcinoma in 10%-15% in nonseminoma germ cell tumors (NSGCT) and 80%-90% necrosis/fibrosis and 10%-20% viable carcinoma in patients with seminoma.[22] An appropriate serologic and radiographic response to first-line chemotherapy is defined as negative tumor markers and residual mass <1 cm in NSGCT and <3 cm in seminomas. These patients are considered low-risk for relapse, and PC-RPLND is not recommended by most experts. Some institutions favor PC-RPLND even in the setting of subcentimeter residual lymph nodes when yolk sac tumor or teratoma are present in the orchiectomy specimen, given their association with finding teratoma or active GCT in the retroperitoneum.[23]

Surgery is typically performed 4-6 weeks after the last cycle of chemotherapy. PC-RPLND is often a very challenging surgery and requires a high level of expertise because of the risk of vascular injury and need for adjunctive procedures. Additional surgical procedures are required in >20% of patients undergoing PC-RPLND. Most common are nephrectomy and vascular procedures, such as inferior vena cava/aortic resection and reconstruction, which may harbor residual disease or teratoma in up to 70% of cases.[24] In patients with bulky pulmonary and/or large-volume retroperitoneal disease with dual marker elevation before chemotherapy, the diagnosis of nonseminoma is usually presumed, and patients are better served with urgent initiation of chemotherapy with delayed orchiectomy, which would be performed at the time of PC-RPLND.

Most patients with IGCCCG poor-risk disease should undergo a bilateral template dissection. An MSKCC study demonstrated that up to 32% of patients can have viable tumor or teratoma outside the boundaries of a modified template with the risk increasing with increasing size of residual masses.[25] Other studies however have demonstrated that nearly all recurrences occur outside the boundaries of a bilateral template, and therefore argue that in select patients, the modified template is sufficient and is associated with reduced morbidity compared with a bilateral template.[26,27] Although a number of series have reported on the feasibility and oncologic outcomes of robotic RPLND, this approach is generally not recommended in patients with more advanced disease given the complex and large masses with associated desmoplastic reaction in the retroperitoneum and the frequent need for vascular repair. In patients who have received bleomycin, the use of supplemental oxygen during the perioperative period should be avoided given the risk of significant pulmonary complications.

For patients with late relapse (>2 years after primary treatment), surgical treatment remains the preferred approach if the disease is resectable, as late relapses are often chemo-resistant and frequently contain teratoma or somatic-type malignancy.[21]

Management of Multifocal Residual Disease

The management of multifocal residual disease after chemotherapy for testicular cancer is complex, with significant pathologic discordance between sites, ranging between 25% and 50%.[28-30] National Comprehensive Cancer Network (NCCN) guidelines recommend surgical resection of all residual masses in NSGCTs with normalized markers after

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chemotherapy as pathology can vary between anatomic sites (NCCN). RPLND is typically performed first in the multifocal setting for several reasons. First, the retroperitoneum is the primary landing zone for testicular cancer and often harbors the largest tumor burden. Second, the pathology from RPLND provides prognostic information that guides subsequent management decisions. Finally, PC-RPLND is a technically complex surgery and is best performed when patients are in optimal condition before other procedures. If pathology from the PC-RPLND does not reveal viable GCT or teratoma and tumor markers remain normal, some centers may opt for a more conservative approach to other sites, although this remains controversial and complete resection of all sites remains standard of care (NCCN). Studies have found that there is a 90% concordance between lung masses and that a 75% reduction in tumor size following chemotherapy is highly predictive of absence of viable tumor or teratoma.[27,31] These patients may be candidates for close observation, particularly in those with multiple pulmonary lesions, allowing for selective extirpation upon growth. However, further research is needed to validate these findings and evaluate how they may shape clinical practice.

Growing Teratoma Syndrome

Patients with enlarging metastatic tumors during chemotherapy with normalized tumor markers typically suggest growing teratoma syndrome (GTS). Management consists of complete surgical resection because teratomas are resistant to chemotherapy and radiation. Although teratomas rarely metastasize, GTS can have rapid growth and cause substantial morbidity and mortality. Typically, patients should complete the appropriate number of chemotherapy cycles before resection of the teratoma, unless patients develop symptomatic growth. It is critical that all sites of disease are fully resected even when invading vascular structures or adjacent organs as recurrence rates are 83% with incomplete resection compared with 4%-9% with complete resection.[32,33]

Desperation Surgery After Chemotherapy

Desperation surgery, defined as resection of nonresponsive or progressive disease with rising tumor markers (typically after exhausting multiple lines of therapy or ineligible for further systemic options), can also achieve long-term durable disease control in those with completely resectable disease. Studies found that patients who developed early relapse (<12 months) who underwent salvage RPLND after chemotherapy had a longer 3-year PFS and a trend toward improved OS compared with those who did not undergo surgery.[34] A study of 153 patients undergoing residual tumor resection following chemotherapy with elevated tumor markers found that 38% of patients were long-term survivors despite the overall poor prognosis of this patient population. Long-term survival ranges between 30% and 70% of completely resected patients following desperation RPLND, with prognostic factors including extent of disease, prior IGCCCG stage, and rising tumor markers leading up to surgery.[35] Patients who are not candidates for complete resection should not undergo desperation surgery, as residual disease portends a worse prognosis.

SALVAGE THERAPY

Although most patients with GCTs are cured with first-line cisplatin-based chemotherapy, up to 30% of patients experience relapse and require salvage treatment.[36] Two principal strategies are used after first-line failure: conventional-dose chemotherapy (CDCT) and high-dose chemotherapy (HDCT), followed by autologous stem cell transplantation (ASCT). Both retain curative potential, but the absence of definitive prospective comparative data has precluded establishment of a universal standard. Evidence supporting HDCT is largely retrospective. The two randomized phase III trials available used different approaches than commonly used in current practice and did not demonstrate a clear OS advantage for HDCT.[37,38] In practice, treatment selection is frequently guided by the International Prognostic Factor Study Group (IPFSG) model, which stratifies patients according to clinical and biologic risk factors[39] (Table 3). Retrospective analyses suggest that HDCT may offer greater benefit in most IPFSG categories except very low- and low-risk disease, where CDCT remains appropriate.[40] Treatment-related mortality must also be considered, with a recent meta-analysis reporting lower mortality for CDCT (3%) compared with HDCT (7.5%).[41] The ongoing TIGER trial (ClinicalTrials.gov identifier: NCT02375204) is expected to clarify the optimal first-salvage approach. Given the treatment complexity, management should be centralized in experienced centers. Patients not cured with HDCT salvage therapy have dismal outcomes with limited activity in subsequent chemotherapy lines.[42] More recent studies of immunotherapy and targeted therapies have not yet shown promise in improving outcomes and remain investigational.[43-45] Genomic sequencing of cisplatin-resistant GCT have identified a low tumor mutation burden and frequent alterations in *TP53* and *MDM2*, the latter as a potential therapeutic target with inhibitors of MDM2 in development.[46]

Standard-Dose Salvage Regimens

The most widely used CDCT regimens are TIP (paclitaxel, ifosfamide, and cisplatin) and VeIP (vinblastine, ifosfamide, and cisplatin). TIP has demonstrated durable efficacy, with complete response rates of 63% and 10-year PFS and OS of 62% and 66%, respectively.[47] Hematologic toxicity is substantial, with febrile neutropenia reported in up to 47% of patients, supporting routine primary G-CSF and antibacterial prophylaxis.

VeIP remains an active salvage regimen but is associated with higher rates of severe hematologic toxicity.[48,49] A randomized comparison of TIP and VeIP closed early because of poor accrual (ClinicalTrials.gov identifier: NCT00072215). In practice, TIP is commonly preferred because of its favorable balance between efficacy and tolerability. Complete

TABLE 3. Prognostic Score for Patients With Relapsed GCT

	Score Points				
Parameter	0	1	2	3	Score
Primary site	Gonadal	Extragonadal	—	Mediastinal nonseminoma	
Prior response	CR/PRm-	PRm+/SD	PD	—	
PFI, months	> 3	≤ 3	—	—	
AFP salvage	Normal	≤ 1,000	> 1,000	—	
hCG salvage	≤ 1,000	> 1,000	—	—	
LBB	No	Yes	—	—	
Score sum (values from 0 to 10)					
Score sum (values from 0 to 10) Regroup score sum into categories: (0) 0; (1 or 2) 1; (3 or 4) 2; (5 or more) 3					
Add histology score points: pure seminoma, -1; nonseminoma or mixed tumors, 0					
Final prognostic score (-1 very low risk; 0 low risk; 1 intermediate risk; 2 high risk; 3 very high risk)					

NOTE. Reproduced From Lorch et al.[39]
Abbreviations: AFP, alpha fetoprotein; CR, complete remission; GCT; germ cell tumor; hCG, human chorionic gonadotrophin; LBB, liver, bone, brain metastases; PD, progressive disease; PFI, progression-free interval; PRm, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease.

surgical resection of residual disease remains essential for cure, particularly in nonseminoma GCT.

Toxicity Management With Ifosfamide-Based Regimens

Ifosfamide is integral to both CDCT and HDCT regimens and is associated with urothelial, neurologic, and renal toxicity related to its metabolites.[50] Hemorrhagic cystitis has become uncommon with routine MESNA administration and adequate hydration. Myelosuppression is frequent and warrants primary G-CSF support and transfusion as indicated. Ifosfamide-induced encephalopathy occurs in approximately 15% of patients, is usually reversible after discontinuation, and may be treated with methylene blue in selected cases.[51]

High-Dose Chemotherapy and Transplant Regimens

High-dose regimens developed in the 1980s and 1990s were associated with substantial toxicity and treatment-related mortality[52,53]; the introduction of peripheral blood stem cell support subsequently enabled safer delivery of sequential high-dose therapy.[54]

Two strategies form the backbone of current practice (Table 4). The Indiana tandem regimen consists of two sequential cycles of high-dose carboplatin and etoposide (CE), each followed by ASCT. Long-term disease-free survival was achieved in 70% of second-line patients and 45% treated in third line or beyond.[54] In a cohort of 364 patients, 2-year PFS and OS were 60% and 66%, respectively, with durable remissions across IPFSG categories, although outcomes were less favorable in very high-risk disease.[56]

The TI-CE regimen incorporates paclitaxel and ifosfamide for cytoreduction and stem cell mobilization followed by sequential high-dose CE. In poor-prognosis patients, 5-year DFS and OS were 47% and 52%, respectively.[55] Other intensified regimens have not demonstrated superiority over standard CE-based HDCT, and routine addition of additional agents is not supported.[57-59] Available data support the use of at least two planned high-dose cycles, as outcomes are inferior with single-cycle approaches.[37,40]

Toxicity Management of HDCT

Acute toxicities of HDCT include profound myelosuppression, mucositis, gastrointestinal toxicity, dehydration, and renal dysfunction. Transfusion support and G-CSF are routinely employed following ASCT. Antimicrobial prophylaxis is administered according to transplant guidelines to reduce infectious morbidity.[60] Nonhematologic toxicities require aggressive antiemetic therapy, careful hydration, and close renal monitoring.

Post-Transplant Monitoring

Specific surveillance guidelines tailored to patients with GCT after HDCT are lacking. Follow-up is generally based on established testicular cancer surveillance frameworks integrated with survivorship principles.[61]

Relapse surveillance is most intensive during the first 2 years after salvage therapy and includes regular clinical assessment, serum tumor markers (AFP, hCG ± LDH), and imaging according to prior disease distribution. Extended follow-up beyond 5 years is appropriate given the possibility of late relapse.

Long-term monitoring must also address late effects of platinum- and etoposide-intensive therapy, including cardiovascular and metabolic morbidity, neurotoxicity, ototoxicity, renal dysfunction, endocrine impairment with potential hypogonadism and infertility, reduced bone mineral density, fatigue, and secondary malignancies.[62,63]

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TABLE 4. Select Studies Evaluating Conventional-Dose Chemotherapy and High-Dose Chemotherapy as Salvage Treatments

Study	Regimen(s) Tested	n	Patients' Characteristic (risk per IPFSG criteria)	EFS	OS	Outcome Time Point (months)
Einhorn et al[54]	CE[a] × 2	184	NR	63%	NR	48
Adra et al[55]	CE[a] × 2	364	Very low, 11% Low, 18% Intermediate, 25.5% High, 25.5% Very high, 20%	60%	66%	48
Feldman et al[55]	TI × 2 + CE[b] × 3	107	NR	47%	52%	60
Gleeson et al[47]	TIP[c] × 4	104	Very low, 15% Low, 25% Intermediate, 45% High, 15%	66%	69%	60
Loehrer et al[48]	VeIP[d] × 4	135	NR	NR	32%	84

Abbreviations: CE, carboplatin and etoposide; G-CSF, granulocyte-colony stimulating factor; NR, not reported; OS, overall survival; TIP, paclitaxel, ifosfamide, and cisplatin.

[a]Carboplatinum 700 mg/m^2 + etoposide 750 mg/m^2, once daily for 3 consecutive days every 21, each one followed by ASCT.

[b]Two cycles of TI 14 days apart (paclitaxel 200 mg/m^2 once daily day 1 + ifosfamide 2,000 mg/m^2 once daily with mesna day 2-4), each one followed by G-CSF daily from day 4 until adequate collection or neutrophil recovery and leukapheresis daily from day 11 until day 14 or adequate stem cell collection; followed by three cycles of CE (carboplatin AUC 7-8, days 1-3 + etoposide 400 mg/m^2 once daily days 1-3), followed by ASCT.

[c]Four cycles of paclitaxel 250 mg/m^2 once daily day 1 + ifosfamide 1,500 mg/m^2 once daily with mesna days 2-5 + cisplatin 25 mg/m^2 once daily days 2-5 every 21.

[d]Four cycles of vinblastine once daily (0.11 mg/kg/d days 1-2), ifosfamide once daily (1.2 g/m/d days 1-5), and cisplatin once daily (20 mg/m^2/d days 1-5), every 3 weeks.

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Cardiovascular risk assessment, endocrine evaluation when clinically indicated, and lifestyle counseling are appropriate components of survivorship care.

Maintenance Strategies After HDCT

In contrast to several hematologic malignancies, no established standard exists for maintenance systemic therapy following HDCT and ASCT in relapsed GCT. Efforts to improve outcomes have focused on optimizing HDCT delivery and surgical resection rather than extending systemic therapy.

Retrospective data from Indiana University evaluated maintenance oral etoposide in 383 patients after HDCT and ASCT. Two-year PFS was 55% versus 46% with observation, and 2-year OS was 61% versus 54%. On multivariable analysis, maintenance therapy remained associated with improved PFS (adjusted hazard ratio, 0.51) and appeared to benefit primarily patients with platinum-refractory disease.[64] Given the retrospective design, these findings require prospective validation. Considering the substantial long-term toxicity burden of HDCT, potential benefit must be balanced against overtreatment. Randomized evaluation is ongoing (NCT04804007; NCT06937866), and until these data mature, maintenance therapy remains investigational.

MANAGEMENT OF BRAIN METASTASES

Incidence

Brain metastases (BM) are present at the time of diagnosis in 0.88% of all patients with testicular GCTs and 7.6% of patients with metastatic testicular cancer in the United States.[65] Over 95% of BM in GCTs occur in nonseminomas, and up to 50% are detected incidentally at diagnosis in the absence of symptoms.[66] Population databases do not reliably report the incidence of BM at relapse.[65] In the randomized GETUG-13 study comparing standard versus dose-dense chemotherapy among patients with poor-risk NSGCT and unfavorable tumor marker decline, BM represented a first progression event in 19% of patients relapsing after first-line chemotherapy.[17] Approximately 50% of all radiographic-only progression events after first-line therapy in GETUG-13 and other series occurred in the brain.[66,67] Single-institution retrospective series suggest that BM overall affect 10%-15% of male patients with poor-risk GCTs.[5,68]

When to Image for BM

Any patient with GCT and neurologic symptoms should undergo imaging to evaluate for BM. In the absence of neurologic symptoms, the benefit of brain imaging at initial GCT diagnosis is less clear. However, NCCN testicular cancer guidelines suggest brain imaging for some IGCCCG intermediate-risk and most poor-risk GCT cases.[21] Specific criteria to consider from NCCN guidelines include the presence of neurologic symptoms, tumor marker elevations (hCG >5,000, AFP >10,00), extensive lung metastases, nonpulmonary visceral metastases, and predominance of choriocarcinoma. In the Global Germ Cell Tumor Group (G3) series, which represents the largest retrospective study of patients with BM from GCT, 95% of patients with BM at diagnosis had nonseminoma, 94% had lung metastases, and

83% had an hCG over 1,000 U/L. More recently, a predictive model for the presence of BM was developed; features associated with an increased risk of BM included age older than 40 years, presence of bone metastases, hCG ≥5,000, choriocarcinoma histology, and pulmonary metastases, especially ≥3 cm.[69] The presence of pulmonary metastases and choriocarcinoma carried the most weight in determining the pretest probability of BM. Other scenarios in which to consider brain imaging in asymptomatic patients with GCT include when tumor markers, especially hCG, are declining slowly after first-line chemotherapy, and at the time of relapse (radiographic or biochemical) following first- or later-line chemotherapy.

Prognosis

Consistent with their designation within the IGCCCG risk stratification schema, the prognosis of GCTs with brain metastases is poor.[4] Importantly, there are differences in clinical features and prognosis depending on whether a patient presents with BM at diagnosis (synchronous) versus at relapse (metachronous). In the G3 series of 523 GCT cases with BM, patients with BM at diagnosis tended to have very high levels of hCG, multiple brain metastases, and higher burden of systemic disease including in the lung, liver, and bone.[66] The presence of BM at diagnosis was associated with a 2-year PFS of 29%, 3-year OS of 48%, and median OS of 29.5 months. Multivariable analysis of clinical features in patients with synchronous BM demonstrated that primary mediastinal nonseminoma, presence of liver or bone metastases, and multiple BM were associated with worse OS. By contrast, patients with metachronous BM were more likely to present with neurologic symptoms (70.5% *v* 53.0%) as compared with patients with synchronous BM. These patients had a 2-year PFS of 21%, a 3-year OS of 27%, and a median OS of 8 months. Multiple BM, concurrent presence of liver or bone metastases, and elevated AFP or hCG were negatively prognostic in the metachronous group.

Treatment

Despite poor prognosis, effective therapy in patients with synchronous or metachronous brain metastases can prevent death from uncontrolled intracranial disease. Given the rarity of BM in GCT and heterogeneity of practice patterns, data are insufficient to define a clear standard of care.[66,70,71] Therefore, the following discussion of treatment options is based on retrospective case series, guideline consensus, and expert opinion. Decisions between specific systemic regimens or radiation approaches (eg, whole brain *v* stereotactic radiation) cannot be covered within the scope of this review.

For asymptomatic synchronous BM at diagnosis, first-line chemotherapy for IGCCCG poor-risk disease is indicated. High-dose chemotherapy is not recommended as first-line therapy in this patient population. If a patient has symptomatic BM at presentation, metastasis-directed therapy before chemotherapy should be considered, either with surgery or radiotherapy. Surgery may be preferred for larger tumors especially if accompanied by hemorrhage or mass effect, or if there is suspicion for metastatic choriocarcinoma that is prone to bleeding especially with lower platelet counts during chemotherapy.[72] Extrapolating from single-institution series that included a few BM and the approach used for residual extracranial masses, many clinicians will observe residual postchemotherapy brain masses ≤1 cm.[73] The aforementioned G3 study did not demonstrate a clear benefit for multimodality therapy (eg, the addition of radiation or surgery) for patients with synchronous BM.[66]

The management of metachronous BM is guided by the clinical context of relapse, with evidence supporting the use of multimodality therapy to improve patient survival.[66] In the case of relapse only in the brain, especially with a solitary BM, focal therapy with surgery or radiation is often preferred when feasible. Adjuvant radiation to the resection bed is often considered after surgery based on neurosurgical literature in other malignancies. Relapse in the brain portends a significant chance of eventual systemic relapse, and it is unclear whether prompt adjuvant chemotherapy after surgery and/or radiation versus waiting for systemic relapse is optimal. With more widespread relapse in the brain and torso, multimodal therapy involves focal therapy to BM as well as high-dose chemotherapy if feasible, with the latter associated with a survival benefit compared with conventional chemotherapy in the large G3 retrospective series.[66] The order of focal therapy versus systemic therapy depends on disease kinetics and if any metastases are symptomatic or associated with hemorrhage.

Hemorrhagic BM, most commonly seen with choriocarcinoma, pose a particular challenge when focal therapy is not feasible because of numerous lesions or when rapidly progressive disease requires urgent chemotherapy. In such situations, whole brain radiation can be considered in combination with chemotherapy, with radiation typically given between chemotherapy cycles. In patients with BM requiring salvage chemotherapy, there is often particular concern about the risk of intracranial hemorrhage during high-dose chemotherapy given the severe and prolonged thrombocytopenia associated with this approach. In one study, transfusion support to maintain a platelet count >30,000/μL was associated with no untoward intracranial hemorrhage events, although this can be difficult to achieve.[74] Based on data from patients with multiple myeloma undergoing autologous stem cell transplantation, thrombopoietin receptor agonists can be considered beginning on day +1 until platelet recovery to ≥50,000/μL, possibly decreasing the duration of severe thrombocytopenia.[75]

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Survivorship

Survivorship care is of particular concern in poor-risk patients, with higher treatment burden and subsequent toxicities. Chemotherapy toxicities, most notably from cisplatin, include increased rates of secondary malignancies, cardiotoxicity, peripheral neuropathy, metabolic dysfunction, and hearing loss with cumulative exposure increasing many toxicities in a dose-dependent manner.[76,77] Discussion and planning of fertility preservation is important for patients, who are commonly in young adulthood, as fertility may be affected by side effects of both chemotherapy and surgery.[78] Long-term follow-up of poor-risk patients should incorporate survivorship care and monitoring of late complications of therapy.[79] Late relapse of GCT occurs in 2%-3% of patients, and chemotherapy-exposed, poor-risk patients in long-term surveillance should have annual monitoring of tumor markers, as late relapse may happen many years after treatment and frequently can be discovered with elevated tumor markers.[80] Late relapse of chemotherapy-exposed GCT is often chemotherapy resistant, and surgical resection ± chemotherapy is required for long-term benefit.

CONCLUSION

Poor-risk GCT have unfavorable outcomes and require expert management to optimize survival. Proper treatment selection based on disease characteristics, evaluation of treatment response, and selection of subsequent therapy requires multidisciplinary collaboration. For these reasons, poor-risk patients are recommended to be evaluated at expert referral centers for optimal outcomes. For patients not cured with current standard-of-care therapies, centralization of patients to expert referral centers improves enrollment of these rare patients in clinical trials of novel targets including surface molecule claudin-6, intracellular kinase signaling, and DNA hypermethylation.[81] In addition, ongoing trials investigating novel first-line therapy approaches and optimal initial salvage therapy are eagerly awaited. With more poor-risk patients being cured of their disease, survivorship care remains critical long-term. Incremental improvements in poor-risk GCT have only been possibly through collaborative efforts in both clinical trials and retrospective analyses informing clinical practice of the unique clinical situations faced by patients with poor-risk GCT. Continued future collaboration is essential.

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Optimizing Care for Patients With Metastatic Castration-Resistant Prostate Cancer

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OVERVIEW

The therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has evolved substantially over the past decade, with androgen receptor pathway inhibitors, taxanes, poly (ADP-ribose) polymerase (PARP) inhibitors, radioisotopes, bone-protecting agents, and emerging targeted therapies improving survival for patients. At the same time, earlier treatment intensification in the hormone-sensitive setting has resulted in heterogeneous clinical presentations at the onset of castration resistance, adding complexity to treatment sequencing and clinical decision making. Here, we propose a pragmatic, patient-centered framework to help guide the management of mCRPC by integrating clinical features, molecular profiling, imaging findings, and supportive care considerations. Confirmation of castration resistance remains a critical first step and requires documented biochemical or radiographic progression in the setting of castrate testosterone levels. Treatment selection should consider prior systemic therapies, disease burden and tempo, symptom profile, comorbidities, and frailty. Molecular characterization, including evaluation for homologous recombination repair alterations and mismatch repair deficiency, is highly important for identifying candidates for PARP inhibitors or immune checkpoint blockade and other emerging biomarker-driven targeted strategies. Prostate-specific membrane antigen (PSMA)–targeted radioligand therapy has emerged as a key treatment. PSMA-positron emission tomography–based selection, incorporating assessment of uptake intensity, tumor heterogeneity, and total tumor volume, may help identify patients who are most likely to benefit from this treatment. Clinical factors such as liver metastases and limited prior response to androgen receptor–directed therapy have been associated with less favorable outcomes. Early on-treatment assessment using prostate-specific antigen response and PSMA-based imaging may support adaptive treatment strategies and earlier recognition of resistance. Given the high prevalence of bone metastases, bone-protecting agents should be considered to reduce skeletal-related events. Early palliative care (EPC) is now widely recognized as a concurrent, patient-centered intervention that improves quality of life, symptom burden, coping, and satisfaction across advanced cancers. Prostate cancer represents an especially compelling setting for EPC because of prolonged advanced disease courses, cumulative symptom burden, repeated treatment transitions, and persistent unmet supportive needs.

FIRST-LINE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: ONE SIZE DOES NOT FIT ALL

Over the past decade, the therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has expanded at an unprecedented pace.[1,2] Androgen receptor pathway inhibitors (ARPIs), taxanes, poly (ADP-ribose) polymerase (PARP) inhibitors, radioisotopes, bone-protecting agents, and emerging targeted agents have collectively transformed outcomes for many patients. Sipuleucel-T is another option. This complex cell therapy is rarely used and, only in the United States, most commonly in patients with early mCRPC.[3] Yet paradoxically, this therapeutic abundance has also exacerbated uncertainties in everyday clinical practice. These uncertainties are partially related to the use of some of these agents in the hormone-sensitive setting, thus creating new clinical situations in mCRPC. The challenge that oncologists are often facing worldwide is no longer whether effective treatments exist, but how to select, sequence, combine, and adapt them for each individual patient.

In this context, a pragmatic and patient-centered approach is needed. Rather than advocating for a rigid treatment algorithm, we propose here a clinically driven checklist designed to mirror real-world practice.

PRACTICAL APPLICATIONS

- The use of next-generation sequencing, performed on tumor tissue or circulating tumor DNA, should be encouraged whenever feasible, as it may increasingly inform biomarker-driven treatment strategies and future therapeutic development.
- The landscape is changing fast with [^{177}Lu]-PSMA moving earlier in the prostate cancer space. Ongoing trials are evaluating combination strategies as well as PSMA targeted alpha therapies.
- Early integration of palliative is now widely recognized as a patient-centered intervention that improves quality of life.

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From Definition to Decision Making: A Checklist for mCRPC

Defining Castration Resistance: Beyond a Semantic Exercise

The first and most critical step in managing mCRPC is ensuring that the diagnosis itself is correct. Castration resistance should never be assumed without confirming adequate androgen deprivation. A serum testosterone level below 0.50 ng/mL (=50 ng/dL = 1.7 nmol/L) remains the accepted threshold. Once castrate levels are confirmed, progression must be clearly documented. This may occur biochemically, with a rising prostate-specific antigen (PSA) characterized by three consecutive increases. Alternatively, radiographic progression may be demonstrated by the appearance of two new bone lesions on a bone scan or progression of measurable soft tissue disease according to RECIST 1.1 criteria. This distinction is not trivial; it may shape therapeutic decisions, prognostic discussions, and eligibility for clinical trials. Progression criteria on next-generation imaging such as prostate-specific membrane antigen-positron emission tomography (PSMA-PET) are less well-established.[4]

Patients Come First: Age, Frailty, and Comorbidities

Similar to many other cancers, mCRPC is predominantly a disease of second half of life. Therefore, many patients have vulnerabilities that may inadequately be captured by the performance status alone. Chronologic age should not dictate treatment intensity, but biological age often does. Simple geriatric screening tools, such as the G8 score, can identify patients who may benefit from a more comprehensive geriatric assessment and tailored therapeutic strategies.[5,6]

Comorbidities are equally influential. Cardiovascular disease, metabolic syndrome, and renal impairment may all affect treatment tolerance and safety, particularly with ARPIs or taxanes. Just as importantly, polypharmacy is common, and drug-drug interactions may compromise both efficacy and toxicity profiles.[7] In this context, involving an oncology-trained pharmacist can be relevant, particularly in complex cases, to ensure prescription safety.

Importantly, beyond clinical and geriatric parameters, patients' preferences and goals of care represent a critical determinant of treatment choice. Shared decision making is essential in this setting, ensuring that therapeutic strategies align with what matters most to the patient, with an emphasis on doing more for the patient rather than to the patient.

Never Overlook the Skeleton

Bone metastases are the dominant site of metastatic spread in castration-resistant prostate cancer, affecting more than 80% of patients and contributing substantially to morbidity, impaired quality of life (QOL), and mortality. The complex interaction between prostate cancer cells and the bone microenvironment leads to both osteoblastic and osteolytic activity, resulting in skeletal-related events (SREs) such as pathologic fractures, spinal cord compression, and the need for bone surgery or radiation therapy. Bone-targeted agents such as bisphosphonates or RANK-ligand inhibitors (denosumab) significantly reduce the risk of SREs and should be considered in an early setting.[8-10] Both play a role in maintaining QOL, reducing pain, and preserving functional independence. Denosumab was shown to be superior to zoledronic acid in a large phase III trial.[8]

Effective management of skeletal health in mCRPC requires a multimodal approach that integrates baseline and follow-up bone mineral density assessment and routine calcium and vitamin D supplementation with appropriate monitoring to mitigate hypocalcemia. Evidence from meta-analyses suggests that calcium and vitamin D supplementation can reduce fracture risk by approximately 7%-20% in at-risk populations, supporting their systematic use.[11] Preventive measures should also include a baseline dental assessment and the maintenance of good oral hygiene throughout treatment to reduce the risk of osteonecrosis of the jaw, a well-known side effect of bone-protecting agents.

In addition to pharmacologic interventions, adapted physical activity plays a critical role in maintaining bone health, reducing risk of falling, and preserving functional status in men with mCRPC. Structured exercise programs have been shown to enhance bone mineral density, improve muscle strength, and reduce the incidence of falls and fractures in patients undergoing androgen deprivation therapy, which itself accelerates bone loss.[12]

Bone-targeted agents should be considered standard care for patients with mCRPC and bone metastases to reduce the risk of SREs.

One Disease Name, Many Clinical Scenarios

mCRPC Is Not a Single Clinical Entity

Prior treatments now vary widely as many patients enter the castration-resistant phase after intensified therapy in the hormone-sensitive setting, including triplet and doublet systemic regimens. Whether a patient has received androgen deprivation alone, combined androgen receptor inhibition, or combined androgen receptor inhibition plus docetaxel profoundly influences subsequent therapeutic choices. In addition, cabazitaxel, Lu-PSMA, and PARP inhibitors (for *BRCA* patients) have all shown improvements in overall survival in mCRPC patients with prior ARPI and docetaxel and therefore shall be regarded as standard options in patients with mCRPC post-triplet for hormone-sensitive prostate cancer.[13–15]

Similarly, clinical presentation matters. At one end of the spectrum is the frail older patient with indolent, minimally symptomatic disease, and at the other, the young, fit patient with rapidly progressive bone and, sometimes, visceral metastases. Applying identical treatment strategies to these fundamentally different situations is neither rational nor patient-centered.

Molecular Profiling: From Optional to Essential

Molecular characterization plays an increasingly important role in the management of mCRPC although it is not yet universally accessible in routine clinical practice. Next-generation sequencing (performed on tumor tissue or circulating tumor DNA) should be strongly encouraged whenever feasible. While actionable alterations are by far not present in every patient, their identification can help guide therapy and support personalized management.

Alterations in homologous recombination repair genes, particularly *BRCA1* and *BRCA2*, represent one of the most clinically impactful molecular subsets. PARP inhibitors have demonstrated meaningful benefit in this population.[15–19] and platinum-based chemotherapy remains an area of active investigation supported by biological and clinical data.[20]

Mismatch repair deficiency or microsatellite instability-high status, although rare, identifies patients who may benefit from immune checkpoint inhibition. Access to immunotherapy remains heterogeneous worldwide, but testing remains essential to identify eligible patients.[21]

Other alterations, including androgen receptor mutations or amplifications, are being actively explored, with multiple investigational agents targeting androgen biosynthesis or receptor signaling which are currently in development (ClinicalTrials.gov identifiers: NCT03436485, NCT06764485, NCT05067140).

Recognizing Aggressive Biology

Certain molecular and clinical features indicate a poor prognosis and require increased vigilance. Loss of *TP53*, *PTEN*, or *RB1* is frequently associated with aggressive tumor behavior, early visceral involvement (particularly liver metastases), and lower sensitivity to androgen receptor–directed therapies. In these cases, closer imaging surveillance and earlier consideration of taxanes may be warranted.

Taxanes remain a standard of care in the mCRPC setting. Docetaxel retains substantial activity post-ARPI, and cabazitaxel provides a valid option after docetaxel failure.[13]

In about 20% of cases, tumors may undergo neuroendocrine differentiation, which is typically characterized by rapid progression, low PSA levels, and visceral disease (often on top of bone metastases). Histologic confirmation should be sought whenever possible. Evidence guiding treatment is limited, and platinum-based regimens are commonly used despite the absence of phase III evidence.

Sequencing Therapies in mCRPC: Matching Disease Biology and Clinical Trajectory

Therapeutic sequencing after progression on an ARPI currently is a central challenge in the management of mCRPC. Beyond molecularly driven strategies, clinical practice increasingly converges toward two distinct therapeutic pathways after ARPI failure.

In patients who are fit and candidates for a taxane, accumulating evidence suggests that early use of docetaxel may confer a survival advantage when administered immediately after ARPI failure, compared with immediate Lu-PSMA and deferred chemotherapy strategies. This benefit appears to be most pronounced in carefully selected populations, typically characterized by preserved performance status, symptomatic disease, and a higher burden of aggressive features, including rapidly evolving bone metastases and/or visceral metastases.[22]

In patients with an indolent disease course, limited symptoms, and demonstrable PSMA expression, PSMA-targeted radioligand therapy represents an emerging alternative, with not only better radiographic progression-free survival but also better QOL outcomes.[22–24]

Selective Radiotherapy in the Era of Systemic Therapy for mCRPC ?

Radiotherapy continues to play a role in selected patients with mCRPC. Metastasis-directed radiotherapy may delay systemic treatment modification in cases of oligoprogression, and local treatment of the primary tumor may provide meaningful control. Although supported mainly by phase II data,[25,26] these approaches reflect a growing

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recognition of spatial and temporal heterogeneity in advanced disease.

Conclusion

In an era of rapidly expanding therapeutic options, the management of mCRPC demands more than guideline adherence. It requires thoughtful integration of clinical judgment, molecular insight, patient vulnerability, and treatment history.

HOW TO BETTER PERSONALIZE TREATMENT WITH [^{177}Lu]Lu-PSMA RADIOLIGAND THERAPY

Aim

To understand how to best select patients for [^{177}Lu]-PSMA therapy including which criteria to use on PSMA-PET and other imaging. What patient and tumor characteristics best predict response. To understand in which line patients profit most from radioligand therapy and how to prevent side effects. To understand how many cycles should be given and how to decide on the optimal number of cycles for a specific patient (dose adaption). To understand how to best monitor patients on treatment (evaluating tumor response and progression).

Before Treatment

Identifying patients who will respond well to PSMA-radioligand therapies (RLT) is important in determining optimal sequencing choices to better personalize the therapeutic journey. With PSMA-RLT, this is best done through a combination of PSMA-PET parameters including both PSMA expression and tumor volume, diagnostic computed tomography (CT), or fluorodeoxyglucose (FDG)-PET to evaluate for metastatic sites that do not express PSMA, clinical features such as prior response to ARPI, the presence of hepatic metastases, and, potentially in the future, circulating tumor DNA (ctDNA) fraction.

PSMA-PET/CT to screen for [^{177}Lu]-PSMA suitability enables measuring both PSMA expression (both lesional and whole body) measured as standardized uptake value (SUV) and total tumor volume. To select patients, trials have used varying PSMA expression criteria. All phase III trials have used a liver-based threshold requiring PSMA expression above liver at a single site with no PSMA-negative soft tissue metastases on CT, an inclusive criterion developed to maximize the number of eligible patients with just a 13% screen failure rate in the VISION trial.[14,23] By contrast, the TheraP trial required an SUVmax (≥20) at one site and SUVmax ≥10 at all sites with no FDG-PET discordance, a more stringent approach that excluded 28% of patients.[27] This approach improved depth of PSA response in TheraP compared with VISION (66% *v* 46%), but not overall survival. At a clinical level, a PSMA-PET criterion that ensures relatively homogenous PSMA expression across all larger metastatic deposits is likely to select patients who will better respond to PSMA-targeted treatment, minimizing the number of men with primary treatment resistance. ENZA-p used middle ground criteria, SUVmax ≥15 at a single site and ≥10 at all larger sites of disease with no soft tissue mismatch on diagnostic CT (particularly in liver), a criterion now adopted in Australia for funded [^{177}Lu]-PSMA selection.[28]

Patient selection may be optimized with PSMA SUVmean, if clinically available. SUVmean gives the average PSMA expression within the total tumor volume and is reflective of

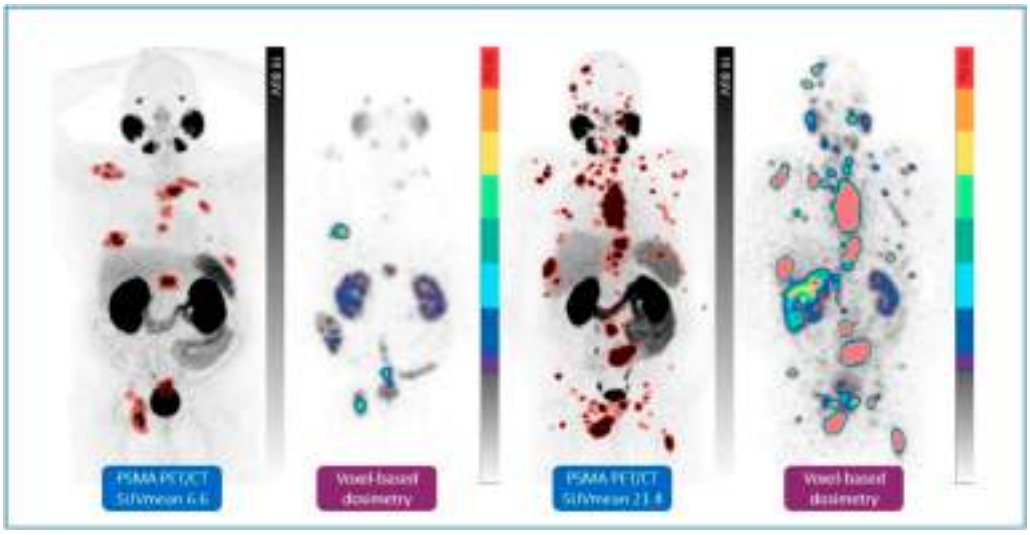

FIG 1. (A) A patient with low PSMA SUVmean in the total tumor burden, segmented in red. (B) On his cycle 1 [^{177}Lu]-PSMA SPECT/CT, there is low radiation-absorbed dose in most metastases (<2 Gy). By contrast, (C) another patient with high PSMA SUVmean has (D) very high radiation-absorbed dose at cycle 1, most 60-80 Gy. CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SPECT, single photon emission computed tomography.

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PSMA intensity and heterogeneity. High SUVmean ≥10 is positively associated with treatment response and radiation absorbed dose from [^{177}Lu]-PSMA and prognostic for overall survival (Fig 1).[29,30] In the TheraP trial, PSMA-SUVmean was predictive of PSA response to [^{177}Lu]-PSMA versus cabazitaxel for the top three quartiles (SUVmean ≥6.9). By contrast, patients with SUVmean <6.9 had a PSA 50% response rate of 29% (6 of 21) with [^{177}Lu]-PSMA versus 43% (12 of 28) with cabazitaxel. This may be a reasonable clinical cutoff below which to consider chemotherapy versus [^{177}Lu]-PSMA or [^{177}Lu]-PSMA in combination with other treatments, such as ARPI. As SUVmean is clinically unavailable for most clinicians, alternative visual methods that derive similar response information have been developed including the HIT score and the PSMA PET tumor-to-salivary glands ratio.[31,32] Automated quantitation of PET including SUVmean is also getting closer to being clinically available.[33-35]

Total tumor volume is another PET parameter that has demonstrated potential for patient selection. Higher baseline PSMA total tumor volume is predictive for overall survival, improving from 20 to 36 months with the addition of [^{177}Lu]-PSMA to enzalutamide in men with high-volume disease in the ENZAp trial (>230 mL).[36] PSMA total tumor volume also demonstrated prognostic benefit with [^{177}Lu]-PSMA monotherapy, with improved overall survival in low- versus high-volume disease.[37,38] Similarly, high pretreatment FDG PET-CT tumor volume (≥200 mL) was prognostic for OS after adjusting for conventional biomarkers in TheraP and may play a future role in identifying patients who would better benefit from combination strategies.[29]

Ultimately, although PSMA-PET screening can identify patients more likely to respond, it cannot identify all nonresponders to [^{177}Lu]-PSMA as this is also dependent on the radiation sensitivity of individual tumoral clones. For this reason, other clinical parameters and early on-treatment response evaluation with [^{177}Lu]-PSMA are clinically valuable.

Other important predictors of poor response include the presence of hepatic metastases and prior limited response to ARPI (<12 months).[37] Patients with liver metastases have a poorer prognosis with [^{177}Lu]-PSMA therapy, and careful evaluation of the diagnostic CT before commencing treatment to ensure that all hepatic lesions are PSMA-avid is important to ensure that patient benefit.[39] A nomogram that incorporates both clinical and imaging parameters has previously been published. ctDNA fraction, when clinically available, has potential as a predictor of treatment response with [^{177}Lu]-PSMA.[40] A baseline low ctDNA fraction (<2% or not detected) is associated with better overall survival in a number of trials.[41-43]

Identifying Patients at Risk of Adverse Events

Low glomerular filtration rate (GFR) is not a specific contraindication for [^{177}Lu]-PSMA therapy although care must be taken to ensure the that cause is not related to renal outflow obstruction before therapy.[44] While a median 20% reduction in GFR is known to occur at 2 years in patients receiving [^{177}Lu]-PSMA, impaired GFR at baseline does not make deterioration in GFR more likely and the treatment appears to be safe even in the presence of baseline renal dysfunction.[45,46]

Patients with baseline high-volume symptomatic disease are at higher risk of significant toxicities related to [^{177}Lu]-PSMA therapy compared with those with lower-volume disease or without baseline pain. The most prominent symptoms are marked fatigue, pain flare, and nausea around the time of treatment. All patients experiencing pain before [^{177}Lu]-PSMA therapy should have a discussion around pain flare and have a pain control plan before their first dose of treatment. Similarly, oral dexamethasone (4-8 mg once daily) with as-required ondansetron on days 1-3 in patients with high-volume disease on PSMA PET (>250 mL) or baseline pain significantly reduces the risk of fatigue, nausea, and pain, particularly at the first dose of treatment.

High-volume metastatic bone disease before [^{177}Lu]-PSMA therapy presents a significant risk of marrow compromise as [^{177}Lu]-PSMA will also affect a small region of marrow surrounding each tumor deposit.[47] Ensuring adequate PSMA expression in the majority of bone deposits and maximizing (not reducing) the first [^{177}Lu]-PSMA dose administered are important in this situation. Improving marrow function in these men requires significant treatment response at involved sites of marrow infiltration. High-volume low-PSMA expression bone involvement may be better treated with a PSMA-targeted alpha radionuclide or Radium-223, where adjacent marrow may be less compromised because of the shorter radionuclide pathlength.[48]

During Treatment

On-treatment biomarkers offer the potential to clinically personalize treatments based on response. The phase III trials of [^{177}Lu]-PSMA have all treated six-cycles, 6-weekly until radiographic progression without allowing treatment pauses or on-treatment biomarkers to evaluate for treatment response or progression.[14,23] ENZA-p evaluated the concept of adaptive dosing using an on-treatment PSMA-PET combined with PSA response. Those patients who had complete metabolic/biochemical responses on a 3-month PSMA-PET/PSA were given two doses rather than 4, continuing on enzalutamide alone.[28] The TheraP and EVOLUTION trials used a single photon emission computed tomography (SPECT)/CT and PSA response to identify marked responders who qualified a treatment pause, with retreatment commencing again at first confirmed PSA rise (ClinicalTrials.gov identifier: NCT05150236). [^{177}Lu]-PSMA SPECT/CT is a whole-body 3D image derived from the [^{177}Lu] emissions that can be undertaken between 4 and 72 hours after each treatment, generally taking around 20 minutes to acquire using a standard gamma camera. A SPECT/CT

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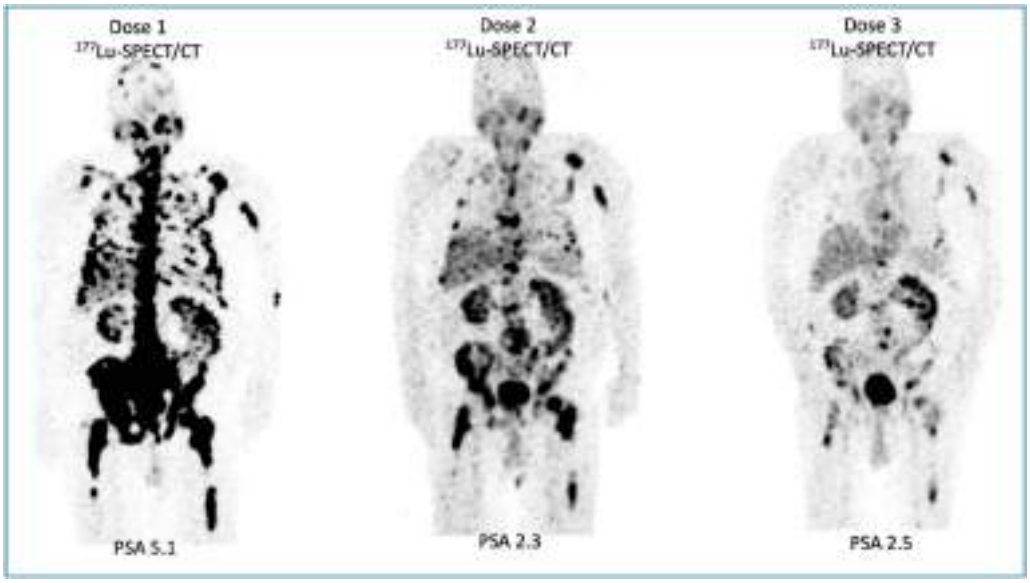

FIG 2. [^{177}Lu]-PSMA SPECT/CT is an additional tool in evaluating treatment response. This is a patient with high-volume metastatic disease in bone with PSA underexpression (PSA 5.1). Measuring PSA in this patient has clinical limitations. However, the SPECT/CT images help confirm that the patient has had a marked response to treatment at all sites of disease involvement despite no measurable soft tissue involvement and an unchanged bone scan. CT, computed tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SPECT, Single photon emission computed tomography.

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undertaken after each therapy dose in conjunction with PSA response allows a dynamic assessment of response/progression that can help decide best ongoing patient management, with both PSA and PSMA response providing independent data (Fig 2).[49-52] Patients with increased PSMA tumor volume and/or new lesions on 177Lu-SPECT/CT at 6 weeks after commencing treatment have significantly shorter progression-free and overall survival than those patients with any reduction in PSMA tumor volume/no new lesions.[49] The 6-week (dose 2) time point SPECT/CT appears to be effective at identifying patients with primary treatment resistance who may benefit from treatment intensification, such as with PSMA-targeted alpha therapy or change to chemotherapy in those with new sites of PSMA-low-expression disease. Conversely, a marked PSMA (and PSA) response on interim PSMA SPECT or PET identifies patients who can safely pause treatment for up to 2 years before responding again at rechallenge. Clinical registries have reported that these patients have repeat PSA50% response rates of between 50% and 80% with [^{177}Lu]-PSMA rechallenge.[53,54] A number of trials are also evaluating dose intensification, using shorter interval induction dosing to deepen and prolong responses (ClinicalTrials.gov identifier: NCT06526299).

While prospective trials have evaluated up to six doses of [^{177}Lu]-PSMA, retrospective studies have reported ongoing treatment responses with a higher number of doses with no significant toxicities.[55] The Flex-MRT trial is evaluating up to 12 doses of [^{177}Lu]-PSMA given using an adaptive dosing schedule (ClinicalTrials.gov identifier: NCT06216249). Ultimately, however, a minority of patients require more than six doses, with early treatment failure before a significant issue with [^{177}Lu]-PSMA therapy, particularly when used in metastatic castration-resistant prostate cancer as a monotherapy.

The landscape is changing fast with [^{177}Lu]-PSMA moving earlier in the prostate cancer space because of the positive findings from the PSMAddition trial, which administered [^{177}Lu]-PSMA in combination with ARPI in metastatic hormone-sensitive prostate cancer (mHSPC).[56] Similarly, the ENZA-p trial found that [^{177}Lu]-PSMA added to first-line enzalutamide therapy in early mCRPC improved overall survival by over 8 months compared with enzalutamide alone.[57] Further trials are evaluating other combinations including cabazitaxel chemotherapy (ClinicalTrials.gov identifier: NCT05340474), PARP inhibitors (ClinicalTrials.gov identifier: NCT03874884), and immune modulators (ClinicalTrials.gov identifier: NCT05150236). Where to fit [^{177}Lu]-PSMA and PSMA-targeted alpha therapies in prostate cancer sequencing is under evaluation (ClinicalTrials.gov identifiers: NCT06855277, NCT06780670).

EARLY INTEGRATION OF PALLIATIVE CARE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: EVIDENCE, RATIONALE, AND A PRACTICAL FRAMEWORK

Early palliative care (EPC) refers to specialist palliative care integrated alongside disease-directed oncology treatment early in the course of advanced cancer. EPC is typically delivered by an interdisciplinary team that focuses on four longitudinal domains: symptom management, coping and psychosocial support, communication and shared decision

making, and future planning including advance care planning (ACP). The team may consist of doctors, advance care providers, nurses, spiritual care providers, social workers, and other supportive care providers.

This model of early integration is consistent both the ASCO Clinical Practice Guideline Update and European guidelines, which recommend that patients with advanced solid tumors and hematologic malignancies receive early integrated specialist palliative care concurrent with active cancer therapy, based on patient needs such as symptom burden, quality-of-life concerns, or psychosocial distress rather than prognosis alone.[58,59]

Evidence of EPC Benefits

EPC improves outcomes that matter most to patients and caregivers while patients continue cancer-directed treatment. The Cochrane review of randomized trials found improved QOL with EPC and lower symptom intensity without consistent survival benefit.[60,61] Additional meta-analyses report better QOL, fewer symptoms, and improved mood.[62]

The landmark randomized trial in metastatic non–small cell lung cancer demonstrated that early outpatient palliative care significantly improved QOL and mood while reducing aggressive end-of-life care.[63] Several other landmark trials reinforce that benefit depends on the intervention structure and intensity. The ENABLE II trial demonstrated that a nurse-led palliative intervention improved QOL and mood.[64] ENABLE III further compared early versus delayed initiation and found improved one-year survival in the early group.[60] Studies of EPC in different cancers showed that QOL improvements differed by cancer type, suggesting that EPC may need tailoring to disease trajectory.[65]

Benefit of EPC in GU Cancers

GU-focused reviews describe low uptake of palliative and supportive care services despite substantial symptom burden and propose structured frameworks for earlier referral.[66] A national survey of individuals living with prostate cancer and their caregivers demonstrated significant unmet needs in communication, symptom management, and care coordination—domains directly targeted by EPC.[67]

Conceptual work further argues that prostate cancer's long disease trajectory and cumulative treatment-related morbidity make it especially amenable to early palliative involvement.[68]

More recent synthesis suggests that palliative and hospice care in prostate cancer is associated with improved QOL, fewer hospitalizations, and reduced high-intensity interventions near the end of life, yet referrals remain delayed.[69]

Taken together, EPC in GU oncology should be viewed as guideline-concordant supportive comanagement rather than a late-stage alternative to therapy.

How Should EPC Be Integrated?

A practical implementation model distinguishes primary palliative care, delivered by oncology clinicians, from secondary or tertiary specialist palliative care, supported by trigger-based workflows consistent with ASCO guidance.[58]

Primary Palliative Care (oncology-led)

Primary palliative care refers to core supportive skills that should occur during routine oncology visits:

- Symptom screening and first-line symptom management
- Serious illness communication
- Medication safety and supportive care planning
- Identification of caregiver needs

ASCO explicitly recognizes that oncology clinicians share responsibility with specialist teams for delivering palliative care across the cancer continuum.[58]

Embedding these skills into routine GU practice is critical given frequent patient contact with the oncology team and palliative care workforce limitations. Primary palliative care can be provided by any member of the primary oncology team, including physicians, advanced care providers, nurses, social workers, pharmacists, and financial counselors. When the primary team is unable to address symptoms and need additional expertise, a referral to a specialist palliative care team is warranted.

Secondary or Specialist Palliative Care

Specialist palliative care should be engaged when needs exceed routine oncology workflows, including

- Refractory or complex symptoms
- Significant psychological or existential distress
- Complex treatment decision making
- Recurrent hospitalizations or ICU consideration.

Trials demonstrating the greatest benefit typically used structured, longitudinal follow-up, underscoring that palliative care should function as comanagement rather than a one-time consultation.[70,71]

Trigger-Based Referral: A Prostate Cancer–Focused Referral Approach

Recent studies have shown trigger-based referral systems to standardize workflow to be better than individual clinician discretion in patient outcomes.[58] Potential triggers are listed below (Table 1). Depending on the expertise and comfort of the primary oncology team's ability to address the four domains of palliative care needs and availability of the

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specialist palliative care team, each institution can establish one or more of the following triggers.

Triggers in Metastatic Castration-Resistant Prostate Cancer

As highlighted above, there are several possible triggers to consider referral for EPC. Disease-based triggers include a new diagnosis of metastatic castration-resistant prostate cancer (mCRPC). Patients developed mCRPC because they had failure of therapies for either mHSPC or nonmetastatic hormone-sensitive or castration-resistant prostate cancer (nmHSPC or nmCRPC). Regardless of how the patient developed mCRPC, the fact that cancer has progressed to mCRPC implies the change in disease status and it has implications for prognosis and therapy choices.

These patients might also have physical symptoms from their disease, such as pain from bone metastasis. The change in disease status and symptoms can be distressing to both patients and caregivers. Routine evaluation for psychosocial symptoms with tools such as patient health questionnaire-9 and National Comprehensive Cancer Network's Distress Thermometer can help identify patients who may benefit from primary or secondary EPC 17. Rarely, the diagnosis of mCRPC occurs when the patient presents to the hospital with severe symptoms of disease progression.

From an oncologic perspective, patients with mCRPC are offered palliative-intent interventions such as RLT, chemotherapies, ARPI, and novel therapies including bispecific antibodies and antibody-drug conjugates (ADC), presenting overwhelming choices with different side effect profiles. Management of side effects can be accomplished by the primary oncologic teams (medical oncology, radiation oncology, or nuclear medicine radiologist) depending on the interventions used. Depending on the therapy used, the symptoms can include dry mouth, neuropathy, hot flashes, fatigue, nausea, vomiting, and immune-mediated toxicities. Primary oncologic providers typically manage these symptoms although collaboration with secondary PC team can be helpful in cases where additional support is needed.

Additional Benefits of Integration of EPC in mCRPC

Scientific advances in finding better targets and treatments such as bispecific antibodies, ADC, radioligands, and immunotherapy will help advance cancer-specific outcomes. There is an opportunity to improve the same cancer-specific outcomes by improving supportive care by advancing science of symptom management and palliative care.

TABLE 1. Potential Triggers for Early Palliative Care Referral

Disease-based triggers
New diagnosis of metastatic prostate cancer, hormone-sensitive or castration-resistant
Progression to castration-resistant prostate cancer
Enrollment in early-phase clinical trials[1]
Symptom and functional triggers
Moderate-to-severe symptoms despite primary palliative care interventions
Escalating opioid requirements
Functional decline (eg, ECOG ≥2)
Psychosocial triggers
Reports of depression, anxiety, demoralization
Caregiver distress
Difficulty in coping with illness trajectory as coping-focused mechanisms likely contribute to improved outcomes[5]
Health system triggers
Emergency department visits
Unplanned hospitalizations
Complex discharge needs

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Integration of EPC has the potential to collaborate on advancing supportive care. Research has focused on symptoms such as fatigue, immune reactions, neurologic toxicities, and other system-based toxicities.

CONCLUSION

EPC is now widely recognized as a concurrent, patient-centered intervention that improves QOL, symptom burden, coping, and satisfaction across advanced cancers.[58,60,61,63]

Prostate cancer represents an especially compelling setting for EPC because of prolonged advanced disease courses, cumulative symptom burden, repeated treatment transitions, and persistent unmet supportive needs.[66,67]

For oncology teams, integrating EPC requires three core strategies:

1. Deliver primary palliative care at every visit.
2. Refer early to specialist palliative care for advanced disease, if such expertise exists and the primary team needs assistance
3. Use trigger-based workflows at major clinical transitions.

When systematically embedded into GU oncology practice, EPC can function as a practical quality standard that optimizes patient-centered care.

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

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Optimizing Care for Patients With Metastatic Castration-Resistant Prostate Cancer

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OVERVIEW

The therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has evolved substantially over the past decade, with androgen receptor pathway inhibitors, taxanes, poly (ADP-ribose) polymerase (PARP) inhibitors, radioisotopes, bone-protecting agents, and emerging targeted therapies improving survival for patients. At the same time, earlier treatment intensification in the hormone-sensitive setting has resulted in heterogeneous clinical presentations at the onset of castration resistance, adding complexity to treatment sequencing and clinical decision making. Here, we propose a pragmatic, patient-centered framework to help guide the management of mCRPC by integrating clinical features, molecular profiling, imaging findings, and supportive care considerations. Confirmation of castration resistance remains a critical first step and requires documented biochemical or radiographic progression in the setting of castrate testosterone levels. Treatment selection should consider prior systemic therapies, disease burden and tempo, symptom profile, comorbidities, and frailty. Molecular characterization, including evaluation for homologous recombination repair alterations and mismatch repair deficiency, is highly important for identifying candidates for PARP inhibitors or immune checkpoint blockade and other emerging biomarker-driven targeted strategies. Prostate-specific membrane antigen (PSMA)–targeted radioligand therapy has emerged as a key treatment. PSMA-positron emission tomography–based selection, incorporating assessment of uptake intensity, tumor heterogeneity, and total tumor volume, may help identify patients who are most likely to benefit from this treatment. Clinical factors such as liver metastases and limited prior response to androgen receptor–directed therapy have been associated with less favorable outcomes. Early on-treatment assessment using prostate-specific antigen response and PSMA-based imaging may support adaptive treatment strategies and earlier recognition of resistance. Given the high prevalence of bone metastases, bone-protecting agents should be considered to reduce skeletal-related events. Early palliative care (EPC) is now widely recognized as a concurrent, patient-centered intervention that improves quality of life, symptom burden, coping, and satisfaction across advanced cancers. Prostate cancer represents an especially compelling setting for EPC because of prolonged advanced disease courses, cumulative symptom burden, repeated treatment transitions, and persistent unmet supportive needs.

FIRST-LINE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: ONE SIZE DOES NOT FIT ALL

Over the past decade, the therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has expanded at an unprecedented pace.[1,2] Androgen receptor pathway inhibitors (ARPIs), taxanes, poly (ADP-ribose) polymerase (PARP) inhibitors, radioisotopes, bone-protecting agents, and emerging targeted agents have collectively transformed outcomes for many patients. Sipuleucel-T is another option. This complex cell therapy is rarely used and, only in the United States, most commonly in patients with early mCRPC.[3] Yet paradoxically, this therapeutic abundance has also exacerbated uncertainties in everyday clinical practice. These uncertainties are partially related to the use of some of these agents in the hormone-sensitive setting, thus creating new clinical situations in mCRPC. The challenge that oncologists are often facing worldwide is no longer whether effective treatments exist, but how to select, sequence, combine, and adapt them for each individual patient.

In this context, a pragmatic and patient-centered approach is needed. Rather than advocating for a rigid treatment algorithm, we propose here a clinically driven checklist designed to mirror real-world practice.

PRACTICAL APPLICATIONS

- The use of next-generation sequencing, performed on tumor tissue or circulating tumor DNA, should be encouraged whenever feasible, as it may increasingly inform biomarker-driven treatment strategies and future therapeutic development.
- The landscape is changing fast with [^{177}Lu]-PSMA moving earlier in the prostate cancer space. Ongoing trials are evaluating combination strategies as well as PSMA targeted alpha therapies.
- Early integration of palliative is now widely recognized as a patient-centered intervention that improves quality of life.

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From Definition to Decision Making: A Checklist for mCRPC

Defining Castration Resistance: Beyond a Semantic Exercise

The first and most critical step in managing mCRPC is ensuring that the diagnosis itself is correct. Castration resistance should never be assumed without confirming adequate androgen deprivation. A serum testosterone level below 0.50 ng/mL (=50 ng/dL = 1.7 nmol/L) remains the accepted threshold. Once castrate levels are confirmed, progression must be clearly documented. This may occur biochemically, with a rising prostate-specific antigen (PSA) characterized by three consecutive increases. Alternatively, radiographic progression may be demonstrated by the appearance of two new bone lesions on a bone scan or progression of measurable soft tissue disease according to RECIST 1.1 criteria. This distinction is not trivial; it may shape therapeutic decisions, prognostic discussions, and eligibility for clinical trials. Progression criteria on next-generation imaging such as prostate-specific membrane antigen-positron emission tomography (PSMA-PET) are less well-established.[4]

Patients Come First: Age, Frailty, and Comorbidities

Similar to many other cancers, mCRPC is predominantly a disease of second half of life. Therefore, many patients have vulnerabilities that may inadequately be captured by the performance status alone. Chronologic age should not dictate treatment intensity, but biological age often does. Simple geriatric screening tools, such as the G8 score, can identify patients who may benefit from a more comprehensive geriatric assessment and tailored therapeutic strategies.[5,6]

Comorbidities are equally influential. Cardiovascular disease, metabolic syndrome, and renal impairment may all affect treatment tolerance and safety, particularly with ARPIs or taxanes. Just as importantly, polypharmacy is common, and drug-drug interactions may compromise both efficacy and toxicity profiles.[7] In this context, involving an oncology-trained pharmacist can be relevant, particularly in complex cases, to ensure prescription safety.

Importantly, beyond clinical and geriatric parameters, patients' preferences and goals of care represent a critical determinant of treatment choice. Shared decision making is essential in this setting, ensuring that therapeutic strategies align with what matters most to the patient, with an emphasis on doing more for the patient rather than to the patient.

Never Overlook the Skeleton

Bone metastases are the dominant site of metastatic spread in castration-resistant prostate cancer, affecting more than 80% of patients and contributing substantially to morbidity, impaired quality of life (QOL), and mortality. The complex interaction between prostate cancer cells and the bone microenvironment leads to both osteoblastic and osteolytic activity, resulting in skeletal-related events (SREs) such as pathologic fractures, spinal cord compression, and the need for bone surgery or radiation therapy. Bone-targeted agents such as bisphosphonates or RANK-ligand inhibitors (denosumab) significantly reduce the risk of SREs and should be considered in an early setting.[8-10] Both play a role in maintaining QOL, reducing pain, and preserving functional independence. Denosumab was shown to be superior to zoledronic acid in a large phase III trial.[8]

Effective management of skeletal health in mCRPC requires a multimodal approach that integrates baseline and follow-up bone mineral density assessment and routine calcium and vitamin D supplementation with appropriate monitoring to mitigate hypocalcemia. Evidence from meta-analyses suggests that calcium and vitamin D supplementation can reduce fracture risk by approximately 7%-20% in at-risk populations, supporting their systematic use.[11] Preventive measures should also include a baseline dental assessment and the maintenance of good oral hygiene throughout treatment to reduce the risk of osteonecrosis of the jaw, a well-known side effect of bone-protecting agents.

In addition to pharmacologic interventions, adapted physical activity plays a critical role in maintaining bone health, reducing risk of falling, and preserving functional status in men with mCRPC. Structured exercise programs have been shown to enhance bone mineral density, improve muscle strength, and reduce the incidence of falls and fractures in patients undergoing androgen deprivation therapy, which itself accelerates bone loss.[12]

Bone-targeted agents should be considered standard care for patients with mCRPC and bone metastases to reduce the risk of SREs.

One Disease Name, Many Clinical Scenarios

mCRPC Is Not a Single Clinical Entity

Prior treatments now vary widely as many patients enter the castration-resistant phase after intensified therapy in the hormone-sensitive setting, including triplet and doublet systemic regimens. Whether a patient has received androgen deprivation alone, combined androgen receptor inhibition, or combined androgen receptor inhibition plus docetaxel profoundly influences subsequent therapeutic choices. In addition, cabazitaxel, Lu-PSMA, and PARP inhibitors (for *BRCA* patients) have all shown improvements in overall survival in mCRPC patients with prior ARPI and docetaxel and therefore shall be regarded as standard options in patients with mCRPC post-triplet for hormone-sensitive prostate cancer.[13–15]

Similarly, clinical presentation matters. At one end of the spectrum is the frail older patient with indolent, minimally symptomatic disease, and at the other, the young, fit patient with rapidly progressive bone and, sometimes, visceral metastases. Applying identical treatment strategies to these fundamentally different situations is neither rational nor patient-centered.

Molecular Profiling: From Optional to Essential

Molecular characterization plays an increasingly important role in the management of mCRPC although it is not yet universally accessible in routine clinical practice. Next-generation sequencing (performed on tumor tissue or circulating tumor DNA) should be strongly encouraged whenever feasible. While actionable alterations are by far not present in every patient, their identification can help guide therapy and support personalized management.

Alterations in homologous recombination repair genes, particularly *BRCA1* and *BRCA2*, represent one of the most clinically impactful molecular subsets. PARP inhibitors have demonstrated meaningful benefit in this population.[15–19] and platinum-based chemotherapy remains an area of active investigation supported by biological and clinical data.[20]

Mismatch repair deficiency or microsatellite instability-high status, although rare, identifies patients who may benefit from immune checkpoint inhibition. Access to immunotherapy remains heterogeneous worldwide, but testing remains essential to identify eligible patients.[21]

Other alterations, including androgen receptor mutations or amplifications, are being actively explored, with multiple investigational agents targeting androgen biosynthesis or receptor signaling which are currently in development (ClinicalTrials.gov identifiers: NCT03436485, NCT06764485, NCT05067140).

Recognizing Aggressive Biology

Certain molecular and clinical features indicate a poor prognosis and require increased vigilance. Loss of *TP53*, *PTEN*, or *RB1* is frequently associated with aggressive tumor behavior, early visceral involvement (particularly liver metastases), and lower sensitivity to androgen receptor–directed therapies. In these cases, closer imaging surveillance and earlier consideration of taxanes may be warranted.

Taxanes remain a standard of care in the mCRPC setting. Docetaxel retains substantial activity post-ARPI, and cabazitaxel provides a valid option after docetaxel failure.[13]

In about 20% of cases, tumors may undergo neuroendocrine differentiation, which is typically characterized by rapid progression, low PSA levels, and visceral disease (often on top of bone metastases). Histologic confirmation should be sought whenever possible. Evidence guiding treatment is limited, and platinum-based regimens are commonly used despite the absence of phase III evidence.

Sequencing Therapies in mCRPC: Matching Disease Biology and Clinical Trajectory

Therapeutic sequencing after progression on an ARPI currently is a central challenge in the management of mCRPC. Beyond molecularly driven strategies, clinical practice increasingly converges toward two distinct therapeutic pathways after ARPI failure.

In patients who are fit and candidates for a taxane, accumulating evidence suggests that early use of docetaxel may confer a survival advantage when administered immediately after ARPI failure, compared with immediate Lu-PSMA and deferred chemotherapy strategies. This benefit appears to be most pronounced in carefully selected populations, typically characterized by preserved performance status, symptomatic disease, and a higher burden of aggressive features, including rapidly evolving bone metastases and/or visceral metastases.[22]

In patients with an indolent disease course, limited symptoms, and demonstrable PSMA expression, PSMA-targeted radioligand therapy represents an emerging alternative, with not only better radiographic progression-free survival but also better QOL outcomes.[22–24]

Selective Radiotherapy in the Era of Systemic Therapy for mCRPC ?

Radiotherapy continues to play a role in selected patients with mCRPC. Metastasis-directed radiotherapy may delay systemic treatment modification in cases of oligoprogression, and local treatment of the primary tumor may provide meaningful control. Although supported mainly by phase II data,[25,26] these approaches reflect a growing

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recognition of spatial and temporal heterogeneity in advanced disease.

Conclusion

In an era of rapidly expanding therapeutic options, the management of mCRPC demands more than guideline adherence. It requires thoughtful integration of clinical judgment, molecular insight, patient vulnerability, and treatment history.

HOW TO BETTER PERSONALIZE TREATMENT WITH [^{177}Lu]Lu-PSMA RADIOLIGAND THERAPY

Aim

To understand how to best select patients for [^{177}Lu]-PSMA therapy including which criteria to use on PSMA-PET and other imaging. What patient and tumor characteristics best predict response. To understand in which line patients profit most from radioligand therapy and how to prevent side effects. To understand how many cycles should be given and how to decide on the optimal number of cycles for a specific patient (dose adaption). To understand how to best monitor patients on treatment (evaluating tumor response and progression).

Before Treatment

Identifying patients who will respond well to PSMA-radioligand therapies (RLT) is important in determining optimal sequencing choices to better personalize the therapeutic journey. With PSMA-RLT, this is best done through a combination of PSMA-PET parameters including both PSMA expression and tumor volume, diagnostic computed tomography (CT), or fluorodeoxyglucose (FDG)-PET to evaluate for metastatic sites that do not express PSMA, clinical features such as prior response to ARPI, the presence of hepatic metastases, and, potentially in the future, circulating tumor DNA (ctDNA) fraction.

PSMA-PET/CT to screen for [^{177}Lu]-PSMA suitability enables measuring both PSMA expression (both lesional and whole body) measured as standardized uptake value (SUV) and total tumor volume. To select patients, trials have used varying PSMA expression criteria. All phase III trials have used a liver-based threshold requiring PSMA expression above liver at a single site with no PSMA-negative soft tissue metastases on CT, an inclusive criterion developed to maximize the number of eligible patients with just a 13% screen failure rate in the VISION trial.[14,23] By contrast, the TheraP trial required an SUVmax (≥20) at one site and SUVmax ≥10 at all sites with no FDG-PET discordance, a more stringent approach that excluded 28% of patients.[27] This approach improved depth of PSA response in TheraP compared with VISION (66% *v* 46%), but not overall survival. At a clinical level, a PSMA-PET criterion that ensures relatively homogenous PSMA expression across all larger metastatic deposits is likely to select patients who will better respond to PSMA-targeted treatment, minimizing the number of men with primary treatment resistance. ENZA-p used middle ground criteria, SUVmax ≥15 at a single site and ≥10 at all larger sites of disease with no soft tissue mismatch on diagnostic CT (particularly in liver), a criterion now adopted in Australia for funded [^{177}Lu]-PSMA selection.[28]

Patient selection may be optimized with PSMA SUVmean, if clinically available. SUVmean gives the average PSMA expression within the total tumor volume and is reflective of

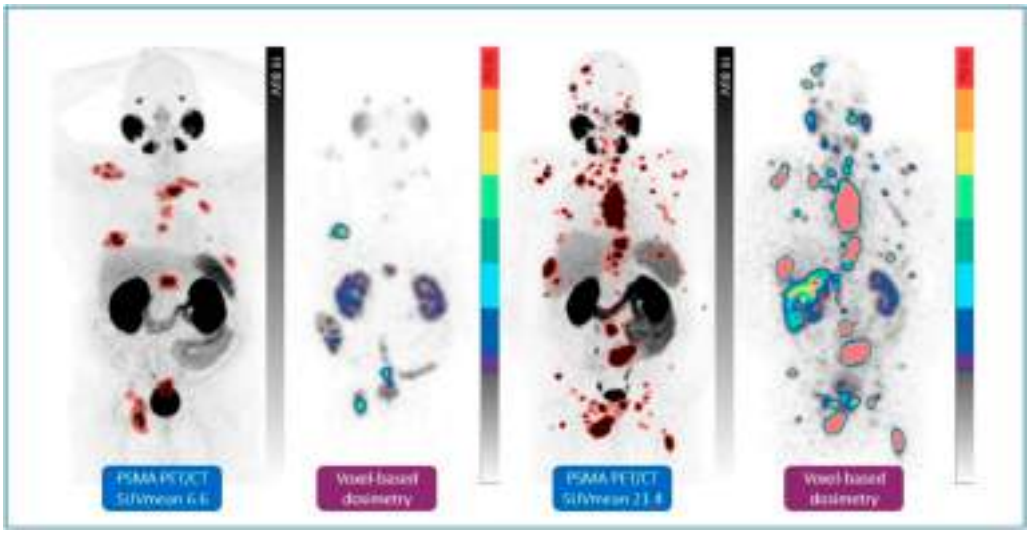

FIG 1. (A) A patient with low PSMA SUVmean in the total tumor burden, segmented in red. (B) On his cycle 1 [^{177}Lu]-PSMA SPECT/CT, there is low radiation-absorbed dose in most metastases (<2 Gy). By contrast, (C) another patient with high PSMA SUVmean has (D) very high radiation-absorbed dose at cycle 1, most 60-80 Gy. CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SPECT, single photon emission computed tomography.

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PSMA intensity and heterogeneity. High SUVmean ≥10 is positively associated with treatment response and radiation absorbed dose from [^{177}Lu]-PSMA and prognostic for overall survival (Fig 1).[29,30] In the TheraP trial, PSMA-SUVmean was predictive of PSA response to [^{177}Lu]-PSMA versus cabazitaxel for the top three quartiles (SUVmean ≥6.9). By contrast, patients with SUVmean <6.9 had a PSA 50% response rate of 29% (6 of 21) with [^{177}Lu]-PSMA versus 43% (12 of 28) with cabazitaxel. This may be a reasonable clinical cutoff below which to consider chemotherapy versus [^{177}Lu]-PSMA or [^{177}Lu]-PSMA in combination with other treatments, such as ARPI. As SUVmean is clinically unavailable for most clinicians, alternative visual methods that derive similar response information have been developed including the HIT score and the PSMA PET tumor-to-salivary glands ratio.[31,32] Automated quantitation of PET including SUVmean is also getting closer to being clinically available.[33-35]

Total tumor volume is another PET parameter that has demonstrated potential for patient selection. Higher baseline PSMA total tumor volume is predictive for overall survival, improving from 20 to 36 months with the addition of [^{177}Lu]-PSMA to enzalutamide in men with high-volume disease in the ENZAp trial (>230 mL).[36] PSMA total tumor volume also demonstrated prognostic benefit with [^{177}Lu]-PSMA monotherapy, with improved overall survival in low- versus high-volume disease.[37,38] Similarly, high pretreatment FDG PET-CT tumor volume (≥200 mL) was prognostic for OS after adjusting for conventional biomarkers in TheraP and may play a future role in identifying patients who would better benefit from combination strategies.[29]

Ultimately, although PSMA-PET screening can identify patients more likely to respond, it cannot identify all nonresponders to [^{177}Lu]-PSMA as this is also dependent on the radiation sensitivity of individual tumoral clones. For this reason, other clinical parameters and early on-treatment response evaluation with [^{177}Lu]-PSMA are clinically valuable.

Other important predictors of poor response include the presence of hepatic metastases and prior limited response to ARPI (<12 months).[37] Patients with liver metastases have a poorer prognosis with [^{177}Lu]-PSMA therapy, and careful evaluation of the diagnostic CT before commencing treatment to ensure that all hepatic lesions are PSMA-avid is important to ensure that patient benefit.[39] A nomogram that incorporates both clinical and imaging parameters has previously been published. ctDNA fraction, when clinically available, has potential as a predictor of treatment response with [^{177}Lu]-PSMA.[40] A baseline low ctDNA fraction (<2% or not detected) is associated with better overall survival in a number of trials.[41-43]

Identifying Patients at Risk of Adverse Events

Low glomerular filtration rate (GFR) is not a specific contraindication for [^{177}Lu]-PSMA therapy although care must be taken to ensure the that cause is not related to renal outflow obstruction before therapy.[44] While a median 20% reduction in GFR is known to occur at 2 years in patients receiving [^{177}Lu]-PSMA, impaired GFR at baseline does not make deterioration in GFR more likely and the treatment appears to be safe even in the presence of baseline renal dysfunction.[45,46]

Patients with baseline high-volume symptomatic disease are at higher risk of significant toxicities related to [^{177}Lu]-PSMA therapy compared with those with lower-volume disease or without baseline pain. The most prominent symptoms are marked fatigue, pain flare, and nausea around the time of treatment. All patients experiencing pain before [^{177}Lu]-PSMA therapy should have a discussion around pain flare and have a pain control plan before their first dose of treatment. Similarly, oral dexamethasone (4-8 mg once daily) with as-required ondansetron on days 1-3 in patients with high-volume disease on PSMA PET (>250 mL) or baseline pain significantly reduces the risk of fatigue, nausea, and pain, particularly at the first dose of treatment.

High-volume metastatic bone disease before [^{177}Lu]-PSMA therapy presents a significant risk of marrow compromise as [^{177}Lu]-PSMA will also affect a small region of marrow surrounding each tumor deposit.[47] Ensuring adequate PSMA expression in the majority of bone deposits and maximizing (not reducing) the first [^{177}Lu]-PSMA dose administered are important in this situation. Improving marrow function in these men requires significant treatment response at involved sites of marrow infiltration. High-volume low-PSMA expression bone involvement may be better treated with a PSMA-targeted alpha radionuclide or Radium-223, where adjacent marrow may be less compromised because of the shorter radionuclide pathlength.[48]

During Treatment

On-treatment biomarkers offer the potential to clinically personalize treatments based on response. The phase III trials of [^{177}Lu]-PSMA have all treated six-cycles, 6-weekly until radiographic progression without allowing treatment pauses or on-treatment biomarkers to evaluate for treatment response or progression.[14,23] ENZA-p evaluated the concept of adaptive dosing using an on-treatment PSMA-PET combined with PSA response. Those patients who had complete metabolic/biochemical responses on a 3-month PSMA-PET/PSA were given two doses rather than 4, continuing on enzalutamide alone.[28] The TheraP and EVOLUTION trials used a single photon emission computed tomography (SPECT)/CT and PSA response to identify marked responders who qualified a treatment pause, with retreatment commencing again at first confirmed PSA rise (ClinicalTrials.gov identifier: NCT05150236). [^{177}Lu]-PSMA SPECT/CT is a whole-body 3D image derived from the [^{177}Lu] emissions that can be undertaken between 4 and 72 hours after each treatment, generally taking around 20 minutes to acquire using a standard gamma camera. A SPECT/CT

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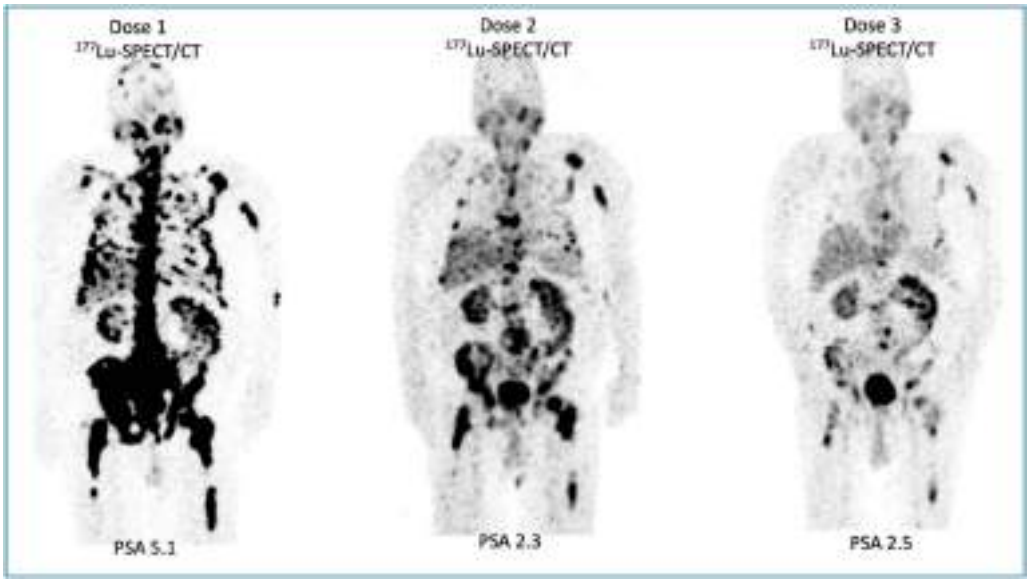

FIG 2. [^{177}Lu]-PSMA SPECT/CT is an additional tool in evaluating treatment response. This is a patient with high-volume metastatic disease in bone with PSA underexpression (PSA 5.1). Measuring PSA in this patient has clinical limitations. However, the SPECT/CT images help confirm that the patient has had a marked response to treatment at all sites of disease involvement despite no measurable soft tissue involvement and an unchanged bone scan. CT, computed tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SPECT, Single photon emission computed tomography.

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undertaken after each therapy dose in conjunction with PSA response allows a dynamic assessment of response/progression that can help decide best ongoing patient management, with both PSA and PSMA response providing independent data (Fig 2).[49-52] Patients with increased PSMA tumor volume and/or new lesions on 177Lu-SPECT/CT at 6 weeks after commencing treatment have significantly shorter progression-free and overall survival than those patients with any reduction in PSMA tumor volume/no new lesions.[49] The 6-week (dose 2) time point SPECT/CT appears to be effective at identifying patients with primary treatment resistance who may benefit from treatment intensification, such as with PSMA-targeted alpha therapy or change to chemotherapy in those with new sites of PSMA-low-expression disease. Conversely, a marked PSMA (and PSA) response on interim PSMA SPECT or PET identifies patients who can safely pause treatment for up to 2 years before responding again at rechallenge. Clinical registries have reported that these patients have repeat PSA50% response rates of between 50% and 80% with [^{177}Lu]-PSMA rechallenge.[53,54] A number of trials are also evaluating dose intensification, using shorter interval induction dosing to deepen and prolong responses (ClinicalTrials.gov identifier: NCT06526299).

While prospective trials have evaluated up to six doses of [^{177}Lu]-PSMA, retrospective studies have reported ongoing treatment responses with a higher number of doses with no significant toxicities.[55] The Flex-MRT trial is evaluating up to 12 doses of [^{177}Lu]-PSMA given using an adaptive dosing schedule (ClinicalTrials.gov identifier: NCT06216249). Ultimately, however, a minority of patients require more than six doses, with early treatment failure before a significant issue with [^{177}Lu]-PSMA therapy, particularly when used in metastatic castration-resistant prostate cancer as a monotherapy.

The landscape is changing fast with [^{177}Lu]-PSMA moving earlier in the prostate cancer space because of the positive findings from the PSMAddition trial, which administered [^{177}Lu]-PSMA in combination with ARPI in metastatic hormone-sensitive prostate cancer (mHSPC).[56] Similarly, the ENZA-p trial found that [^{177}Lu]-PSMA added to first-line enzalutamide therapy in early mCRPC improved overall survival by over 8 months compared with enzalutamide alone.[57] Further trials are evaluating other combinations including cabazitaxel chemotherapy (ClinicalTrials.gov identifier: NCT05340474), PARP inhibitors (ClinicalTrials.gov identifier: NCT03874884), and immune modulators (ClinicalTrials.gov identifier: NCT05150236). Where to fit [^{177}Lu]-PSMA and PSMA-targeted alpha therapies in prostate cancer sequencing is under evaluation (ClinicalTrials.gov identifiers: NCT06855277, NCT06780670).

EARLY INTEGRATION OF PALLIATIVE CARE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: EVIDENCE, RATIONALE, AND A PRACTICAL FRAMEWORK

Early palliative care (EPC) refers to specialist palliative care integrated alongside disease-directed oncology treatment early in the course of advanced cancer. EPC is typically delivered by an interdisciplinary team that focuses on four longitudinal domains: symptom management, coping and psychosocial support, communication and shared decision

making, and future planning including advance care planning (ACP). The team may consist of doctors, advance care providers, nurses, spiritual care providers, social workers, and other supportive care providers.

This model of early integration is consistent both the ASCO Clinical Practice Guideline Update and European guidelines, which recommend that patients with advanced solid tumors and hematologic malignancies receive early integrated specialist palliative care concurrent with active cancer therapy, based on patient needs such as symptom burden, quality-of-life concerns, or psychosocial distress rather than prognosis alone.[58,59]

Evidence of EPC Benefits

EPC improves outcomes that matter most to patients and caregivers while patients continue cancer-directed treatment. The Cochrane review of randomized trials found improved QOL with EPC and lower symptom intensity without consistent survival benefit.[60,61] Additional meta-analyses report better QOL, fewer symptoms, and improved mood.[62]

The landmark randomized trial in metastatic non–small cell lung cancer demonstrated that early outpatient palliative care significantly improved QOL and mood while reducing aggressive end-of-life care.[63] Several other landmark trials reinforce that benefit depends on the intervention structure and intensity. The ENABLE II trial demonstrated that a nurse-led palliative intervention improved QOL and mood.[64] ENABLE III further compared early versus delayed initiation and found improved one-year survival in the early group.[60] Studies of EPC in different cancers showed that QOL improvements differed by cancer type, suggesting that EPC may need tailoring to disease trajectory.[65]

Benefit of EPC in GU Cancers

GU-focused reviews describe low uptake of palliative and supportive care services despite substantial symptom burden and propose structured frameworks for earlier referral.[66] A national survey of individuals living with prostate cancer and their caregivers demonstrated significant unmet needs in communication, symptom management, and care coordination—domains directly targeted by EPC.[67]

Conceptual work further argues that prostate cancer's long disease trajectory and cumulative treatment-related morbidity make it especially amenable to early palliative involvement.[68]

More recent synthesis suggests that palliative and hospice care in prostate cancer is associated with improved QOL, fewer hospitalizations, and reduced high-intensity interventions near the end of life, yet referrals remain delayed.[69]

Taken together, EPC in GU oncology should be viewed as guideline-concordant supportive comanagement rather than a late-stage alternative to therapy.

How Should EPC Be Integrated?

A practical implementation model distinguishes primary palliative care, delivered by oncology clinicians, from secondary or tertiary specialist palliative care, supported by trigger-based workflows consistent with ASCO guidance.[58]

Primary Palliative Care (oncology-led)

Primary palliative care refers to core supportive skills that should occur during routine oncology visits:

- Symptom screening and first-line symptom management
- Serious illness communication
- Medication safety and supportive care planning
- Identification of caregiver needs

ASCO explicitly recognizes that oncology clinicians share responsibility with specialist teams for delivering palliative care across the cancer continuum.[58]

Embedding these skills into routine GU practice is critical given frequent patient contact with the oncology team and palliative care workforce limitations. Primary palliative care can be provided by any member of the primary oncology team, including physicians, advanced care providers, nurses, social workers, pharmacists, and financial counselors. When the primary team is unable to address symptoms and need additional expertise, a referral to a specialist palliative care team is warranted.

Secondary or Specialist Palliative Care

Specialist palliative care should be engaged when needs exceed routine oncology workflows, including

- Refractory or complex symptoms
- Significant psychological or existential distress
- Complex treatment decision making
- Recurrent hospitalizations or ICU consideration.

Trials demonstrating the greatest benefit typically used structured, longitudinal follow-up, underscoring that palliative care should function as comanagement rather than a one-time consultation.[70,71]

Trigger-Based Referral: A Prostate Cancer–Focused Referral Approach

Recent studies have shown trigger-based referral systems to standardize workflow to be better than individual clinician discretion in patient outcomes.[58] Potential triggers are listed below (Table 1). Depending on the expertise and comfort of the primary oncology team's ability to address the four domains of palliative care needs and availability of the

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specialist palliative care team, each institution can establish one or more of the following triggers.

Triggers in Metastatic Castration-Resistant Prostate Cancer

As highlighted above, there are several possible triggers to consider referral for EPC. Disease-based triggers include a new diagnosis of metastatic castration-resistant prostate cancer (mCRPC). Patients developed mCRPC because they had failure of therapies for either mHSPC or nonmetastatic hormone-sensitive or castration-resistant prostate cancer (nmHSPC or nmCRPC). Regardless of how the patient developed mCRPC, the fact that cancer has progressed to mCRPC implies the change in disease status and it has implications for prognosis and therapy choices.

These patients might also have physical symptoms from their disease, such as pain from bone metastasis. The change in disease status and symptoms can be distressing to both patients and caregivers. Routine evaluation for psychosocial symptoms with tools such as patient health questionnaire-9 and National Comprehensive Cancer Network's Distress Thermometer can help identify patients who may benefit from primary or secondary EPC 17. Rarely, the diagnosis of mCRPC occurs when the patient presents to the hospital with severe symptoms of disease progression.

From an oncologic perspective, patients with mCRPC are offered palliative-intent interventions such as RLT, chemotherapies, ARPI, and novel therapies including bispecific antibodies and antibody-drug conjugates (ADC), presenting overwhelming choices with different side effect profiles. Management of side effects can be accomplished by the primary oncologic teams (medical oncology, radiation oncology, or nuclear medicine radiologist) depending on the interventions used. Depending on the therapy used, the symptoms can include dry mouth, neuropathy, hot flashes, fatigue, nausea, vomiting, and immune-mediated toxicities. Primary oncologic providers typically manage these symptoms although collaboration with secondary PC team can be helpful in cases where additional support is needed.

Additional Benefits of Integration of EPC in mCRPC

Scientific advances in finding better targets and treatments such as bispecific antibodies, ADC, radioligands, and immunotherapy will help advance cancer-specific outcomes. There is an opportunity to improve the same cancer-specific outcomes by improving supportive care by advancing science of symptom management and palliative care.

TABLE 1. Potential Triggers for Early Palliative Care Referral

Disease-based triggers
New diagnosis of metastatic prostate cancer, hormone-sensitive or castration-resistant
Progression to castration-resistant prostate cancer
Enrollment in early-phase clinical trials[1]
Symptom and functional triggers
Moderate-to-severe symptoms despite primary palliative care interventions
Escalating opioid requirements
Functional decline (eg, ECOG ≥2)
Psychosocial triggers
Reports of depression, anxiety, demoralization
Caregiver distress
Difficulty in coping with illness trajectory as coping-focused mechanisms likely contribute to improved outcomes[5]
Health system triggers
Emergency department visits
Unplanned hospitalizations
Complex discharge needs

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Integration of EPC has the potential to collaborate on advancing supportive care. Research has focused on symptoms such as fatigue, immune reactions, neurologic toxicities, and other system-based toxicities.

CONCLUSION

EPC is now widely recognized as a concurrent, patient-centered intervention that improves QOL, symptom burden, coping, and satisfaction across advanced cancers.[58,60,61,63]

Prostate cancer represents an especially compelling setting for EPC because of prolonged advanced disease courses, cumulative symptom burden, repeated treatment transitions, and persistent unmet supportive needs.[66,67]

For oncology teams, integrating EPC requires three core strategies:

1. Deliver primary palliative care at every visit.
2. Refer early to specialist palliative care for advanced disease, if such expertise exists and the primary team needs assistance
3. Use trigger-based workflows at major clinical transitions.

When systematically embedded into GU oncology practice, EPC can function as a practical quality standard that optimizes patient-centered care.

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Unique Considerations in Rare Gynecologic Tumors: Gestational Trophoblastic Neoplasia, Germ Cell Tumors, and Clear Cell Ovarian Cancers

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OVERVIEW

Rare cancers are usually defined as an incidence of <6/100,000 persons per year. Gynecological oncology is characterized by a paradoxical high prevalence of rare cancer subtypes, especially in ovarian tumors. Ovarian germ cell tumors, clear cell ovarian cancer and gestational trophoblastic disease encompass this set of gynecologic tumors. The WHO classification distinguishes epithelial cell tumors (85% of malignant tumors) from non-epithelial tumors, sex cord stromal tumors (8% of malignant tumors), and germ cell tumors (6% of malignant tumors). The current treatment for these tumors is similar to that for ovarian cancer but advancing quickly to incorporate targeted therapy. Gestational trophoblastic tumors are usually curable, even when widely metastatic disease is present. Ovarian clear-cell carcinoma (OCCC) remains a challenging disease characterized by intrinsic chemoresistance and distinct molecular features. A more biologically aligned treatment strategy has emerged. Continued integration of molecular selection and microenvironmental modulation will likely define the next phase of therapeutic development in OCCC. The clinical features, staging, and current treatment of each of these tumors is reviewed.

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Rare cancers are usually defined as an incidence of <6 per 100,000 persons per year. Gynecologic oncology is characterized by a paradoxical high prevalence of rare cancer subtypes, especially in ovarian tumors.[1,2] Ovarian germ cell tumors (OGCTs), clear cell ovarian cancer, and gestational trophoblastic disease encompass this set of gynecologic tumors. The World Health Organization (WHO) classifies ovarian primary cancers into three main subtypes according to the cell type of origin: epithelial cells, sex cord and stromal cells, and germ cells.[1] Consistent with the three main functions and compartments of the ovaries, the WHO classification distinguishes epithelial cell tumors (85% of malignant tumors) from nonepithelial tumors, sex cord stromal tumors (8% of malignant tumors), and germ cell tumors (6% of malignant tumors). The current treatment for these tumors is similar to that for ovarian cancer but is advancing quickly to incorporate targeted therapy. Gestational trophoblastic tumors are usually curable, even when widely metastatic disease is present. The clinical features, staging, and current treatment of each of these tumors are reviewed.

MALIGNANT OVARIAN GERM CELL TUMOR

Malignant ovarian germ cell tumor (MOGCT) accounts for approximately 1%-3% of malignant ovarian tumors, with an annual incidence rate of 3.7 per 1,000,000 worldwide.[3] Unlike epithelial ovarian cancer, which is more common in adult women, germ cell tumors primarily affect younger individuals, often occurring in the first three decades of life.[4] Germ cell tumors are often International Federation of Gynecology and Obstetrics (FIGO) stage I and may potentially spread to lymph nodes rather than to the peritoneum. The subtypes include dysgerminomas (equivalent to the male seminoma, 1%-2% of all ovarian cancers), immature teratomas (0.9%), yolk sac tumors (1%), and mixed germ cell tumors (0.9%).[1,5] In addition, there are very rare embryonal carcinomas, choriocarcinomas, and malignant struma ovarii tumors. Their histologic diversity and unique characteristics present distinct challenges in diagnosis and treatment. The most frequent genetic alteration across all MOGCT subtypes, except for pure immature teratomas, is a gain in chromosome 12p.[6] Additional genetic changes include frequent KIT and KRAS mutations. KIT mutations are commonly observed in ovarian dysgerminomas and KRAS mutations, along with PIK3CA and AKT1 amplifications, and are frequently found in yolk sac tumors.[6] Early diagnosis and prompt, effective treatment are paramount in managing OGCTs. Understanding the latest trends and advancements in diagnosing and treating these tumors is crucial for improving patient outcomes.

Management of germ cell tumors has been based on data from testicular germ cell tumor trials.[1,7] Surgery involves unilateral adnexectomy and peritoneal staging, including biopsies and cytology. The staging procedure includes

PRACTICAL APPLICATIONS

- Staging and treatment strategy for ovarian germ cell tumors.
- Staging and treatment strategy for clear cell ovarian cancers.
- Staging and treatment strategy for high-risk, refractory gestational trophoblastic disease.

infracolic omentectomy, biopsies of the peritoneum (diaphragmatic, paracolic gutters, and pelvic), and peritoneal washing in cases of macroscopic stage I disease.[6] Survival impact of pelvic/aortic lymphadenectomy is controversial across series and should not be proposed systematically.[1,8] According to European Society for Medical Oncology (ESMO) guidelines, in early-stage disease that does not require adjuvant chemotherapy, lymph node dissection is recommended only for suspicious lymph nodes detected intraoperatively or lymphadenopathies identified on preoperative imaging.[6,7] Data obtained from the National Cancer Institute registry from 1988 to 2006 have also been analyzed. In all, 1,083 patients with OGCTs who had undergone surgical treatment and deemed at the time of the surgery to have disease clinically confined to the ovary were included.[8] Five hundred and ninety (54.48%) had no lymphadenectomy (LND 1), and 493 (45.52%) had lymphadenectomy. Of the 493 patients who had lymphadenectomy, 441 (89.5%) were FIGO surgical stage I and 52 (10.5%) were upstaged to FIGO stage IIIC because of nodal metastasis. The 5-year survival was 96.9% for the no-lymphadenectomy group, and 97.7% for the stage I lymphadenectomy group, and 93.4% for the stage III lymphadenectomy group. On multivariate analysis, lymphadenectomy was not an independent predictor of survival when controlling for age, histology, and race. Moreover, the presence of lymph node metastasis had no significant effect on survival. It appeared that neither lymphadenectomy nor lymph node metastasis was an independent predictor of survival in patients with OGCT confined to the ovary. This probably reflects the highly chemosensitive nature of these tumors.

Fertility-sparing surgery, sparing one ovary and uterus, does not adversely affect overall survival (OS) and may be proposed in young patients with localized disease.[1] Adjuvant chemotherapy in the form of bleomycin-etoposide-platinum was recommended to all patients, except for stage IA.[1,7] Park evaluated the oncologic and reproductive outcomes after fertility-sparing surgery in patients with early and advanced MOGCTs.[9] The study included 171 patients who underwent fertility-sparing surgery. Twenty-five patients (14.6%) had recurrent disease, and five patients (2.9%) died of disease during the median follow-up time of 86 months.[9] The 5-year OS was 97%. The 5-year OS was 99% for stage I and 91% for stage II to IV. In multivariate analysis, yolk sac tumor, incomplete staging surgery, and residual tumor were independent risk factors for reduced disease-free survival (DFS), and yolk sac tumor and residual tumor were independent risk factors for reduced OS. Reproductive and obstetric outcomes were evaluable in 124 patients, and six patients (4.8%) had premature menopause. Twenty patients tried to conceive, 15 patients (75%) succeeded in achieving 21 pregnancies, and 13 of the patients (65%) gave birth to 20 healthy babies. Park concluded that fertility-sparing surgery has excellent survival outcomes in young women with MOGCTs, even in advanced stages. Yolk sac tumor, incomplete surgical staging, and residual tumor were independent prognostic factors. Retrospective data have supported active surveillance for patients with stages IB to C.[7]

The MaGIC (Malignant Germ Cell International consortium) conducted a detailed analysis of germ cell tumors in children and adolescents and concluded that onset at or after 11 years is a risk factor for poor prognosis.[3,10] In terms of pathology, dysgerminoma has the best prognosis, and mixed germ cell tumors have a poorer prognosis. Immature teratomas with malignant transformation have an extremely poor prognosis. The prognostic stratification of MOGCT is primarily adapted from the IGCCCG (International Germ Cell Cancer Collaborative Group) classification for testicular germ cell tumors as modified IGCCCG.[3,11] The modified IGCCCG classification triages patients to dysgerminoma and nondysgerminoma and categorizes female genital germ cell tumors into three risk groups. Data from the Memorial Sloan Kettering Cancer Center showed that the 3-year progression-free survival (PFS) rates for groups at low, intermediate, and high risk were 88%, 78%, and 31%, respectively; the 3-year OS rates were 91%, 80%, and 50%, respectively.[3,12]

According to the ESMO guidelines, stage IA dysgerminomas and properly staged stage IA grade 1 immature teratomas should be treated with surgery alone, followed by postoperative surveillance.[6,7] Stage IB and IC dysgerminomas can be closely monitored. The treatment of immature teratomas in stage IA grade 2 to 3 and stage IB to IC remains controversial.[6,7] A large series of stage I pure immature teratomas showed that surveillance did not decrease survival compared with adjuvant chemotherapy even in patients at higher risk of recurrence properly staged and with negative postoperative tumor markers (IC grade 2 to 3 immature teratomas).[6,13] There was no significant increase in the risk of malignant (grade 2 to 3 immature teratoma) relapse (9 of 81 *v* 2 of 27; $P = .72$) or in DFS or OS in the surveillance *v* chemotherapy groups. A 2021 prospective observational study by Mangili et al reported a low relapse rate (3.2%) in patients with well-staged stage IA to IC dysgerminomas, stage IA to IC grade 1 to 3 immature teratomas, and stage IA mixed malignant germ cell tumors who underwent surveillance alone underlining the importance of surgical restaging too.[6,14]

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Yolk sac tumors have been shown to be a poor prognostic indicator. All yolk sac tumors and mixed histologies with yolk sac elements should be treated with adjuvant chemotherapy after surgery.[6] Only properly staged stage IA to IB yolk sac tumor patients with negative postoperative tumor markers may be considered for close surveillance, but robust data on this histology are lacking.

For all other advanced stages and MOGCT histotypes, such as embryonal carcinoma, the standard treatment is 5-day adjuvant bleomycin, etoposide, and cisplatin chemotherapy. The 2020 European Society of Gynaecological Oncology-European Society of Paediatric Oncology guidelines recommend that the standard chemotherapy regimen for stage III to IV disease in adolescents and young adults follows adult protocols with bleomycin, etoposide, and platinum for three to four cycles. For pediatric patients, carboplatin may be substituted for cisplatin.[6,15] An alternative regimen used for high-risk patients is cisplatin, vincristine, methotrexate, bleomycin, actinomycin D (ACT-D), cyclophosphamide, and etoposide (POMB/ACE). Because of the high pulmonary toxicity of bleomycin, it is generally omitted after three cycles, reaching a maximum total cumulative dose of 270 IU. Bleomycin should also be avoided in patients with pre-existing pulmonary conditions and in those older than 40 years because of a drug-related mortality rate of 3%.[1,5] There are studies that suggest that early administration of adjuvant chemotherapy for patients with advanced-stage MOGCTs is associated with an OS benefit.[16] A National Cancer Database study evaluated patients diagnosed between 2004 and 2015 with stage III to IV MOGCTs who underwent primary surgery and received adjuvant chemotherapy. Survival was compared between patients who received adjuvant chemotherapy 1-4 weeks (early administration group) and 4.1-12 weeks (delayed administration group). Delay in adjuvant chemotherapy administration was associated with worse OS; 5-year OS rates were 87.5% for the early group and 77.6% for the delayed administration group. After controlling for confounders, delay in adjuvant chemotherapy administration was associated with worse OS (hazard ratio = 1.99).

Without adjuvant chemotherapy, relapse rates are generally 15%-25% within 1 or 2 years from surgery and, if detected early, salvage chemotherapy in pediatric and adolescent cases may offer similar survival to that of patients who received initial chemotherapy. In one study, girls age 0-16 years with stage I MOGCT were enrolled onto Children's Oncology Group study AGCT0132 between November 2003 and July 2011.[17] AGCT0132 was a study with the goal of assessing whether a surveillance strategy with strictly defined surgical guidelines could be extended to stage I MOGCTs in pediatric and adolescent girls. Twenty-five girls (median age, 12 years) with stage I MOGCT were enrolled onto AGCT0132. After a median follow-up of 42 months, 12 patients had evidence of persistent or recurrent disease (4-year event free survival, 52% [95% CI, 31% to 69%]). The median time to recurrence was 2 months. All patients had elevated AFP at recurrence; six had localized disease, two had metastatic disease, and four had tumor marker elevation only. Eleven of 12 patients experiencing relapse received successful salvage chemotherapy (4-year OS, 96% [95% CI, 74% to 99%]).[17] This finding is lacking in adult's cases.[1,17] Patients with advanced disease should also be treated with surgery, based on retrospective data, and chemotherapy in the form of four cycles of bleomycin-etoposide-platinum.[7]

There are no standard recommendations for patients with refractory or recurrent disease. Patients with persistent disease or relapse after primary chemotherapy are considered to have a less favorable prognosis.[3] Germ cell tumors are highly chemosensitive even at recurrence. Conventional-dose chemotherapy or high-dose chemotherapy is an acceptable option for first-salvage chemotherapy in testicular germ cell tumors.[3,18] For patients who have surgically resectable residual tumors, cytoreductive surgery should be performed with the goal of achieving complete resection. Paclitaxel/ifosfamide/cisplatin is recommended as a second-line treatment in patients with refractory or recurrent disease.[3,19] Other conventional-dose chemotherapy regimens include etoposide/ifosfamide/cisplatin and vinblastine/ifosfamide/cisplatin. High-dose chemotherapy with stem cell rescue may offer a benefit to patients with platinum sensitive recurrence.[20] They conducted a retrospective review of 184 consecutive patients with metastatic testicular cancer that had progressed after they received cisplatin-containing combination chemotherapy. The patients then received high-dose chemotherapy. In 110 patients, cytoreduction with one or two courses of vinblastine plus ifosfamide plus cisplatin preceded the high-dose chemotherapy. Of the 184 patients, 116 had complete remission of disease without relapsing during a median follow-up of 48 months (range, 14-118). Of the 135 patients who received the treatment as second-line therapy, 94 (70%) were disease-free during follow-up; 22 of 49 (45%) patients who received treatment as third-line or later therapy were disease-free. Of 40 patients with cancer that was refractory to standard-dose platinum, 18 (45%) were disease-free. Among the 184 patients, there were three drug-related deaths during therapy and acute leukemia developed in three additional patients after therapy. This study provided evidence that testicular tumors are potentially curable by means of high-dose chemotherapy plus hematopoietic stem-cell rescue, even when this regimen is used as third-line or later therapy or in patients with platinum-refractory disease.

GESTATION TROPHOBLASTIC DISEASE

Gestation trophoblastic disease (GTD) is a group of conditions that encompass both benign and malignant entities. Gestational trophoblastic neoplasia (GTN) is used to refer to malignant diseases and includes postmolar GTN/invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).

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TABLE 1. Diagnosis of gestational trophoblastic neoplasia

Plateau of hCG of 4 values + or −10% for 4 values over a 3-week duration (days 1, 7, 14, 21)
Rise in hCG of ≥10% for ≥3 values over at least 2 weeks (days 1, 7, 14)
Histologic confirmation of choriocarcinoma and/or radiographic evidence of metastases

Abbreviation: hCG, human chorionic gonadotropin.

These malignancies are rare but highly curable, even with widespread metastases, if women are managed appropriately.[21-23] Globally, treatment for GTD often occurs at or in consultation with a trophoblastic disease reference center.[24]

Unlike any other malignancy that requires a tissue diagnosis, GTN is most commonly diagnosed by a rising or plateau in human chorionic gonadotropin (hCG) during surveillance after a molar pregnancy. The rise or plateau in hCG that qualifies for GTN is strictly defined. GTN can also be diagnosed when there is histopathology confirmation of choriocarcinoma or radiographic evidence of metastases (Table 1).[21-23] Once GTN has been diagnosed, patients must undergo appropriate staging. Current FIGO staging consists of two components: anatomic staging and calculation of the WHO risk score[25] (Table 2). This risk score takes into account various clinical factors (age, type of antecedent pregnancy, time from antecedent pregnancy, hCG level, tumor size, sites of metastases, and number of metastases) and is a reflection of how likely disease will respond to single-agent chemotherapy and is a surrogate for prognosis.[22] Since PSTT and ETT originate from intermediate trophoblast rather than syncytiotrophoblast or cytotrophoblast like invasive mole and choriocarcinoma, they produce less hCG and have a different natural history. As such, there is a separate staging system that does not rely on the WHO risk score. Instead, staging for PSTT and ETT is anatomic and incorporates time from antecedent pregnancy of ≥48 months, a significant risk factor for these malignancies.[26-28] FIGO staging is being updated in 2026 and will incorporate lymph nodes that are ≥1 cm in short axis (Presentation at FIGO 2025 World Congress).

TABLE 2. International Federation of Gynecology and Obstetrics Staging and WHO Risk Score 2000

I	Disease confined to the uterus
II	Disease extends outside the uterus, but limited to the genital structures (adnexa, vagina, broad ligament)
III	Disease extends to the lungs, with or without known genital tract involvement
IV	All other metastatic sites

	Score			
Risk Factor	0	1	2	4
Age, years	<40	≥40	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval, months	4	4-6	7-12	>12
Pretreatment hCG, mIU/mL	<1,000	1,000 to <10,000	10,000-100,000	>100,000
Largest tumor (including uterus), cm	—	3-4	>5	—
Site of metastases	Lungs	Spleen, kidney	GI tract	Liver, brain
No. of metastases	0	1-4	5-8	>8
Prior failed chemotherapy	—	—	Single agent	2 or more

NOTE. Report as stage: risk score.
Abbreviation: hCG, human chorionic gonadotropin.

Using the calculated risk score, patients with GTN are assigned to a risk group which influences the choice of treatment. As GTN is uniquely sensitive to chemotherapy, this is typically the modality of treatment. This allows for excellent cure rates often with fertility still intact. The exception to this is PSTT and ETT which, although not resistant to chemotherapy, have lower response rates and are preferentially managed with surgery and chemotherapy.[26-28] Patients can have low-risk disease (score, 0-6), high-risk disease (score, 7-12), or ultrahigh-risk disease (score, ≥13).[22,23] Those with low-risk disease are typically treated with single-agent chemotherapy (methotrexate or ACT-D),[29] those with high-risk disease receive multiagent chemotherapy,[30-32] and those with ultra high-risk get induction chemotherapy followed by multiagent regimens.[33] The focus of this study will be on treatment for high-risk, ultrahigh-risk, and recurrent disease and chemotherapy for resistant low-risk disease or those with risk scores of 5 and 6.

Chemotherapy for low-risk disease typically consists of treatment with methotrexate (MTX) or ACT-D. There are many different doses and infusion schedules, but the most active are multiday MTX (8-day or 5-day) and pulse ACT-D administered every 2 weeks.[23,29,34] Complete response rates to these agents across a large number of clinical trials are estimated to be approximately 75%-90% with neither agent considered superior to the other; however, a 2016 Cochrane Review suggested that ACT-D is superior to MTX.[29] Despite this, given the ease of delivery and minimal toxicity, MTX tends to be the first-line therapy of choice internationally.[22] If patients develop resistance to one of the agents, usually complete remission can be achieved with the other single agent.[22,23] Some centers use the hCG level at the time of resistance to determine whether to use single-agent or multiagent regimens.[35] Alternatively, the response rate to avelumab in patients with MTX resistance was noted to be 50%-60%.[36]

Although low-risk GTN is treated with single-agent chemotherapy, patients with risk scores of 5 or 6 are noted to have particularly low response rates of approximately ≤30%.[37]

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In a multicenter retrospective study evaluating 430 patients with scores of 5 or 6, response rates to either first-line or second-line single-agent chemotherapy was noted to be 60%. Given this high response rate, first-line multiagent chemotherapy should be reserved for patients with FIGO 5/6 only for the following: (1) those with no metastatic disease and no choriocarcinoma, who have pretreatment hCG concentrations of 410,000 IU/L or higher, (2) those with metastatic disease or histopathologic evidence of choriocarcinoma and pretreatment hCG concentrations of 150,000 IU/L or higher, and (3) those with metastatic disease and choriocarcinoma.[38]

The mainstay of treatment for patients with high-risk disease is a multiagent chemotherapy regimen consisting of etoposide, methotrexate, ACT-D, cyclophosphamide, and vincristine (EMC-CO; 10-12; Table 2). This regimen has produced complete responses/cure rates of approximately 75%-85%. For women with brain metastases, it is important to increase the methotrexate dose to 1 g/m^2 on day 1 of EMC-CO regimen over 24 hours. In addition, adding intrathecal methotrexate (12.5 mg) once on day 8 has produced the best survival rates for those with brain metastasis.[39,40] Another multiagent chemotherapy regimen, commonly used in Asia, is FAEV (Floxuridine, ACT-D, etoposide, vincristine) which has been shown to have a complete remission rate of nearly 70%.[41] In a randomized trial comparing FAEV with EMA-CO, Ji et al[42] reported equivalent complete response and relapse rates and similar survival with no difference in toxicity.

Approximately 30%-40% of patients will have resistance to EMA-CO or relapse after first-line therapy.[30] There is no standard second-line therapy, but two platinum-containing regimens are often used. EMA-EP (etoposide, methotrexate, and ACT-D, and cisplatin)[43,44] and TE/TP (taxol/etoposide, taxol/cisplatin)[45] have not been compared head-to-head but have similar response rates and outcomes. Given the addition of paclitaxel and cisplatin, to the every 2-week schedule, and improved toxicity profile, TE/TP is often the preferred regimen at many reference centers, particularly for those who did not respond to EMA-CO or have persistent toxicities.

Despite the excellent response to EMA-CO in the series by Bower et al, there was an early death rate of approximately 7%.[31] Analysis noted that patients who presented with high disease volume including (multiple metastasis including lungs, liver, the brain; hCG >1 million) were at highest risk of early death. These early deaths were thought to be due to hemorrhage. In a follow-up series by Alfrangis, patients who presented with these features were treated with induction etoposide (100 mg/m^2) and cisplatin (25 mg/m^2; EP, days 1 and 2 every 7 days) for 2-3 weeks before initiation of EMA-CO.[33] Using this approach the early death rate decreased to <1% and the improved OS to 88%. This group of patients is now captured in the new ultrahigh-risk group (WHO risk score ≥13) where the standard treatment should be with induction EP followed by EMA-CO or EMA-EP.

TABLE 3. Multiagent Chemotherapy Regimens

EMA-CO		
Day 1	Etoposide	100 mg/m^2 IV bolus once
	Actinomycin D	500 mcg IV push once
	Methotrexate IV push	100 mg/m^2 once
		200 mg/m^2 IV once 12 hours
Day 2	Actinomycin D	500 mcg IV push once
	Etoposide	100 mg/m^2 IV bolus once
	Leucovorin	15 mg PO once every 12 hours
Day 8	Vincristine	1.0 mg/m^2 once
	Cyclophosphamide	600 mg/m^2 once
EMA-EP		
Day 1	Etoposide	100 mg/m^2 IV bolus once
	Actinomycin D	500 mcg IV push once
	Methotrexate	100 mg/m^2 IV push once
		200 mg/m^2 IV once over 12 hours
Day 2	Actinomycin D	500 mcg IV push once
	Etoposide	100 mg/m^2 IV bolus once
	Leucovorin	15 mg PO once q 12 hours
Day 8	Etoposide	150 mg/m^2 IV bolus once
	Cisplatin	75 mg/m^2 IV over 1-3 hours once
TP/TE		
Day 1	Paclitaxel	135 mg/m^2 IV once
	Cisplatin	60 mg/m^2 IV once
	Day 15 paclitaxel	135 mg/m^2 IV once
	Etoposide	150 mg/m^2 IV once
FAEV		
Day 1	Vincristine	2 mg IV once
Day 1-5	Etoposide	100 mg/m^2 IV drip once
	Actinomycin D	200 μg/m^2 IV drip once
	Floxuridine	800 mg/m^2 IV drip once

Despite excellent response rates to chemotherapy, there are some who develop resistance or experience relapse and need salvage therapy (Table 3). After several failed lines of therapy, high-dose chemotherapy with autologous hematopoietic stem-cell support has been used. In the largest series of 32 patients, 13 (41%) achieved complete remission with responders having an hCG ≤12 IU/L.[46] Surgery also plays an important role in patients with chemotherapy-resistant disease. Hysterectomy or resection of oligometastatic resistant disease can help achieve cure when chemotherapy has failed (Table 4).[47,48]

Over the past 10 years, immunotherapy, in particular, check point inhibitors, has emerged as a novel treatment of high-risk or relapse GTN that is capable of inducing durable remissions.[49] Given the immunosuppressive state of normal pregnancy, it is not surprising that there are near universal elevated expression of PDL-1 in normal placenta, molar pregnancy, choriocarcinoma, and PSTT/ETT.[50-52] By blocking the PD-1/PD-L1 axis, immune checkpoint inhibitors effectively reverse trophoblastic immune evasion, restore cytotoxic T-cell activity, and re-establish antitumor

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TABLE 4. Salvage Chemotherapy Options

EMA-EP (also used for PSTT/ETT)
BEP
TE/TP
Carboplatin with or without gemcitabine
ICE
5-FU (capecitabine, FAEV)
Liposomal doxorubicin
High-dose chemotherapy with stem-cell support
Immunotherapy—pembrolizumab, avelumab

Abbreviations: 5-FU, fluorouracil; BEP, bleomycin, etoposide, and cisplatin; ETT, epithelioid trophoblastic tumor; ICE, ifosfamide, carbo, and etoposide; PSTT, placental site trophoblastic tumor; TE/TP, taxol/etoposide, taxol/cisplatin.

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immune surveillance. Originally used in heavily pretreated patients,[53] the use of pembrolizumab has expanded to a wide range of treatment scenarios including consolidation after EMA-EP for patients with high-risk PSTT/ETT (advance stage or diagnosis ≥48 months). Across all scenarios, response rates have ranged from 60% to 80%.[53-56] In a recent meta-analysis including 15 studies, pembrolizumab induced complete sustained remission in 71.5% of cases (95% CI, 53.2 to 84.7, $P = .9$) and had similar performance regardless of age (<40 years *v* ≥40 years), GTN histopathology (PSTT, ETT, noninvasive mole/others versus invasive mole/choriocarcinoma), time to initiating immunotherapy (<4 years *v* ≥4 years), and use of pembrolizumab as single agent versus with chemotherapy.[55] Although most of the data are generated from single-agent pembrolizumab, there is emerging evidence that combining immunotherapy with chemotherapy may enhance activity, increasing tumor immunogenicity and overcoming resistance. Retrospective data indicate higher response rates with chemoimmunotherapy combinations compared with immunotherapy alone, without substantial increases in toxicity.[56] Although most patients respond to immunotherapy, there is a proportion in whom it fails. Lack of tumor-infiltrating lymphocytes, absent expression of nonclassical MHC class I protein HLA-G, and natural killer cells lacking high-affinity FcγR3Apolymorphism are markers of poor response to immunotherapy.[57,58] Impact on future fertility after the use of immunotherapy is an issue that has been raised. Data from the Frech Trophoblastic Disease Group presented at the XXXI World ISSTD Congress in 2022 showed that among the 42 women treated with avelumab, 13 attempted to achieve pregnancy, of whom seven had term delivery, three miscarried, and three were trying to conceive. There is one reported pregnancy after the use of pembrolizumab.[59]

Despite the success of immunotherapy, some patients remain refractory to treatment. As a result, novel therapeutic regimens are needed. Recent advances in understanding the molecular etiology of GTN, through next-generation sequencing on circulating cell-free tumor DNA, has highlighted potential therapeutic targets such as c-MYC, EGFR, mTOR/PI3K.AKT/PTEN pathway, and BLC2. Some of these targets have existing agents, whereas others need further development and all need to be investigated.[60,61]

Although short-term toxicities associated with multiagent chemotherapy are usually management with supportive care, there are data that there is an elevated risk of secondary malignancies that appear to be associated with exposure to etoposide in a dose, time, and age-dependent manner.[62] Importantly, most women with GTN are cured and can expect normal reproductive outcomes in the future.[63]

OVARIAN CLEAR CELL CARCINOMA

Ovarian clear cell carcinoma (OCCC) is a biologically and clinically distinct subtype of epithelial ovarian cancer. Although relatively uncommon in Western populations, OCCC accounts for approximately 20%-25% of ovarian cancers in Japan and other parts of East Asia, making it a major contributor to ovarian cancer morbidity in these regions. Clinically, OCCC is characterized by intrinsic resistance to platinum-based chemotherapy, younger age at onset, and a strong association with endometriosis, clearly distinguishing it from high-grade serous carcinoma (HGSC).[64]

OCCC exhibits a characteristic bimodal clinical course. Patients diagnosed with early-stage disease, particularly those with stage I tumors that are completely resected, may experience relatively favorable outcomes. By contrast, advanced-stage and recurrent OCCC is associated with a markedly poor prognosis, largely driven by limited responsiveness to conventional cytotoxic chemotherapy and the absence of established effective treatments beyond first-line therapy. Standard first-line treatment with carboplatin and paclitaxel yields objective response rates of only 20%-30% in OCCC, substantially lower than those observed in HGSC.[65] Alternative cytotoxic strategies have been explored, including the JGOG3017 randomized phase III trial comparing irinotecan plus cisplatin with paclitaxel plus carboplatin in OCCC. This study failed to demonstrate the superiority of the irinotecan-based regimen in terms of PFS or OS, confirming the limited efficacy of cytotoxic intensification in this histologic subtype.[66] These findings underscore a central clinical challenge in OCCC: how to improve outcomes once the disease becomes systemically resistant.

At the molecular level, OCCC is characterized by frequent loss-of-function mutations in *ARID1A* and activation of the *PI3K-AKT* signaling pathway, most commonly through co-occurring PIK3CA mutations, distinguishing it molecularly from homologous recombination deficiency (HRD)–driven ovarian cancer subtypes such as HGSC.[67] This constellation of alterations reflects a tumor biology driven more by

epigenetic dysregulation and oncogenic signaling than by genomic instability. Consistent with this biology, comprehensive genomic profiling studies have demonstrated that most OCCC tumors lack defects in homologous recombination repair, resulting in a predominantly HRD–negative phenotype.[68] These molecular characteristics are thought to contribute to the typically immune-cold to immune-intermediate tumor microenvironment observed in OCCC, characterized by limited baseline immune infiltration and relative resistance to immune checkpoint blockade.[67]

Given the high prevalence of *PI3K* pathway activation, pathway-targeted therapy has long been considered an attractive strategy in OCCC. However, early clinical attempts to target this pathway without molecular selection have yielded disappointing results. A notable example is the phase II trial led by Farley et al,[69] in which the mTOR inhibitor temsirolimus was combined with chemotherapy in patients with recurrent OCCC. Despite the strong preclinical rationale, this strategy failed to improve PFS or OS.

These negative results are best interpreted as reflecting downstream pathway inhibition applied to a molecularly unselected patient population rather than pathway irrelevance. mTOR inhibitors target a distal node of the PI3K-AKT-mTOR axis and do not directly suppress oncogenic PI3K signaling driven by *PIK3CA* mutations. Moreover, inhibition at the level of mTORC1 may release negative feedback mechanisms, resulting in compensatory reactivation of upstream PI3K-AKT signaling.[70]

Building on these lessons, selective targeting of upstream oncogenic drivers represents a more rational therapeutic approach in OCCC. Among such strategies, inhibition of *PI3Kα* has emerged as a promising precision oncology paradigm, given the high frequency of activating *PIK3CA* mutations in this histology.

CYH33 (risovalisib) is a next-generation, selective PI3Kα inhibitor designed to directly suppress oncogenic PI3K signaling driven by *PIK3CA* mutations while minimizing off-target inhibition of other PI3K isoforms. By targeting the pathway at its functional entry point, PI3Kα inhibition offers the potential for more complete and durable pathway suppression than downstream mTOR inhibition.

Early-phase clinical studies of CYH33 have demonstrated manageable safety and preliminary antitumor activity in patients with advanced solid tumors harboring *PIK3CA* mutations, providing proof of mechanism for selective PI3Kα inhibition.[71] A global phase II study (CYH33-G201) enrolling patients with recurrent or persistent OCCC harboring *PIK3CA* hotspot mutations demonstrated clinically meaningful antitumor activity.[72] This study provides the primary clinical evidence supporting the Japanese new drug application for risovalisib in advanced or recurrent *PIK3CA*-mutant OCCC after prior chemotherapy, submitted in 2025 with orphan drug designation.

The monotherapy experience with immune checkpoint blockade in OCCC has been disappointing. The randomized MOCCA trial demonstrated no improvement in PFS with durvalumab monotherapy (ORR, 9.7%).[73]

The PEACOCC phase II study of pembrolizumab monotherapy demonstrated modest activity with occasional durable responses.[74] The low response rates observed with immune checkpoint inhibitor monotherapy in OCCC have prompted evaluation of dual immune checkpoint blockade strategies. The BrUOG 354 randomized phase II trial demonstrated that nivolumab plus ipilimumab achieved an ORR of 33% in recurrent OCCC, including four complete responses, with a median PFS of 5.6 months.[75] The DART/SWOG S1609 trial reported an ORR of 36.8% and a median PFS of 3.7 months with nivolumab plus ipilimumab.[76]

The MoST-CIRCUIT phase II study reported an ORR of 55% (95% CI, 35 to 73) in patients with OCCC treated with nivolumab plus ipilimumab.[77] The NRG-GY016 trial evaluated pembrolizumab plus epacadostat and reported an ORR of 21% with a median PFS of 4.8 months.[78] Notably, dual PD-1 and CTLA-4 blockade has been associated with substantial immune-related toxicity. In MoST-CIRCUIT, 35% of patients experienced grade 3-4 immune-related adverse events and one grade 5 myocarditis occurred.[77]

Bevacizumab improved PFS in unselected ovarian cancer populations.[79,80] The concept of vascular normalization suggests that angiogenesis inhibition may alleviate hypoxia and facilitate immune infiltration.[81,82] In this context, combining antiangiogenic therapy with immune checkpoint blockade represents a biologically rational strategy to overcome immune exclusion and achieve meaningful antitumor activity. The LARA phase II study demonstrated a confirmed ORR of 44% and a median PFS of 23.4 weeks with pembrolizumab plus lenvatinib.[83] The INOVA phase II study of sintilimab plus bevacizumab similarly demonstrated clinically meaningful activity in relapsed OCCC.[84] The success observed in LARA and INOVA provides clinical validation that angiogenesis inhibition can enable immunotherapy by normalizing tumor vasculature, alleviating hypoxia, and enhancing immune cell infiltration.[81,82] The DOVE randomized phase II study is an ongoing trial evaluating dostarlimab with or without bevacizumab compared with chemotherapy.[85] OCCC remains a challenging disease characterized by intrinsic chemoresistance and distinct molecular features. Early attempts to intensify cytotoxic therapy or inhibit downstream mTOR signaling were insufficient to meaningfully alter outcomes. A more biologically aligned strategy has emerged, centered on precision targeting of PIK3CA-driven signaling and rational immune-based combinations. Selective PI3Kα inhibition represents a histology-specific precision approach in molecularly defined patients. Immune checkpoint inhibitor-antiangiogenic combinations have provided clinical validation of vascular normalization as a means to enhance immunotherapy. Dual immune checkpoint blockade demonstrates higher response rates but

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at the cost of increased immune-related toxicity. Continued integration of molecular selection and microenvironmental modulation will likely define the next phase of therapeutic development in OCCC.

The current treatment for these rare ovarian tumors is similar to that for high-grade epithelial ovarian cancer but is advancing quickly to incorporate targeted therapy. Gestational trophoblastic tumors are usually curable, even when widely metastatic disease is present. Despite excellent response rates to chemotherapy, there are some who develop resistance or experience relapse and need salvage therapy. These patients should be evaluated and treated by experienced trophoblastic disease centers.

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Less Is More, But Me-Too Should Not Be the Strategy for Lung Cancer Treatment in 2026

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OVERVIEW

Although immune checkpoint inhibitors (ICIs) and targeted therapies (TTs) have transformed the treatment of non–small cell lung cancer (NSCLC) across disease stages, real-world access remains highly unequal worldwide. Persistent cost barriers, fragmented reimbursement frameworks, and heterogeneous regulatory pathways limit equitable availability. The rapid proliferation of me-too agents has been proposed to counter monopolies; yet, this expansion has not consistently improved affordability. Heterogeneous evidentiary requirements—along with differences in clinical end points, comparator selection, crossover policies, and treatment duration—fragment therapeutic markets and complicate assessment of incremental clinical benefit. Divergent regulatory decisions, particularly between the US Food and Drug Administration and European Medicines Agency, underscore how trial design and geographic representation influence drug availability, especially when approvals rely on single-country data sets. These challenges are amplified in perioperative treatment strategies and rare oncogene-defined subgroups, where feasibility constraints and limited clinical equipoise hinder large randomized trials. As a result, an increasingly crowded therapeutic landscape makes cross-trial comparisons difficult and allows disparities in patient access to persist despite multiple approved therapies. Dose selection has historically followed maximum tolerated dose principles, even when preclinical and pharmacologic data suggest activity plateaus at lower exposure of ICI and TT. Dose and schedule optimization—through reduced dosing, extended intervals, or other deintensified strategies—therefore represents a rational and ethically grounded approach with a meaningful clinical impact. Such strategies may preserve efficacy while improving tolerability, reducing treatment burden, and mitigating financial toxicity, particularly in resource-limited settings. Aligning regulatory frameworks with dose optimization could promote more scalable, equitable, and sustainable NSCLC innovation.

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INTRODUCTION

Over the past decade, substantial improvements in 5-year overall survival (OS) have been achieved among patients with non–small cell lung cancer (NSCLC)[1] and the introduction of targeted therapies (TTs) and immunotherapies has markedly shifted treatment paradigms and improved clinical outcomes.[2] The implementation of these strategies in earlier disease stages is expected to further enhance survival. Although these breakthroughs have improved outcomes for some, the reality is that many of these treatments remain inaccessible to most patients with lung cancer globally. According to the International Agency for Research on Cancer, more than 60% of new lung cancer cases occur in low- and middle-income countries (LMICs),[3] and facilitating access to effective therapies is crucial to improve treatment outcomes globally.

Early phase drug development in NSCLC has traditionally followed the principles of cytotoxic therapy, where doses are selected based on the maximum tolerated dose (MTD) under the assumption of a direct correlation between drug exposure and efficacy. However, this correlation is not consistently observed with newer agents such as immune checkpoint inhibitors (ICIs) and TT.[4,5] Even for novel therapies with a chemotherapy component such as antibody-drug conjugates, higher doses do not always translate to better objective response rates (ORRs).[6] Consequently, patients may be exposed to unnecessarily high treatment doses that worsen toxicity without improving efficacy, further contributing to increased costs and widening disparities in health care access. While various me-too agents encompassing ICI and TT have been developed to expand treatment options and reduce a market monopoly, a key challenge is defining what metrics should be used to evaluate these agents for broad regulatory approval. This is especially relevant for me-too therapies developed in single-country studies, which do not permit robust assessment of treatment effects across diverse geographic regions and patient populations and may hence limit regulatory approval, even if

PRACTICAL APPLICATIONS

- Clinicians and policymakers should critically evaluate differences in trial design, end points, and regulatory decisions when interpreting approvals of immune checkpoint inhibitors and targeted therapies in non–small cell lung cancer as these factors directly influence comparative value, access, and reimbursement in routine practice.
- Incorporating dose and schedule optimization strategies—such as reduced dosing or extended treatment intervals—into clinical care may preserve efficacy while improving tolerability, decreasing treatment burden, and mitigating financial toxicity, particularly in resource-limited settings.
- Regulatory agencies, payers, and cooperative groups should prioritize harmonized evidentiary standards and prospective dose-optimization studies to support scalable, cost-conscious innovation and promote more equitable global access to effective non–small cell lung cancer therapies.

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priced more competitively. This chapter reviews the emergence of me-too ICI and TT in NSCLC, with a focus on agents that share similar mechanisms of action and the metrics used to evaluate their clinical value. We also assess how the growing number of mechanistically similar treatments influences patient access, contributes to financial toxicity, and shapes therapeutic decision making. Importantly, we discuss the nonuniform criteria adopted by various health authorities regarding the approval of novel therapies across disease stages and the need for phase III trials to obtain regulatory approval despite concerns regarding the ethical justification and true equipoise of these study designs, especially for TT in specific oncogene subsets. In addition, the chapter discusses fixed-dose versus exposure-based dosing strategies and their relevance to global treatment practices. Together, these sections provide a critical analysis of current challenges and considerations in the development, evaluation, and implementation of novel systemic therapies for lung cancer (Fig 1).

ME-TOO ICI COMPOUNDS

Regulatory decisions governing the approval of ICI for NSCLC vary substantially across major agencies such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Differences in evidentiary requirements, trial end points, and approval pathways have resulted in nonuniform criteria for authorizing these therapies worldwide. Consequently, many patients have difficulty in accessing life-prolonging treatments in a timely manner, partly because of affordability concerns.[7] Furthermore, the lack of harmonization across regulatory bodies contributes to fragmented markets, which may conversely increase treatment costs despite the availability of multiple me-too ICIs that should theoretically encourage competitive pricing.

Since 2016, numerous ICI-based regimens have received first-line approval from the FDA and EMA for patients with advanced NSCLC without druggable genomic alterations (Fig 2). Despite this crowded scenario, it has not alleviated the substantial annual health care expenditure related to these agents,[8] nor has it reduced global inequalities in cancer drug access.[9] The early-stage NSCLC treatment landscape has also followed suit, where several me-too ICIs have been approved by the FDA and EMA as neoadjuvant or perioperative strategies, despite reporting similar efficacy parameters in terms of pathologic complete response (pCR) and event-free survival (EFS) compared with chemotherapy alone (Fig 3).[10-17]

In China, four additional me-too ICIs have been developed: three anti–PD-1 antibodies (camrelizumab, sintilimab, and tislelizumab) and one anti–PD-L1 antibody (sugemalimab).[18] Although the availability of these compounds could theoretically help with price negotiations to improve affordability,[19] none of these me-too ICIs have been granted FDA approval. In the case of sintilimab, FDA denied its approval citing concerns regarding the single-country trial design, the choice of chemotherapy alone as the comparator arm that did not reflect the standard of care (SoC) in the United States, and the sponsor's decision not to use OS as the primary end point.

By contrast, the EMA granted approval for tislelizumab in the metastatic and perioperative setting and sugemalimab for metastatic disease (Figs 2 and 3) and more recently as consolidation treatment after chemoradiotherapy in unresectable stage III PD-L1≥1% NSCLCs.[20] Yet, it remains to be seen whether these approvals will positively affect health care financing in Europe. For example, physicians will need to change their prescribing practices to less-familiar ICI for cost-effectiveness to be appreciable, which may pose a challenge especially if differences in cost and treatment outcomes are marginal. Similarly, in unresectable stage III NSCLC, the EMA has recently approved sugemalimab after definitive chemoradiotherapy based on the GEMSTONE trial for PD-L1 expression ≥1%.[20] Although the trial evaluated up to 2 years of sugemalimab in this setting, the EMA approval allows treatment until disease progression or unacceptable toxicity.[21] This decision is somewhat unexpected as the survival outcomes in GEMSTONE appear to be similar to that of consolidation durvalumab in the PACIFIC trial, which is given for a shorter duration of one year.[22,23] Furthermore, as both consolidation durvalumab and sugemalimab are only approved by the EMA for PD-L1 expression ≥1% tumors, the approval of sugemalimab in Europe does not overcome the treatment gap for unresectable stage III NSCLC with PD-L1 expression <1% after chemoradiotherapy. Considering the longer treatment duration with sugemalimab and more

FIG 1. Considerations when evaluating me-too drugs and alternative strategies.

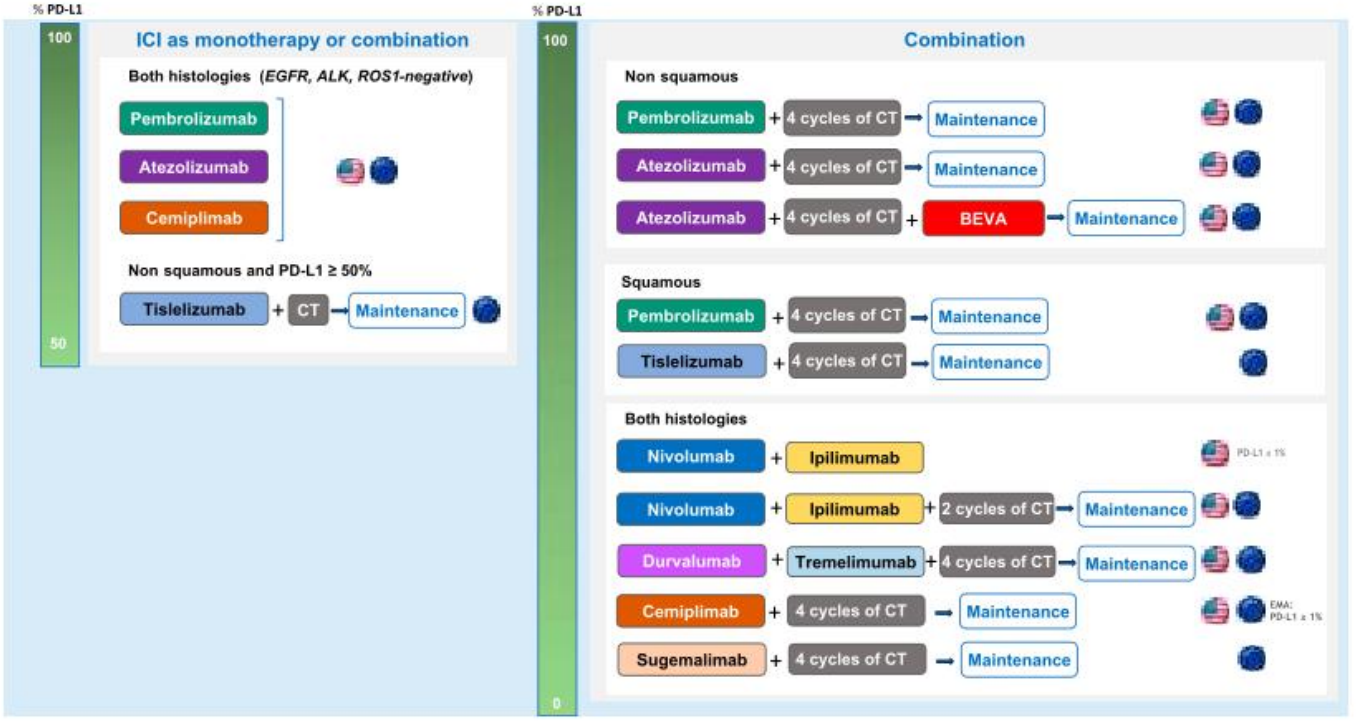

FIG 2. Clinical trials with immune checkpoint inhibitors in metastatic non–small cell lung cancer. BEVA, bevacizumab; CT, computed tomography; EMA, European Medicines Agency; ICI, immune checkpoint inhibitor.

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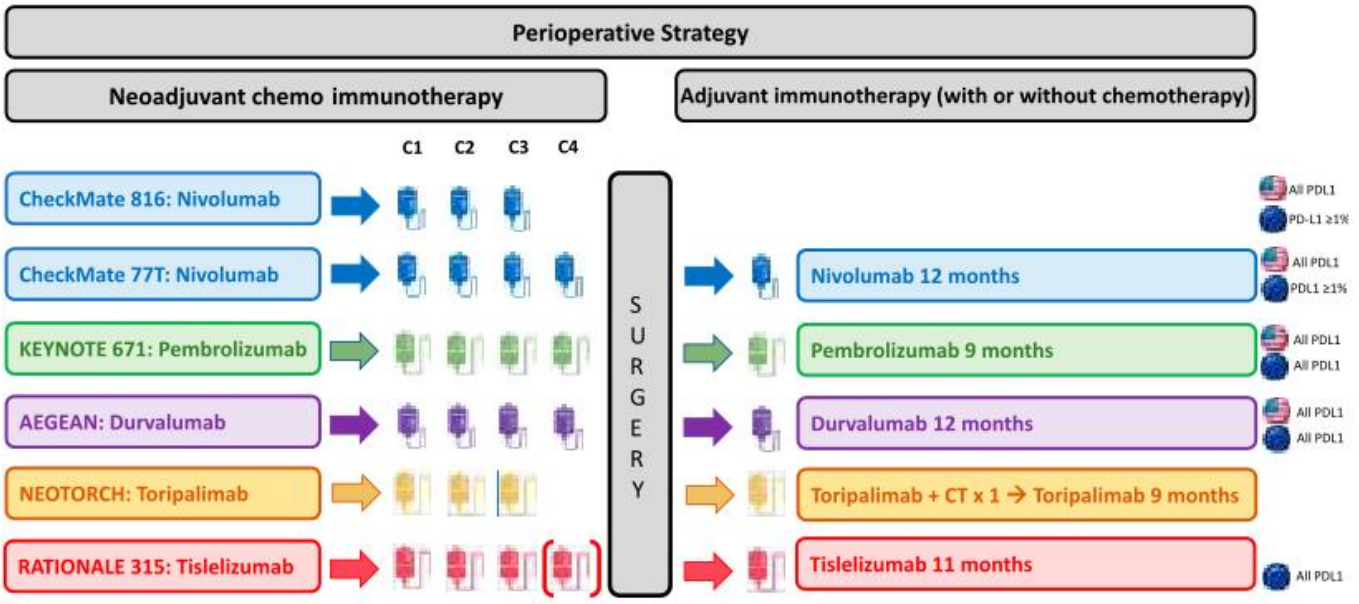

FIG 3. Clinical trials with neoadjuvant and perioperative chemoimmunotherapy in early-stage non–small cell lung cancer. CT, computed tomography.

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frequent dosing schedule (every 3 weeks *v* every 4 weeks) compared with durvalumab, the cost-benefit ratio of sugemalimab over durvalumab remains uncertain.[24] Finally, the efficacy of sugemalimab has not been proven in non-Chinese populations, and therefore, it is pertinent to consider the potential overestimation of treatment effects in single-country trials. Most of the pivotal trials evaluating ICI in resectable early-stage NSCLC (Fig 3) enrolled a geographically diverse population, typically including 25%-50% Asian, 25%-40% European, and 10%-23% North American patients,[12-15] all consistently reporting pCR rates of approximately 20%. By contrast, RATIONALE-315, evaluating perioperative tislelizumab and conducted exclusively in China, reported a pCR rate of 41%.[16] These observations question the generalizability of the results to non-Chinese populations and underscore the limitations of single-country studies for regulatory decisions in other populations. Despite these concerns, the EMA approved perioperative tislelizumab based on the magnitude of EFS and OS improvement that was broadly similar to other trials.[12,13,17,25]

Collectively, these disparities in ICI approvals for NSCLC across disease stages highlight an urgent need for greater global regulatory alignment to ensure equitable access to effective cancer therapies. Notably, China has positioned itself as an emerging leader in global drug development with multiple clinical trials involving novel compounds.[26] It is crucial for regulatory agencies to consider how global pharmaceutical innovation and regulation should evolve such that novel effective therapies can be made accessible to more patients worldwide.[26] Moreover, despite recent EMA approvals based on China-only studies reflecting the importance of cost consideration in health care regulatory decisions, me-too compounds are unlikely to increase the proportion of patients with access to ICI in LMICs and other strategies of deintensification need to be explored, as discussed below.

In the perioperative strategy for early-stage NSCLC, it is important to recognize that the specific contribution of each treatment component (neoadjuvant and adjuvant) to improving patient outcomes remains unknown. Therefore, some patients are likely overtreated using this approach, especially those who achieve a pCR after neoadjuvant treatment as up to 90% of these patients remain alive and disease-free at 5 years.[25] In July 2024, the FDA's Oncologic Drugs Advisory Committee unanimously recommended that future trial designs should include adequate assessments of the individual contributions of both the neoadjuvant and adjuvant immunotherapy phases. Yet, multiple perioperative ICI approaches including me-too compounds have already been FDA- and EMA-approved and the treatment landscape is unlikely to change in the near future. This highlights the challenges of regulatory approvals, which may adopt different benchmarks over time.

ME-TOO TT COMPOUNDS

Classical epidermal growth factor receptor (*EGFR*) mutations (exon 19 deletion and L858R point mutation) are the most common actionable oncogenic drivers in NSCLC worldwide, and third-generation EGFR tyrosine kinase inhibitors (TKIs) form the backbone of treatment across disease stages.[27] Similar to ICI, numerous me-too EGFR TKIs have been developed, some exclusively in mainland China such as aumolertinib, furmonertinib and befotertinib,[28] but none of

these compounds has been approved by regulatory health authorities outside of China.

Multiple me-too TKIs in other rarer oncogene subsets have also been developed. For example, there are currently nine ALK TKIs in the market (crizotinib, ceritinib, alectinib, brigatinib, ensartinib, lorlatinib, iruplinalkib, envonalkib, and foritinib), of which the latter three are developed and approved only in mainland China.[29-32] Notably, many of these ALK TKIs have received regulatory approval despite the choice of suboptimal control arms in the registrational trials. One example is the CROWN trial, which compared lorlatinib versus crizotinib in the first-line setting, although the FDA and EMA had already approved alectinib as the preferred SoC when patient enrollment began.[33,34] Similarly, the ongoing phase III ALKAZAR trial (ClinicalTrials.gov identifier: NCT06765109) is evaluating the efficacy of neladalkib in treatment-naïve advanced *ALK*-positive NSCLC with alectinib as the control arm; this choice is contentious given that first-line lorlatinib has demonstrated longest progression-free survival (PFS) to date and should be the preferred choice for otherwise fit patients.[33] However, based on the long PFS, head-to-head comparisons between neladalkib and lorlatinib would take several years and would be a too much expensive clinical trial. Therefore, how the next generation of clinical trials with TT in different oncogene subsets should be designed is a relevant question, including how regulatory authorities evaluate the choice of comparator arm given the availability of multiple treatment options. Similarly, there are at least four FDA-approved ROS1 TKIs (crizotinib, entrectinib, repotrectinib, taletrectinib), with others in development such as zidesamtinib, despite a prevalence of only 1%-2% of *ROS1* fusions in NSCLC.[35] While having competitor drugs should theoretically drive down market prices, treatment costs unfortunately remain high and whether it is rational for so many TTs to be developed for a rare patient population remains an open question.

Many of these me-too TTs are developed exclusively in mainland China. However, the FDA, unlike the EMA, generally does not approve drugs evaluated in single-country studies, underscoring discrepancies in global regulatory approvals as discussed above. Furthermore, although LASER301 was a global multicountry trial that enrolled at least one third of non-Asian patients[36] and had a similar trial design (first-line lazertinib *v* gefitinib) and treatment outcomes to FLAURA (osimertinib *v* erlotinib or gefitinib),[37] lazertinib monotherapy is approved only in Korea, but is neither FDA- nor EMA-approved as monotherapy. By contrast, for *ROS1*-positive NSCLC, despite the fact that only 17.2% of the study population in the combined analysis of TRUST-I and TRUST-II was Western,[38] the FDA approved taletrectinib in this setting. Altogether, this highlights other factors that regulatory authorities may consider besides geographical representation, such as costs and the availability of other treatment options, especially for rare oncogene subsets. Cost and toxicity concerns are undoubtedly major factors that drive regulatory decisions, and despite robust phase III data, novel therapies may not be approved or reimbursed even in high-income countries. For example, in *EGFR*-mutant NSCLC, while first-line amivantamab and lazertinib are approved by the EMA based on the significant improvement in PFS and OS over osimertinib reported in the global multicounty MARIPOSA trial,[39,40] this combination is not reimbursed in some European countries such as France at present. If these reimbursement issues are encountered for high income countries, then patients from LMICs are much less likely to be able to access these novel therapies in the foreseeable future.

For rare genomic alterations, the choice of optimal comparator arm and appropriate end points in clinical trials to obtain regulatory approval of TT remains an important question. There are ethical concerns in conducting randomized controlled trials in earlier treatment lines when the TT has already proven substantive benefit in the later-line setting, and it is expected that the comparator arm will perform worse because of lack of clinical equipoise,[41] especially if crossover is not permitted. For example, sevabertinib recently obtained FDA approval for patients with human epidermal growth factor receptor 2 (*HER2*)–mutated NSCLC who had received prior treatment based on substantial efficacy observed in pretreated patients.[42] The ongoing SOHO-02 trial (ClinicalTrials.gov identifier: NCT06452277) evaluating sevabertinib in the first-line setting with PFS as the primary end point initially did not permit crossover, raising ethical concerns especially for patients who are unable to access sevabertinib outside of a clinical trial, which eventually led to a protocol amendment allowing crossover from the control arm. Indeed, in February 2026, the FDA approved zongertinib, another HER2 TKI, for first-line treatment of *HER2*-mutant advanced NSCLC based on data from 74 patients.[43] Although this approval represents an step forward for patients to have access to personalized treatment up front, it may complicate enrollment in the phase III Beamion LUNG-2 trial (ClinicalTrials.gov identifier: NCT06151574), which is evaluating zongertinib versus chemoimmunotherapy in the first-line setting, at least in the United States.

The complexity of trial designs and appropriate end points is further compounded in the early-stage setting. Although it is unsurprising that a TT that has proven efficacy in the metastatic setting will outperform chemotherapy or placebo in the adjuvant setting, regulatory authorities will not approve these therapies unless a significant survival benefit is demonstrated in a randomized controlled trial, which are expensive and time-consuming to conduct. Yet, it is arguably unethical to conduct these trials, particularly if patients in the control arm are not provided access to the appropriate TT at relapse. In that light, health care authorities need to work with investigators, pharmaceutical companies, and patient advocacy groups to overcome these challenges and decide on the minimum burden of evidence that needs to be generated for regulatory approval for TT in rare oncogene subsets and early-stage disease, while

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ensuring that clinical trial designs are ethical and patient-centric.

LOW-DOSE IMMUNOTHERAPY IN LUNG CANCER

Despite the significant improvement in survival outcomes across multiple tumor types including NSCLC, the high cost of ICIs severely limits access, with utilization rates below 5% in LMICs such as India.[44] Given the challenges of using me-too compounds as detailed above, low-dose ICI has been proposed as an alternative solution. Cost-effectiveness aside, this approach is also biologically rational as a clear dose-response relationship has not been demonstrated for ICI, particularly for antibodies targeting PD-1.[4,45-52] Clinical efficacy is achieved primarily through saturation and sustained blockade of the target receptor,[53] with T lymphocytes representing the principal cellular targets. Approximately 20%-40% of peripheral blood T cells express PD-1, and effective immune activation requires occupancy of about 70%-75% of PD-1 receptors. Phase I studies of anti–PD-1 agents indicate prolonged pharmacokinetics (PKs), with half-lives of up to 20 days.[4] Pharmacodynamic (PD) analyses further demonstrate that a mean PD-1 receptor occupancy of approximately 70% on circulating T cells can be maintained for more than 2 months after a single infusion, largely independent of dose.[4,45,54,55] Therefore, alternative ICI dosing strategies including dose reduction and extended dosing intervals can potentially achieve similar survival outcomes as standard dosing at a fraction of the cost. This is clinically relevant as the global expenditure on oncology drugs reached $252 billion US dollars (USD) in 2024 and is projected to rise to $441 billion USD by 2029, underscoring the need for cost-effective treatment.[56]

As reported, the PK and PD profiles of anti–PD-1 antibodies such as nivolumab and pembrolizumab are characterized by a flat exposure-response relationship, indicating that maximal efficacy is achieved at doses significantly lower than the MTD.[57] For nivolumab, peripheral receptor occupancy has been shown to be saturated at doses as low as 0.3 mg/kg once. Furthermore, PK modeling has shown that the trough concentration maintained at a standard 3 mg/kg dose once (16 μg/dL) is approximately 160-fold higher than that required for maximal receptor binding; notably, a concentration of only 0.04 μg/dL is sufficient to occupy >70% of PD-L1 receptors.[4,45] Similarly, pembrolizumab exhibits a plateau in interleukin-2 production beyond 0.3 mg/kg once in preclinical models and achieves 95% target engagement with a single dose of 1 mg/kg dose. Clinical simulations of tumor size dynamics further corroborate that there is no significant difference in therapeutic efficacy across dosing ranges from 2 mg/kg to 10 mg/kg once every 3 weeks.[46,47] These data collectively suggest that lower-dose regimens (eg, 1 mg/kg once) may be sufficient to maintain therapeutic activity. An analysis of four clinical trials comprising patients with both squamous and non-squamous metastatic NSCLC demonstrated a flat exposure-response relationship to nivolumab, with no association between nivolumab exposure and OS across doses ranging from 1 to 10 mg/kg once every 2 weeks.[55] In a systematic evaluation of pembrolizumab dosing at 2 mg/kg once every 3 weeks, 10 mg/kg once every 2 weeks, and 10 mg/kg once every 3 weeks, higher dosage or dose intensity did not translate to additional efficacy,[58] and similar findings have been shown in other tumor types.[46,59]

There are several clinical trials and real-world data (RWD) supporting that lower doses of ICI do not negatively affect patients' outcomes.[60,61] The first example was in metastatic head-and-neck cancer where the addition of low-dose nivolumab (20 mg flat dosage) to metronomic chemotherapy achieved similar benefit to historical data using full doses of nivolumab.[62] Recently, the phase III DELII study compared ultralow-dose nivolumab (20 mg once every 2 weeks) with standard chemotherapy in 500 patients with advanced solid tumors, including NSCLC (n = 182). Although the overall response rate was similar in both arms (7.7% *v* 8.1%), nivolumab reduced the risk of mortality by 20% (hazard ratio [HR], 0.80 [95% CI, 0.66 to 0.97]; P = .022), with up to one third of patients being alive at 12 months in the nivolumab arm compared with 17% with chemotherapy.[63] This is also reinforced by encouraging initial data coming from the ongoing phase III noninferiority DEDICATION-1 trial (NVALT-30, ClinicalTrials.gov identifier: NCT04909684). In the interim analysis, no safety or efficacy signals suggesting inferiority of the reduced-dose regimens (pembrolizumab 300 mg every 6 weeks and 100 mg every 3 weeks) compared with the SoC doses (pembrolizumab 400 mg once every 6 weeks, or 200 mg onvce every 3 weeks and 150 mg once every 3 weeks -the latter dose is in accordance with the Dutch Society for Medical Oncology recommendations) were observed.[64] RWD in lung and other tumor types from countries including Korea, China, Taiwan, Singapore, Brazil, and India has similarly supported the use of low-dose ICI in NSCLC.[65-71] Ongoing clinical trials evaluating low-dose ICI in NSCLC are given in Table 1. Notably, the role of low-dose ICI potentially extends to all stages of NSCLC. In a retrospective study from India, neoadjuvant treatment with 20-40 mg of nivolumab plus chemotherapy in stage III NSCLC has reported a pCR of 25%,[78] mirroring the pCR rate reported in the phase III CheckMate 816 trial using 360 mg of nivolumab once every 3 weeks.[12] This observation is consistent in other tumor types such as early-stage breast cancer. The phase IIb PLANET trial demonstrated that low-dose neoadjuvant pembrolizumab (50 mg once every 6 weeks, for three doses) with dose-dense chemotherapy in triple-negative early-stage breast cancer achieved a pCR rate of 54%,[79] which was comparable with that of KEYNOTE-522 using full dose of pembrolizumab.[80]

Finally, in SCLC, low-dose ICI could also be feasible. For SCLC, atezolizumab was approved at the dose of 1,200 mg every 3 weeks, and for durvalumab the standard dose is 1,500 mg once every 3 weeks. However, as per cost, access, delivery, affordability, toxicity, and health outcomes analysis, durvalumab dosed at 10 mg/kg once every 2 weeks and

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TABLE 1. Ongoing Clinical Trials Evaluating Low Dose or Reduced Dose Intensity in Lung Cancer

Trial (Country)	Author/Trial Group	Study Design/Phase	Eligible Patients	Proposed Low-Dose Strategy	End Points	Current Status
REFINE-Lung (United Kingdom)—NCT05085028[72]	Ghorani E. et al; NIHR/NCRI	Phase III, multiarm, randomized, open-label	Advanced/unresectable NSCLC; no targetable drivers; disease control after approximately 6 months of pembrolizumab-based therapy	Frequency de-escalation: Extended pembrolizumab intervals (every 9 weeks to every 18 weeks) *v* standard	PFS/OS-based framework to define optimal interval	Recruiting
PULSE (Belgium–France–Spain–Luxembourg)—NCT05692999[73]	Belgian KCE/multinational investigators	Phase III, randomized, open-label, noninferiority	Nonsquamous stage III to IV NSCLC; disease control after 3-4 cycles platinum-pemetrexed-pembrolizumab	Interval reduction: Pembrolizumab 200 mg once every 6 weeks *v* standard maintenance	Primary OS (noninferiority); PFS, QoL, toxicity, cost	Recruiting
DIAL/IFCT-2103 (France)—NCT05255302[74]	IFCT (Intergroupe Francophone de Cancérologie Thoracique)	Phase II/III, randomized, open-label	Stage IV NSCLC; ECOG 0-1; disease control after 6 months chemoimmunotherapy	Duration de-escalation: Stop pembrolizumab at 6 months *v* continuation up to 2 years	Primary PFS; OS, QoL, toxicity, cost-effectiveness	Recruiting
LEDANG (Malaysia)—NCT07050043[75]	Arvindran K. et al; MOH Malaysia	Phase III, multicenter, randomized	Stage IIIB to IV NSCLC; first-line treatment	True low-dose strategy: Nivolumab 40 mg once fixed dose every 6 weeks + chemotherapy	Primary OS (superiority); PFS, ORR, safety, health-economic outcomes	Recruiting
ELON (India; neoadjuvant)—Ann Oncol TiP[76]	Biswal S. et al	Phase II, randomised, open-label	Resectable/locally advanced NSCLC planned for surgery	Low-dose nivolumab (protocol-defined) + chemotherapy *v* chemotherapy alone	MPR/pCR; EFS, DFS, OS, surgical outcomes	Not publicly reported
Low-dose IL-2 + pembrolizumab (USA)—NCT05493566[77]	Winship cancer Institute (Emory University)	Phase I, single-arm, open-label	Previously untreated metastatic NSCLC	Immunomodulatory approach: Low-dose IL-2 (aldesleukin) + standard pembrolizumab	Immune correlates (primary); ORR, PFS, OS, safety	Recruiting

Abbreviations: DFS, disease free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; IL-2, interleukin-2; MPR, major pathological responses; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; QoL, quality of life.

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15 mg/kg once every 3 weeks would result in similar drug exposure as compared with standard flat dose. Therefore, the drug dose can theoretically be halved using weight-based dosage without comprising efficacy. This is supported by RWD from India, which reported that low-dose durvalumab (120 mg once every 3 weeks) with platinum doublet showed similar outcomes to standard doses used in NSCLC.[81]

These data collectively support the role of low-dose ICI across disease stages and tumor types including lung cancer, especially in resource-constrained settings where access to full dose anti-PD1 and anti-PDL1 remains challenging.

LOW-DOSE TTs IN LUNG CANCER

The introduction of TT has yielded substantial improvements in survival outcomes for tumors harboring actionable genomic alterations, which has extended across all disease stages in oncogene subsets such as *EGFR*-mutant NSCLC.[37,82-85] Given the mechanism of action, TTs are often administered indefinitely, which is a stark contrast to ICI where the induction of memory T cells allows a fixed and often shorter duration of treatment. This paradigm highlights the need to balance between efficacy and long-term tolerability, minimize cumulative toxicity, reduce treatment burden, and ensure equitable access across diverse health care systems.

Historically, approved TT dosing regimens were based on early-phase trials that focused on identifying the MTD rather than the minimum effective dose (MED).[86] Consequently, the approved dosage of certain TT could exceed the minimum dose needed to maintain adequate target inhibition in a subset of patients. This is supported by RWD and emerging PK/PD data, which suggest that adequate target inhibition may be achieved at exposures below standard approved doses of TT and that exposure beyond this range can increase toxicity without proportional gains in efficacy.[87] Fueled by escalating treatment costs with novel compounds and longer treatment durations, this has led to growing interest in exploring lower-dose strategies for TTs that maintain quality of life and mitigate financial toxicity without compromising efficacy.

One of the clearest examples of potential overdosing with TT is for patients with NSCLC harboring *KRAS* G12C mutations. Sotorasib, a *KRAS* G12G off inhibitor, is approved in this setting at a dose of 960 mg once daily. However, a phase II, randomized study comparing 960 mg with 240 mg once daily in this population reported that patients treated with higher doses of sotorasib had numerically higher ORR than patients treated with lower doses, without significant differences in PFS and OS, but with a higher risk of grade ≥3 treatment-related adverse events (TRAEs) with higher doses (39% *v* 19% with sotorasib at 960 mg once daily or 240 mg once daily, respectively).[88]

Among EGFR TKIs, afatinib is a well-established example of successful dose optimization. Post hoc analyses of the phase III LUX-Lung 3 and 6 trials showed that tolerability-guided dose reduction from 40 mg once daily to 30 mg once daily reduced the incidence and severity of TRAEs without compromising PFS.[89] In this analysis, patients requiring early dose reductions were more likely to have higher afatinib trough concentrations at 40 mg once daily and therefore overexposed, but dose adjustments did not affect systemic exposure as afatinib concentrations at day 43 were similar for those patients with dose reduction to 30 mg versus those remaining at 40 mg once daily (23.3 *v* 22.8 ng/mL).[89] This evidence has been confirmed in RWD cohorts, showing that starting or reducing afatinib to 30 mg once daily maintains clinical outcomes comparable with those with the standard dose of 40 mg once daily, while reducing severe gastrointestinal and dermatologic toxicities.[90,91] Doses can even be reduced up to ≥20 mg once daily without compromising outcomes.[92] These data may suggest that a patient-specific tolerability-guided dose adjustment of afatinib is feasible.

Osimertinib, a third-generation CNS-penetrant EGFR TKI, is prescribed at a standard dose of 80 mg once daily, for common sensitizing *EGFR*-mutant NSCLC. Exposure-response and integrated PK/PD analyses suggest no clear improvement in extracranial efficacy with increasing osimertinib dose,[93] whereas higher exposure is primarily associated with increased toxicity, including rash, diarrhea, and QTc prolongation.[94-96] In the phase I study with osimertinib, the ORRs were broadly similar at each of the dose levels analyzed (52% with 20 mg, 43% with 40 mg, 52% with 80 mg, 58% with 160 mg, and 52% with 240 mg, all doses once daily), whereas adverse events (AEs) increased in frequency in a dose-dependent manner.[97] A similar pattern emerges for CNS control. In *EGFR*-mutated NSCLC with leptomeningeal (LM) disease, the phase II BLOSSOM trial reported meaningful CNS activity with osimertinib at the standard 80 mg once daily dose regardless of T790M status (LM ORR 51.6%, median PFS 11.2 months, OS 15.0 months),[98] comparable with that observed in the BLOOM study using 160 mg once daily (LM ORR 62%, median PFS 8.6 months, OS 11.0 months).[99] Consistently, retrospective analyses from the AURA program suggest that dose escalation does not necessarily confer superior CNS efficacy,[100] and the phase II OCEAN trial did not find an association between osimertinib plasma trough concentrations and CNS progression or efficacy.[101] Indeed, the intracranial efficacy of a drug primarily depends on its ability to penetrate the blood-brain barrier, its interaction with efflux transporters (and the presence of germline variants in these transporters),[102] and its capacity to maintain therapeutic concentrations within the CNS. Accordingly, dose escalation to improve intracranial outcomes is most plausible for TT with limited CNS penetration (ie, a low cerebro-spinal fluid [CSF]:plasma ratio), whereas for most newer-generation agents—where CSF and plasma concentrations are near equilibrium (CSF:plasma approximately equal to 1)—this rationale is less compelling. Finally, retrospective RWD cohorts suggest that tolerability-driven dose reductions of osimertinib from 80 mg once daily —even when performed early—may preserve clinical outcomes, particularly in elderly, low-body-weight,

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comorbid, or otherwise frail patients, in whom de-escalation can mitigate toxicity and help prevent premature treatment discontinuation.[103,104]

Based on the half-life of osimertinib of 60 hours,[97] reduced-frequency schedules (eg, every-other-day [EOD] or every-third-day dosing) may represent a further promising approach for deintensified treatment approaches. A small real-world retrospective study (N = 22) proved the efficacy of alternative schedules of osimertinib (80 mg EOD, 40 mg daily, 40 mg EOD) in previously treated patients, with the longest median OS achieved in the 80-mg once daily EOD group (14 months, 10 months for 40 mg EOD, and 13 months for 40 mg once daily).[105] However, RWD is limited, and only noncomparative trials are available. Therefore, this approach should be reserved for selected patients.[106]

Similarly, for *ALK*-positive NSCLC, in the dose-escalation studies of alectinib—a second-generation *ALK* inhibitor—no clear relationship was found between drug exposure and efficacy. Across the evaluated dose range (300-900 mg twice a day), all alectinib doses demonstrated systemic activity. However, while no dose-limiting toxicities were reported with 600 mg twice a day, 2 of 13 patients treated with 900 mg twice a day had grade 3 TRAEs that led to dose reduction, supporting that greater exposure was associated with a higher toxicity.[107]

Of note, alectinib exhibits substantial interpatient PK variability, largely driven by body weight and ethnicity differences. This suggests that a single dose level may not account for interpersonal differences and may be safely reduced for specific subgroups. Alectinib is currently approved at a fixed dose of 600 mg twice a day for non-Japanese patients, whereas it is approved at a lower dose of 300 mg twice a day in Japan. Indeed, even if cross-trial comparison requires caution, the Japanese J-ALEX trial investigating alectinib 300 mg twice a day versus crizotinib reported outcomes (PFS 34.1 months *v* 10.2 months, HR, 0.37 [95% CI, 0.26 to 0.52])[108] similar to those from the Asian subgroup analysis of the ALEX trial, which tested alectinib 600 mg twice a day versus crizotinib (PFS 34.8 months *v* 9.6 months, HR, 0.43 [95% CI, 0.27 to 0.67]).[109] Consistently, in a recent Korean RWD cohort comparing alectinib at 300 mg twice daily versus 600 mg twice a day, broadly similar PFS and OS were reported, with fewer toxicities and dose modifications at 300 mg, particularly among patients with body weight ≤60 kg and no baseline brain metastases. However, plasmatic levels of the drug were not assessed.[110] Together, these data question whether a lower dose of alectinib could achieve comparable efficacy with 600 mg twice a day in other populations.

Regarding the intracranial activity of alectinib, no clear dose-response relationship was observed in the phase I trial,[107] because of its high CNS penetration (CSF:plasma ratio of 0.86). In the previous Korean study, CNS failure was numerically more frequent in the 300-mg than 600-mg twice-a-day group, although not statistically significant (HR, 1.76 [95% CI, 0.53 to 5.80]).[110] By contrast, for crizotinib-refractory *ALK*-positive NSCLC, brigatinib dosed at 180 mg once daily (after a 7-day lead-in at 90 mg) yielded higher intracranial efficacy than 90 mg once daily (intracranial confirmed response rate 67% *v* 50%; median intracranial response duration 16.6 *v* 9.4 months).[111]

More recently, in the phase III CROWN trial, lorlatinib, a highly CNS-penetrant third-generation ALK/ROS1 inhibitor, has notably improved PFS outcomes versus crizotinib in patients with untreated *ALK*-positive metastatic NSCLC. Post hoc analysis from the trial showed that early dose reductions of lorlatinib did not compromise outcomes in a 16-week landmark analysis, with similar 12-month PFS and intracranial efficacy in patients who reduced dose versus those maintained at 100 mg once daily.[112] Similar results were observed in a real-world cohort, where landmark PFS did not differ between patients with dose modifications within 16 weeks because of TRAEs and those without (median 24.8 *v* 10.1 months, $P = .46$).[113] Importantly, lorlatinib serum concentrations were significantly higher in patients with grade ≥3 TRAEs (462 *v* 177 ng/mL, $P < .01$) and dose modification reduced serum concentrations with improved toxicity control.[113] Overall, these findings support the value of therapeutic drug monitoring to anticipate and mitigate toxicity; however, for lorlatinib, dose reduction appears most justifiable when exposure is high, and evidence for exposure-independent de-escalation remains modest. Unfortunately, no evidence is available on dose optimization strategies for TT targeting other druggable fusions like *ROS1*, *RET*, and *NTRK*.

The incidence of *MET* exon-14 skipping mutation (*MET*ex14) is more common in older patients with NSCLC, raising the relevance of dose optimization of MET inhibitors (capmatinib or tepotinib) to reduce toxicity and avoiding dose discontinuations that may compromise treatment efficacy. In a small RWD cohort of *MET*ex14 advanced NSCLC (N = 17) treated with capmatinib or tepotinib in the first line, dose reduction was required in 14 of 17 patients, including 3 of 14 who started therapy at a reduced dose and were subsequently further reduced to mitigate toxicity and enable treatment continuation. Notably, only one CNS-only progression event was observed while on dose-reduced therapy, supporting the feasibility of toxicity-driven dose modification in selected patients, although conclusions are limited by the small, noncomparative design.[114]

Therefore, across TT, dose reductions frequently improve tolerability, preserve health-related quality of life, and improve treatment adherence.

Currently, the available literature remains insufficient to endorse systematic dose reduction as a default strategy or to definitively quantify its impact on long-term systemic and CNS outcomes across TT and clinical settings. More academic clinical trials are necessary to prove the validity of this approach in daily practice. FDA has launched the OPTIMUS project, which aims to evaluate the optimal dosing of various

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TTs with a holistic approach, including efficacy, safety, PK, and PD data.[115] Therefore, this project wants to reform the paradigm of dose selection in oncology drug development. This initiative emphasizes the identification of an optimal biological dose rather than relying solely on the MTD, encouraging more comprehensive dose-exploration strategies and randomized dose-ranging studies early in development. Such an approach aims to better characterize the benefit-risk profile of anticancer agents and improve long-term tolerability for patients receiving chronic TTs. Although no formal equivalent initiative currently exists at the EMA, similar concerns regarding insufficient dose optimization in drug development were highlighted in the EMA-EFPIA dose-finding workshop report in 2014.[116]

Exposure-response–based multiattribute clinical utility score frameworks, combining efficacy and toxicity data of the investigated drug into a single measurement, could represent another promising tool to more accurately select TT doses/schedules.[117]

Dose optimization also has important implications for financial toxicity and global equity. Reducing drug exposure may decrease overall treatment costs and toxicity-related health care utilization, thereby enhancing affordability and expanding access, particularly in resource-limited settings.

CONCLUSIONS

As TTs increasingly follow a chronic disease paradigm across all stages of the disease, prospective randomized trials, pragmatic comparative-effectiveness studies, and model-informed precision dosing will be essential to define minimal effective exposure thresholds. Such trials should integrate PKs, longitudinal toxicity trajectories, and patient-reported outcomes to ensure the validity of lower-dose strategies before their routine clinical implementation. Similarly, current evidence supports the clinical efficacy of low-dose ICI, and when implemented with informed patient consent, these approaches represent a rational, ethical, and high-impact strategy—particularly in resource-limited settings—without compromising patient care.[118] Ultimately, the value of cancer therapeutics lies not only in the development of new drugs but also in their capacity to deliver meaningful benefit to individual patients while balancing clinical decision making, health-policy considerations, and industry sustainability. To translate this principle into everyday practice, regulatory and professional frameworks must evolve potentially through expanded labeling to include validated lower-dose regimens or, at minimum, incorporation into clinical practice guidelines supported by robust noninferiority trial evidence.

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

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From Silos to Synergy: Building Resilient Multidisciplinary Oncology Teams

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OVERVIEW

Modern cancer care is highly complex and interdependent, requiring coordination across specialties, settings, and time points. When interdependence is not intentionally managed, care delivery becomes fragmented, resulting in delays, inefficiencies, and increased burden on clinicians and patients. High-functioning multidisciplinary teams are essential for delivering timely, patient-centered oncology care and sustaining the oncology workforce. However, practical approaches for establishing and operating these teams remain limited. This article presents a practical roadmap for establishing and sustaining high-functioning oncology teams using the 4R oncology model (right information, right care, right patient, right time). The model operationalizes teamwork by centering the team goals and actions around explicitly managing the timing and sequencing of interdependent care through a structured tool, the Care Sequence, which provides a patient-centered roadmap of guideline-concordant care across specialties. Implementation includes team formation, collaborative optimization of care processes, and integration of coordinated workflows into routine clinical practice, including continuous learning processes that support adaptation over time. We highlight the central roles of patients as active members of the care team with capacity for self-management, and of nonphysician professionals essential for reliable team-based care delivery. Because multidisciplinary collaboration generates differing perspectives, we discuss structured approaches to conflict resolution that transform disagreement into productive problem-solving and system improvement. Finally, as oncology practice becomes increasingly interconnected across institutions and countries, we consider how team-based structures support collaboration across diverse settings and geographies. Together, these principles offer an actionable framework for transforming siloed structures into coordinated, resilient oncology teams capable of delivering high-quality cancer care.

INTRODUCTION

Advances in cancer biology, diagnostics, and therapeutics have transformed oncology practice, enabling personalized treatment strategies and comprehensive care across domains and specialties. As a result, contemporary cancer care has become highly interdependent, requiring coordinated actions across disciplines, settings, and time points.[1,2] When this interdependence is not deliberately managed, specialization can devolve into silos, causing fragmented workflows, misaligned timing of care, and unclear accountability.[3-5] These failures lead to care delays, omissions, and breakdowns that compromise outcomes and intensify clinician burden, which in turn contributes to burnout.[1,6-9]

Traditional multidisciplinary structures, including tumor boards and multidisciplinary clinics, remain essential for treatment decision making,[10,11] but are not designed to ensure timely execution of care.[12-14] Systematic approaches are needed to translate multidisciplinary decisions into coordinated, time-sensitive action across the care continuum. In their absence, care delivery remains[15,16] fragmented, often leaving patients and families to bridge coordination gaps and exacerbating the burden of a cancer journey.[17]

These challenges are unfolding amid a global oncology workforce shortage. Staffing constraints reduce capacity and resilience, increase reliance on informal workarounds, and heighten vulnerability to changes such as staff turnover, rising demand, or the introduction of new diagnostics and treatments.[8,15,18,19] Under these conditions, coordinating the timing and sequencing of interdependent care across specialties becomes increasingly difficult.

High-functioning teams have emerged as a cornerstone of effective cancer care delivery.[16,20-22] Team-based approaches provide a mechanism to explicitly manage interdependence, enabling coordinated, patient-centered care while reducing the operational burden on clinicians and patients.[4,8,17] High-

PRACTICAL APPLICATIONS

- High-functioning oncology teams should be established to translate multidisciplinary treatment decisions into coordinated team-based cross-specialty care delivery processes. The 4R oncology model provides a practical framework and a set of steps to establish high-functioning teams, align the timing and sequencing of care, and optimize care delivery.
- Nonphysician professionals should be actively engaged in the design of the team and optimizations of oncology care processes. Nurses, advanced practice providers, pharmacists, social workers, and navigators provide operational insights that are essential for reliable team-based care.
- Patients should serve as members of oncology care teams and should be provided with clear care roadmaps and expectations for self-management. This clarity can improve engagement, adherence, and continuity of care, while reducing clinician burden.
- Resilient oncology teams should develop structured approaches to conflict resolution. Constructive management of disagreement can strengthen psychological safety and help teams refine care pathways and improve collective performance.
- Standardized team-based frameworks can support collaboration across increasingly interconnected oncology systems in research and patient care. Multidisciplinary, cross-institutional and international collaboration models provide examples for advancing cancer research and care globally.

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functioning teams are characterized by (1) recognition as a team internally and externally, (2) commitment to an explicit shared goal, (3) enablement of interdependent work to achieve that goal, and (4) regular reflection to adapt objectives and processes over time.[8,23] Among these characteristics, the ability to manage interdependent care is crucial and represents a central principle of contemporary teamwork.[8,23–25]

Together, these attributes define not only effective but also resilient teams. In oncology, resilience is the capacity of care teams to anticipate and adapt to clinical, operational, and organizational pressures while maintaining timely, high-quality, patient-centered care.[26–29] This aligns with health care resilience frameworks that emphasize sustained system-level capabilities, rather than individual effort, to manage interdependence and effective care delivery.[8,30,31]

High-functioning, resilient teams must reflect the realities of contemporary oncology practice. Timely care delivery requires recognizing patients as members of the care team. As care pathways become more complex, patient participation and self-management, including understanding and following timing/sequencing of care, are essential.[32–34] Equally important is the role of nonphysician professionals, including nurses, advanced practice providers (APPs), navigators, social workers, genetic counselors, and pharmacists, whose contributions are central to care coordination and continuity.[14–16,35]

Although the attributes of high-functioning teams may appear intuitive, their implementation is challenging. Managing interdependent care requires systematic and adaptable approaches rather than reliance on ad hoc efforts.[4,17,20] One such approach is the 4R oncology model (right information and right care for the right patient at the right time), which operationalizes teamwork through explicit attention to care timing/sequencing and has demonstrated effectiveness in establishing high-functioning teams and improving patient self-management.[6,7,36–38]

The learning objective of this article was to describe how the characteristics of high-functioning teams and related team science principles can be translated into practice in oncology care. We present an actionable roadmap for establishing and sustaining high-functioning oncology teams across diverse practice settings and global contexts, using the 4R model as an organizing construct. We address core requirements of team-based care, including the roles of patients and nonphysician professionals, approaches to conflict management essential for sustainability, and strategies for cross-institutional, cross-regional, and transnational collaboration. Together, these elements aim to advance practical pathways from siloed excellence toward coordinated, resilient cancer care delivery. Our intended audience includes physician and nonphysician professionals across cancer care specialties, spanning surgical, medical, and radiation oncology, as well as supportive and social care, along with oncology practice leaders and administrators.

This article contributes to the field of oncology education by addressing a critical gap in knowledge: the lack of approaches to implementing team science principles and high-functioning teams in cancer care. This gap has been highlighted by leaders of the NCI–ASCO Teams in Cancer Care Initiative, who noted that, despite prior progress, new and actionable strategies are needed to apply team science to the evolving challenges of oncology care delivery.[21]

ESTABLISHING AND SUSTAINING HIGH-FUNCTIONING TEAMS: A PRACTICAL AND EFFECTIVE APPROACH USING THE 4R ONCOLOGY MODEL

Team-Enabling Framework to Implement Team Science: 4R Oncology Model

4R oncology is rooted in team science: It facilitates one of the central principles of teamwork—intentional management of

work interdependence.[6] 4R provides a structured approach to establishing and sustaining high-functioning teams by explicitly managing interdependent care. It organizes teamwork around a patient's care trajectory as a coordinated set of interrelated tasks rather than a series of specialty encounters.[6,7] The core tool, the Care Sequence, is a patient-facing roadmap that depicts guideline-concordant care across disciplines, clarifies timing and dependencies, and defines responsibilities (Fig 1). It shifts focus from specialty workflows to a patient-centered chronology, making interdependence explicit and operational, and forming the foundation of team function.

Teams are implemented through two iterative steps (Fig 2). Step 1, 4R optimization, supports team formation, adaptation of Care Sequences and timing/sequencing optimizations. Step 2, 4R clinical use, enacts teamwork and care optimizations and integrates Care Sequences into routine care, with real-world performance informing continuous refinement.[37-39]

A comprehensive 4R evaluation demonstrated successful formation of a multidisciplinary team (MDT) spanning 24 specialties and 40 targeted care optimizations.[37] Although team formation and subsequent care optimizations required team members' time and effort, the 4R methodology enabled efficient use of these resources: Half of optimizations required minimal effort and 20% required moderate effort, while nearly 80% improved care process efficiency.[37] These care optimizations resulted in actual improvements in timing and sequencing of 22 types of interdependent care across lung and breast cancers, as measured post-Step 2 4R launch.[39] Additionally, multicenter studies showed improved patient-level timing and sequencing of care and patient self-management in breast cancer, with comparable or greater benefit in safety-net settings.[36]

Roadmap to Building a High-Functioning Team Along the 4 Characteristics (4R Step 1)

The actions, participants, and outputs of building a high-functioning team are described below and summarized in Table 1.

Forming the Team

High-functioning teams require shared accountability for timely care delivery. Membership should be defined by care interdependencies rather than departmental boundaries, engaging specialties across the cancer continuum, including oncologic, diagnostic, supportive, and social care, based on how they influence upstream and downstream care. Care Sequences identify participating specialties and assign accountability for each care element. When delivery depends on external services, such as fertility preservation, genetics or rehabilitation, these partners should be integrated with defined roles and responsibilities. Leadership endorsement reinforces external team recognition, legitimizes shared responsibility, and enables cross-specialty workflow optimization to ensure care is delivered as intended.

Building Commitment to Shared Goals

Commitment to teamwork is built through active participation in design and use of Care Sequences, with each specialty defining timing and dependencies of their services within the patient-centered timeline. Commitment is reinforced through targeted timing/sequencing optimizations. A patient's trajectory encompasses successive Care Sequences, each focused on a treatment-specific episode, for example, surgery, systemic therapy, and radiation (Fig 3). The succession is based on guideline-recommended care pathways and should be reviewed and agreed upon by the team. Care Sequences should reflect institutional context and be disease specific in specialized programs and pan-cancer in general settings (Fig 3 illustrates a pan-cancer example).

Enabling Interdependent Work

Care Sequences provide a structured method for identifying care breakdowns, delays, or misaligned sequencing across specialties. The team should use these insights to identify and prioritize care optimizations. Optimizations should be pragmatic, targeted, and feasible within existing resources. Examples of optimization methods include advancing care earlier in the trajectory, establishing shared sequencing standards, prioritizing scheduling for time-sensitive services, and/or removing unnecessary steps that introduce delay. 4R implementation experience demonstrates that many high-impact optimizations require modest effort yet yield substantial improvements in reliability and efficiency.

Embedding Reflection and Adaptation Into Team Practice

This is achieved by regularly comparing delivered care with Care Sequences and assessing whether intended timing/sequencing was achieved. Teams use these comparisons to examine system-level causes, such as workflow misalignment or unclear responsibilities. Gaps are addressed through iterative refinements to Care Sequences, workflows, or coordination processes (Fig 2). These adjustments are tested in practice, monitored, and revised as needed, creating a continuous feedback loop. The standard quality improvement methods, such as plan-do-study-act (PDSA), may be used for iterative improvements. By institutionalizing this cycle, teams sustain reliable performance over time and remain responsive to evolving clinical standards, operational conditions, and patient needs.

Team Functioning: Using Care Sequencing and Optimized Care Processes in the Clinic (4R Step 2)

Ongoing team operation is achieved by activating optimized processes and integrating Care Sequences into care planning and delivery. Care Sequences are introduced at treatment

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FIG 1. Example of a care sequence: pan-cancer neoadjuvant therapy. Care Sequences contain a preprinted list of care, which is personalized for each patient by checking boxes and making notes. This Care Sequence is intended for patients indicated for neoadjuvant therapy. Patients receive a subsequent Care Sequence specific to the treatment decision following neoadjuvant therapy, such as surgery, additional systemic therapy or radiation. Squares are shorter events, such as tests or appointments; bars are longer care processes, such as biomarker testing. Arrows indicate care dependencies: what care events should be completed before other care starts. This is an abbreviated schematic for illustration purposes, not an actual Care Sequence template. Actual Care Sequences may contain additional care. DOB, date of birth; MRN, medical record number.

planning encounters across the care continuum (Fig 2). During in-person or telehealth visits, clinicians review and personalize the Care Sequence with the patient, confirming indicated care, timing/sequencing, and responsibilities. The document is provided to the patient and incorporated into the electronic medical record to guide coordinated execution. Care Sequences serve as a shared reference: clinicians deliver care according to agreed timing/sequencing, and patients use the document to anticipate next steps and actively manage their care.

Step 2 embeds a feedback loop into routine practice: teams compare delivered care with intended timing and sequencing using quantitative metrics (eg, time to treatment, biomarker availability before decisions, completion of pretreatment care) and qualitative input from clinicians and patients.

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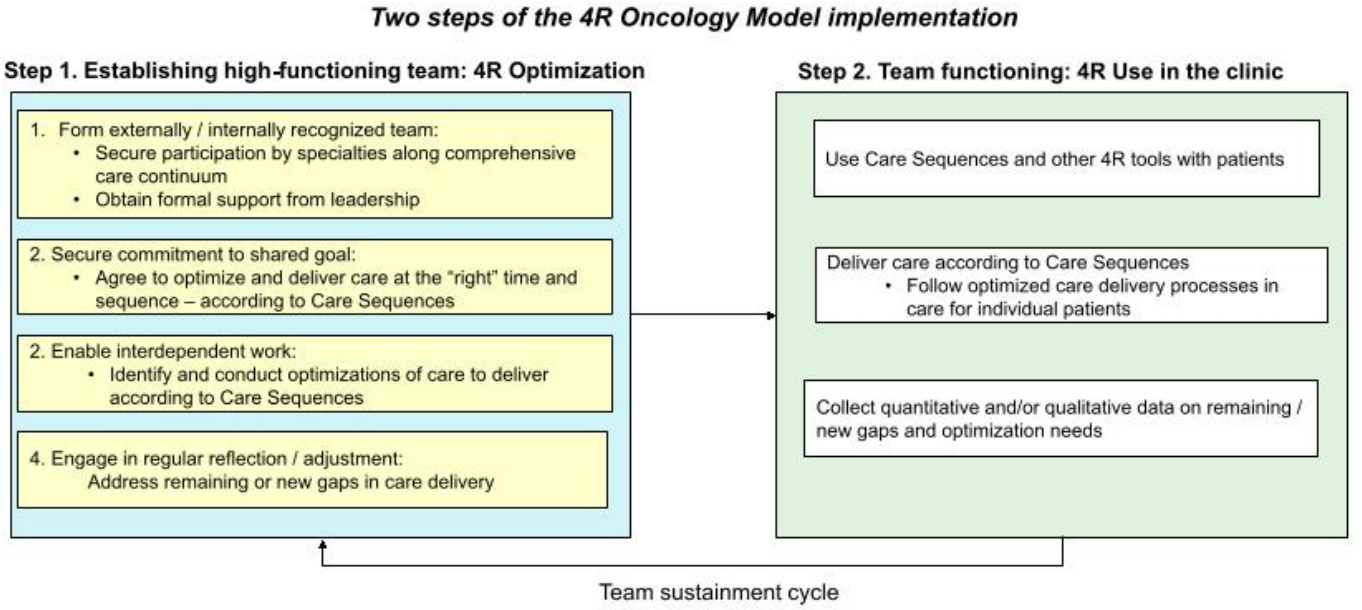

FIG 2. 4R oncology model as a mechanism for establishing and operating high-functioning teams. Items 1-4 are the four characteristics of high-functioning teams (Vogel et al).[23]

Deviations, delays, or unmet referrals serve as feedback to step 1, as described above.

Supporting Team Resilience Across Diverse Settings and Geographies

By explicitly mapping care interdependence, 4R strengthens team-level resilience across diverse settings by allowing teams to anticipate bottlenecks, adjust workflows in response to staffing or capacity constraints, and recover from disruptions. Shared structures, particularly Care Sequences, reduce reliance on informal workarounds and shift coordination from individual effort to collective accountability. Resilience thus becomes a team capability rather than an individual attribute.

The model is adaptable across academic, community, safety-net, and low- and middle-income country settings. Care Sequences are grounded in internationally used guidelines, such as National Comprehensive Cancer Network (NCCN), ASCO, and European Society for Medical Oncology, and can be tailored to local workforce and infrastructure availability. In LMICs, where resources may be limited, Care Sequences can define feasible care pathways, clarify referral networks, and prioritize time-sensitive interventions. Their visual format supports understanding across language and health literacy differences and facilitates coordination among distributed teams. Teams can focus on high-impact interdependencies, such as timely pathology review or treatment initiation. Even with limited capacity, explicit management of timing/sequencing reduces fragmentation and improves reliability. 4R therefore serves as scalable infrastructure for resilient cancer care delivery across resource levels.

Nevertheless, success of 4R implementation depends on infrastructure, data systems, workforce capacity, and institutional readiness, including leadership support and multidisciplinary collaboration. Implementation may be constrained by local resources and context, requiring context-specific adaptation and, in some settings, incremental adoption to achieve full benefit.

THE IMPERATIVE OF PATIENT AS MEMBER OF THE CARE TEAM WITH CAPACITY FOR SELF-MANAGEMENT

Effective oncology care requires not only coordinated clinicians but also engaged patients who function as active members of the care team. Contemporary cancer care spans specialties, settings, and time points, with most symptom monitoring, appointment coordination, and transition management occurring outside the clinic. Reliable care delivery therefore depends on patients who understand the care plan, its timing and sequencing, and their role within it.[32]

It is recognized that patients and families assume responsibility for managing cancer as both an acute and chronic condition and must be supported as members of the care team.[34] This requires that patients have capacity for self-management, defined as the individual's ability to manage symptoms, treatment, and the physical and psychosocial consequences of disease. In cancer, this extends beyond symptom control to include monitoring one's condition, adhering to complex regimens, coordinating across providers and settings, and sustaining health behaviors over time.[34] Importantly, patient self-management is an evolving and distinct field focused on patients' capacity to manage illness and care processes and should be distinguished from self-efficacy as applied to health professionals or educators.

Cancer disrupts a person's sense of control. Diagnosis, complex treatment decisions, symptoms, uncertainty, and

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TABLE 1. Team Formation: Actions and Output

Action	What the Team Does in Practice	Role of Care Sequences	Typical Participants	Practical Output
Forming the team	Identify all specialties and external partners whose actions affect care timing or sequencing across the patient's care trajectory	Make interdependencies explicit and assign responsibility for each element of care	Disease-specific clinicians, diagnostics, nursing/navigation, supportive care, external service providers; institutional and practice leadership	Clearly defined team membership, roles, and accountability for care delivery in the optimal time and sequence
Building commitment to shared goals	Jointly define when care should occur and how different care activities depend on one another	Provide a shared, patient-centered timeline that aligns specialty input	Same as above, with clinical leads	Agreed timing and sequencing of care, shared understanding of responsibilities
Enabling interdependent work	Identify delays, omissions, or misaligned sequencing and prioritize feasible improvements	Highlight where delivered care deviates from intended sequence	Multidisciplinary subgroups formed around specific interdependencies	Targeted care optimizations that improve reliability and efficiency
Embedding reflection and adaptation	Regularly review delivered care against intended timing and sequencing and adjust processes as needed	Serve as the reference point for monitoring, learning, and refinement	Core team, with leadership involvement as needed	Updated care sequences, workflows, and sustained team performance over time

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fear of recurrence leave patients feeling overwhelmed or dependent. Fostering self-management restores agency—the belief that one can understand the care plan, participate in decisions, and respond to symptoms and life changes.[40]

Psychologically, self-management promotes lower distress and greater resilience. Patients capable of managing symptoms, navigating appointments, and coping with uncertainty experience less helplessness.[41,42] For survivors, confidence in monitoring symptoms and seeking help appropriately reduces hypervigilance and fear of recurrence.[43-45]

Behaviorally, self-management enables health-promoting actions: Patients are more likely to adhere to medications, attend follow-up visits, engage in physical activity, and manage fatigue or pain proactively. These behaviors depend not only on information but also on the belief that one's actions matter. Without self-management, even well-designed care plans can feel burdensome.[46]

Clinically, supporting self-management reflects the chronic nature of modern cancer care. Many patients live for years with surveillance, late effects, or long-term therapy. Self-management enables patients to distinguish manageable symptoms from those requiring medical attention, promoting appropriate care use.[43]

Ethically, promoting self-management respects autonomy without abandoning patients to complexity. It reframes autonomy as supported capability—the ability to make informed choices and express preferences with confidence, particularly for those facing structural barriers within health care.[40]

Self-management requires a willing and able patient who assumes responsibility in collaboration with clinicians. For team-based care, two aspects are central: the ability to organize care and to follow the agreed plan. Organizing care entails understanding the sequence of diagnostic and therapeutic steps, scheduling and preparing for appointments, tracking results, coordinating referrals, and anticipating transitions. Following the care plan requires clarity about timing, dependencies, and medication and referral completion.[6]

Promoting self-management benefits all members of the cancer clinical team. Patients who feel capable and engaged often communicate more clearly, participate more productively in shared decision making, and experience less decisional regret. This can support more trusting, collaborative relationships.[40] Patients capable of self-management can better understand and follow the care plan, thus improving care adherence and contributing to better outcomes. This benefits not only care team but also the institution.[8,33]

Recognizing patients as team members is therefore operationally necessary. High-functioning teams must equip patients with the structure and support needed to understand, organize, and execute their care, thereby strengthening timing, sequencing, and overall reliability of care delivery. Embedding patient self-management into clinical care pathways requires thoughtful implementation approaches and may require structural changes at the organizational level.[7]

Although oncology patients typically receive education about their diagnosis, treatment, and possible side effects, there is a shortage of strategies and tools to facilitate patient self-management and engagement as care team members.[32-34] The 4R model addresses this need and operationalizes the imperative of patient self-management by positioning the Care Sequence as a tool for both care team and the patient. Introducing and personalizing Care Sequences at key planning encounters, teams transform abstract treatment plans

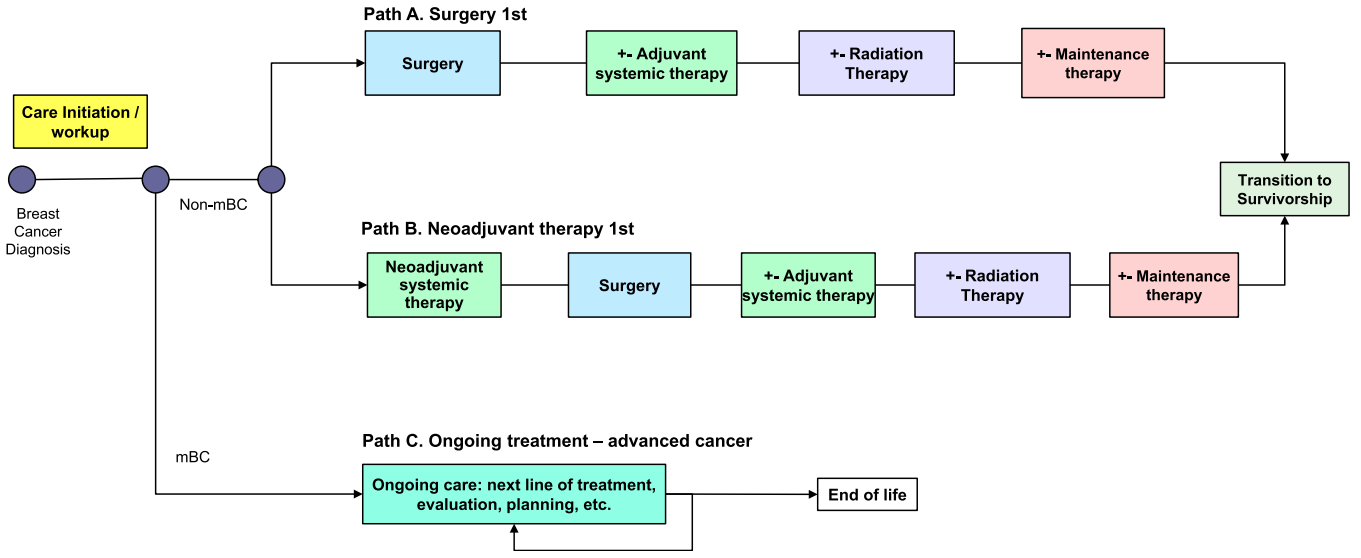

FIG 3. Succession of Care Sequences along the cancer care continuum: example of breast cancer. Each box corresponds to a specific 4R Care Sequence template. Use of specific Care Sequence templates is based on the point in a patient's care continuum. One patient may receive multiple Care Sequences over time. mBC, metastatic breast cancer.

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into a shared, time-anchored trajectory.[6,7] This enables patients to anticipate milestones, prepare for transitions, track completion of indicated services, and recognize when care is off-sequence.

Prior multicenter evaluation of 4R in early-stage breast cancer demonstrated that patients receiving Care Sequences reported significantly greater clarity of their overall care plan and of the timing and sequencing of care, as well as improved ability to manage and organize their care, compared with historical controls. Patients also reported greater knowledge of their cancer stage and were less likely to feel overwhelmed or not in control, underscoring the model's impact on core dimensions of self-management.[36]

Critically, patient understanding of timing and sequencing is not ancillary, but foundational to effective team participation. When patients know what should happen next and why, they are better equipped to coordinate appointments, follow through on referrals, report missing results, and raise concerns about delays. In this way, self-management reinforces team reliability and reduces fragmentation, while reducing clinicians' burden.[8] Embedding Care Sequences into routine workflows thus strengthens both patient agency and team performance, advancing high-functioning, resilient cancer care.

NONPHYSICIAN PROFESSIONALS AS MEMBERS OF A HIGH-FUNCTIONING TEAM: WORKING WITH YOUR EXISTING RESOURCES TO DELIVER TEAM-BASED CARE

Comprehensive cancer care is widely recognized as a hallmark of quality. Yet, multidisciplinary collaboration is often operationalized primarily among physician specialties through tumor boards or multidisciplinary clinics. Although physician alignment is essential for treatment decisions, it is insufficient for reliable care execution across the continuum. High-functioning oncology teams require a broader composition that integrates nonphysician professionals whose work directly shapes timing, sequencing, and continuity of care.[14,35]

Nurses, APPs, social workers, genetic counselors, patient navigators, community health workers, nutritionists, rehabilitation specialists, pharmacists, palliative care clinicians, and psychologists address clinical, psychosocial, and logistical needs that influence treatment adherence, symptom burden, and outcomes. When these roles are not systematically integrated, care coordination becomes informal and vulnerable, and patients and families are left to bridge gaps. Intentional inclusion of nonphysician professionals strengthens reliability, reduces fragmentation, and distributes coordination workload, supporting workforce sustainability and well-being.[47]

National and international guidelines underscore this broader definition of team-based care.[48] Recommendations from NCCN, ASCO, and accreditation bodies emphasize distress screening, navigation, psychosocial services, survivorship planning, and supportive care as core program components.[49–51] Social determinants of health—such as transportation barriers, financial toxicity, housing instability, and caregiver strain—directly affect timely care delivery.[52,53] Social workers and navigators are often central to identifying and mitigating these risks. Similarly, nutrition, rehabilitation, behavioral health, and palliative services influence treatment tolerance, functional status, and goal-concordant care. Failure to integrate these domains undermines patient-centered care and compromises outcomes.[3]

Because of their essential roles in care, nonphysician professionals must be positioned not merely as executors of care plans but as active contributors to team design and

performance. Teams that rely exclusively on physician leadership for workflow redesign risk overlooking frontline operational realities. High-functioning teams incorporate the perspectives of those who manage day-to-day coordination, symptom monitoring, and patient communication, thereby aligning strategy with practice.[14,54]

The 4R oncology model illustrates how nonphysician professionals can be structurally embedded into high-functioning teams. In formal evaluations, implementation of 4R engaged diverse professionals—including nurses, navigators, pharmacists, social workers, and external partners—across 24 specialties in targeted optimizations of interdependent care.[37]

Within 4R step 1 (optimization), nonphysician professionals should participate in defining Care Sequences, identifying breakdowns in timing and sequencing, and designing feasible workflow optimizations (Fig 2). For example, nurses, navigators, and other relevant nonphysician professionals often identify delays in genetic testing, biomarker reporting, distress referrals, or vaccinations. In prior implementations, optimizations included moving supportive services earlier in the trajectory, standardizing referral triggers, and clarifying accountability for delivery of care. By engaging nonphysician professionals in care optimizations, teams enable interdependent work across clinical and supportive domains.

Within 4R step 2 (clinical use), nonphysician professionals serve as stewards of Care Sequences in daily practice. Nurses, APPs, and/or navigators review Care Sequences with patients, confirm milestones, track completion of indicated services, and coordinate referrals. Navigators and social workers address identified barriers—transportation, financial assistance, or caregiver support—before they disrupt treatment timing. Pharmacists and rehabilitation specialists ensure that supportive care aligns with scheduled therapy. These professionals report deviations from intended timing/sequencing through feedback loops for system-level refinement. In this way, nonphysician professionals operationalize interdependence, transforming Care Sequences from static documents into active coordination tools.

Staffing models vary across academic centers, community practices, safety-net institutions, and global settings. High-functioning teams do not depend on idealized staffing but on intentional role design. Institutions may deploy role-sharing, cross-training, telehealth, or community partnerships to deliver key supportive functions. Clarity is essential regarding who is accountable for distress screening, comorbidity optimization, vaccination, dental evaluation, functional assessment, and survivorship transition—and how these services connect to disease-directed therapy within the care sequence.

As oncology complexity grows and workforce pressures intensify, integration of nonphysician professionals becomes foundational to resilience.[16] By distributing coordination responsibilities across defined roles and embedding supportive care into shared structures, teams reduce reliance on individual ad hoc efforts and informal workarounds.[4] Structured engagement of nonphysician professionals strengthens anticipation of bottlenecks, adaptation to constraints, and recovery from disruption—core components of resilient cancer care delivery.

FROM FRICTION TO FUNCTION: GUIDING TEAMS THROUGH CONFLICT

High-functioning oncology teams are not defined by the absence of conflict, but by how they navigate it. In interdependent cancer care, friction reflects diverse expertise, competing priorities, and professional identities interacting around complex decisions. The objective is not to eliminate disagreement but to transform it into learning, alignment, and system improvement.

The Hidden Costs of Team Dysfunction

Conflict in time- and resource-constrained MDT environments compounds existing burdens. Health care workers spend an average of 2.8 hours weekly managing workplace conflict,[55] and 40% of team conflicts carry potential consequences for patient care quality.[56] Direct costs include rework from sequencing errors, duplicated tests, delayed treatment starts, and coordination failures.[57] Evidence from teamwork training interventions demonstrates improvements in safety culture and reductions in adverse events,[58] suggesting dysfunction imposes substantial waste.

Traditional frameworks categorize conflict as task-focused or relational.[59] This binary fails in practice—disagreements about care pathways, clinical decisions, and science feel different when shaped by relational history or hierarchies, and emotions, power dynamics, and systemic pressures.[60] Navigating conflict well requires understanding its sources, our cognitive approach to it, and how we use it productively.

A Multidimensional Framework for Teams: The SOCS Approach

We can help our teams function by using a framework to understand the domain of complex conflict we need to address. The SOCS Framework—self, others, content, and situation—provides structure for navigating this complexity.[61]

Self (intrapersonal): What each person brings—cognitive dissonance, emotional responses, and identity tensions. Self-work asks: *What am I making this mean? How is my perspective shaping this conflict?*

Others (interpersonal): Relational history, communication patterns, and authority dynamics. Others work asks: *What structural pressures are they navigating?*

Content (substantive): The actual technical problem—contested evidence, process disagreements, and competing

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priorities.[59] Content work asks: *Where does genuine uncertainty exist*?

Situation (contextual): Forces beyond individual or team control—resource constraints, cultural norms, and systemic inequities.[62] Situation work asks: *What systemic forces are shaping this*?

These domains interact continuously. A Care Sequence timing disagreement intensifies when one clinician carries unacknowledged uncertainty (self), relational history exists between specialties (others), the clinical question lacks consensus (content), and institutional metrics prioritize throughput (situation).

A Critical Pattern: When Uncertainty Activates Self and Others

Teams primarily focus on content and situation during interdisciplinary care—these domains contain the science and logistics. However, when conflict arises, self and others can become disproportionately prominent—especially amid clinical uncertainty. When data cannot settle the question, individuals can shift from what is right for the patient to whether they are right, which becomes fundamentally about who they are. This shift from patient-centered content to identity protective self explains why technically sound solutions meet resistance.

Data alone rarely resolve conflicts where self-dimensions remain unaddressed. A clinician facing identity threat may resist even clear evidence. The SOCS framework becomes essential: Before examining data objectively, individuals must recognize their own framing and defensive reactions. Data work most effectively paired with reflection in action—noticing one's resistance and moving one's interpretive lens from subject to object.

A Coaching Stance: Leading Through Questions

The impulse when facing conflict is to solve it. This fails because it locates expertise in the leader rather than developing team capacity.[63] A coaching stance leads through questions that help teams navigate complexity.[64] Conflict competence becomes a *team capability, not just a leadership skill*. Through dynamic subordination,[65] leadership flows to whoever holds the most relevant expertise regardless of formal authority, and the SOCS framework distributes this capacity rather than concentrating it in hierarchy.

The discipline lies in not rushing to content before exploring self and others—premature problem-solving breeds resentment.[66] Each domain offers leverage but poses limits when over-emphasized: excessive self-focus pathologizes individuals for systemic problems; excessive content focus creates the illusion that protocol alone resolves conflicts; excessive situation focus excuses harmful behavior.

Implications for Team Resilience

SOCS and coaching techniques enhance capacity to build resilient teams by addressing conflict as opportunity for learning rather than failure.[67] Coaching questions surface concerns early (*anticipation*). When Care Sequences reveal gaps, SOCS helps teams explore dimensions before revising workflows (*adaptation*). When conflicts escalate, coaching prevents fragmentation through dynamic subordination (*recovery*). We should continue learning from existing conflict management frameworks,[59,68] and adding a coaching perspective integrated with SOCS enhances leaders' and teams' capacity to reduce conflict and build resilience.

UNITING ACROSS TIME ZONES: BUILDING TEAMS FOR GLOBAL CANCER CARE

The world is increasingly interconnected and nowhere is this interdependence more evident than in cancer care. As cancer incidence rises globally and disparities in outcomes persist, transnational collaboration has become essential to advancing equitable, high-quality oncology care. Building effective teams across time zones enables the sharing of scientific knowledge, clinical expertise, and educational resources, accelerating progress in both research and patient care.

Cancer epidemiology and tumor biology vary substantially across populations because of differences in genetic ancestry, environmental exposures, and infectious etiologies. International consortia and biorepository networks allow investigators to pool biospecimens, genomic data, and clinical outcomes, increasing statistical power and enabling discoveries that would otherwise be impossible. For example, the National Institutes of Health partnered with AfrECC, a consortium of more than 80 physicians and scientists across nine African countries, to conduct large genome-wide association studies that led to the identification of novel genetic risk factors in esophageal cancer.[69] These findings not only advance our understanding of esophageal cancer in African populations but also expand the knowledge of cancer biology more broadly. ASCO has supported similar efforts through global research initiatives, collaborative grants, and partnerships that promote data sharing and capacity building across diverse health systems.

Clinical collaboration is equally important. Many low- and middle-income countries face shortages of oncology specialists, health care infrastructure, diagnostic tools, and access to essential medicines. Transnational partnerships can strengthen health systems by building capacity and developing sustainable programs. For example, World Child Cancer uses the concept of twinning to bring together top-notch institutions in high-income countries with hospitals in LMICs to help facilitate training of local expertise, sharing clinical and research protocols and expanding infrastructure.[70] Partnerships like that of St Jude's Children's Hospital with a public hospital in Recife, Brazil, have significantly reduced relapse and improved event-free survival in children with ALL.[71] Other examples include the

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work of the Academic Model Providing Access to Healthcare and Indiana University with Moi University and Moi Teaching and Referral Hospital in Eldoret, Kenya.[72-75]

Beyond these types of formal one-on-one institutional partnerships, there are other models of facilitating international clinical collaborations. For example, ASCO partnered with the World Economic Forum, World Bank, and the NCI among other academic and pharmaceutical organizations to become a founding partner of City Cancer Challenge (C/Can) 2025, which seeks to increase access to quality cancer care in cities throughout the world.[76] ASCO's multidisciplinary cancer management courses also promote cross-border collaboration by bringing local and international experts together to address regionally relevant clinical challenges, strengthen local tumor boards, and improve care delivery. Workshops have highlighted the need for multidisciplinary collaboration and shared best practices on making tumor boards work more efficiently.[77] Where needed, virtual multidisciplinary tumor boards and Project ECHO initiatives allow ongoing consultation across geographic boundaries.[78] Given the considerable variability in resource settings worldwide, collaboration on resource-stratified clinical guidelines is also essential. Initiatives such as the Global Breast Health Initiative have helped establish evidence-based standards tailored to differing levels of health care infrastructure.[79]

Finally, international educational exchanges expose trainees and faculty to diverse disease patterns, care models, and cultural contexts. ASCO's international education programs, including the International Development and Education Award which pairs junior faculty from low- and middle-income countries with mentors in the United States, promote bidirectional knowledge exchange and workforce development while strengthening local leadership capacity.

Across all domains, building effective international teams requires intentional effort. Conferences like ASCO's Annual Meeting facilitate initial connections and collaboration. Sustained partnerships, however, demand thoughtful coordination across time zones. Cultural and intellectual humility, shared goal setting, and realistic expectations regarding institutional capacity are all critical. Despite these challenges, transnational collaboration offers a powerful opportunity to advance research, improve clinical care, and strengthen oncology education, all of which ultimately improves cancer care for patients worldwide.

CONCLUSION

Delivering contemporary cancer care requires coordinated action across specialties, settings, and time points. High-functioning teams provide the structure needed to translate multidisciplinary decisions into reliable execution of care across the cancer continuum. The 4R oncology model offers a practical framework for operationalizing such teamwork by explicitly managing the timing and sequencing of interdependent care and aligning clinicians and patients around shared Care Sequence plans denoting care trajectory. Implementation experience demonstrates that targeted workflow optimizations can improve care reliability and efficiency while strengthening collaboration across specialties.

Effective teams also extend beyond physician collaboration. Patients and nonphysician professionals, including nurses, navigators, and supportive care specialists, play essential roles in coordinating care and sustaining continuity throughout the cancer care trajectory.

As oncology becomes increasingly interconnected, the ability to navigate disagreement constructively and collaborate across institutions and geographies is critical. Approaches that transform conflict into learning, along with teamwork that spans organizations and time zones, will help build resilient oncology teams capable of advancing coordinated cancer care worldwide.

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Improving Affordability in Cancer Care for Resource-Limited Settings: Highlights From *JCO Global Oncology*

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OVERVIEW

By 2045, more than three quarters of global cancer deaths are projected to occur in low- and middle-income countries (LMICs); however, the global availability of cancer care remains constrained by high costs and inequitable access. Value-based frameworks that integrate clinical benefit with affordability, feasibility, and equity are essential to better guide research prioritization, resource allocation, and regulatory policies in LMICs. A key component of a value-based approach is the generation of high-quality, locally relevant data to support evidence-based implementation of cancer prevention and control strategies. Herein, we provide three contemporary examples from *JCO Global Oncology* which demonstrate how economic evaluation in cancer research can address locally relevant, health system–specific questions.

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INTRODUCTION

Cancer exerts a disproportionate burden in low- and middle-income countries (LMICs), accounting for approximately 61% of global cancer cases and 71% of cancer deaths globally.[1,2] By 2045, more than three quarters of global cancer deaths are projected to occur in LMICs.[3] By contrast, LMICs receive <5% of global cancer control resources.[4] Patients in LMICs face profound barriers to timely cancer diagnosis and treatment, including limited screening programs, inadequate diagnostic imaging and pathology capacity, and restricted access to cancer therapies.

Globally, the availability of cancer therapies remains constrained by high costs and inequitable access, particularly in LMICs. Access to radiotherapy—a cornerstone of curative therapy—is especially constrained, with LMICs possessing only 9% of global radiotherapy resources.[5] Systemic therapies represent another critical gap, with only 32%-58% of anticancer drugs listed on the WHO Essential Medicines List routinely available.[6] High prices and low coverage result in substantial out-of-pocket expenditures.[7] Financial toxicity associated with cancer diagnosis represents a major structural barrier in LMICs and may drive up to 100 million individuals into poverty annually.[8,9] Consequently, high rates of treatment abandonment contribute to substantial disparities in survival outcomes.[7]

Concurrently, the costs of cancer care continue to increase because of scientific discovery, increasing cancer burden, and longer life expectancies. In 2023, global cancer care expenditures reached $223 billion US dollars (USD) and are projected to increase to $409 billion USD by 2028.[10] Multiple studies have demonstrated weak or even negative correlations between treatment costs and survival gains.[11-13] Furthermore, the traditional efficacy-driven paradigms are insufficient for resource-limited health care systems, where infrastructure constraints and competing health priorities must also be considered.[14] Value-based frameworks that integrate clinical benefit (eg, survival and quality of life) with affordability, feasibility, and equity are thus essential to better guide research prioritization, resource allocation, and regulatory policies in LMICs.[15]

A key component of this value-based approach is the generation of high-quality, locally relevant data to support evidence-based implementation of cancer prevention and control strategies. However, LMIC populations remain substantially under-represented in clinical trials, with only 8% of randomized controlled trials globally led by LMIC investigators. Among trials led by high-income countries, only 29% include patient recruitment from LMICs.[16,17] Moreover, a few randomized trials explicitly aim to improve the equity, affordability, or feasibility of cancer care in LMIC settings.[17,18] Given substantial differences in cancer epidemiology, health system capacity, sociocultural context, medicine availability, and tumor biology between LMICs and HICs, pragmatic and context-appropriate trials are urgently needed to generate evidence that is directly applicable to resource-constrained settings.

Thus, robust data on the efficacy and cost-effectiveness of alternative approaches are essential to guide clinical practice and policy in resource-constrained settings. In this article,

PRACTICAL APPLICATIONS

- Value-based oncology frameworks that integrate clinical benefit with affordability, feasibility, and equity can more effectively guide research priorities, resource allocation, and policy decisions in LMICs.
- Cost-effectiveness and budget-impact analyses from Brazil show that using OncotypeDX to guide adjuvant chemotherapy decisions for patients with early stage breast cancer is likely to have a long-term positive economic impact, despite up-front costs.
- Real-world data and emerging trials of low-dose immunotherapy show that dose de-escalation strategies can help expand access to ICIs while reducing financial toxicity in resource-constrained settings.
- LMIC-led randomized trials of oral metronomic regimens provide level I evidence for low-cost, feasible treatment options for head and neck cancers that have already influenced regional practices and guidelines.
- Other value-focused approaches include optimizing treatment sequencing and rigorous evaluation of biosimilars and generics to lower costs and toxicity without compromising survival outcomes.

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we review three recent studies published in *JCO Global Oncology* that evaluate diagnostic and therapeutic strategies designed to improve the value of cancer care in LMICs. Each study provides insights into value-based oncology frameworks for resource-constrained health systems, with important implications for future research agendas and policy development.

Case 1: Oncotype DX Breast Recurrence Score Test

Health technology assessment (HTA) plays a pivotal role in promoting the sustainability of health systems, particularly in LMICs, where finite resources must be carefully allocated to maximizing population health. Molecular tests pose significant challenges to HTA, in that they may lead to higher immediate costs (eg, purchase costs) and/or indirect costs (eg, increases in determining appropriateness of access to costly therapies). Oncotype DX is a widely used molecular assay in high-income settings which is included in guidelines for use in refining prognostic information and predicting benefit from adjuvant chemotherapy in patients with early-stage breast cancer.[19] However, reimbursement has been an issue in Brazil and other countries because its up-front purchase cost is perceived as too high by payors. The objective of this study was to evaluate the clinical and economic impact of the Oncotype DX genomic test in patients with breast cancer from the perspective of the Brazilian private health insurance system.

The Brazilian health system comprises two major subsystems with distinct financing structures: the Unified Health System (Sistema Único de Saúde [SUS]), a tax-funded universal public system, and the private health insurance sector, which is regulated by the National Supplementary Health Agency (ANS). For both, the incorporation of new technologies depends on formal HTA processes that evaluate clinical effectiveness, safety, cost-effectiveness, and budget impact to support coverage decisions and ensure financial sustainability.

Currently, the Oncotype DX genomic assay is not routinely reimbursed in Brazil by either SUS or the private sector. Breast cancer represents a substantial disease burden in the country.[20] In early-stage hormone receptor–positive, human epidermal growth factor receptor 2–negative disease, adjuvant chemotherapy is frequently prescribed based on clinical-pathologic criteria, which may lead to overtreatment and unnecessary toxicity for a portion of patients. Genomic testing has emerged internationally as a strategy to risk stratify and guide treatment decisions.[21,22] The authors hypothesized that by identifying patients unlikely to benefit from chemotherapy, Oncotype DX would reduce chemotherapy utilization and its associated costs and adverse events. Conversely, it can also identify a subset of patients initially considered to be at low clinical risk who harbor higher genomic risk and may benefit from chemotherapy, thereby improving the precision of treatment allocation.

Zimmermann et al[23] conducted a cost-effectiveness analysis to estimate the economic impact of incorporating Oncotype DX to guide adjuvant chemotherapy decisions in the Brazilian private health care system. The model combined a decision tree with a Markov structure, including transitions among recurrence-free survival, distant recurrence, acute myeloid leukemia, and death. Distant recurrence probabilities were derived from the TAILORx[21] and RxPONDER[22] trials and complemented with local data on utilities and overall survival (OS).[24] Deterministic scenario analyses and probabilistic sensitivity analyses using Monte Carlo simulations were performed.

Compared with clinical-pathologic risk assessment alone, the use of Oncotype DX in both node-negative (N0) and node-positive (N1) patients resulted in gains of 0.15 quality-adjusted life-years (QALYs) and lower overall costs (−$4,469.44 USD), indicating dominance (greater effectiveness at lower cost). The main drivers of results were chemotherapy costs, chemotherapy prescription rates, and test price. Considering the Brazilian cost-effectiveness thresholds ($8,000-$24,000 USD per QALY), probabilistic sensitivity analyses showed a high probability of cost-effectiveness across all evaluated scenarios.

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A complementary budget impact analysis was conducted using a hybrid decision tree-Markov model with the same clinical transitions.[25] The eligible population was estimated using epidemiologic data. Subgroup analyses included N0 patients stratified by age and clinical risk and N1 patients stratified by menopausal status. Direct medical costs were assessed over 5 years without discounting. Two scenarios were evaluated: (1) progressive market uptake (40%-80% over 5 years) and (2) universal testing. The introduction of Oncotype DX was associated with 5-year cost savings of approximately $19.3 million USD in scenario 1 and $26.7 million USD in scenario 2. Incremental costs were observed only in N0 low-risk patients 50 years and younger ($9.5-$16.9 million USD) and premenopausal N1 patients ($2.2-$4.4 million USD). Overall, reductions in chemotherapy-related expenditures were expected to fully or partially offset the cost of testing, generating net savings in most subgroups.

This study supports the up-front reimbursement of Oncotype DX in the Brazilian private health care system with potential to reduce downstream expenditures through risk stratification of patients unlikely and most likely to benefit from adjuvant chemotherapy. Beyond its economic findings, it serves as an example of good scientific practice in HTA. This approach illustrates how rigorous evidence generation before regulatory submission can support more informed coverage decisions while contributing to the financial sustainability of health systems.

Case 2: Alternate Dosing Strategies for Immunotherapy

Since the approval of the first immune checkpoint inhibitor (ICI), ipilimumab, for patients with advanced melanoma, immunotherapy has led to transformative outcomes for a subset of cancers.[26] With annual treatment expenses estimated at $150,000-$200,000 USD per patient,[27] costs of ICIs at standard doses are prohibitive for the majority of patients in LMICs. In the absence of universal health coverage and sustainable financing mechanisms, access to ICIs is therefore extremely limited, contributing to major disparities in outcomes.

Unlike cytotoxic agents, ICIs do not exhibit a clear dose-response relationship.[28] Thus, alternate dosing strategies for ICIs based on known pharmacokinetic (PK) and pharmacodynamic (PD) characteristics have emerged as a potential opportunity to improve affordability. In *JCO Global Oncology*, Hoyek et al[29] published a comprehensive systematic review of the emerging body of data on what is currently known regarding the efficacy and safety of low-dose immunotherapy.

According to the phase I KEYNOTE-001 trial, ex vivo interleukin-2 stimulation assays, which are used to evaluate cytokine production as a surrogate marker of anti–PD-1 activity, showed near-complete peripheral PD-1 receptor target engagement at weight-based pembrolizumab doses as low as 1 mg/kg every 2 weeks, with sustained engagement for at least 21 days.[30] Notably, no discernible differences in target engagement were observed between doses of 1, 3, and 10 mg/kg, with dosing intervals ranging from every 2 to 3 weeks across cohorts. In addition, among patients treated across these dose levels, no dose-limiting toxicities were identified during dose escalation and a maximum tolerated dose was not reached.

Real-world and prospective data support the potential utility of reduced-dose ICIs. Multiple retrospective analyses using flat and weight-based dose reductions in NSCLC reported comparable survival outcomes with standard dosing (Table 1).[31-36] In addition, the interim results of the Dutch NVALT-30 noninferiority trial found similar outcomes between low-dose (300 mg once every 6 weeks or 100 mg once every 3 weeks) and standard-dose pembrolizumab (400 mg once every 6 weeks or 150-200 mg once every 3 weeks), with the 1-year OS of 53.4% versus 56.6% and the median OS of 13.1 versus 15.9 months (P = .45), respectively.[34] In head and neck squamous cell carcinoma, Patil et al[35] found that adding low-dose nivolumab (20 mg once every 3 weeks) to metronomic chemotherapy significantly improved 1-year OS (43.4% *v* 16.3%; hazard ratio, 0.545; P = .0036) and median OS (10.1 *v* 6.7 months; P = .0052) without increasing grade ≥ 3 toxicity. The 20 mg once every 3 weeks flat dose was selected based on PK/PD studies showing ≥70% PD-1 receptor occupancy at 0.3 mg/kg. Therefore, cost savings of 95%-99% were achieved through flat reduced dosing and vial sharing. Evidence extends to other tumor types, including renal cell carcinoma, where comparable outcomes were observed with nivolumab given once daily every 2 weeks at doses <2.15 mg/kg versus higher doses.[36]

As dose reduction is the primary strategy to improve cost efficiency, supporting evidence has been limited to retrospective analyses. Given limited generalizability of such data, a potentially more applicable strategy is the use of weight-based dosing rather than fixed dosing. Originally, pembrolizumab was approved by the US Food and Drug Administration at a weight-based dose of 2 mg/kg once every 3 weeks.[28] However, PK analyses supported a shift from weight-based dosing to a fixed dose of 200 mg once every 3 weeks or an extended-interval regimen of 400 mg once every 6 weeks. For example, in Taiwan, Chang et al reported a mean patient weight of 61.5 kg, consistent with population-level data showing average body weights of 72.2 kg in men and 57.4 kg in women.[32] By following a weight-based dosing strategy of 2 mg/kg once every 3 weeks, the estimated pembrolizumab dose required would be approximately 144 mg once every 3 weeks for men and 128 mg once every 3 weeks for women, corresponding to dose reductions of approximately 28%-36%, respectively. Adoption of weight-based dosing strategies for ICIs may better account for interpatient pharmacokinetic variability, substantially reducing treatment costs and improving accessibility in LMICs.

TABLE 1. Comparative Outcomes of Reduced-Dose Versus Standard-Dose Anti–PD-1 Therapy in Advanced Solid Tumors

Study	Design	Tumor Type	Low-Dose Regimen	Comparator	Key Outcomes
Yoo et al,[31] 2018 (Korea)	Retrospective	NSCLC	Nivolumab 20 or 100 mg once every 3 weeks	Nivolumab 3 mg/kg once every 2 weeks	OS: 12.5 *v* 8.2 months PFS: 3 *v* 1 months
Chang et al,[32] 2022 (Taiwan)	Retrospective	NSCLC	Pembrolizumab <2 mg/kg	Pembrolizumab ≥ 2 mg/kg	OS: 14.3 *v* 19.3 months (HR, 0.84 [95% CI, 0.62 to 1.14]) PFS: 2.8 *v* 3.4 months
Low et al,[33] 2021 (Singapore)	Retrospective	NSCLC	Pembrolizumab 100 mg once every 3 weeks	Pembrolizumab 200 mg once every 3 weeks	OS: 14.3 *v* 19.8 months (HR, 1.08 [95% CI, 0.48 to 2.41]) PFS: 6.8 *v* 4.2 months (HR, 0.72 [95% CI, 0.36 to 1.46])
NVALT30, 2024 (Netherlands)[34]	Prospective	Metastatic NSCLC	Pembrolizumab 300 mg once every 6 weeks or 100 mg once every 3 weeks	Pembrolizumab 400 mg once every 6 weeks or 150-200 mg once every 3 weeks	1-year OS 53.4% *v* 56.6%; mOS 13.1 *v* 15.9 months (P = .45)
Patil et al,[35] 2023 (India)	Prospective	HNSCC	Nivolumab 20 mg once every 3 weeks + TMC	TMC alone	1-year OS 43.4% *v* 16.3% (HR, 0.545; P = .0036)
Zhao et al,[36] 2021 (Singapore)	Retrospective	RCC	Nivolumab 2.15 mg/kg	Nivolumab ≥ 2.15 mg/kg	OS: not reached *v* 28.0 months (HR, 0.24 [95% CI, 0.05 to 1.15]) PFS: 7.0 *v* 7.0 (HR, 0.56 [95% CI, 0.24 to 1.30])

Abbreviations: HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TMC, metronomic chemotherapy.

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Despite the emerging evidence from multiple retrospective studies evaluating alternative dosing strategies, guideline adoption in Southeast Asia and Latin America has remained limited because of the methodological limitations and risk of bias inherent in retrospective studies, as well as the limited number of randomized noninferiority trials. In addition, guideline adoption in these regions is often influenced by Western guidelines, which generally continue to recommend standard approved dosing.[37-39] In addition to the ongoing NVALT-30 trial, other studies will further inform and optimize the delivery of ICIs in different patient populations. For example, REFINE-Lung and PULSE studies are investigating lower frequency of ICI administration at the same dose in lung cancer.[40,41]

Collectively, while prospective validation of low-dose regimens is pending, weight-based dosing may offer an immediately actionable, evidence-aligned approach that could reduce drug consumption by 25%-45% without compromising efficacy. The success of investigator-initiated trials shows that meaningful dose optimization research is achievable outside traditional industry sponsorship. Expanding these collaborative models through academic partnerships, philanthropic funding, and health system–supported initiatives will be critical to generating the robust evidence needed to inform guideline changes and broaden global access to cost-effective immunotherapy.

Case 3: Oral Metronomic Chemotherapy in Advanced Head and Neck Cancer

Recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) after platinum failure represents a therapeutic setting marked by limited durability of response, substantial symptom burden, and historically poor survival. Although ICIs and targeted therapies have demonstrated survival benefit in pivotal global trials, access to these agents remains inconsistent across many LMICs. Given that India and parts of Southeast Asia carry a disproportionately high burden of tobacco-associated HNSCC, the disconnect between evidence and access has meaningful public health implications. The development of triple oral metronomic chemotherapy (OMCT) emerged directly from this gap—with investigators seeking to determine whether a rational, low-cost, orally administered regimen could meaningfully improve survival compared with conventional salvage chemotherapy in platinum-refractory disease.

Metronomic chemotherapy refers to the continuous administration of low-dose cytotoxic agents at frequent intervals without prolonged drug-free breaks. Unlike conventional maximum tolerated dose chemotherapy, metronomic dosing primarily exerts antiangiogenic and immunomodulatory effects rather than direct tumor cytotoxicity.[42] In HNSCC, angiogenesis, EGFR signaling, and inflammation play central roles in tumor progression. Triple OMCT combines low-dose methotrexate (antiangiogenic effect), erlotinib (EGFR inhibition), and celecoxib (COX-2 pathway modulation), thereby targeting complementary oncogenic pathways.

This strategy was grounded in three principles: (1) sustained microenvironment modulation may provide durable disease control, (2) continuous low-dose therapy may reduce severe toxicity compared with conventional chemotherapy, and (3) use of widely available generic drugs enhances affordability and scalability. Importantly, the

TABLE 2. Key Clinical Studies Evaluating Oral Metronomic Chemotherapy Strategies in Head and Neck Squamous Cell Carcinoma

Study	Design	Tumor Type	Regimen	Comparator	No. of Patients and Key Outcomes	Clinical Significance
Patil et al,[43] 2019 (India)	Phase I/II, single-arm	R/M HNSCC, platinum-refractory	Low-dose methotrexate-based metronomic regimen	Historical control	N = 91 Feasible; acceptable toxicity; signal of survival benefit	Established safety and biological rationale for metronomic approach
Patil et al,[35] 2023 (India)	Phase III randomized	R/M HNSCC	Triple OMCT with or without low-dose nivolumab	OMCT alone	N = 151; improved 1-year OS from 16.3% to 43.4% with addition of low-dose ICI; manageable toxicity	Demonstrated immunologic synergy and feasibility of the low-dose ICI strategy
Kapoor et al,[44] 2025 (METRO-CHASE) (India)	Phase III randomized	R/M HNSCC, postplatinum	Triple OMCT (celecoxib + methotrexate + erlotinib)	Physician's choice chemotherapy	N = 214 Improved OS and PFS; favorable toxicity profile	Provided level I evidence supporting OMCT in platinum-refractory disease
Kapoor et al,[45] 2026 (METRO-PLUS) (India)	Phase III randomized	Advanced unresectable HNSCC	Paclitaxel + carboplatin + triple OMCT	Paclitaxel + carboplatin	N = 238; improved disease control and survival end points; acceptable toxicity	Validated metronomic therapy as augmentation to the chemotherapy backbone
Kashyap et al,[46] 2021 (India)	Prospective study	Technically unresectable OSCC (neoadjuvant)	Paclitaxel + carboplatin + triple OMCT	None (single-arm)	N = 14 High response rate; achieved resectability in 65%; tolerable toxicity	Supported role of OMCT in borderline/locally advanced disease
Ongoing TMCi RCT (India)	Randomized controlled trial (recruiting)	Resectable HNSCC	Triple OMCT + low-dose nivolumab	Up-front surgery followed by standard adjuvant (no IO)	Planned n = 348, presently recruiting	Evaluating affordability-conscious intensification in the curative setting
Marimuthu et al,[48] 2026 (India)	Prospective phase II study	Borderline resectable OSCC	Nab-paclitaxel + carboplatin + triple OMCT + low-dose nivolumab	None	N = 34, 90.3% conversion rates	Affordable, outpatient chemo-immunotherapy approach that improves surgical conversion

NOTE. Please note that the outcomes summarized represent the primary efficacy findings reported in the respective studies.

Abbreviations: HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; OMCT (triple OMCT), oral metronomic chemotherapy consisting of low-dose methotrexate, erlotinib, and celecoxib administered continuously without prolonged treatment breaks; OS, overall survival; OSCC, oral squamous cell carcinoma; PFS, progression-free survival; R/M, recurrent or metastatic disease; RCT, randomized controlled trial; TMCi, triple metronomic chemotherapy combined with immunotherapy.

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regimen was designed with implementation feasibility in high-volume public sector oncology centers in mind; the oral administration reduces infusion infrastructure demands and limits hospital visits.

The development of triple OMCT evolved through a stepwise clinical research pathway beginning with early phase I/II studies.[43] Initial single-arm phase I/II trials evaluated low-dose methotrexate-based metronomic regimens in recurrent/metastatic HNSCC, establishing feasibility, safety, and signals of durable disease control in heavily pretreated patients.[43] These early studies demonstrated acceptable toxicity, improved symptom control, and encouraging survival outcomes compared with historical controls, thereby providing biological and clinical justification for the addition of erlotinib and celecoxib. The favorable safety profile and preliminary efficacy observed in these exploratory trials laid the foundation for subsequent randomized phase III evaluation in the METRO-CHASE study, representing a methodical progression from proof-of-concept to level I evidence.

The METRO-CHASE phase III randomized study compared triple OMCT with physician's choice chemotherapy in patients with R/M HNSCC progressing after platinum-based therapy.[44] The trial demonstrated a statistically significant improvement in OS and progression-free survival in the metronomic arm, alongside a manageable toxicity profile. Compliance rates were favorable, reflecting the practicality of oral administration.

The clinical significance of METRO-CHASE lies in several domains. First, it represents one of the few randomized phase III trials conducted in a resource-constrained setting addressing platinum-refractory HNSCC. Second, the comparator arm reflected real-world salvage options rather than idealized trial conditions, enhancing external validity for LMIC practice. Third, the survival benefit was achieved without escalating toxicity or resource utilization.

These findings challenged the assumption that incremental survival gains in refractory HNSCC require high-cost biologics. Instead, they demonstrated that rational repurposing of existing agents, tested in a rigorous randomized framework, can generate clinically meaningful outcomes.

Triple OMCT has become an accepted therapeutic option in India for platinum-refractory R/M HNSCC, particularly in settings where ICIs are not accessible. Its advantages include the following: (1) oral administration with minimal requirement for infusion infrastructure, (2) lower drug acquisition cost for generically available drugs, (3) lower rates of high-grade myelosuppression relative to many cytotoxic regimens, and (4) improved feasibility in nutritionally compromised and frail patients. Beyond individual patient benefit, the regimen results in lower financial toxicity and indirect costs, including travel and caregiver burden. In public health terms, OMCT improved the incremental value proposition of second-line systemic therapy in HNSCC.

The success of triple OMCT catalyzed further investigation into metronomic therapy as a combinatorial platform. Subsequent phase III investigations performed by our group have evaluated the addition of triple OMCT to paclitaxel-carboplatin in advanced unresectable HNSCC. A randomized, open-label study demonstrated improved disease control when metronomic therapy was added to chemotherapy, without disproportionate toxicity.[45] These findings support the hypothesis that continuous antiangiogenic and microenvironment modulation may enhance the efficacy of cytotoxic backbones. This strategy is particularly relevant in LMIC settings where platinum-taxane combinations remain widely used. Incorporating a low-cost oral metronomic layer may augment therapeutic benefit while preserving cost-effectiveness.

As discussed in case 2, emerging pharmacokinetic and pharmacodynamic evidence suggests that meaningful PD-1 receptor engagement can be achieved with substantially lower doses of immune checkpoint inhibitors. This rationale provided the foundation for evaluating low-dose nivolumab in combination with metronomic chemotherapy, creating a biologically synergistic and economically feasible chemo-immunotherapy strategy for resource-constrained settings. A randomized study evaluating low-dose nivolumab added to metronomic therapy demonstrated improved 1-year OS compared with metronomic therapy alone, with acceptable safety.[35] This later approach represents a pragmatic compromise: harnessing immune checkpoint inhibition while attenuating drug cost. In health systems where full-dose ICIs are financially inaccessible, low-dose strategies combined with metronomic backbones may expand immunotherapy access. Together, these studies position metronomic therapy not as a static regimen but as a flexible scaffolding for integration of chemotherapies and/or immunotherapies to incrementally improve outcomes.

Building on its activity in the recurrent/metastatic setting, the metronomic platform has progressively moved earlier in the disease continuum. The combination of metronomic chemotherapy with standard cytotoxic backbones is now being explored in borderline resectable head and neck cancers with the aim of improving response rates, facilitating surgical resectability, and enhancing pathologic response without substantially increasing toxicity or cost. Early evidence supporting this strategy includes a prospective study demonstrating that neoadjuvant paclitaxel-carboplatin combined with oral metronomic chemotherapy achieved meaningful response rates and enabled resectability in patients with technically unresectable oral squamous cell carcinoma, with acceptable toxicity.[46] Although perioperative immunotherapy, as evaluated in KEYNOTE-689, has emerged as an approved option in resectable locally advanced head and neck cancer, its adoption in many LMIC settings remains limited by cost and access constraints.[47]

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Moreover, a proportion of patients experience early progression during the neoadjuvant phase, potentially compromising surgical outcomes. In this context, a randomized-controlled clinical trial evaluating triple metronomic chemotherapy plus immunotherapy in resectable head and neck cancer is ongoing, representing a strategic effort to develop a biologically rational, more affordable intensification approach within curative-intent treatment pathways.

The accumulation of evidence in support of the effectiveness of OMCT has influenced practice patterns and regional recommendations in India and parts of Southeast Asia. Table 2 summarizes the important studies of metronomic therapy in head and neck cancers. Institutional and regional guidelines now include triple OMCT as a valid option for platinum-refractory advanced/metastatic HNSCC not eligible to receive any curative-intent therapy, particularly when ICIs/biologics are not feasible.[49] The inclusion of metronomic strategies reflects (1) availability of phase III evidence generated within comparable health systems, (2) alignment with economic constraints of public oncology programs, and (3) scalability across tertiary and secondary oncology centers in resource-constrained settings. Importantly, this represents a paradigm shift from empiric salvage approaches to evidence-based, more affordable care.

OMCT in advanced HNSCC exemplifies a research model in which biological insight, scientific rigor, and economic pragmatism coexist. Rather than adapting high-income country standards with incremental benefits to resource-limited environments, this work originated from the realities of resource constraints in India. The metronomic program demonstrates that innovation can involve optimization of existing agents, dose modulation, and combinatorial strategies rather than exclusive reliance on novel high-cost drugs.

CONCLUSION

The three cases reviewed here each demonstrate how economic evaluation in cancer research can address locally relevant, health system–specific questions in resource-constrained settings. These examples span cost-effectiveness and budget-impact analyses of precision oncology testing, the development of locally feasible alternative chemotherapy regimens, and immunotherapy dose de-escalation studies. Collectively, these studies demonstrate how innovative, context-sensitive research can inform clinical guidelines, reimbursement decisions, and health policy, ultimately improving access to high-quality, evidence-based cancer care. Additional approaches may include optimizing treatment sequencing to reduce costs and treatment-related toxicity without compromising survival and rigorous evaluation of biosimilars and generic medicines to improve access to essential anticancer therapies.[50,51]

Looking ahead, research priorities in LMICs must focus on strengthening local capacity to generate rigorous evidence addressing context-specific questions about how best to implement high-quality, high-value cancer care. Achieving this goal will require several strategies: (1) conducting pragmatic trials to evaluate when treatment de-escalation is noninferior while reducing toxicity, (2) expanding the use of implementation science and real-world data to evaluate how global advances and guidelines can be adapted to local care pathways, and (3) integrating cost-effectiveness and budget-impact analyses into clinical trials to inform guideline development and policy decisions. By placing affordability, feasibility, and equity at the center of research priorities, these approaches offer a pragmatic roadmap for reducing global cancer disparities while maintaining the long-term sustainability of cancer care systems.

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From Passion to Persistence: Nurturing Idealistic Roots to Extinguish Burnout

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OVERVIEW

Oncology clinicians often enter oncology with a strong sense of passion rooted in curiosity, service, and early formative experiences. Over time, however, this passion is tested by escalating clinical complexity, administrative burden, workforce shortages, and competing personal and organizational demands. Evidence consistently links these pressures to moral distress, burnout, and attrition, threatening both clinician well-being and the quality of cancer care. This chapter examines the current state of well-being within the oncology workforce and explores how sustained alignment with values and purpose can transform early passion into long-term professional persistence. Drawing on the literature from oncology, organizational psychology, and behavioral science, this work reframes well-being as a dynamic interaction between individuals, teams, and systems. The chapter also introduces contemporary concepts including values-based practice, harmonious versus obsessive passion, advocacy as a form of spiritual and meaning-centered activity, and personal growth through embracing discomfort. Practical, evidence-informed interventions are presented at individual, team, organizational, and system levels, emphasizing psychological flexibility, codesign, enabling systems, and continuous quality improvement. A three-tiered implementation framework is proposed to clarify accountability and reduce overreliance on individual resilience. Ultimately, this chapter highlights that while passion may ignite a career, it is purpose, values alignment, and supportive cultures that sustain clinicians—protecting well-being and maintaining a compassionate and future-ready oncology workforce.

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INTRODUCTION

> "A young oncologist moved to a regional cancer centre, driven by a deep passion to improve access to care and outcomes for rural and Indigenous communities. Alongside just one other medical oncologist, they shared a strong commitment to health equity and began developing new models of care, including decentralized clinical trial models aimed at bringing research closer to patients.
>
> Despite this shared vision, progress was met with persistent and systemic barriers. Workforce turnover was high, leadership support was limited, and bureaucratic processes made it extraordinarily difficult to secure approvals for trial staffing, workforce training, and the conduct of clinical research. These obstacles stood in stark contrast to the stated commitments of healthcare organizations, regulatory bodies, and government agencies to improving health equity and access to care.
>
> All of this unfolded while the two oncologists were managing heavy clinical workloads and attempting to advocate for system-level change. Over the following three years, the cumulative strain led to growing disillusionment and brought them close to burnout.
>
> What ultimately shifted the trajectory was the introduction of mindfulness and purpose-aligned practices, knowledge and application of implementation science and clinician levers. These approaches helped them reconnect with their original values, restore emotional energy, and create a more sustainable balance between work and life. Rather than disengaging, they found renewed capacity for advocacy, a deeper sense of meaning in their work, and a revitalized passion for both their profession and life beyond it".

As exemplified in the story, oncology clinicians often enter their careers with a deep sense of passion—a spark that emerges from early exposure in school, university, or postgraduate training. This passion may stem from a fascination with science, curiosity about new models of care, involvement in clinical trials, a drive toward innovation, or a commitment to service, advocacy, and health equity. For many clinicians, especially those working in oncology, early personal experiences with illness or inspiring mentors solidify this calling.

However, passion is dynamic—it evolves over time, deepening and expanding to include diverse aspects of oncology,

PRACTICAL APPLICATIONS

- Embedding value-to-action practices in daily work can help clinicians align daily tasks with personal and professional values, sustaining meaning and reducing burnout risk.
- Shifting from individual resilience to team-based well-being infrastructure could distribute stress, reduce isolation, and normalize collective responsibility for well-being.
- Designing enabling systems that protect meaning-centered clinical work, so clinicians can spend more time in patient care, teaching, research, and advocacy—activities most closely aligned with professional purpose.
- Reframing advocacy as sustainable, meaning-centered practice can help sustain engagement and reduce moral distress.
- Institutionalizing purpose, culture, and well-being as quality indicators may ensure accountability at macro-, meso-, and micro-levels rather than reliance on individual coping strategies.

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health systems, and the wider human systems in which we live and work. As oncology clinicians move through their careers, competing demands begin to surface, increasing administrative burden, workforce shortages, political and organizational pressures, and personal responsibilities. These persistent stressors can slowly erode even the strongest intrinsic motivation. Literature consistently shows that such pressures contribute to moral distress, emotional fatigue, and burnout across oncology and other high-acuity specialties.[1-5]

This chapter focuses on the well-being of oncology clinicians. It outlines the current state of the oncology workforce, the significance of the values and purpose of the clinician, and the present-day factors driving burnout in the profession. The chapter subsequently presents value-based individual and organizational interventions that can be readily implemented to foster and maintain the sense of purpose and protect, enhance, and preserve the well-being of the oncology workforce.

THE CURRENT STATE OF THE ONCOLOGY WORKFORCE

The cancer care workforce is facing an unprecedented crisis that may affect the quality of care of patients with cancer.[6,7] Workforce shortages, combined with the growing complexity of cancer treatment, can compromise care quality and patient safety. While therapeutic advances in oncology are improving outcomes, they also require more time, coordination, and specialized expertise. However, the workforce is not expanding at a pace that matches these demands.[8] For example, in the United States, 38 states had fewer oncologists per capita in 2024 than in 2014 with many experiencing limited rural workforce coverage.[8] This trend reflects broader challenges within the global health workforce. The WHO projects a global shortage of 18 million health care workers by 2030, signaling a structural challenge that demands urgent attention.[9]

Recent crises including COVID-19 pandemic and conflicts across the globe have further exacerbated the pressures on clinicians, leaving a lasting impact on their mental health and on service delivery.[10] The cancer workforce faces further specific challenges, including the emotional burden of caring for patients diagnosed with cancer and those approaching the end of life and interacting with concerned and bereaved families.[11,12]

Several professional cancer societies, such as ASCO, European Cancer Organization, Clinical Oncology Society of Australia, and European Society of Medical Oncology, have analyzed the situation. For example, they have examined the workload of oncologists across regions, the working conditions, the impact of the COVID-19 pandemic, and the mental well-being and burnout of oncology workers.[10,13,14] These studies use the empiric definition of burnout as an occupational-related syndrome characterized by signs of physical and emotional exhaustion, cynicism and depersonalization (sense of detachment/disengagement), and a low sense of professional accomplishment.[11] Oncology clinicians enter the field with a mission to help patients with cancer. Inevitably, the shortage of cancer care colleagues with whom to share the burden can negatively affect patients.[15] Oncologists and other oncology team members such as nurses, psychologists, physician assistants, pharmacists, pathologists, and many others continue to struggle to cope.[16,17] More oncology professionals are reporting mental health issues, such as burnout, secondary traumatic stress, moral distress, grief, and anxiety, forcing them to leave their professions.[5] Those who remain are given additional responsibilities and larger workloads, resulting in less time and attention for patients. Medical errors under these conditions are inevitable and further compromise patient care. Stress, burnout, and staff shortages can lead to unintended consequences that undermine the quality of care and life of those affected by cancer.[11]

A pan-European survey of 700 clinicians from 30 countries provides a snapshot of the cumulative strain.[7] Fifty-two percent reports endless workloads, 55% says that administrative procedures make their job too difficult, 51% feels that decision-makers do not care about their well-being, 43% lacks sufficient personal time because of work, 19% reports high levels of burnout, and 8% intends to leave cancer care within 5 years. Younger professionals report

greater challenges across most domains. Satisfaction and support are higher in Western and Northern Europe than in Eastern and Southern Europe, where stress and burnout are more prevalent, signaling unequal risk across the continent.[7]

Similarly, in the United States, a 2023 study identified that 59% of ASCO member oncologists experienced burnout, with rates significantly higher than oncologists in 2013 (59% in 2023 *v* 45% in 2013 [$P < .01$]). In 2023, consistent with oncologists across the world, burnout was significantly associated with younger age (<age 50 years), serving in a familial/parental caregiver role, and working >60 h/wk ($P < .05$). Oncologists reported less satisfaction with work-life balance, and more than 20% of oncologists reported a greater likelihood of a reduction of clinical hours in the next year.[13]

To summarize, beginning of an oncology career is a particularly vulnerable period as clinicians are simultaneously establishing clinical competence, managing research expectations in an academic career, caring for young children or aging parents, and trying to build academic credibility. Root causes of burnout are multifactorial and can be categorized across system, organizational, and individual levels.[11,12,14] At the system level, contributors include chronic underfunding of cancer services, workforce planning failures, regulatory burden, productivity-driven funding models, and inequitable access in rural and regional settings. At the organizational level, poor workplace culture and leadership, discrimination, workforce shortages, administrative overload, and poorly designed electronic health systems intensify emotional and cognitive strain. At the individual level, moral distress, emotional labor, conflict with patients, families and colleagues, role overload, cumulative grief, and work-life conflict compound vulnerability, leading to burnout as a predictable system outcome rather than an individual failing. While this chapter focuses primarily on oncology clinicians, it is important to recognize that the sustainability of health systems ultimately depends on the well-being of all patients who contribute to and are affected by the system.

When oncology workforce faces regulatory hurdles, administrative burden, workflow inefficiencies, punitive behaviors from leadership following medical errors, workplace conflict, or patient complaints, it becomes easy to lose sight of their deeper meaning. This raises an essential workforce question: How do oncology professionals sustain passion when confronted by adversity, complexity, and competing demands?

ALIGNMENT WITH VALUES AND PURPOSE

A critical foundation lies in sustained alignment with purpose and values—character traits, moral qualities, and elements repeatedly shown to support resilience, meaning, and long-term professional engagement.[2,18–21] In virtue ethics, examples of physician values in medicine empirically described include kindness, compassion, wisdom, honesty, respect, confidentiality, trust, and professional integrity.[22] At the organizational level, examples of purpose may include high-quality service delivery, patient and psychological safety, research, education and training, and health equity. Clinicians typically choose oncology or related fields because of a strong sense of meaning. They enter the profession knowing that the health system is imperfect, expecting barriers and inefficiencies. However, experiencing these barriers repeatedly—especially alongside the emotional toll of caring for patients with cancer—can gradually disconnect clinicians from the reasons they entered the field. Studies show that this disconnection is a major contributor to burnout.[6] When daily work becomes misaligned with purpose or values, clinicians experience reduced engagement, diminished job satisfaction, and compromised well-being.

Some examples of individual and organizational actions that contravene common values such as kindness, gratitude, and respect are listed in Table 1. They act as psychosocial hazards and therefore impact well-being.

TABLE 1. Examples of Actions by Individuals and Organizations That Contradict Purpose and Values

Operational and Personal Behaviors that Contradict Values and Purpose
At the organizational level
Items on the strategic plans are not implemented
Same items discussed repeatedly without progressing actions
Decisions made without consultation or consensus
Multiple, repeated, and duplicative steps for recruitment, finance, and research approvals
Rostering staff without fatigue considerations and not addressing vacancies in a timely manner
Last minute alteration to meeting schedules
Reprisals for staff who raise safety concerns
The inappropriate use of regulatory processes to marginalize individuals
The misapplication of professional development planning processes to revisit past issues, rather than to enable meaningful, constructive development and future-focused growth
At the individual level
Dismissing ideas and saying no as the first response to ideas
Characterizing advocates for improvement as "difficult" rather than recognizing their contribution to positive change
Negative feedback being given in inappropriate settings and in front of other colleagues
Showing up late to clinics and meetings
Attending meetings without sufficient preparation
Not responding to e-mails in a timely manner
Defamatory statements about colleagues outside of the workplace setting

NOTE. Adapted from Ref. 23.

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TABLE 2. Examples of Domains of Value, Purpose, and Meaning for Oncology Clinicians

Domains of Value, Purpose, and Meaning for Oncology Clinicians
Advancing research, quality improvement, and innovation
Teaching and mentorship
Developing protocols that improve care, strengthening professional relationships
Supporting patients and families through uncertainty
Health equity
Cost-effective care delivery

Purpose in clinical practice is rarely singular. It includes advancing research and innovation, teaching and mentorship, developing protocols that improve care, strengthening professional relationships, and supporting patients and their families through uncertainty. Other examples are listed in Table 2. These everyday expressions of meaning often become the very experiences that sustain long-term engagement. Frankl's[20] concept of searching for "meaning in suffering" and contemporary organizational psychology both emphasize that such small, repeated expressions of purpose act as stabilizing forces during adversity.

VALUES AND PURPOSE ALIGNED INTERVENTIONS BY INDIVIDUALS

Literature across medicine and organizational psychology consistently shows that alignment of daily work with personal values is one of the strongest predictors of fulfilment and resilience.[2,11,21,22,24,25] This values-to-action alignment enables clinicians to reinterpret challenges not as distractions but as part of their broader mission—patient care, system improvement, and scientific progress. Some examples of values and purpose aligned actions are listed in Table 3. Recent work on meaning-centered interventions in oncology demonstrates that even brief opportunities to reconnect clinicians with core values can reduce burnout markers and improve well-being.[2] Other interventions consistently shown to add benefit to oncologists include coaching and mindfulness-based stress reduction (MBSR) programs.[2,5,11,12,25] MBSR is a protective practice that empowers oncologists to cultivate nonjudgmental awareness in the present moment during clinical care. This routine practice can address the burnout-related exhaustion, thereby supporting resilience. By fostering mindful compassion, oncologists enhance their moral cognition, harmonize their personal values with clinical actions, and improve the overall quality of cancer care.[2,5,11,12,25]

Approaches such as acceptance and commitment therapy (ACT) have added further clarity.[26,27] ACT emphasizes psychological flexibility: acknowledging what is outside our control while committing to actions guided by deeply held values. Clinicians who cultivate this flexibility experience lower burnout, greater engagement, and improved emotional well-being. Returning to these anchors during moments of stress—a difficult complaint, an interpersonal conflict, or a systems frustration—helps clinicians remain grounded and intentional rather than reactive. Importantly, acceptance in ACT does not equal passive tolerance of flawed systems. It simply acknowledges that challenges exist and then uses purpose and values to guide constructive and meaningful action.

PERSONAL GROWTH BY EMBRACING DISCOMFORT

The lives and professional roles of oncology clinicians are filled with experiences that trigger discomfort. These are often labeled as "negative emotions" and avoided in the belief that comfort equates well-being. However, growing evidence suggests the opposite: facing and leaning into discomfort—rather than avoiding or numbing it—can foster personal growth, resilience, and long-term sustainability in demanding careers such as oncology.[27,34]

Embracing discomfort as a catalyst for growth requires discernment and skill. Not all discomfort is beneficial; some signals the need for protection or boundaries, whereas others point toward learning, adaptation, and change. Developing the capacity to distinguish between growth-promoting and damaging discomfort is therefore critical. This includes accepting discomfort as a meaningful signal, reframing triggers as opportunities for reflection and development, and translating insight into actions that are aligned with one's values and sense of purpose.

An important and emerging question is whether embracing discomfort has enduring effects beyond a single moment of challenge. Specifically, does this approach strengthen intrinsic motivation, sustain engagement, and support long-term professional fulfilment? Exploring this question may offer valuable insights into how clinicians can not only cope with adversity but also grow through it.

HARMONIOUS VERSUS OBSESSIVE PASSION

It seems that passion also needs to be managed carefully or strategically. Concepts of harmonious passion and obsessive passion are useful for navigating and choosing our purpose.[28] Obsessive passion is an inflexible compulsion that governs the individual's identity, often producing conflict with other personal values and life fields. Alternately harmonious passion is an autonomous, healthy drive that integrates a treasured healthy activity into the individual's life, aligning with one's overall values. Harmonious passion means that our careers are integrated with the rest of our life, allowing joy to arise in every aspect of life. This also reminds us that we should strive to find meaning and joy in all the things we do, including those we dismiss as mundane. A practical approach is to find activities within the domains of well-being to create balance. These activities should cover the physical, emotional, social, intellectual, vocational, financial, environmental, and spiritual aspects of health-related well-being.[29]

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TABLE 3. Examples of Purpose- and Value-Aligned Personal Actions

Actions	Purpose	Values
Obtaining authorization and insurance coverage and completing discharge summaries or patient updates in a timely manner	Helping patients with financial situations, helping colleagues to be updated of patient's condition	Kindness, respect
Allowing opportunity for raising ideas by others	Empowering colleagues, quality improvement	Kindness, respect
Completing communication loops in a timely manner	Completion of tasks in a timely manner	Integrity, kindness
Reading papers before and attending the meetings on time	Making correct decisions and in a timely manner	Integrity, respect, and kindness
Functioning as high performing teams, collaboration, and mentoring	Empowering colleagues, operational efficiency, fostering a sense of belonging	Kindness, collaboration
Considering others' circumstances before making judgments and statements of their actions	Fostering teams and human-centered cultures	Kindness
Reframing frustrating situations through values and purpose. For example, when systems are slow, cultivating gratitude for having electronic infrastructure at all and using the pause to connect, reflect, or share a quick teaching point rather than defaulting to frustration	To maintain own mental energy without discharging energy on low-value activities	Kindness (to self)

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ADVOCACY AS A SPIRITUAL ACTIVITY

Advocacy is a fundamental responsibility of health professionals, especially oncology clinicians[30]—and, arguably, of all humans. It is often misunderstood as "fighting" or "activism," terms that can imply confrontation, emotional exhaustion, and a win-lose outcome. When efforts fall short, or when apathy and structural inertia seem overwhelming, advocacy framed in this way can lead to disillusionment, frustration, and eventual disengagement.

If, however, advocacy is understood as the leading change or advancing quality improvement, it can be approached as a spiritual activity. At its core, advocacy is grounded in purpose—the purpose of improving the lives of others. It inherently involves working with and for other human beings, which requires acceptance, kindness, patience, and gratitude. These qualities are central to spiritual practice across cultures and belief systems.

When oncology clinicians adopt this perspective, advocacy becomes less about resistance and more about service and less about victory and more about meaning. Implementation science reinforces this approach, showing that sustainable improvements arise when clinicians focus on identifying the right problem, using the right methodology, engaging the right network of patients, and grounding solutions in evidence, partnerships, and patient outcomes. Identifying and applying clinician levers are important for keeping stakeholders engaged and achieve win-win outcomes for all.[31,32]

We as authors have found this approach to be life-altering—sustaining personal well-being, deepening connection with others, and ultimately making advocacy more rewarding and effective. At the same time, most health system issues are complex and adaptive, not linear.[33] They require teamwork, shared leadership, and codesigned solutions rather than individual effort alone. While individuals must nurture their own passion, purpose, and values, organizations also hold responsibility for creating environments that support rather than undermine clinicians.

VALUES- AND PURPOSE-ALIGNED ORGANIZATIONAL INTERVENTIONS

Values- and purpose-aligned health systems are increasingly recognized as essential for sustainable oncology cultures.[33,35,36] Organizational research shows that when workplace values align with clinician values, engagement increases, turnover decreases, and well-being improves.[35,36] The impact of poor organizational culture is summarized in Figure 1 using an analogy of cancer and its symptoms. A review in 2025 by Lapen et al[1] listed several examples of organizational-level interventions under following themes: eliminating low value work, team restructuring, clinician work-life integration, psychological safety in the workplace, practice setting stressors, and fostering community.

Using themes identified in the literature, and culture and well-being frameworks around the world, professional organizations such as the Clinical Oncology Society of Australia, ASCO, and the European Cancer Organization now make culture tangible by defining healthy clinical workplace cultures as environments in which humans care for and enable each other to achieve organizational purpose, structured around four core inter-related pillars.[35,36]

First, teams as the foundation of collective purpose. Effective teams offer psychological safety, shared decision making, and collective responsibility—all linked to improved well-being and patient outcomes.[35,36] Most organizations adopt purposes aligned with community needs: research, training, innovation, and equity. Individuals do not need to contribute to every purpose; instead, they contribute in complementary ways to a shared mission. This reflects the idea that "everyone is an incomplete leader and therefore needs a complete team."[38] Within teams, each individual has unique and equally important contribution to offer in line with

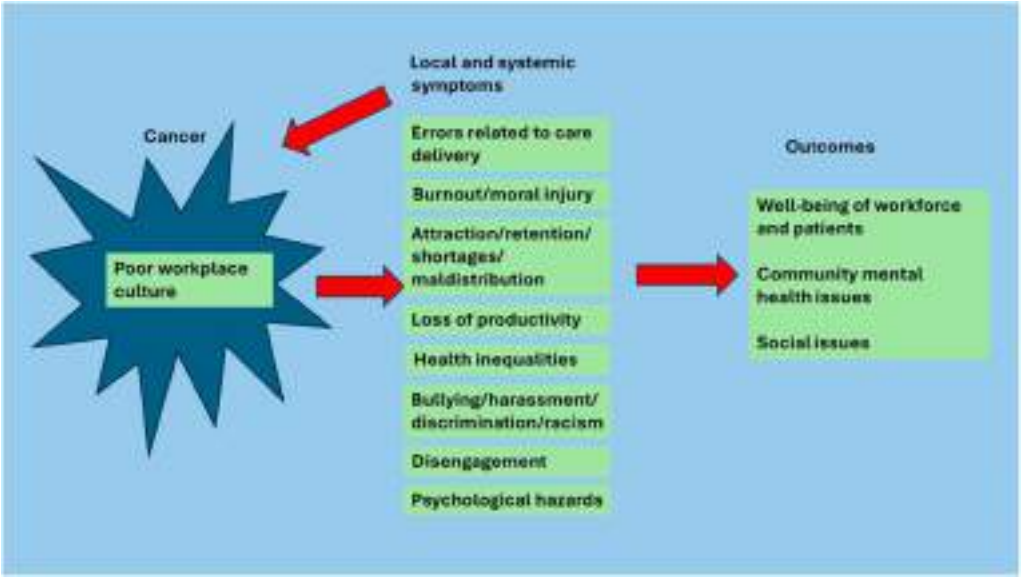

FIG 1. Impact of poor workplace culture on workforce, patients, and community (extracted from Clinical Oncology Society's healthy workplace culture in the health systems framework).

concepts such as "insignificant being and significant existence" grounded in values and purpose.[39] Therefore, when teams operate with mutual respect and equal importance—even if roles differ—cultures of belonging, empowerment, kindness, and collaboration naturally emerge.

Second, codesign as a central method for problem solving. Well-planned codesign processes bring clinicians, patients, administrators, and researchers together to create solutions. Evidence shows that it increases trust and cultural cohesion, boosting the rate of adoption of new processes.[35,36]

Third, enabling systems—interactions, policies, processes, and resources—that make meaningful work possible. Values-aligned systems reduce unnecessary administrative burden and promote equity, safety, and collaboration.[1,35,36]

Several organizations have identified and suggested similar themes of actions. As an example of enabling systems, we have listed actions proposed by the European Cancer Organization's workforce network and ASCO:[7,11]

1. Prioritize training and professional development: Ensure dedicated time for oncology staff to engage in training and professional development. This includes participation in scientific congresses and research. This is essential for keeping up with the latest advancements in cancer care and fostering a culture of lifelong learning and career support.
2. Implement work-life balance policies: Implement work-life balance policies that promote a healthy work-life balance for oncology professionals to reduce stress and prevent burnout. Maintaining a balanced life is crucial for the long-term well-being of staff and the quality of care they provide.
3. Foster positive, growth-oriented work cultures: Create a work culture that actively promotes positivity, collaboration, and professional growth. Encourage open communication, recognition, and personal development opportunities to boost morale and promote retention.
4. Streamline reporting and administrative tasks: Revise bureaucratic reporting requirements to reduce administrative burdens on oncology professionals. Consider redistributing certain reporting duties across different health care roles to streamline processes and enable staff to focus more on direct patient care.
5. Accessible psychological care and promotion of healthy lifestyle: Guarantee access to psychological care and stress management training at all stages of an oncology professional's career. Promote healthy lifestyles to contribute to general well-being. Regular mental health support is vital for sustaining a resilient and capable workforce. The approach should be tailored to the personal and professional needs and experiences of each health care professional.
6. Reduce administrative burdens: Simplify and streamline administrative processes to free up valuable time for oncology professionals to dedicate to patient care. Reducing paperwork and nonclinical duties allows staff to focus on providing high-quality care. This includes the effective and integrated digitization of medication management. This process should be conducted in close consultation with oncology professionals to reduce administrative tasks and waiting times for medication treatment and minimize the risk of medication errors.
7. Support technology integration: Investing in technology integration in cancer care can improve the quality of care, support health care professionals, and improve patient outcomes. It can also reduce medical errors and increase efficiency. Supporting the adoption of these innovations allows health care systems to better address the growing

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demand for cancer care while improving the experience for patients and health care professionals.
8. Improve working conditions: Enhance working conditions for oncology staff by ensuring that they have the appropriate resources, a manageable workload, and a supportive environment. This will enable them to provide the best care to their patients.
9. Promote mentorship and training programs: Establish robust mentorship programs for oncology trainees across health care facilities. These programs are also critical for early and mid-career faculty who are particularly vulnerable to burnout. Pairing experienced professionals with trainees ensures the transfer of knowledge, fosters career growth, and helps mitigate the effects of workforce shortages.

Fourth, monitoring and quality improvement mechanisms that continuously track culture, well-being, equity, and outcomes, ensuring that systems evolve in ways that support clinicians and communities.

A SYSTEMS FRAMEWORK FOR IMPLEMENTATION

To avoid placing the onus on individuals, we propose a macro-meso-micro level or layer framework that sequences practical levers with clear accountability. While workforce and well-being matters are global and complex, we have included some examples at each level/layer.

1. Macro (national):
   a. Workforce planning capacity and funding to match projected needs
   b. Regulatory support for task shifting and cross-border training and accreditation
   c. National dashboards that incorporate burnout and intention to leave as safety indicators
   d. Embed healthy workplace culture into regulatory mechanisms and professional curriculum
2. Meso (organizations/cancer centers):
   a. Foster healthy workplace culture to create psychological safety
   b. Protected professional development time embedded in job plans, with leadership accountability for engagement and well-being
   c. Redesign of documentation with frontline cocreation, removal of duplicate steps, and role optimization (eg, pharmacy techs, navigators, and scribes)
   d. Psychological safety, peer support, and access to timely mental health resources
3. Micro (teams/individuals):
   a. Leverage contemporary team frameworks to foster team-based culture
   b. Structured mentorship, onboarding curricula, MBSR programs, and coaching
   c. Incorporating protected recovery time into clinical schedules
   d. Team huddles and escalation protocols that distribute cognitive load
   e. Access to confidential support without stigma, tailored to oncology roles and career stages

Together, the four pillars of healthy workplace culture embedded at macro-meso-micro levels create environments where individual purpose and organizational purpose reinforce one another. This enables clinicians not only to sustain passion but also to transform early enthusiasm into persistent, meaningful contribution across a career.

CONCLUSION

Ultimately, passion may ignite a career, and persisting passion is critical in oncology, but purpose and values are key for sustaining it. As oncology becomes more complex, with rapid scientific advances and intensifying systemic pressures, long-term fulfilment depends on clinicians' ability to reconnect with meaning and align action with values. By recognizing that passion changes over time—and intentionally grounding our work in purpose and values—clinicians can move from passion to persistence, forming the foundation of a compassionate and future-ready oncology workforce.

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Beyond Routine Surveillance Imaging for Melanoma: Emerging Technologies for Detecting Early Recurrence and Guiding Clinical Management

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OVERVIEW

Melanoma recurrence risk is highest within the first 2 years after diagnosis and progressively declines thereafter. Current surveillance strategies remain largely guided by clinicopathologic risk stratification, with the comprehensive medical history, physical examination, and complete skin assessment forming the cornerstone of follow-up. Although cross-sectional imaging and lymph node ultrasound are used in selected higher-risk patients, routine intensive imaging has not consistently demonstrated survival benefit and may increase costs and false-positive findings. Emerging technologies are reshaping melanoma surveillance and clinical management. Circulating tumor DNA (ctDNA) has shown promise as a minimally invasive biomarker capable of detecting molecular residual disease and anticipating clinical recurrence. Persistent or newly positive ctDNA after surgery is consistently associated with inferior recurrence-free survival. However, ctDNA does not reliably detect all recurrence patterns and its sensitivity varies according to disease burden and metastatic site. Prospective validation and clarification of how ctDNA should guide adjuvant therapy or imaging strategies remain necessary. In parallel, CD8-targeted positron emission tomography (CD8 PET) has emerged as a novel functional imaging modality capable of noninvasively visualizing whole-body T-cell dynamics. By differentiating tumor burden from immune infiltration and capturing early T-cell recruitment, CD8 PET offers predictive insights into immunotherapy response. Nevertheless, limitations of this technique include dependence on optimal imaging timing, limited tracer availability, cost, and an inability to directly assess T-cell functionality. Together, ctDNA and immune-focused imaging approaches represent promising steps toward precision surveillance and management of melanoma. Further robust prospective studies are required to define their integration into clinical decision making and optimize patient outcomes.

INTRODUCTION

Melanoma is a malignant tumor originating from melanocytes and most commonly arises in the skin.[1] It represents a significant global health burden, accounting for more than 300,000 new cases annually, with the highest incidence observed in Europe, North America, and Australia.[2,3] Over recent decades, melanoma incidence has continued to rise steadily.[4] Given that the median age at diagnosis is approximately 59 years, melanoma is associated with a high number of potential years of life lost, estimated at 20.4 years, compared with 16.6 years for all malignancies combined.[5]

Clinical outcomes in melanoma are strongly influenced by the stage at diagnosis. In the United States, approximately 84% of patients are diagnosed with localized disease, whereas 4% present with distant metastatic disease.[5] These distributions differ substantially in regions with lower melanoma prevalence and more limited health care infrastructure, where systems may be less prepared for early diagnosis and comprehensive staging. For instance, in Brazil, nearly one quarter of melanoma cases are diagnosed at a metastatic stage.[6] These figures underscore a significant socioeconomic disparity between high- and middle-income countries, highlighting the impact of delayed diagnosis on both treatment-related costs and loss of productivity.

CONTEMPORARY APPROACHES TO MELANOMA SURVEILLANCE

Evidence and International Guideline Recommendations

Because of the lack of robust evidence supporting intensive surveillance strategies or routine imaging and laboratory testing for patients with resected melanoma, current follow-

PRACTICAL APPLICATIONS

- Key objectives of follow-up of patients with melanoma include early detection of recurrence, detection of secondary skin cancers, prevention and patient education, management of treatment-related toxicities, and psychosocial support.
- Surveillance should be risk-adapted and stage-specific, prioritizing intensive clinical and dermatologic examination in the first 2-3 years, selective use of imaging for stage ≥IIB or symptomatic patients, and avoiding routine laboratory testing in asymptomatic individuals.
- The use of circulating tumor DNA for detection of recurrent melanoma represents an emerging technology to aid in disease monitoring for selected patients although further study is needed to determine how to best incorporate this tool into clinical decision making.
- CD8 positron emission tomography imaging represents a clinically predictive, longitudinal, and noninvasive modality for monitoring antitumor responses and enhancing long-term surveillance across the entire body.

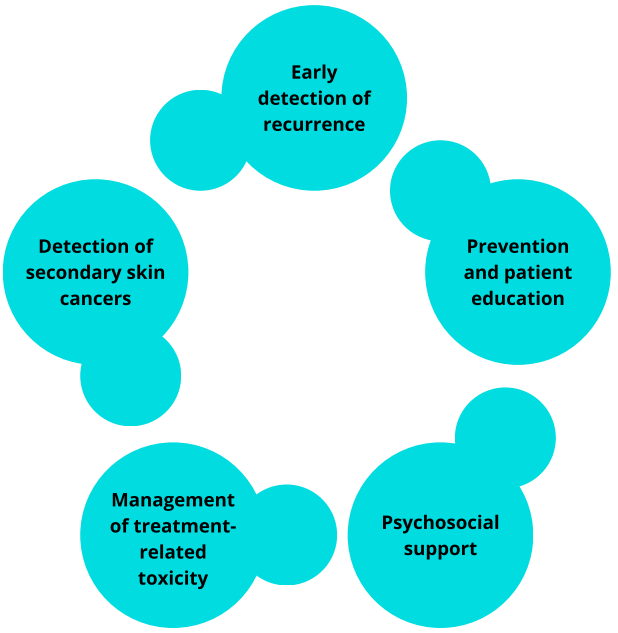

FIG 1. Key objectives of melanoma follow-up.

up recommendations rely on expert opinion. Therefore, respective national clinical practice guidelines should be consulted to guide surveillance strategies.[5-7]

Within this framework, it is important to highlight the main clinical objectives of melanoma surveillance, summarized in Figure 1, which include the following:

1. Identification of local, regional, or distant disease recurrence at the earliest possible stage;
2. Surveillance for subsequent primary melanomas and nonmelanoma skin cancers;
3. Education on primary prevention strategies and skin self-examination for patients and first-degree relatives;
4. Recognition and management of adverse events related to systemic therapies;
5. Assessment and support of psychosocial needs throughout follow-up.[6]

The first years after excision of the primary cutaneous melanoma are particularly critical as the risk of recurrence is highest during this period. According to the American Joint Committee on Cancer version 8 (AJCCv8) cohort, 10-year melanoma-specific survival rates range from 98% to 94% for stage I disease (IA and IB, respectively) and from 88% to 75% for stage II disease, depending on subclassification. In stage III melanoma, survival rates vary widely, reaching 77% for stage IIIB, 60% for IIIC, and 24% for IIID.[8] Importantly, real-world evidence suggests a higher recurrence burden than that reported in AJCCv8 cohorts.[9]

Consistent with these observations, the median time from diagnosis to recurrence is approximately 2 years, with locoregional and distant recurrences occurring at comparable frequencies. By 5 years after diagnosis and excision of primary lesion, 82%-90% of all recurrences have already occurred, underscoring the importance of intensified surveillance during the early follow-up period.[6,10]

In recent years, prognostic tools based on machine learning algorithms have been developed to improve the prediction of recurrence in early-stage melanoma. These tools may support clinicians in patient counseling and in tailoring surveillance strategies. Among clinicopathologic factors, tumor thickness and mitotic rate appear to have the greatest impact on recurrence risk in stage I-II melanoma.[10,11] Overall, follow-up schedules should be individualized, considering disease stage, individual risk, and patient-specific needs. Surveillance strategies include clinical and dermatologic examinations, regional lymph node ultrasonography, laboratory testing, and imaging studies, as suggested in Table 1.[7] The following sections discuss each surveillance modality in greater detail.

Clinical and Dermatologic Examination

A prospective 10-year cohort study demonstrated that 18% of melanoma recurrences were detected by patients themselves, whereas an additional 24% was identified by physicians during routine follow-up visits, without the need for complementary diagnostic tests. These recurrences were predominantly local, satellite/in-transit, or regional nodal;

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TABLE 1. Suggested Follow-Up Schedule According to the Disease Stage

Stage	Clinical and Dermatologic Examination	Lymph Node Ultrasound	LDH/S-100	Cross-Sectional Imaging[a]
IA	Every 6 months (years 1-3), annually thereafter	Not recommended	Not recommended	Not recommended
IB-IIA	Every 3-6 months (years 1-3), every 6 months (years 4-10), annually thereafter	Every 6 months (years 1-3)	Not routinely recommended	Not routinely recommended
IIB-IIIC	Every 3 months (years 1-3), every 6 months (years 4-10), annually thereafter	Every 3-6 months (years 1-3)	Every 3-6 months (years 1-3)	Every 6 months (years 1-3)†
IIID	Every 3 months (years 1-3), every 6 months (years 4-10), annually thereafter	Every 3-6 months (years 1-3)	Every 3-6 months (years 1-3)	Every 3-6 months (years 1-3)†
Stage IV NED	Every 3 months (years 1-3), every 6 months (years 4-10), annually thereafter	Every 3-6 months (years 1-3)	Every 3-6 months (years 1-3)	Every 3 months (years 1-3)†
Stage IV (M1a-1d)	Individualized follow-up	Individualized	Individualized	Imaging every 8-12 weeks[b,c]

NOTE. This table is adapted from the study by Garbe et al.[6] Differences reflect the authors' interpretation of available evidence and alignment with selected NCCN recommendations, particularly around the consideration of the use of brain MRI for surveillance in IIB-IIID melanoma.[5] In contrast to the study by Garbe et al,[6] which recommends LDH and S-100 assessment every 6 months for stages IB-IIA (years 1-3), the authors do not routinely recommend use of these biomarkers given the limited evidence supporting their clinical utility. S-100 is not routinely recommended at any stage.
Abbreviations: LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NED, no evidence of disease after complete resection or complete response under systemic therapy; PET, positron emission tomography.
[a]CT of chest, abdomen, and pelvis (including neck according to the primary melanoma site) or PET-CT.
[b]Brain MRI for stage III or as clinically indicated.
[c]Standard of care in clinical trials.

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by contrast, recurrences detected through imaging or laboratory tests were predominantly distant.[6,12]

A comprehensive medical history, thorough physical examination, and complete skin assessment represent the cornerstone of melanoma surveillance. It includes inspection of the primary excision scar, palpation of regional lymph nodes, and full-body skin examination using dermoscopy. Ideally, these assessments are performed by a multidisciplinary team involving medical oncologists and dermatologists. In regions with limited access to specialists, trained primary care physicians may perform these examinations, including dermatoscopic evaluation when appropriately trained.[6,7] Most experts recommend clinical surveillance for at least 5 years. Some advocate extending follow-up to 10 years, whereas others transition patients to routine primary care after the initial surveillance period.

Engagement of nursing professionals to support patient education, self-examination skills, and coping strategies for fear of cancer recurrence may improve patient satisfaction, quality of life, and adherence to surveillance.[13] Structured patient-led surveillance programs have also been shown to facilitate early detection of local recurrences and new primary melanomas, sometimes preceding scheduled follow-up visits.[14]

Imaging Examinations

Previous data indicate that regional lymph node ultrasound is more sensitive than physical examination, computed tomography (CT), or positron emission tomography (PET)/CT for detecting subclinical nodal recurrences.[6] However, despite its higher detection rate, the use of ultrasound alone has not demonstrated a survival benefit in patients with stage IB-IIA melanoma.[15] Although the role of imaging in early-stage disease remains controversial, most studies and guidelines do not support routine imaging surveillance for patients with stage 0 to IIA melanoma in the absence of clinical signs and symptoms suggestive of recurrence or metastatic disease.[16] Nevertheless, recent international guidelines recommend the use of lymph node ultrasound for the evaluation of nodal involvement in patients with T1b disease (stage IB) and higher.[6]

For patients with stage IIB melanoma and above, an individualized approach to surveillance imaging should be discussed. This may include periodic CT scans of chest, abdomen, and pelvis, targeted to anatomic regions based on the location of the primary tumor (eg, neck CT in head and neck melanoma), or PET/CT imaging.[6,16,17] Evidence suggests that CT imaging performed every 6 months is a cost-effective strategy for detecting recurrence during the first 3 years of follow-up in patients with stage IIB, IIC, and III melanoma.[18]

Patients considered at high risk of CNS involvement, such as those with stage III disease and/or a history of brain metastases, should undergo brain magnetic resonance imaging (MRI) as part of their surveillance strategy.[6,17] However, cost-effectiveness analyses indicate that this approach

provides benefit primarily during the first year of follow-up in patients with stage IIC and III melanoma.

Laboratory Examinations

Isolated laboratory testing has a very limited ability to detect melanoma recurrence.[12] Consequently, routine blood tests are not recommended as part of standard post-treatment surveillance.[5] Nonetheless, some clinical guidelines acknowledge laboratory assessments, particularly serum S100B and lactate dehydrogenase, as optional surveillance tools in selected high-risk patients.[17,19] Overall, the clinical utility of laboratory biomarkers in melanoma follow-up remains constrained by the absence of highly sensitive and specific markers and by significant limitations such as false-positive results, which may lead to unnecessary investigations and patient anxiety.[20] Therefore, laboratory examinations should not be used in isolation and must be interpreted cautiously within the broader clinical context.

Global Approaches to Melanoma Surveillance in the Modern Era: the Feasible, the Practical, and the Affordable

One of the most debated areas in melanoma care currently concerns the optimal follow-up strategy for patients with melanoma. A major challenge globally lies in balancing efficient follow-up strategies that improve overall survival (OS) with cost-effectiveness, particularly considering the rising incidence of melanoma, which imposes an increasing economic and logistical burden on health care systems. Risk-stratified surveillance approaches may allow for more rational resource allocation, ensuring appropriate vigilance for high-risk patients without overburdening the system. However, the lack of robust evidence-based data has hindered the development of internationally uniform guidelines, resulting in multiple, often discordant recommendations. Many of the currently available guidelines are based on retrospective data assessing recurrence risk over specific follow-up periods. Because of the heterogeneity of these data, authors have proposed surveillance schedules of varying intensities—ranging from conservative approaches to more intensive monitoring.[21,22]

More recently, prospective studies have provided new evidence on melanoma management, fueling discussions on the feasibility of de-escalating imaging and clinic visit frequency. The notion that frequent consultations lead to better outcomes has been challenged by studies demonstrating that most recurrences are detected by patients or their relatives between scheduled visits, typically through the appearance of symptoms or palpable lesions. This observation underscores a crucial shift in surveillance paradigms, particularly for patients with high-risk primary tumors who present with negative sentinel lymph node biopsies. Despite generally favorable prognoses, this subgroup constitutes a large portion of the melanoma population and paradoxically accounts for nearly one third of disease-specific mortality—a phenomenon referred to as the low-risk paradox.[23,24]

The MELFO trial assessed 388 patients from the Netherlands and the United Kingdom who were randomly assigned to either a low-intensity follow-up schedule or a traditional surveillance plan for AJCC stage IB-IIC patients (7th edition). Patients received instructions for self-inspection of the skin and regional lymph nodes. After 5 years, no significant differences were observed between the groups in terms of OS, melanoma specific survival, disease-free survival, or distant metastasis-free survival (DMFS). However, the low-intensity arm had a 39% cost reduction. Notably, over 97% of patients reported satisfaction regardless of visit frequency, and approximately 75% of recurrences in both groups were identified by the patients themselves. These findings emphasize that effective follow-up relies on educating patients to recognize skin or nodal changes and ensuring rapid access to referral centers when needed.[25,26]

The use of imaging in asymptomatic patients remains one of the most controversial aspects of follow-up. While imaging recommendations are based on the high sensitivity for detecting recurrence,[27] in thin melanomas (Breslow thickness ≤0.8 mm), the risk of metastasis is extremely low, rendering routine imaging unnecessary.[6,28] In more advanced stages (IIB-III), although systemic recurrence risk is higher, the effectiveness of routine imaging in improving survival remains limited.[29] Cost-effectiveness analyses indicate that imaging in stage I-II patients yields marginal survival benefits—typically <2 months—while being associated with high false-positive rates. Up to 20% of CT scans and 9% of PET-CTs in asymptomatic patients show suspicious findings that require further, sometimes invasive, investigations, which do not confirm melanoma recurrence. A cohort study at the Melanoma Institute Australia reported false-positive findings in at least 50% of patients. This phenomenon, known as incidentaloma, contributes to psychological stress and significantly increases health care costs without clear clinical benefit.[29,30] This issue was directly addressed in the TRIM Trial, a randomized phase III study conducted in Sweden that compared physical-examination-only follow-up with schedules incorporating routine imaging in resected stage IIB, IIC, and III patients. Interim analysis demonstrated no significant benefit from imaging-based surveillance in terms of recurrence-free survival, OS, or DMFS. Moreover, diagnostic intensification did not improve psychosocial outcomes as anxiety and depression levels were equivalent between groups, challenging the assumption that frequent imaging reassures patients. Similarly, retrospective studies of resected stage III patients showed no survival benefit from radiologic screening every 3-4 months compared with intervals of 6 or 12 months.[31,32] The current trend favors reserving imaging for clinical suspicion or ultrahigh-risk subgroups, avoiding indiscriminate screening.

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Emerging Strategies: Digital Monitoring and Blood-Based Biomarkers

Simultaneously, digital technologies are creating novel pathways for remote monitoring. Patient-led surveillance models using smartphone apps for image capture and teledermatology have shown early success in detecting new primary tumors and recurrences. The MEL-SELF trial demonstrated that structured patient-led surveillance, supported by digital tools and remote clinical guidance, is a feasible and safe strategy for patients with localized melanoma.[14] This intervention significantly improved the frequency and quality of skin self-examinations without negatively affecting psychological outcomes. Most new melanomas were detected early, often during unscheduled visits prompted by patient-initiated self-assessment. These findings support guided self-monitoring and digital tools as effective complements to traditional follow-up, particularly for lower-risk patients.[14]

Given that routine laboratory tests have not shown to be clinically useful in monitoring for melanoma recurrence, technologies using circulating tumor DNA (ctDNA) have the potential to detect recurrences at the molecular level. It is clinically appealing to have a minimally invasive, scalable method for diagnosing recurrence before the development of clinical disease, with the hopes that earlier intervention may lead to improved outcomes. However, this must be weighed against concerns about increased costs associated with testing and the potential for lead time bias when earlier treatment is initiated. Several studies have investigated the utility of ctDNA monitoring patients with surgically resectable melanoma, and these results are discussed in more detail in the subsequent section.

WHERE DO WE STAND WITH ctDNA FOR DISEASE MONITORING AND RECURRENCE PREDICTION IN MELANOMA?

The therapeutic landscape for patients with high-risk and unresectable melanoma has seen tremendous advances over the past several years, now with numerous new indications for treatment with both targeted and immunotherapies.[33-35] With these promising changes, multiple new questions now arise, centered around risk prediction, treatment choice, and optimal timing of therapy. Outside of traditional, often tissue-based, molecular analyses to guide selection of targeted therapies, however, robust biomarker data to guide therapeutic decision making are currently lacking.[36] The use of blood-based biomarkers has several advantages over traditional tissue sampling, including less invasive testing and the ability to obtain longitudinal samples over a patient's clinical course.[37]

Cell-free DNA (cfDNA) refers to fragments of DNA that circulate freely in the bloodstream and can be seen in healthy volunteers at low levels although patients with cancer have been shown to have cfDNA fragments detectable at higher levels.[38] The term ctDNA refers to tumor-derived DNA fragments which are also detectable in blood; ctDNA represents a portion of the total cfDNA although the relative percentage can vary widely.[39] While it has long been established that these ctDNA fragments have the same genomic alterations as a patient's primary tumor, technological advances have now moved the use of ctDNA closer to clinical application.[40]

Initial challenges included the relatively low levels of ctDNA compared with total cfDNA and concerns about stability and the potential for contamination, which have largely been overcome with modern technologies.[37-41] Given that the fraction of ctDNA in the background of normal cfDNA has been reported in some cases to be well under 1%, specialized and ultrasensitive techniques to analyze ctDNA are necessary to detect relevant alterations.[42,43] At a high level, these can be categorized into allele-specific techniques using polymerase chain reaction (PCR)–based analyses, such as droplet digital PCR (ddPCR) or BEAMing (bead emulsion amplification and magnetics), which are highly sensitive, but are limited in that they typically can only detect a single established genomic alteration.[27,44] Next-generation sequencing techniques can also be used, allowing for more comprehensive analyses, although they are limited by the relative lack of sensitivity, in addition to cost and longer turnaround time, consequently limiting the potential clinical applicability.[45,46] The use of ctDNA in melanoma has been investigated in a number of settings, including in patients with metastatic disease where ctDNA levels have been shown to correlate with disease status and treatment response.[47,48]

The Use of ctDNA in Risk Assessment and Disease Surveillance for Surgically Resected Melanoma

Adjuvant therapy now represents a standard-of-care option for patients with high-risk stage II and III melanoma, with PD-1–based checkpoint inhibitor therapy showing improvements in relapse-free survival (RFS).[49-52] In addition, patients with *BRAF*^{V600}-mutated stage III melanoma are also eligible for adjuvant therapy with dabrafenib and trametinib.[53] However, these therapies are also associated with toxicity and, in the case of checkpoint inhibitors, potentially irreversible immune-related adverse events which have important therapeutic considerations, especially in a patient population that may be cured by surgery alone.[54,55] Currently, the decision to pursue adjuvant therapy is complex and is based on clinical factors such as staging and medical history, as well as patient and provider preference. A series of small studies and correlative analyses of adjuvant therapy trials have explored the potential role of both baseline and serial ctDNA measurements as a prognostic marker for minimal residual disease in patients with high-risk resected melanoma to further inform risk beyond traditional clinicopathologic features (Table 2).

A single-institution prospective study of 30 patients with resected stage II-III melanoma demonstrated that

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measuring ctDNA in this setting was feasible. Preoperative ctDNA positivity was seen in seven patients and was associated with a higher Breslow depth (6.5 *v* 3.3 mm, $P < .01$).[56] Only three of these patients had persistent detectable ctDNA at the first postoperative time point. A total of 13 patients recurred, and elevated ctDNA levels were detected in eight patients before clinical or radiographic recurrence, with a median lead time of 2.1 months (IQR, 1-2.9). Patients who had detectable ctDNA levels at the first postoperative time point had worse RFS compared with patients without detectable ctDNA (hazard ratio [HR], 7.7 [95% CI, 1.8 to 33.1], $P < .01$). A similar study of 28 patients with resected stage II-III melanoma also demonstrated that preoperative ctDNA positivity correlated with higher stage, but that the majority of patients cleared and became ctDNA-negative within 4 weeks postoperatively.[57] A total of 30% of patients developed detectable ctDNA while on surveillance, and all subsequently recurred. ctDNA detection preceded the detection of clinical recurrence in three of six patients, but was notably negative in a patient who recurred with brain metastases.[57]

More recently, a multi-institutional retrospective analysis of 190 patients with resected stage I-IIIB melanoma analyzed the utility of serial ctDNA monitoring as part of a surveillance strategy. This study used a personalized, tumor-informed ctDNA assay, and decisions around adjuvant therapy were made at the treating physician's discretion. ctDNA positivity at any time point was significantly associated with a shorter RFS compared with patients whose ctDNA remained undetectable (RFS HR, 40.63 [95% CI, 19.9 to 82.96], $P < .0001$).[58] Similarly, for patients who received adjuvant therapy, ctDNA positivity was also correlated with a shorter RFS (HR, 20.21 [95% CI, 6.04 to 67.63]; $P < .0001$). A total of 33 patients developed a clinical recurrence throughout the time course of this study, with 72.7% (24 of 33) having a positive ctDNA before or concurrent with (within 2 weeks) a clinical recurrence. On multivariate analysis, ctDNA positivity at any time point postoperatively was the most significant predictor of RFS when compared with traditional clinicopathologic features. Notably, however, nine patients developed recurrent disease yet remained ctDNA-negative at the time of recurrence although two of these patients eventually were noted to have positive ctDNA. The majority of these patients (5) recurred locally, with an additional two patients each developing regional and distant metastases. In addition, this study is one of the first to begin to explore how ctDNA results influence clinical decision making as the treating physician had access to the ctDNA results. In this analysis, a resulting positive ctDNA affected clinical decision making for 24 of 33 patients although the extent varied widely and included adjusting surveillance intervals or changes in therapeutic regimen.

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TABLE 2. Selected Studies Analyzing the Utility of ctDNA in Monitoring for Disease Recurrence in Patients With Surgically Resected Melanoma

Study	Patient Population	Sample Collection	Findings
Rhodin et al[56]	30 patients Stage IIB-III	Preoperatively 2-3 weeks 3 months postoperatively Every 6 months for 3 years	13 of 30 patients recurred Elevated ctDNA at the first postoperative time point was associated with worse RFS 62% (8 of 13) of patients with recurrence had detectable ctDNA before clinical/radiographic recurrence
Brunsgaard et al[57]	28 patients 20 patients (surveillance cohort) Stage IIB-III	Preoperatively Within 4 weeks postoperatively Every 3-6 months	6 of 20 patients recurred 50% (3 of 6) of patients with recurrence had detectable ctDNA before clinical/radiographic recurrence 1 patient developed brain metastases and remained ctDNA-negative
Ansstas et al[58]	190 patients Stage I-III	Varied Required to have at least 1 postoperative sample for inclusion	ctDNA positivity at any time point was associated with worse RFS and was the most significant factor associated with RFS
Tan et al[59]	99 patients Stage III	Preoperatively Up to 12 weeks postoperatively	ctDNA was detectable in 37 of 99 patients ctDNA positivity at baseline or postoperatively was associated with worse RFS and DMFS
Syeda et al[60]	597 patients 94 patients with longitudinal samples Stage III	Baseline 3, 6, 9, and 12 months after treatment initiation	ctDNA was detectable in 79 (13%) of baseline samples ctDNA positivity was associated with worse RFS irrespective of adjuvant therapy
Lee et al[61]	161 patients Stage II/III		ctDNA detected in 15 of 132 (11%) *BRAF*-mutant samples ctDNA detected in 4 of 29 (14%) *NRAS*-mutant samples Patients with detectable ctDNA had worse RFS and DMFS The 5-year OS for detectable ctDNA was 33% The 5-year OS for undetectable ctDNA was 65%

Abbreviations: ctDNA, circulating tumor DNA; DMFS, distant metastasis-free survival; OS, overall survival; RFS, relapse-free survival.

In a study of prospectively collected samples from patients with stage III melanoma, somatic mutations were identified through tumor tissue sequencing, and then personalized ddPCR assays were developed to detect corresponding ctDNA.[59] In a cohort of 81 patients who did not receive adjuvant therapy, 58 and 52 patients had pre- and postoperative plasma available, respectively. ctDNA was detectable in 21 of 58 (36%) of patients preoperatively and 13 of 52 (25%) of patients postoperatively. Having detectable ctDNA at this baseline time point was predictive of relapse, with 19 of 21 patients recurring (RFS HR, 2.9 [95% CI, 1.5 to 5.6]; $P = .002$), although postoperative ctDNA elevations were more strongly correlated with a worse RFS compared with baseline elevation (RFS HR, 10 [95% CI, 4.3 to 24], $P < .001$).

The COMBI-AD trial was a randomized phase III study in patients with resected stage III $BRAF^{V600}$-mutated melanoma, which demonstrated an improvement in RFS and DMFS with 1 year of adjuvant dabrafenib plus trametinib compared with placebo.[53] The utility of a ddPCR assay designed to detect $BRAF^{V600E/K}$ as a prognostic biomarker in this context was recently reported.[60] Baseline samples were available for 597 of 890 patients, and serial samples drawn at 3, 6, 9, and 12 months were available for 94 patients. With a median follow-up of nearly 5 years, ctDNA was detectable in 79 of 597 (13%) baseline samples and higher levels of ctDNA correlated with higher stage. Baseline ctDNA positivity was associated with both shorter RFS and decreased OS, compared with patients whose ctDNA remained negative. In the placebo group, the median RFS was 3.71 months (95% CI, 2.39 to 6.89) for ctDNA-positive patients, versus 24.41 months (95% CI, 17.28 to 43.13), with a HR of 2.91 (95% CI, 1.99 to 4.25 $P < .0001$) for ctDNA-negative patients. In the dabrafenib/trametinib arm, the median RFS was 16.59 months (95% CI, 12.02 to 26.8) versus 68.11 months (95% CI, 50.36 to not reached; HR, 2.98 [95% CI, 1.95 to 4.54], $P < .0001$). Similarly, in the placebo arm, OS was worse in patients with positive ctDNA, with a median OS of 33.9 months (95% CI, 13.96 to not reached [NR]), versus not reached in ctDNA-negative patients. In the adjuvant therapy group, the median OS for ctDNA-positive patients was 40.31 months (95% CI, 24.9 to NR) versus not reached in patients with undetectable ctDNA throughout the study. Overall, patients who received adjuvant dabrafenib/trametinib demonstrated improved RFS and OS compared with placebo, irrespective of risk, consistent with the established benefit of adjuvant therapy in this patient population.

In summary, ctDNA represents an exciting tool which is emerging as being potentially clinically useful in helping to further refine clinical management for patients with melanoma. Across several studies, it is clear that patients who demonstrate certain ctDNA patterns, such as persistent positivity after surgery, or those who convert from being ctDNA-negative to ctDNA-positive, have an unfavorable prognosis compared with patients who remain ctDNA-negative. However, ctDNA does not appear to reliably detect all types of recurrences with equal sensitivity, and further study is needed around how ctDNA monitoring can be optimally integrated with traditional surveillance modalities. Moreover, the use of ctDNA to inform decisions around adjuvant therapy warrants further evaluation.

VISUALIZING THE IMMUNE RESPONSE: CLINICAL UTILITY AND PREDICTIVE VALUE OF CD8$^+$ T-CELL PET IMAGING IN SOLID TUMORS

The introduction of immunotherapy has fundamentally altered the clinical landscape of oncology, conferring durable benefits and even cures in a subset of patients with advanced malignancies.[62] Despite the improvement in clinical responses, resistance is very common, and the mechanisms underlying immunotherapy are poorly understood. CD8$^+$ T cells play a central role in antitumor immunity and are the primary effector in many immunotherapies, including immune checkpoint blockade, mRNA vaccine therapy, adoptive cell therapy, chimeric antigen receptor T-cell therapy, and T cell-receptor therapy. Consequently, CD8 PET imaging has emerged as a powerful, noninvasive tool that captures whole-body immune dynamics longitudinally. By quantifying CD8$^+$ T-cell distribution, it offers unique value in identifying early immune activity and predicting clinical response. Furthermore, it serves as a critical adjunct for longitudinal surveillance by differentiating tumor burden from treatment-related inflammation.

CD8-Targeted PET Probes and Biodistribution

The development of CD8-targeted imaging probes has focused on optimizing pharmacokinetics and biological inertness by engineering smaller CD8-binding antibody fragments.[63] Compared with full-length antibodies, these fragments exhibit improved tissue distribution and faster clearance and lack the Fc domain, thereby preventing antibody-dependent cellular cytotoxicity while retaining high binding affinity.[64]

Four major PET probes have progressed from preclinical studies to human trials, including the minibody ^{89}Zr-crefmirlimab berdoxam, the one-armed antibody ^{89}ZED88082A, and smaller nanobody-based tracers like ^{18}F-GEH200521 and ^{68}Ga-NODAGA-SNA006.[65-69] Their key imaging properties are largely defined by their molecular format:

- Zirconium-89 probes: The long half-life of Zr-89 (approximately 78 hours) pairs well with larger imaging probes such as minibodies and one-armed antibodies, which exhibit slower clearance, prolonged blood-pool activity, and increased liver signal reflecting hepatic clearance. Imaging is typically performed 24-48 hours postinjection for optimal contrast, and the longer half-life results in higher radiation doses, generally limiting repeat

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imaging to intervals of > 12 days (approximately 4 half-lives).[65]

- Fluorine-18 and Gallium-68 probes: Smaller antibody fragments such as nanobodies clear rapidly through the kidneys, minimizing nonspecific background signal and permitting the use of radioisotopes with shorter half-lives such as F-18 (110 minutes) and Ga-68 (68 minutes). This pairing enables same-day imaging 1-2 hours post-injection with lower effective radiation doses, making these tracers well-suited for serial imaging and longitudinal monitoring.[70]

Critically, biodistribution studies across these probe formats have revealed a consistent pattern reflecting the physiologic reservoirs of $CD8^+$ T cells, with high uptake observed in the spleen, lymph nodes, and bone marrow. Current dosing strategies incorporate a small amount of unlabeled probe to partially saturate these peripheral antigen sinks, thereby enhancing tumor bioavailability while maintaining rapid blood clearance and high tumor-to-background contrast.[66,71] Phase I and II trials have established a favorable safety profile for these agents, with no significant drug-related adverse events.[65-68,71]

Clinical Validation

In prospective cohorts of metastatic melanoma, non–small cell lung cancer, and renal cell carcinoma, the CD8 PET signal has demonstrated strong concordance with the gold standard of biopsy-derived immunohistochemistry.[66,67,72] However, CD8 PET offers several advantages over tissue biopsy. By quantifying $CD8^+$ T-cell infiltration across entire lesions, it avoids the sampling bias inherent to single-site biopsies and better accounts for intratumoral heterogeneity.[65] Moreover, CD8 PET enables simultaneous assessment of all tumor lesions and can be repeated to monitor dynamic changes in CD8 signal over time.

Clinical Utility and Predictive Value of CD8 Imaging

Baseline CD8 PET imaging categorizes tumors into inflamed versus immune desert phenotypes. High baseline SUV_{max} is associated with improved OS across a wide range of tumor types.[66,73-75] This noninvasive stratification has utility in patient selection as patients with immunologically cold tumors are less likely to benefit from monotherapy and may instead be candidates for rational combinatorial strategies designed to prime the tumor microenvironment (TME).[76]

Changes in CD8 signal after treatment with immunotherapy are also clinically predictive. Retrospective analyses using machine learning have shown that recruitment of $CD8^+$ T cells to the peritumoral ring, corresponding to the biological invasive margin, is highly predictive of best overall response.[77] This increase in CD8 signal likely reflects effective trafficking of T cells into the TME, which is associated with clinical response.[76,78,79] An early phase trial of CD8 PET/CT imaging supports this observation, with high CD8 tumor uptake correlating with durable clinical benefit, including complete and partial responses.[71]

A consistent observation across CD8 PET studies performed after initiation of immunotherapy is significant interlesional heterogeneity within individual patients, with some metastases demonstrating intense CD8 uptake, while others remain near background activity (Fig 2). Importantly, lesions with a low CD8 signal can still demonstrate a response to therapy, suggesting that variable uptake reflects differences in the kinetics of immune activation and tumor infiltration across tumor sites rather than therapeutic resistance.[66,71] Notably, several studies have reported no correlation between tumor CD8 uptake and clinical response when imaging was performed >4 weeks after treatment initiation.[66,80,81] This apparent discrepancy likely reflects suboptimal imaging timing as scans obtained at later time points may miss the transient peak of T-cell recruitment that accompanies early immune activation. In addition, divergent lesion-specific immune dynamics may obscure relationships between CD8 signal intensity and eventual response. Together, these findings indicate that CD8 PET/CT is highly sensitive to dynamic immune processes, but that its predictive value likely depends on the timing of imaging relative to immunotherapy initiation.

Beyond its current applications in baseline stratification and early response prediction, CD8 PET shows promise for longitudinal monitoring. During early restaging, anatomic imaging may struggle to differentiate true progression from transient immune infiltration, whereas in long-term

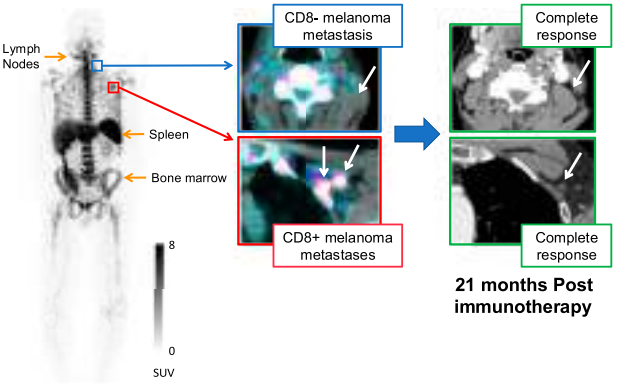

FIG 2. Heterogeneous CD8 signal across metastatic lesions during pembrolizumab treatment. Maximum intensity projection CD8 PET image (left) and fused CD8 PET/CT images (center) acquired using the CD8-targeted radiotracer ^{89}Zr-crefmirlimab berdoxam in a patient with metastatic melanoma 4 weeks after starting pembrolizumab. Increased CD8 PET signal is seen in two axillary metastases (lower center; SUVmax = 9.5-10), whereas neck metastases demonstrate background uptake (upper center; SUVmax = 0.4-1.0). Follow-up imaging using contrast-enhanced CT at 21 months (right) demonstrated a durable complete response to therapy across all lesions. Adapted from the study by Farwell et al.[71] PET, positron emission tomography; SUVmax, maximum standardized uptake value.

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surveillance, diagnostic challenges shift toward evaluating persistent residual masses or newly arising equivocal lesions. By distinguishing localized treatment-related inflammation from active malignancy, CD8 PET may help resolve diagnostic ambiguity and better inform clinical management.

Challenges and Future Directions

Despite its utility, a key limitation of CD8 PET is that a positive signal indicates the presence of $CD8^+$ T cells but not their functional state. A hot tumor on PET may be composed of terminally exhausted $CD8^+$ T cells with impaired proliferative capacity and limited effector function.[82] To address this limitation, PET imaging probes targeting markers of immune activation and function, including granzyme B, AraG, and 4-1BB (CD137), are currently being explored in clinical trials to visualize functional immune activity in vivo.[83–85] Complementing these approaches, PET imaging probes targeting PD-L1 have been developed to noninvasively assess PD-L1 expression as a predictive biomarker before treatment, enabling rational therapy selection.[86,87]

However, these emerging PET agents remain investigational and are associated with limited availability, higher cost, and logistical complexity, which constrain their implementation in multicenter therapy trials. A further challenge is their dependence on imaging timing: scans performed too early or too late relative to the peak immune response may underestimate immune engagement and lead to false-negative interpretations.

By contrast, early ^{18}F-fluorodeoxyglucose (FDG) PET/CT imaging, typically performed 1-2 weeks post-treatment, represents a widely available and cost-effective alternative that is also predictive of response to immunotherapy.[88] Because FDG uptake captures metabolic activity from both tumor cells and activated immune cells, early post-treatment scan timing is less critical than with lineage-specific probes. Imaging during peak immune activation may reveal increased uptake (metabolic flare), whereas later imaging demonstrates decreased uptake associated with tumor cell death and resolution of immune activity (metabolic response).[88,89]

Finally, integration of CD8 PET with complementary imaging modalities, such as diffusion-weighted MRI or metabolic imaging, enables a more comprehensive multiparametric assessment of the TME.[80] Radiomic approaches are also being explored to extract additional quantitative features from imaging studies although their incremental clinical value remains under investigation.[77]

Summary

CD8 PET imaging represents a clinically predictive, longitudinal, and noninvasive modality for monitoring antitumor immune responses across the entire body. Unlike anatomic imaging, which offers only lagging indicators of size, CD8 PET provides the biological specificity to distinguish active T-cell infiltration from tumor burden, which informs both initial therapeutic response and longitudinal surveillance. This capability facilitates a shift from a reactive wait-and-see approach to proactive, mechanism-based precision oncology. Furthermore, CD8 PET captures a dimension of the immune response that is not accessible through blood- or biopsy-based analyses, providing a whole-body view of heterogeneous immune activity. Emerging imaging probes targeting immune activation further highlight the growing ability of molecular imaging to characterize immune biology in vivo. By enabling immune phenotyping and real-time assessment of T-cell recruitment, CD8 PET may help guide treatment for individual patients, ultimately improving clinical outcomes.

CONCLUSION

In an era where effective systemic therapies for melanoma have transformed clinical outcomes for patients, it will be critical to continue to refine and advance optimal surveillance strategies. Currently available guidelines center around risk-based approaches using clinicopathologic features although clinical practice varies widely. As technologies advance, emerging tools such as ctDNA may provide a minimally invasive biomarker to allow for more tailored monitoring, particularly in high-risk patients. Concurrently, CD8 PET represents a functional approach to visualize intratumoral T-cell engagement, which may help assess the potential benefit of treatment at an earlier time point in a patient's clinical course and precise monitoring during long-term follow-up. Together, these advances represent an important step toward a more personalized approach to clinical decision making, with a goal of further improving patient care.

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

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Tech That Scales: A Practical Framework for Artificial Intelligence–Enabled Cancer Care in Low- and Middle-Income Countries and Underserved US Counties

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OVERVIEW

Cancer outcomes remain starkly unequal: 5-year survival rates for common malignancies in low- and middle-income countries (LMICs) often lag 20-40 percentage points behind high-income benchmarks, and similar disparities persist between well-resourced metropolitan centers and rural or safety-net settings within high-income countries. The gap is driven less by the absence of effective interventions than by workforce shortages, fragmented referral pathways, limited infrastructure, and loss to follow-up after abnormal screens. Technologies that scale must therefore function as deployable workflows integrating staffing, logistics, quality assurance (QA), governance, and monitoring not merely as stand-alone algorithms or devices.[1] This review synthesizes evidence across four complementary technology families that address these constraints across the continuum of care: artificial intelligence (AI)-supported screening and triage as the population entry-point layer; Project ECHO telementoring as the workforce-capacity layer; electronic patient-reported outcomes and remote symptom monitoring as the longitudinal continuity layer; and AI-powered clinical trial prescreening hubs as the access-to-innovation layer. The technologies do not carry equal evidentiary weight, and they should not be deployed identically in every setting. Our aim is to show how oncology leaders can sequence them pragmatically inside a common operating logic while adapting to local infrastructure and governance. We organize the framework in patient journey order entry into care through screening, workforce support through telementoring, continuity through remote monitoring, and access to innovation through trial prescreening, and draw examples from both LMIC programs and underserved US settings. We therefore present a practical implementation playbook, including a 90-day launch checklist, staffing models, QA frameworks, equity and bias monitoring metrics, and a program outcomes dashboard designed for oncology leaders seeking to move beyond pilots toward durable, monitored deployment.

INTRODUCTION

Cancer remains a formidable global challenge. Approximately 20 million new cases and 9.7 million deaths were recorded in 2022, and the burden falls disproportionately on populations with the fewest resources.[1] In high-income countries, five-year lung cancer survival can reach 20%-25%, whereas in many low- and middle-income countries (LMICs), it languishes at 5%-10%; similar gradients exist for breast, cervical, and colorectal cancers.[2] Within the United States, rural counties and safety-net systems face a different but related pattern of inequity: Patients are less likely to have local access to subspecialists, multidisciplinary support, and research infrastructure.

ASCO's commitment to driving knowledge into action demands that emerging artificial intelligence (AI)–driven technologies be evaluated not only for algorithmic accuracy but also for deployability the capacity to integrate into real-world workflows with appropriate staffing, training, quality systems, governance, and equity safeguards. This review addresses four complementary technology families that meet this criterion: AI-supported screening and triage, telementoring for workforce scaling, digital remote follow-up, and AI-powered clinical trial prescreening hubs. We present an implementation playbook suitable for oncology leaders working in low-resource counties and LMIC clinics, and we propose an outcomes dashboard to track program performance and detect inequities early.

Scope, Setting, and Maturity of the Evidence

This study is a narrative review and implementation framework rather than a report of a single empirical study. The examples therefore come from different programs, health systems, and geographies. Rather than conducting a

PRACTICAL APPLICATIONS

- Deploy human papillomavirus self-collection programs, with artificial intelligence (AI)–assisted visual triage considered where locally validated and operationally supported, to increase cervical screening coverage while reducing dependence on scarce specialist colposcopy capacity.
- Use Project ECHO telementoring to extend multidisciplinary oncology expertise to community clinicians without requiring patient travel, with benefits across diagnosis, treatment planning, survivorship, and palliative care.
- Build electronic patient-reported outcomes monitoring programs around patient onboarding, escalation protocols, and fallback nondigital pathways so that remote monitoring strengthens rather than fragments care.
- Frame AI-powered clinical trial prescreening hubs as human-supervised prioritization tools that may reduce screening burden, and when paired with navigation, expand equitable access to investigational therapies in settings where manual screening is infeasible.
- Organize scalable programs around a hub-and-spoke operating model centralizing logistics, quality assurance, and tracking at the hub while embedding explicit metrics in governance to monitor uptake gaps, algorithmic bias, and performance drift.

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systematic review, we selected representative evidence and implementation examples that illustrate four operational bottlenecks across the cancer care continuum: entry into care, extension of expertise, continuity between visits, and access to investigational therapy. We group these examples deliberately because they address adjacent bottlenecks across the continuum of cancer care, but we do not argue that they are equally mature. Project ECHO and electronic patient-reported outcomes (ePRO) monitoring have the strongest practice-based implementation literature; human papillomavirus (HPV) self-collection is established, whereas AI-assisted cervical triage remains emerging and still requires robust external validation; and AI-driven trial prescreening hubs should currently be regarded as promising early-stage tools rather than established standards of care.[3–22]

We also do not equate LMICs and underserved US counties. They share some access problems workforce scarcity, geographic distance, fragmented referral pathways, and loss to follow-up, but they differ materially in broadband reliability, laboratory capacity, record architecture, privacy law, device regulation, reimbursement, and medicolegal accountability. These differences are not peripheral. In AI-enabled care, they determine what can be integrated locally, what must be centralized, who is accountable for oversight, and which safeguards are necessary before scale.[23–27] Although the infrastructural realities differ markedly between LMIC clinics and underserved US counties paper-based records versus fragmented electronic health records (EHRs), intermittent connectivity versus siloed health-information technology systems the underlying data architecture of a hub-and-spoke workflow is intentionally adaptable: hub functions such as centralized quality assurance (QA), AI inference, and navigation can operate on cloud-based or offline-first platforms, while spoke-level data capture can range from structured mobile forms to fast healthcare interoperability resources-enabled EHR feeds depending on local capacity.

AI-SUPPORTED SCREENING: HPV SELF-COLLECTION AND AI-ASSISTED TRIAGE

HPV Self-Collection as a Scalable Entry Point

Cervical cancer is the paradigmatic "screenable" malignancy: A validated high-accuracy primary screening test (HPV detection test), an effective triage pathway for the HPV-positive women, and curative treatment for precancer are all available. Yet, cervical cancer remains the leading cause of cancer death among women in many LMICs because screening coverage is critically low. The International Agency for Research on Cancer (IARC) Handbook on cervical cancer screening provides the comprehensive evidence base for HPV detection-based approaches,[3] and the IARC perspective published in the New England Journal of Medicine underscores that self-sampling combined with a point-of-care triage represents a transformative opportunity for global scale-up.[4] WHO guidance supports HPV DNA testing as the primary screening method and explicitly endorses self-collected specimens,[5,6] and the ASCO resource-stratified guideline update which now includes self-collection as an option across all resource levels provides a practical clinical framework for implementation in diverse settings.[7] IARC's practical HPV testing atlas offers detailed instruction on test selection, specimen handling, and management of HPV-positive women.[8] Studies have shown that community health workers can effectively counsel women to self-collect samples for HPV testing in the privacy of their homes.[28] Critically, perspectives from local health policymakers in sub-Saharan Africa underscore that sustainable scale-up of cervical screening requires attention not only to test accuracy but also to workforce training, supply chain reliability, community engagement, and political commitment at the national level.[9]

Regulatory momentum in the United States further strengthens deployability. The US Food and Drug Administration (FDA)

approvals now permit clinic-based self-collection for specific HPV assays that are polymerase chain reaction-based, with collection feasible in primary care offices, urgent care, pharmacies, and mobile clinics.[10,11] A de novo authorization for a home self-collection device signals expanding at-home options that could reach underserved populations who face transportation or time barriers.

The implementation lesson is straightforward: Self-collection only helps if programs also solve the last mile. Patients need simple instructions, language-concordant education, a clear explanation of what a positive result means, reliable specimen routing, and an accountable process for getting from abnormal result to triage and treatment. In both LMIC and underserved US settings, trusted local partners community health workers, public health teams, navigators, or community clinics often determine whether a screening strategy becomes a closed loop rather than another point of attrition.[9,29]

AI-Assisted Cervical Triage: Promise, Limits, and Appropriate Use

A pioneering study to develop and validate an AI-supported technology for cervical screening automated visual examination (AVE) was conducted by Hu et al[13] from the National Cancer Institute. They trained a deep learning model using digitized cervical images obtained with a fixed-focus camera from a population-based screening study conducted in Latin America. The model was designed to distinguish cervical intraepithelial neoplasia grade 2 or worse (CIN2+) from normal or low-grade disease (<CIN2). The algorithm demonstrated superior performance compared with Pap smear cytology or cervicography for detecting CIN2+, achieving an area under the receiver operating characteristic curve (AUC) of 0.91 (95% CI, 0.89 to 0.93).

Subsequent studies have evaluated AVE using archival cervical images captured by smartphones and trained against expert-determined ground-truth diagnoses, with one study distinguishing biopsy-confirmed CIN2+ from CIN1/normal with an AUC of 0.87 (95% CI, 0.81 to 0.92).[30] However, performance has varied when AVE is applied in real-world screening settings. A multicountry study conducted in sub-Saharan Africa compared AVE, visual inspection with acetic acid (VIA), and HPV testing for detecting histopathology-confirmed CIN2+ lesions; AVE demonstrated a sensitivity of only 60.1% (95% CI, 55.5 to 64.5) and a specificity of 81.9% (95% CI, 81.3 to 82.5).[31]

It is now well recognized that several benign or non-precancerous cervical conditions such as squamous metaplasia, severe cervicitis, and condylomas can mimic precancerous lesions and lead to substantial false-positive results with AVE-based visual assessment.[14] Given the high sensitivity, objectivity, and feasibility of HPV detection on self-collected samples, HPV testing represents a more logical primary screening approach. In this context, AI-supported visual evaluation is better positioned as an adjunctive triage tool among HPV-positive women to identify those who require treatment or further diagnostic evaluation.[32]

AI-assisted visual triaging strategy operationalizes a structured screen-triage-treat pathway for resource-constrained settings: (1) self-sampled HPV screening, (2) triage of HPV-positive women using partial genotyping combined with deep learning–based automated visual evaluation of cervical images, and (3) treatment via thermal ablation or excision.[12] Triaging with AI-assisted technology addresses the central limitation of VIA subjectivity and poor reproducibility by applying convolutional neural networks to classify cervical images with diagnostic accuracy that, in development datasets, has matched or exceeded expert colposcopists.[32]

However, the literature consistently emphasizes that rigorous clinical validation and external evaluation are required before broad deployment.[14,15] Distribution shift degraded performance when algorithms trained in one setting are applied in another, which is a particular concern for AI triage tools deployed across heterogeneous populations, devices, and lighting conditions. Mitigation strategies include site-specific calibration, ongoing drift surveillance, and transparent reporting of subgroup performance. Through a project supported by the National Cancer Institute/National Institutes of Health (Award number 1R37CA275824-01), the IARC/WHO, France has developed a light-weight, high-acuity, image-capturing device, which has been used to collect images from more than 2,500 HPV-positive women across multiple countries (Thailand, India, Zambia, and Zimbabwe) to train and validate an algorithm. The device is undergoing field trial in Zimbabwe and the United States for field validation (ClinicalTrials.gov identifier: NCT06042543). At the same time, IARC has created a bank of anonymized cervical images with histopathology results that can be shared with any AI developer for their model development.

Comparative AI Screening Exemplars

AI-Assisted Mammography

The MASAI randomized trial demonstrated that AI-supported screen reading in population mammography achieved similar cancer detection rates compared with standard double reading by radiologists, with a 44% reduction in screen-reading workload.[16] Nationwide implementation in Germany further confirmed improved detection without increased false positives.[17] The European Guidelines on Breast Cancer Screening recommends the use of AI for the second reading of mammograms interpreted as normal on first reading by technicians or radiologists.[33] For low-resource settings, a centralized reading hub + AI triage model could extend screening access where radiologists are scarce, although dependency on imaging infrastructure and standardized acquisition protocols remains a barrier. These examples are more mature in high-resource imaging

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environments than in most LMIC settings and should be interpreted accordingly.

AI-Assisted Low-Dose Computed Tomography Lung Screening

AI can support risk stratification, nodule detection as a concurrent or second reader, and characterization in low-dose computed tomography programs. Reviews emphasize strong dependence on validation across scanners and populations, integration into Lung-RADS workflows, and monitoring for false reassurance in underserved subgroups.[18] In counties with existing computed tomography capacity, AI as a second reader may improve consistency and reduce radiologist burden.

PROJECT ECHO: DEMOCRATIZING BEST-PRACTICE CANCER CARE THROUGH TELEMENTORING

Model and Mechanisms

Project ECHO was developed at the University of New Mexico to address specialty care gaps by building capacity among community clinicians through virtual clinics combining brief didactics with case consultation.[19,20] Its defining features include a hub-and-spoke architecture connecting a multidisciplinary specialist team with community sites that retain clinical responsibility; a standardized learning cadence of recurring video-based sessions; case-based bidirectional mentorship where spokes present real cases and hubs provide evidence-adapted recommendations (all teach, all learn); and measurement for improvement through participation tracking, learner assessments, and, increasingly, practice and patient-level outcomes.[21]

The foundational ECHO study demonstrated that primary care providers treating hepatitis C through the ECHO model achieved sustained virologic response rates comparable with those at the university specialty clinic,[22] establishing the model's force multiplier premise: moving knowledge rather than patients. That last point is especially important: ECHO is not tele-referral in disguise. It is a workforce-scaling model that keeps care local while standardizing access to specialist input. Over the past decade, oncology ECHO programs have expanded across the cancer continuum.

Evidence Across the Cancer Continuum

Prevention and Early Detection

A Cameroon cervical cancer prevention ECHO launched in 2018 found substantially higher knowledge among prior attendees compared with newcomers and greater uptake of screening and treatment procedures.[34] In the United States, American Cancer Society (ACS) ECHO programs targeting tobacco cessation and screening topics reported significant increases in knowledge and confidence among 431 participants, with 59% planning to apply learning within 1 month.[35] A cancer prevention, screening, and survivorship ECHO in Indiana expanded to 32 states and four countries across 2 years, demonstrating scalable reach with strong multidisciplinary engagement.[36,37]

Diagnosis and Linkage to Care

In western Kenya, a pediatric oncology ECHO engaged 148 participants across 22 sessions and coincided with a 33% increase in new pediatric cancer diagnoses at the regional hub compared with the prior 3-year average an important signal where underdiagnosis is the norm.[38,39] A multiple myeloma ECHO in the same region reported 24 spoke sites across 15 counties and a 35% increase in myeloma diagnoses at the hub.[40] In high-income settings, a rural survivorship pilot pairing ECHO with patient navigation demonstrated high knowledge gains among providers and navigation services delivered to 164 rural survivors across four sites.[41]

Treatment and Supportive Care

A virtual gastrointestinal tumor board in Argentina used the ECHO model across 37 centers over 3 years; 75% of 80 patients were managed locally after multidisciplinary discussion, while 25% were appropriately referred.[42] International Gynecologic Cancer Society programs incorporate monthly ECHO tumor boards at LMIC fellowship sites, reviewing over 300 cases per year.[43] For complex therapeutics like immune checkpoint inhibitors, ECHO has been deployed to support community teams in recognizing and managing immune-related adverse events.[12]

Survivorship and Palliative Care

The ECHO-PACA program provided a 16-month palliative care series across multiple African countries with documented increases in self-reported confidence.[44] The PC-PAICE collaborative in India engaged 22 palliative care programs and evolved into a national effort integrated with India's National Cancer Grid.[45] CDC-linked rural survivorship pilots in multiple US states demonstrated that pairing ECHO with patient navigation addresses both provider capability and structural barriers to follow-up.[41]

Why ECHO Matters in This Framework

ECHO is central here because the other technologies do not implement themselves. Screening programs, ePRO alerts, and AI-supported trial matching all depend on local teams that can interpret outputs, explain them to patients, escalate concern appropriately, and sustain trust capabilities that ECHO is uniquely positioned to build.[46] Successful oncology ECHO programs share several design principles. First, multiprofessional participation including physicians, nurses, pharmacists, navigators, and allied health professionals reflects how cancer care is actually delivered and ensures that best practices translate as team behaviors rather than siloed clinician actions.[37,38,40–42] Second,

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codesign with spokes is decisive; curriculum development should incorporate spokes' perceived skill gaps and context-specific barriers.[38,40] Third, recruitment and protected time for specialists remain persistent constraints; programs that provide continuing medical education/continuing education credit, explicit leadership endorsement, and operational support demonstrate better sustainability.[47] Fourth, evaluation should move beyond attendance and satisfaction toward implementation, practice, and patient-level outcomes, with standardized data collection enabled by platforms such as iECHO.[21,35,48] Selected outcomes are summarized in Table 1.

ePRO AND REMOTE SYMPTOM MONITORING

Evidence and Operational Prerequisites

In a scalable cancer-care model, ePRO monitoring functions as the continuity layer: It keeps patients visible between visits, converts symptom reporting into actionable escalation, and reduces the risk that limited staffing or geography will fracture follow-up.

ePRO-based remote symptom monitoring has strong evidence as a follow-up and early intervention tool in oncology. Randomized trials demonstrate that systematic symptom monitoring using validated instruments such as PROs version of the Common Terminology Criteria for Adverse Events and the Edmonton Symptom Assessment System improves quality of life and clinical outcomes, including survival signals, when paired with responsive clinical workflows that include timely nurse or clinician escalation.[49,50] More recent trials in metastatic cancer confirmed effects on patient-reported outcomes,[51] and implementation studies suggest associations with reduced hospitalizations and improved value metrics, reinforcing that staffing, escalation protocols, and integration into routine care are determinants of effectiveness. ePRO is therefore one of the most implementation-ready technologies discussed in this article.

For resource-constrained settings, the critical design question is not whether ePRO monitoring works but how to make escalation workflows reliable with constrained staff. Simplified multilingual symptom sets, offline-first mobile tools, and explicit service-level agreements who responds, within what timeframe, and according to which protocol are prerequisites for equitable deployment. Without those elements, digital symptom capture can create false reassurance rather than safer continuity. WHO digital health guidance supports remote monitoring as a mechanism for overcoming geographic barriers, with emphasis on legal frameworks, interoperability, workforce training, and patient consent.

Patient Onboarding and Community Support

Patient education is critical. Remote monitoring only works when patients understand what the tool is for, what kinds of symptoms should be entered, how quickly someone will respond, and what to do if symptoms worsen before a callback occurs. A practical onboarding package should include a short teach-back demonstration, language-concordant written or pictorial instructions, a telephone alternative, and a named contact for urgent escalation. This is especially important in settings with variable health literacy, shared devices, or intermittent connectivity.

Published ePRO trials do not uniformly describe formal partnerships with community organizations, and this manuscript should not be read as claiming that every program used the same community support structure. However, for underserved settings, implementation is usually stronger when digital monitoring is reinforced by human navigation and trusted local support such as community health workers, county or tribal public-health teams, community clinics, or advocacy partners that can help patients stay engaged

TABLE 1. Selected Project ECHO Oncology Program Outcomes

Program	Region	Focus Area	Key Outcomes	References
Cameroon Cervical Cancer Prevention ECHO	Cameroon	HPV, screening, treatment	Prior attendees: 53.8% *v* 4.5% knowledge; approximately 69% applied ECHO learning	34
ACS ECHO (tobacco + screening)	The United States	Prevention and screening	431 participants; mean knowledge +0.84, confidence +0.77 (5-pt scale)	35
AMPATH Pediatric Oncology ECHO	Kenya	Diagnosis, referral	33% increase in new pediatric cancer diagnoses at hub	38
AMPATH Multiple Myeloma ECHO	Kenya	Hematologic malignancy	35% increase in myeloma diagnoses; 24 spoke sites, 15 counties	40
Virtual GI Tumor Board (ECHO)	Argentina	Multidisciplinary treatment	80 patients, 37 centers; 75% managed locally	42
Rural Survivorship ECHO + Navigation	The United States	Survivorship, linkage	93% enhanced knowledge; 164 survivors navigated	41
ECHO-PACA	Sub-Saharan Africa	Palliative care	Increased confidence in palliative care delivery	44
ICCP ECHO	Multicountry LMIC	Cancer control planning	Significant pre-post knowledge/confidence gains across 12 strategies	46

Abbreviations: ACS, American Cancer Society; HPV, human papillomavirus; LMICs, low- and middle-income countries.

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between visits. The same principle is visible in rural survivorship navigation and community-based self-collection efforts: Digital tools succeed more often when embedded inside a human support network.[41]

Why ePRO Belongs in the Same Framework

In this sense, ePRO is not an optional digital add-on; it is the mechanism that sustains continuity once screening, treatment initiation, or symptom-triggered intervention has begun. Critically, ePRO data can also feed back dynamically into AI prescreening hubs: patient-reported symptoms signaling disease progression, treatment intolerance, or performance status decline can trigger automated rematching against updated trial databases, ensuring that the transition from active treatment to investigational therapy is recognized in real time rather than discovered at the next scheduled visit. This bidirectional integration between the continuity layer and the access-to-innovation layer exemplifies how the four technology families function most powerfully as a connected system rather than parallel silos.

FROM TOOL TO PROGRAM: AN IMPLEMENTATION PLAYBOOK FOR SCALABLE CANCER CARE

Defining the Hub-and-Spoke Model: Operational Definition

We do not argue that hub-and-spoke is universally superior for every oncology service. We argue that it is usually the best fit when three conditions coexist: scarce expertise, geographic dispersion, and a need for closed-loop tracking. Under those conditions, a fully centralized model concentrates expertise but increases travel burden and queuing, whereas a fully decentralized model preserves local autonomy but duplicates scarce specialist capacity and makes QA inconsistent.

A recurring finding across successful screening programs is that scale lives in the hub. England's bowel cancer screening program provides a canonical model: regional hubs manage call/recall, kit dispatch and processing, helplines, results reporting, and audit/key performance indicator monitoring, while community spokes focus on access and patient relationships.[52] For HPV testing in LMICs, hub-and-spoke logistics (spoke sample collection, hub testing, and referral) are feasible and compatible with self-collection scale-up.[29] Centralized colorectal cancer outreach and navigation programs in US safety-net settings provide an additional operational blueprint: Mailed fecal immunochemical test outreach with structured abnormal-result navigation improved screening completion and generated measurable end-to-end outcomes.[53]

Operationally, the hub performs the functions that benefit most from centralization:

- Clinical governance: triage thresholds, exception handling, patient-safety oversight, downtime plans, and vendor or model oversight.
- Shared operations: registry management, kit or device procurement, result routing, scheduling support, and abnormal-result tracking.
- Specialist support: multidisciplinary consultation, ECHO-style case review, escalation backup, and trial prescreening verification.
- Quality and analytics: audit, drift surveillance, subgroup review, equity monitoring, dashboarding, and reporting.
- Navigation infrastructure: follow-up outreach, barrier assessment, and coordination of referrals or trial screening.

The spoke performs the functions that must remain close to the patient:

- Community outreach and patient education, using trusted local partners where appropriate.
- Local sample collection, symptom capture, counseling, and protocol-driven treatment steps that do not require central specialist review.
- Context adaptation, including language support, transport planning, clinic workflow integration, and relationship building with local clinicians and patients.
- Rapid escalation back to the hub when predefined thresholds are met.

Accountability should be explicit rather than assumed. The hub owns standards, audit, technology governance, and performance monitoring. The spoke owns local execution, patient contact, and contextual adaptation. Figure 1 summarizes this operating model.

Community Engagement and Patient Education Are Part of the Operating Model

Patient-facing technology should never be introduced as a black box. Whether the program involves self-collection, ePRO monitoring, or trial prescreening, patients need a plain-language explanation of what the tool does, what data are being used, what a human clinician or navigator will still do, and what happens if the technology fails. In practice, the local spoke should identify at least one trusted community channel—such as a community health worker network, community clinic, county public health team, advocacy organization, or faith or tribal partner, depending on the locale—to reinforce uptake and follow-up. Because this study is a narrative review and implementation framework rather than a primary implementation study, we did not conduct direct stakeholder interviews or formal community-partner outreach for this study; instead, we translated published implementation experience into practical recommendations.

This is one of the main reasons a common architecture can work across very different settings without pretending they are identical. The hub can standardize safety, logistics, and

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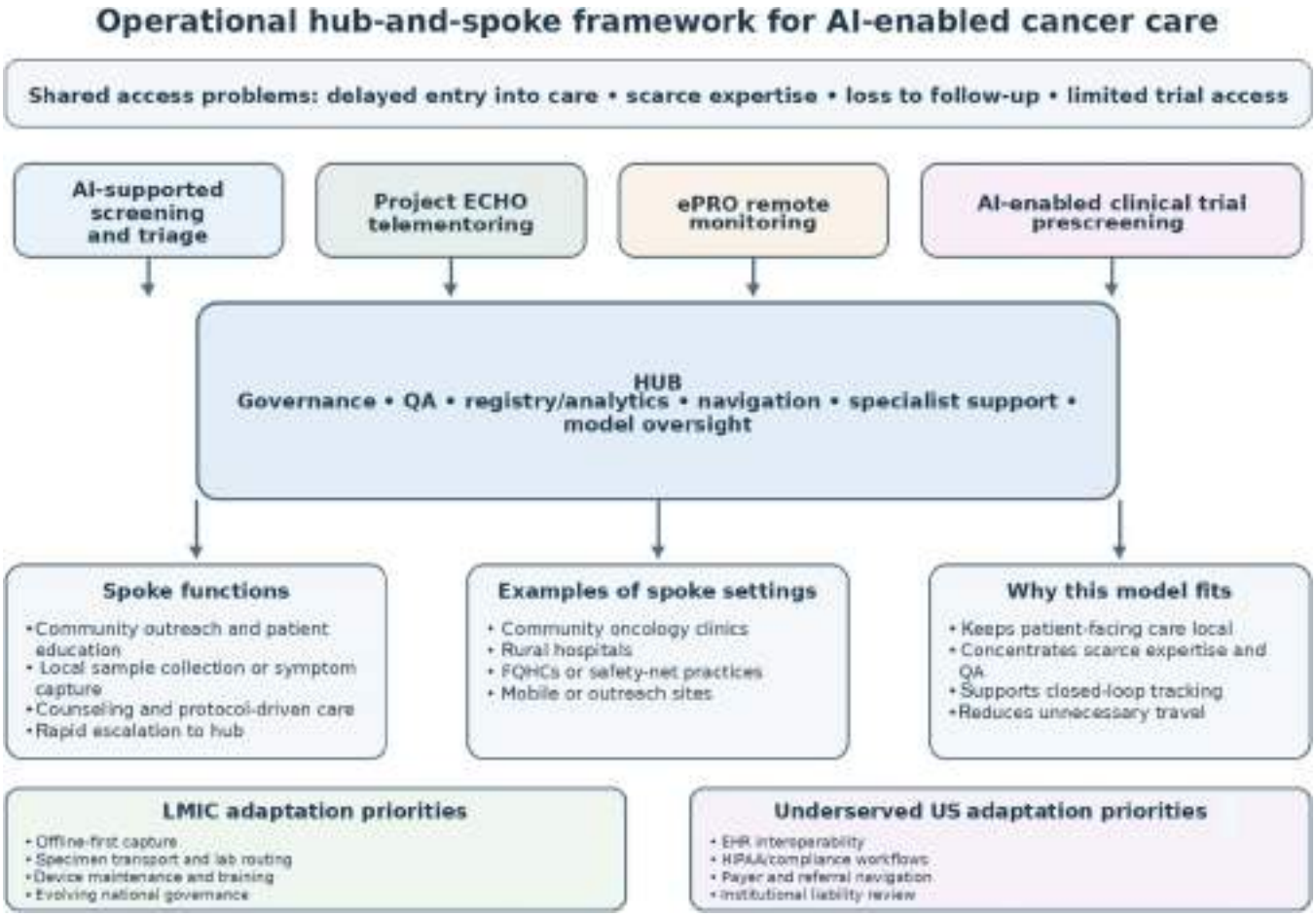

FIG 1. Operational hub-and-spoke framework for AI-enabled cancer care. AI, artificial intelligence; EHR, electronic health record; ePRO, electronic patient-reported outcomes; FQHCs, Federally Qualified Health Centers; HIPAA, Health Insurance Portability and Accountability Act; LMIC, low- and middle-income countries; QA, quality assurance.

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analytics, while the spoke adapts patient communication and support to local language, trust, and transportation realities.

AI-Powered Patient-Centric Prescreening Hubs

Clinical trial prescreening represents a parallel hub application whose relevance to low-resource settings is increasingly compelling. Despite more than 14,900 active cancer clinical trials globally and over 18 million new cancer diagnoses per year, only approximately 0.1% of patients with cancer in the National Cancer Database were enrolled in trials, and roughly 55% of trials close prematurely because of enrollment shortfalls.[54,55] The paradox is acute in underserved communities: 51% of US counties have no active cancer trials and no oncologists, while 85% of patients diagnosed with cancer receive care at community-based practices far from academic research centers.[56]

The concept of patient-centric prescreening hubs—first presented at the 2025 ASCO/ESMO Educational Session (2)—represents a proposed shift from static trial listings to active, AI-driven triage. These digital hubs collect key eligibility data (EMR, laboratory values, next-generation sequencing results, demographics) and apply multiagent AI systems with domain-specific knowledge graphs to compare each patient against live trial criteria in real time, flagging high-probability matches for expert review. Unlike conventional trial finders, prescreening hubs are designed to address data drift—the reality that trial criteria change (amendments, site openings/closures, regulatory holds), patient status evolves (disease progression, new biomarkers, changing performance status), and standard-of-care shifts alter the treatment landscape continuously. Manual tracking may be difficult to sustain in this dynamic environment.

A prospective evaluation of a multiagent AI platform incorporating an oncology-specific knowledge graph, specialized large language model (LLM) agents, and a hybrid recommendation engine was conducted across 3,804 patients with metastatic or progressing cancers.[57] The system processed 157,367 pages of deidentified medical records, achieving 80.29% parameter extraction accuracy and 82.06% trial matching accuracy substantially outperforming GPT-4o (63.15% and 47.00%, respectively) and GPT-4 (57.03% and 38.68%). The AI platform achieved an F1 score

of 0.8246 with a sensitivity of 0.8375 and a specificity of 0.8359. The average time per patient evaluation decreased from 120 minutes to 30 minutes—a fourfold efficiency gain—with human-in-the-loop validation used to support clinical review. In an earlier study of 5,707 patients, the same AI-enabled multitrial matching system demonstrated a 1.82-fold increase in trial matches per patient and a 99.9% reduction in screening effort compared with manual methods.[58] These results are encouraging, but important caveats apply: Both studies are conference abstract-level and author-linked, and neither establishes consistent downstream improvement in enrollment rates, diversity of enrolled participants, time to consent, or cost-effectiveness. These data should therefore be interpreted as proof-of-concept evidence for workflow efficiency gains rather than as established real-world benefit.

The operational model of these hubs follows a hybrid click-and-mortar design: Digital outreach and AI-driven prescreening provide scalable reach to patients anytime and anywhere, while human navigators and study coordinators manage the last mile follow-up calls, consent, laboratory coordination, and enrollment logistics. Triggers can fire automatically at diagnosis, disease progression, or relapse, ensuring real-time rematching as clinical status changes.

Additional practical constraints deserve explicit emphasis before scale. First, external validation across institutions and record systems remains limited. Second, interoperability is often the rate-limiting step, because pathology reports, genomic data, and evolving trial criteria do not arrive in one uniform format. Third, medicolegal accountability is unresolved if an automated system fails to surface an eligible study or misclassifies exclusion criteria. Fourth, cost and maintenance matter: Even a technically strong system will not reduce inequity if only well-resourced centers can support integration, curation, and human verification.[23–27] For those reasons, prescreening hubs should currently be framed as human-supervised prioritization systems rather than autonomous enrollment engines.

ACS ACTS: Scaling Trial Access Through Navigation and AI Matching

The ACS's Access to Clinical Trials and Support (ACTS) program provides a national proof-of-concept for prescreening hubs at population scale. Launched in 2025, ACS ACTS combines AI-powered clinical trial matching with comprehensive support services, clinical trials education, health-related social needs screening, eligibility and enrollment navigation, and transportation and lodging assistance to reduce structural barriers to trial participation.[59,60] ACS ACTS illustrates a critical principle for deployability in low-resource contexts: Effective trial access technology must be embedded within a sociotechnical service model that addresses the social determinants, logistical barriers, and trust deficits that prevent patients from reaching cycle 1, day 1.

The prescreening hub model aligns with the Cancer Moonshot's mandate to bring trials to patients and is increasingly integrated into multi-stakeholder initiatives including the ACS CAN/CodeX Integrated Trial Matching collaboration, which uses mCODE standards to embed trial matching into EHR workflows at community oncology sites.[61] Federated learning approaches where AI models are trained across institutions without sharing raw patient data offer a privacy-preserving pathway for scaling these platforms across international settings while maintaining compliance with Health Insurance Portability and Accountability Act (HIPAA), general data protection regulation (GDPR), and local regulatory frameworks.[62] The convergence of decentralized clinical trial methods with prescreening hubs further extends reach: hubs can identify candidates suitable for remote consent and monitoring, enabling just-in-time site activation in locations far from traditional research centers.

Staffing Model for Low-Resource Settings

Hub roles (fractional FTEs in small programs) include Program Director, Operations Manager, Clinical Lead, QA/Patient Safety Lead, Data/Registry Analyst, Logistics Coordinator, Navigation Lead, and an AI/Tech Steward responsible for model documentation, versioning, and performance monitoring.

Spoke roles (community-proximate) include community health workers or outreach staff, specimen collection facilitators, nurses/advanced practice providers (or applications) for triage and counseling, and navigators who manage appointments and address barriers.

Small programs do not need full-time personnel in every role at launch, but they do need named ownership. What should not be fractional is accountability for closed-loop tracking. Programs that attempt to launch multiple technologies at once often stall; in practice, it is usually better to start with one high-yield use case, validate the workflow, and then extend the same operating model to adjacent services (Table 2).

QA for AI-Supported Screening

AI-supported screening requires QA at three layers: (1) input quality image or specimen quality checks, standardized acquisition protocols, and reject and repeat thresholds; (2) model performance routine recalibration, drift surveillance by site and device, and external validation in new geographies; and (3) clinical workflow performance audits of triage decisions, confirmatory testing rates, and timeliness of referrals.[14,15] For regulated AI/machine learning medical devices, FDA guidance emphasizes managing iterative improvements through predetermined change control plans and transparency expectations.[23,24] The International Medical Device Regulators Forum framework for Software as a Medical Device (SaMD) specifies scientific validity, analytical

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TABLE 2. Ninety-Day Implementation Checklist

Phase	Deliverable	Operational Detail	Primary Owner
Weeks 1-2	Define target population and pathway	Eligibility rules, sites, referral partners, hub *v* spoke responsibilities	Program Director + Clinical Lead
Weeks 1-2	Baseline data pull	Current screening uptake, abnormal result resolution times, no-show rates	Data/Registry Analyst
Weeks 1-3	Governance and risk register	Consent/privacy, clinical safety, downtime plan, equity risks	QA/Safety lead
Weeks 2-4	Workforce plan	Staffing coverage, escalation SLAs, role descriptions	Ops Manager + Navigation lead
Weeks 3-6	Build hub logistics	Kit/device procurement, transport, laboratory agreements, result routing	Logistics Coordinator
Weeks 3-6	Training and competency	Collection QC, triage protocols, navigation scripts, ePRO escalation	Training lead
Weeks 4-8	Pilot closed-loop tracking	Every screen tracked through result, referral, and completion	Data + Navigation
Weeks 6-10	QA launch	Sampling audits, discrepancy review, adverse event review	QA/Safety lead
Weeks 8-12	Go-live and stabilize	Weekly ops huddles, dashboard review, iteration on bottlenecks	Program Director
Day 90	First performance report	Uptake, time-to-diagnosis, follow-up completion, equity stratification	Program Director + Analyst

Abbreviations: ePRO, electronic patient-reported outcomes; QA, quality assurance; QC, quality control; SLA, service level agreement.

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validity, and clinical performance as pillars of clinical evaluation.[25]

Governance and Sustainability

A deployable governance plan includes clinical oversight with a named lead accountable for triage thresholds and exception handling; data governance aligned with local privacy laws and international standards (HIPAA, GDPR); model/version governance through model cards documenting intended use, limitations, data set provenance, and subgroup performance; and sustainability planning including cost models, maintenance schedules, and fallback workflows for system downtime. WHO's ethics and governance framework for health AI emphasizes human rights, transparency, accountability, and inclusion,[26] whereas the NIST AI Risk Management Framework provides a voluntary structure for trustworthy AI deployment.[27]

Governance requirements also differ by setting. In many LMIC implementations, the pressing issues may be offline-first data capture, device maintenance, specimen transport, training, and governance in environments where national AI rules are still evolving. In underserved US settings, priorities more often include HIPAA-compliant data flows, EHR integration, institutional liability review, and reimbursement or payer navigation. The architectural logic can be shared, but the control environment cannot be assumed to be the same.

Equity and Bias Monitoring

Clinical equity metrics (monthly/quarterly): Screening uptake gap ratio (lowest-access subgroup divided by highest-access subgroup); abnormal-result resolution gap; time-to-diagnosis gap; time-to-treatment gap each stratified by rurality, race/ethnicity, language, insurance proxy, and clinic site.

Algorithmic performance metrics (quarterly): Sensitivity/specificity proxies in audited samples; false-negative rates by subgroup; calibration drift by device/site; unknown/ungradable output rates (an early warning for unequal input quality). Transparency artifacts should document intended use, known limitations, and updates aligned with FDA guiding principles.[24]

OUTCOMES DASHBOARD

A scalable program should treat measurement as part of the intervention. The dashboard in Table 3 is organized around access, quality, timeliness, patient-centered care, AI safety, and equity. The goal is not merely to prove activity, but to detect where the workflow is failing, for whom it is failing, and whether technology is reducing or widening existing disparities.

GAPS AND FUTURE DIRECTIONS

The next research agenda should be matched to the maturity of each technology family. For AI triage in cervical screening, the priority is multisite effectiveness studies with explicit evaluation of distribution shift and transparent reporting of subgroup performance in LMIC and rural settings.[15] For self-collection programs, the central unanswered question is not acceptability but closed-loop performance: How often do programs succeed in moving HPV-positive women through triage and treatment within clinically appropriate time windows, particularly in decentralized settings?

For AI mammography and lung screening, a major gap in low-resource contexts is not algorithmic capability but

TABLE 3. Outcomes Dashboard

Domain	Metric	Suggested Stratifiers	Data Source	Cadence
Access	Screening uptake (% eligible completing screening)	County, race/ethnicity, age, site	Registry/EHR	Monthly
Access	Closed-loop completion (% with definitive result + plan)	Same	Registry/EHR	Monthly
Quality	Specimen rejection rate	Site, collector, kit type	Lab LIS	Weekly
Timeliness	Time to diagnosis (median days)	Site, subgroup	EHR/registry	Quarterly
Timeliness	Time to treatment (median days)	Site, subgroup	EHR	Quarterly
Utilization	Avoidable acute care (ED visits/hospitalizations per 100 pts)	Site, subgroup	Claims/EHR	Quarterly
Patient-centered	ePRO completion rate	Language, digital access	ePRO platform	Monthly
Patient-centered	Symptom escalation response time	Site, staffing	ePRO + ticketing	Monthly
AI safety	AI triage sensitivity proxy (audit sample)	Device/site	Audit registry	Quarterly
AI safety	Drift signal (performance change over time)	Site/device	AI logs	Quarterly
Equity	Screening gap ratio (lowest *v* highest access)	Race/ethnicity, rurality	Dashboard	Quarterly
Equity	Follow-up gap (resolution time difference)	Race/ethnicity, rurality	Dashboard	Quarterly

Abbreviations: AI, artificial intelligence; ED, emergency department; EHR, electronic health record; ePRO, electronic patient-reported outcomes.

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dependency on imaging infrastructure and centralized reading capacity. Research should assess whether reading hub + AI triage + local navigation can meaningfully expand access without widening disparities.[17] For AI-powered clinical trial prescreening hubs, although prospective data demonstrate efficiency gains and accuracy above general-purpose LLMs,[57] peer-reviewed evidence on downstream enrollment outcomes, diversity impact, and cost-effectiveness remains limited. Future studies should evaluate whether hub-enabled matching translates into measurably higher enrollment rates and more representative trial populations in LMIC and underserved US county settings and should address barriers to EHR interoperability and NGS data integration that currently constrain real-time matching at scale. Comparative studies of organizational models would also be valuable: Hub-and-spoke is often a strong fit, but some settings may be better served by more centralized referral pathways or by shared regional service collaboratives.

For Project ECHO, future work should link participation to patient-level outcomes in prevention and early detection not only provider satisfaction and evaluate how ECHO pairs with navigation and digital tracking to reduce loss to follow-up.[21,48] For ePRO monitoring, research should focus on implementation in low-resource settings including simplified multilingual symptom sets, offline-first tools, and cost-effectiveness analyses.[49]

Across all four domains, the next frontier is not proving that isolated tools can work, but demonstrating that integrated, hub-based workflows can deliver closed-loop, equitable cancer care at scale across heterogeneous low-resource settings.

CONCLUSION

Technology that scales in cancer care is not defined by algorithmic sophistication alone, but by the capacity to function as a deployable workflow with staffing, logistics, QA, governance, and equity monitoring built into the operating model from inception. The evidence reviewed here shows that HPV self-collection paired with AI triage, Project ECHO telementoring, ePRO-based remote monitoring, and AI-powered clinical trial prescreening hubs each offer scalable, evidence-supported approaches to narrowing disparities in low-resource settings. Their greatest value emerges not in isolation, but in combination: Screening expands entry into care, ECHO expands workforce capacity, ePRO sustains continuity between visits, and prescreening hubs expand access to investigational therapies. A hub-and-spoke architecture offers a pragmatic organizational scaffold across all four.

The framework presented here is intentionally practical. It distinguishes technologies that are ready for broader deployment from those that still require cautious validation, defines the hub-and-spoke model operationally, and separates shared access problems from the very real differences between LMICs and underserved US counties. The 90-day implementation checklist, staffing models, QA frameworks, and outcomes dashboard are intended to be immediately actionable for oncology leaders in LMIC clinics and underserved US counties. The next step for the field is to move beyond demonstration projects toward scaled, monitored, and equitable deployment of integrated care-delivery models. In that transition, AI should augment not replace human judgment, extending the reach of oncology teams while preserving the empathy, contextual reasoning, and trust on which cancer care depends.[63]

DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer/WHO, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer /WHO.

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Desmoid Tumors—Biology-Driven Management and Treatment Selection

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OVERVIEW

Desmoid tumors (DTs) are rare fibroblastic neoplasms driven by altered Wnt signaling pathways, through activating mutations in β-catenin (*CTNNB1*) or loss of repressive *APC*. DTs are considered as intermediate neoplasms that can be locally aggressive, with potential for significant medical complications that can threaten life and limb, as well as impact on patient function, quality of life, and emotional well-being. Historically, DTs were treated with similar paradigms as soft tissue sarcomas, with complete surgical resection the priority despite frequent postoperative recurrences, or use of radiation or cytotoxic chemotherapies for refractory/recurrent cases. Today, improved understanding of DT biology and natural history, along with the development of molecularly targeted therapies, has greatly changed the recommended approach to DT management. In this review, we highlight the role of active surveillance for initial management of most DTs, recognizing the potential for tumor stability or spontaneous regression. In the case of highly symptomatic or progressive tumors, we review the spectrum of treatment options, including surgery for select cases, systemic therapies such as novel gamma secretase inhibitors and tyrosine kinase inhibitors, and emerging local treatment options including cryoablation and high-intensity focused ultrasound. Through a multidisciplinary approach and careful assessment of the individual patient's DT biology and symptomatic impacts, the optimal treatment strategy can be selected to minimize unnecessary morbidity and toxicity and to improve outcomes and quality of life for this unique patient population.

INTRODUCTION

Desmoid tumors (DTs), also known as desmoid fibromatosis or aggressive/deep fibromatosis, are rare soft tissue neoplasms composed of proliferative monoclonal fibroblasts or myofibroblasts, and classified as "intermediate" neoplasms in the WHO 2020 Classification of Soft Tissue Tumors.[1-3] The incidence of DT is approximately five cases per 1 million persons per year, with a greater incidence in women.[4] Although DTs can affect the entire age range including pediatric patients and the elderly population, it most commonly affects patients age 30-40 years. DTs arise in the context of altered Wnt signaling pathways (Fig 1), either through conserved activating mutations in β-catenin (*CTNNB1*) that occur in sporadic tumors or deletion of suppressive *APC* in hereditary polyposis syndromes.[1,5,6] Other pathways implicated in DT pathogenesis include estrogen, particularly in the setting of pregnancy, and NOTCH signaling, though exact mechanisms of cross-talk with *WNT*/*CTNNB1* remain uncertain.[7,8]

DTs tend to arise in deep soft tissues and can occur at essentially any anatomic location, including intra- and extra-abdominal sites.[6] Owing to their locally invasive and infiltrative nature, DTs can cause significant morbidity and symptoms, including pain and functional impairment, catastrophic infections/obstructions, particularly in mesenteric sites, and substantial psychological and socioeconomic impacts.[2,9-11] Recognizing the unique nature and treatment of DTs, dedicated location-specific International Classification of Diseases-10 codes were implemented by the CDC in the United States in October 2023 to distinguish them from benign entities or malignant sarcomas, an effort spearheaded by the Desmoid Tumor Research Foundation.

Owing to their variable clinical presentations and unpredictable behavior, the management of DTs can be complex, often requiring the involvement of multiple disciplines. Given this, the Desmoid Tumor Working Group has published an international evidence-based consensus guideline outlining optimal management strategies for DF[12] (Fig 2). Historically, DT management focused on complete surgical resection similarly to sarcoma paradigms. However, in recent years, this has shifted toward a more conservative approach. Active surveillance (AS), or watchful waiting, has been recommended as the initial treatment strategy for newly diagnosed,

PRACTICAL APPLICATIONS

- Most desmoid tumors (DTs) can be managed with active surveillance at initial diagnosis, reserving treatment for symptomatic, high-risk, or progressing tumors.
- Surgical resection should be reserved for the management of life-threatening complications, such as bowel obstruction for mesenteric DTs, or for low-morbidity sites such as the abdominal wall.
- Highly active systemic therapies, including nirogacestat or sorafenib, offer less toxicity and improved efficacy over the historical use of cytotoxic chemotherapy.
- Interventional radiology locoregional approaches, such as percutaneous cryoablation, are emerging strategies to address extra-abdominal DTs.
- Optimal selection of treatment requires multidisciplinary input, assessment of the individual patient's disease biology, symptoms, and treatment preferences.

asymptomatic DTs.[12] The United States National Comprehensive Cancer Network (NCCN) guidelines also emphasized initial surveillance for patients who are asymptomatic and without progressive disease.[13] This paradigm shift was driven in part by high rates of progression-free survival (PFS; 36%-44% at 2 years) or even spontaneous regressions (overall response rate [ORR], 8%-20%) documented in placebo arms of randomized clinical trials for DTs.[14,15]

In cases of radiographic disease progression with associated morbidity and symptoms, further treatment may be warranted.[12,13] Despite the trend toward nonsurgical management, surgery remains essential in select clinical situations. Surgical intervention is recommended for managing ongoing or potential gastrointestinal complications in patients with sporadic mesenteric DT, such as bowel perforation, obstruction, and bleeding.[12] Additionally, surgical intervention may be considered in DTs that have progressed despite medical treatment or AS, depending on the clinical situation. In particular, surgery remains an option for low-morbidity small abdominal wall DTs.[12] Historically, aggressive DTs could also be treated with cytotoxic chemotherapies; however, long-term toxicities and risks from chemotherapy in the setting of a nonmalignant disease were problematic. Today, novel molecularly targeted therapies and/or interventional radiology locoregional approaches, such as percutaneous cryoablation, have emerged as more appealing options in the management of progressive DTs.

In summary, owing to the complexity of DTs, a multidisciplinary team is essential, and treatment is ultimately determined through consensus and a comprehensive assessment of the patient's symptoms and treatment preferences. Although the disease can be progressive, the guiding principle remains to treat gently and with a patient-centered approach. Various treatment options and general considerations for selection of therapy are discussed in the remainder of this review.

ACTIVE SURVEILLANCE STRATEGIES

Surgical resection has been the mainstay of treatment for resectable DTs for decades. However, surgery in DTs may lead to significant functional impairment, chronic sequelae including pain and deformity, and is associated with high local recurrence rates of up to 30%-50%, potentially from

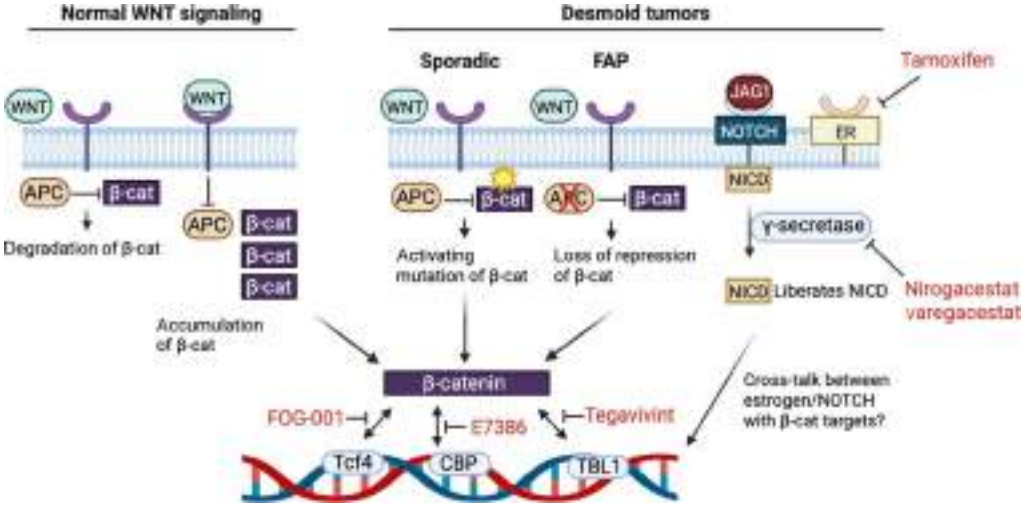

FIG 1. Schema of molecular pathways and treatment targets in desmoid tumors. Created with Biorender. Red text represents agents either approved or in clinical development. β-cat, beta catenin, *CTNNB1*; ER, estrogen receptor; FAP, familial adenomatous polyposis.

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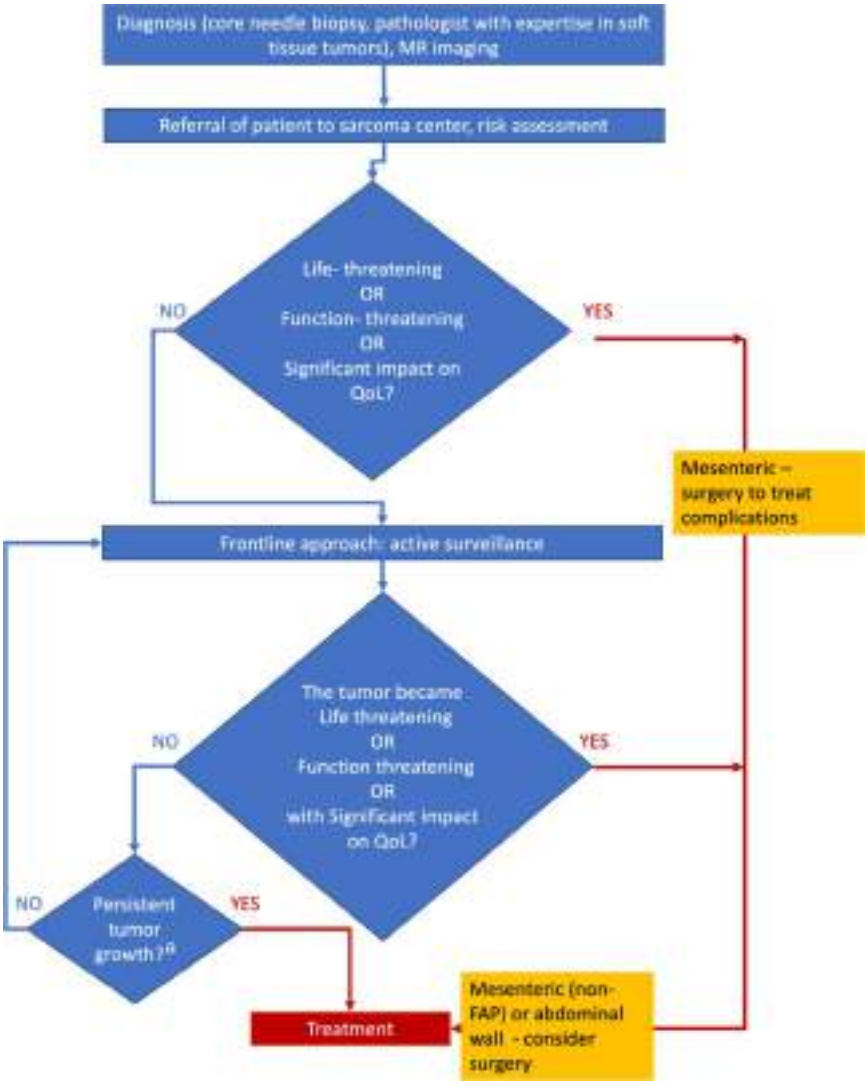

FIG 2. Management of patients with desmoids from diagnosis to treatment including the role of surgery (modified from Kasper et al[11]). [a]A persistent tumor growth is characterized by the observation of tumor size increase at multiple (>2) consecutive follow-up appointments with an impact on either QoL or function or when further enlargement poses a potential risk to the feasibility or efficacy of first-line treatment. MRI, magnetic resonance imaging; QoL, quality of life.

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reactivation of wound healing pathways leading to further mutated fibroblastic growth.[16-19] Thus, surgery is no longer the standard first-line approach, and surgical interventions are currently limited to selected cases, with a global paradigm shift toward more conservative management. AS was first proposed for patients presenting with limb recurrences when extremity salvage was not possible. Thereafter, several multicenter (including prospective) studies confirmed that up to 50%-60% of DTs do not progress or regress on AS.[20-25] Importantly, 20%-30% of patients could achieve spontaneous and even complete regression despite initial progression of the tumors[20,26] (Fig 3A). According to current international guidelines, AS may be offered up-front to almost all patients, depending on the anatomical location, presence of familial adenomatous polyposis (FAP), severity of symptoms, and potential morbidity in the event of ongoing progression.[12,13]

Contrast-enhanced magnetic resonance imaging (MRI) or alternatively computed tomography (CT) for certain tumor locations are the preferred modalities for monitoring DTs on AS, typically within the first 2 months after diagnosis and then at every 3-6 months intervals (in case of stabilization or regression) up to 2-3 years. So far, there are no reliable clinical, radiological, or biological markers that can be used to predict DT behavior or to guide treatment selections. A large prospective French study identified the site of the tumor as a major prognostic factor for local progression classifying sites as favorable (abdominal wall, breast, intra-abdominal, and lower limb) or unfavorable (head and neck,

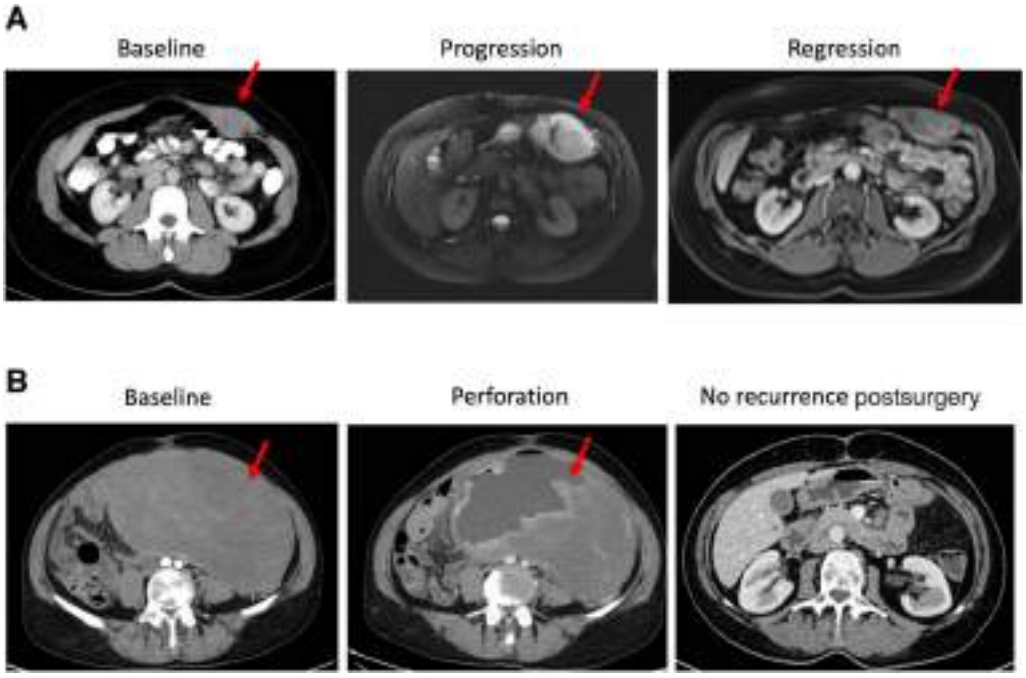

FIG 3. Representative desmoid tumor cases. (A) CT imaging showing spontaneous regression with active surveillance despite initial progression. (B) Large mesenteric desmoid tumor requiring surgery because of jejunal perforation, which occurred 1 month after doxorubicin treatment initiation. No evidence of recurrence after 5 years of follow-up. CT, computed tomography.

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thoracic wall and upper limb).[27] Italian and Dutch studies added tumor size to tumor location as a possible prognostic factor.[21,24] Finally, three recent studies evaluated correlations with specific hotspot mutations in *CTNNB1* or *APC* deletions as prognostic/predictive biomarkers for DTs, but apart from identification of FAP-associated *APC* mutations which exhibit a more aggressive clinical course, sporadic *CTNNB1* mutations did not specifically associate with worse prognosis or response to various systemic therapies.[21,28,29]

In summary, it is strongly recommended that outside of an emergency context, the management of DT should be discussed by a multidisciplinary tumor board at sarcoma reference centers for individualized treatment plans, recognizing that up to 70% of patients do not require active treatment beyond symptom management to maintain quality of life.

INDICATIONS FOR SURGERY

Although watch-and-wait approaches or medical therapy are emerging as preferred strategies, surgery is still potentially indicated for life-threatening acute complications or interval tumor growth of DTs adjacent to critical structures, or progression of symptoms in locations not associated with potentially morbid resection, including very small tumors. Additionally, a substantial number of DTs are still diagnosed in up-front exploratory laparotomies where a malignancy is anticipated based on imaging.[30-32] The general rule is that surgical resection should not be mutilating and should focus on preserving function. Reconstruction, especially in the abdominal wall (fascia-preserving technique preferred) should be considered immediately. After marginal resection with positive margins (R1), AS should be undertaken and not re-excision or radiotherapy. Additionally, in case of recurrence after initial surgery, AS or medical treatment should be implemented. Although surgery is effective in specific cases, it may be associated with poor long-term functional sequelae and higher economic costs.[33] A validated prognostic nomogram is also available for predicting local relapses after surgery, helping in clinical decision making.[34]

The most common indications for surgery are acute complications of mesenteric DTs including bleeding, bowel obstruction, intestinal perforation/tumor abscess (Fig 3B), and mesenteric ischemia. Resection of the tumor should be performed in parallel with treatment of the complication, avoiding extensive resection of the bowel (which may lead to short-gut syndrome). When radical tumor resection is not feasible (eg, because of involvement of mesentery vasculature, or patients after colectomy for FAP), the surgical goal should be to manage complications, even leaving DTs in place. Similarly, patients with DTs in critical structures (mesentery) may be considered for surgical resection if further progression or residual disease before disease stabilization or with resistance to medical therapy is anticipated to lead to complications such as impending bowel

obstruction. It is important to remember that in such cases, patients may be offered medical therapies postoperatively. The second widely accepted indication for surgery can be in the setting of resistance to treatment, mostly for patients with peripheral/superficial DTs (particularly abdominal wall) with progression when surgery may be simply performed without extensive morbidity or for cosmetic/aesthetic purposes per patient preference.

SYSTEMIC THERAPIES

The decision to initiate systemic therapy is a shared decision between the patient and the treatment team. Various factors that can influence the decision to initiate medical treatment rather than continuing AS include (1) DT risk and location as previously discussed, including size and proximity to vital structures; (2) evidence of radiographic disease progression by MRI or CT, including not only tumor size but MRI T1-weighted enhancement and T2-weighted signal characteristics which support active DT rather than collagenization; and (3) current symptomatic and psychosocial impacts to the patient. While typically pain, discomfort, and limitations to function are clear indicators for treatment, other cited patient quality-of-life measures including emotional impacts (ie, depression, anxiety, altered body image related to DT), timing for fertility decisions, socioeconomic factors such as ability to hold job, or need to take care of family members or children may also drive treatment decisions.[9,10] Selection of treatment should take into account individual patient preferences and tolerances for side effects including unique profiles associated with different agents, duration of therapy likely to be required, and medical comorbidities (Table 1).

Current standard systemic therapies include the following:

γ-Secretase Inhibitor: Nirogacestat

Nirogacestat is a selective γ-secretase inhibitor that modulates NOTCH signaling (Fig 1) and, to our knowledge, is the first therapy specifically approved for DTs by the US Food and Drug Administration (FDA) and the European Medicines Agency. In the DeFi phase III trial, oral nirogacestat 150 mg twice daily significantly improved PFS and ORR compared with placebo in adults with progressing DTs, with a favorable impact on patient-reported symptoms and quality of life, specifically reduction in pain.[14] The 2-year PFS rate was 76% with nirogacestat, compared with 44% with placebo, and tumor responses were observed in 41% of patients receiving nirogacestat, significantly exceeding placebo responses at 8%. The median time to response was 5.6 months with nirogacestat. Efficacy was observed in patients with sporadic and FAP-associated DTs. A recently published update reported further increases in the ORR to 45.7% with an 11.4% rate of complete response with a median exposure time to nirogacestat treatment of 33.6 months (range, 0.3-61.8).[35] Furthermore, patient-reported outcomes continued with sustained benefit with additional follow-up.

Despite its efficacy, side effects include frequent gastrointestinal symptoms (ie, diarrhea, nausea), fatigue, hypophosphatemia, rash, and ovarian dysfunction occurring in 75% of women of childbearing potential. Most ovarian dysfunction events appear within the first year of treatment and are largely reversible with treatment discontinuation or sometimes spontaneously resolve with dose reduction.[37] However, with longer follow-up, ovarian function can recur or emerge later than the first year of treatment.[36] Thus, this toxicity may deter women of childbearing potential from proceeding with this treatment option. Additional unanswered questions include the minimum duration of treatment necessary to initiate DT reprogramming and obtain durable disease control and whether responses can occur with reinitiation of treatment after drug interruption. Furthermore, mechanisms of resistance are poorly understood and are the subject of ongoing investigation.

Tyrosine Kinase Inhibitors: Sorafenib

Sorafenib, a multitargeted tyrosine kinase inhibitor, has demonstrated significant clinical activity in DTs. A randomized phase III trial showed that sorafenib 400 mg once daily significantly improved PFS at 2 years (81%) compared with placebo (36%) with median time to response 9.6 months.[15] Subgroup analysis evaluating efficacy by mutation type was not reported; however, activity in patients with FAP has been observed in clinical practice. Common toxicities include rash, fatigue, hypertension, and diarrhea in more than 50% of patients; however, in practice, responses can be achieved or maintained with dose reductions to sorafenib 200 mg once daily or even every other day, which greatly improves toxicities. Sorafenib remains a frequently used option, especially when nirogacestat is unavailable, ineffective, contraindicated, or poorly tolerated and is listed as a preferred agent in the NCCN guidelines for US centers.[38]

Cytotoxic Chemotherapy: Liposomal Doxorubicin

Conventional chemotherapy with pegylated liposomal doxorubicin can induce tumor regression, particularly in aggressive or refractory disease. Multiple retrospective studies have suggested up to a 75% disease control rate including favorable activity in patients with FAP.[28,39-42] Recently, a randomized, double-blind, phase III investigator-initiated trial compared liposomal doxorubicin with placebo with permitted crossover. Among 73 patients with advanced/refractory DTs, patients who received liposomal doxorubicin had significantly improved mPFS compared with placebo (not reached *v* 4.3 months, hazard ratio, 0.05 [95% CI, 0.01 to 0.17]; $P < .001$).[35] The ORR with liposomal doxorubicin was 40.4% with liposomal doxorubicin compared with 4.3% with the placebo group. Common toxicities of this treatment include fatigue, rash, mucositis, nausea, and hand-foot syndrome. Additionally, while rates are much lower than traditional doxorubicin, potential risks include cardiotoxicity, myelosuppression (10.6% rate of grade ≥3 neutropenia[35]), fertility impairment, and

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TABLE 1. Summary of Desmoid Tumor Treatment Options and Selected Considerations for Treatment Selection

Treatment	Advantages	Challenges
Active surveillance	No treatment toxicity Up to 20% spontaneous regression rate	Potential anxiety for patient Potential for progression causing symptoms or limiting future options
Surgery	Potential cure Accepted option for low morbidity tumors (ie, abdominal wall) Critical for mesenteric DTs with obstructive complications	Potentially harmful if done without preceding diagnosis High risks of recurrence (up to 30%-50%)[16-19]
Cryoablation	Potential cure if technically feasible Can repeat if marginal recurrence postprocedure	Location limits feasibility Short-term frostbite nerve/skin injury, pain, swelling May require multiple treatments for large tumors Insurance authorization, expert center availability and access
Liposomal doxorubicin	90.4% PFS rate at 2 years[35] Shorter/finite treatment course (4-6 months typically needed to response) Patients who are not interested in daily pill regimens Potential activity in nirogacestat-refractory patients and patients with FAP	Toxicities (rashes, infusion reactions, potential for cardiotoxicity, myelosuppression, fertility impairment) Requires infusion center, ±central venous access
Sorafenib	Up to 81% PFS rate at 2 years[15] Rapid improvement in pain even before tumor response Flexible dosing for toxicity Improved toxicity profile compared with other TKIs (ie, pazopanib) Oral agent Potential activity in nirogacestat-refractory patients and patients with FAP	Typically longer-term therapy (at least 1 year) to maximum response Toxicity profile with alopecia/hair whitening, rashes, hypertension, hand-foot syndrome can be problematic for some patients Requires delay for attempts at pregnancy, unknown fertility impacts long term Not approved although listed in guidelines
Nirogacestat	76% PFS rate at 2 years and 45.7% response rate with up to 4 years of exposure[14,36] Only agent approved for DTs Flexible dosing for toxicity Oral agent	Typically longer-term therapy (at least 1 year) to maximum response Fertility disruptions and ovarian insufficiency symptoms Long-term effects on fertility understudied More gastrointestinal toxicities, skin lesions, rashes Not all patients respond—resistance mechanisms understudied

Abbreviations: DTs, desmoid tumors; FAP, familial adenomatous polyposis; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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secondary malignancies. In practice, liposomal doxorubicin often leads to early MRI changes in enhancement or size within four to six cycles, and treatment can often be stopped with continued regression of the DT over months to even years.

Historical and Less Commonly Used Therapies

Before the era of targeted agents, various systemic therapies were employed with variable success:

- Hormonal agents and nonsteroidal anti-inflammatory drugs: Tamoxifen, sulindac, and similar agents showed anecdotal and modest activity in small case series but lacked robust efficacy in controlled studies.[43] Without randomized studies, it is difficult to compare activity of tamoxifen to rates of stability/regression that occurs on AS.
- Tyrosine kinase inhibitors imatinib and pazopanib both have demonstrated activity in DTs. A single-arm phase II trial of imatinib 800 mg once daily showed a progression-arrest rate at 6 months of 65%, with an ORR of 19%.[44] Pazopanib was also studied in a noncomparative randomized phase II study (DESMOPAZ) against methotrexate-vinblastine. Patients receiving pazopanib 800 mg once daily achieved a PFS rate at 6 months of 83.7%; however, adverse events were significant with 23% of patients having at least one serious adverse event.[45] Overall, typically sorafenib is used over imatinib and pazopanib based on superior efficacy and toxicity profile; however, these agents remain an option for patients with resistance or intolerability to sorafenib.
- Cytotoxic chemotherapy: Low-dose methotrexate (MTX) and vinblastine/vinorelbine and anthracycline-based regimens such as doxorubicin with or without dacarbazine were widely used before the advent of molecularly targeted therapies. MTX/vinblastine administered weekly for 6 months and then every other week for 6 months demonstrated a PFS rate at 6 months of 45% in the DESMOPAZ study.[45] Doxorubicin plus dacarbazine has most commonly been used in highly aggressive or symptomatic DTs, such as mesenteric DTs observed in FAP, with retrospective data suggesting response rates of 20%-30% and disease control rates of nearly 100%.[28] However, these regimens are associated with significant toxicities and are now rarely used outside of refractory cases.

Selected Ongoing Clinical Trials

Deeper understanding of tumor biology is leading to a rapidly expanding landscape of investigational systemic therapies for DTs.

1. Varegacestat/AL102 (RINGSIDE Trial): Varegacestat, a next-generation gamma-secretase inhibitor, has been studied against placebo controls in the randomized

phase II/III RINGSIDE trial (ClinicalTrials.gov identifier: NCT04871282). While final efficacy and toxicity outcomes have not yet been presented, preliminary data have shown response rates ranging from 43% to 78% across various subgroups, potentially positioning varegacestat as a highly active oral option.[46]

2. FOG-001 (β-catenin:T-cell factor [TCF] Inhibitor): FOG-001 is direct inhibitor of the β-catenin and TCF interaction, the first of its kind, targeting a critical driver of DT pathogenesis. The agent has received FDA fast track designation, underscoring its potential to address an unmet biological target in DTs. An ongoing phase I/II study includes dedicated cohorts for patients with DT patients, along with other solid tumors exhibiting Wnt pathway abnormalities, including colorectal cancer (ClinicalTrials.gov identifier: NCT05919264). Preliminary results presented at the 2025 European Society of Oncology meeting reported acceptable tolerability and responses in two of four patients with efficacy evaluable DT, including a nirogacestat refractory patient, with the other two patients achieving stable disease.[47]
3. E7386 and tegavivint: Additional Wnt pathway modulators are being studied in clinical trials that include DTs. E7386 is an oral inhibitor that blocks the interaction between β-catenin and the transcriptional coactivator CREB-binding protein (ClinicalTrials.gov identifier: NCT03264664). Tegavivint blocks binding between β-catenin and TBL1 and is currently being studied in a Childrens Oncology Group trial (ClinicalTrials.gov identifier: NCT04851119).

NONSURGICAL ALTERNATIVES

Percutaneous Cryoablation

Percutaneous cryoablation has been widely used for both palliative and curative intent in patients with small- or moderate-sized DTs.[48] The technique uses argon gas to induce rapid cooling through an insulated probe.[49] The procedure can be performed under CT or MRI guidance, with and without adjunctive ultrasound guidance. Cryoablation may be performed under various sedation regimens, including local anesthesia and moderate or conscious sedation. The treatment usually consists of two consecutive cycles of a 10-minute freeze with a 5-8 minute interval passive thaw. The ablative zone or ice ball is often visible under both ultrasound and CT guidance, enabling intermittent, close monitoring of the treatment zone and adjacent critical structures (Figs 4B and 4C). The use of cryoablation may be limited in larger-sized DTs, particularly when it involves vital structures or is closely adjacent to them, such as nerves.[12] However, the risk of injury to adjacent critical structures, including the skin surface, can be decreased through hydrodissection. Hydrodissection can be achieved by injecting sterile saline, sterile local anesthetics, or diluted water-soluble contrast to increase the separation between the tumor and adjacent critical structures. Postablation imaging is typically performed 3 months after initial

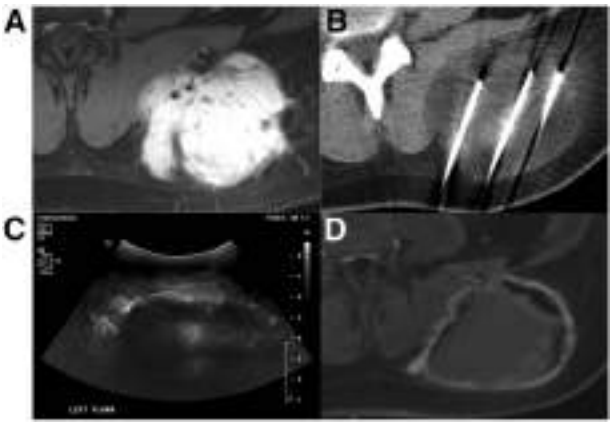

FIG 4. Eighteen-year-old female patient with (A) an enlarging biopsy-proven desmoid tumor involving the left flank (axial T1-weighted fat-suppressed postcontrast MRI). (B, C) Cryoablation was performed with a total of six probes with the ablation zone monitored under both CT and US imaging. Skin protection with hydrodissection was also performed. (D) Five-month follow-up axial MRI (VIBE venous phase with contrast and fat-suppression) shows positive treatment responses with no internal enhancement. Patient reports no worsening pain and is able to perform all activities of daily living. CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

cryoablation and every 6 months thereafter until stability, with variability because of patient factors. Postablation imaging is often performed with contrast-enhanced MRI, as it allows clear delination of ablation changes and viable residual tumor (Fig 4D).

In patients with extra-abdominal DTs, percutaneous cryoablation has been used as first-line or salvage treatment for patients with extra-abdominal tumors. A retrospective study demonstrated symptom improvement in 89% of patients who underwent cryoablation as first-line or salvage treatment for extra-abdominal DTs.[50] Further evidence supporting the safety and efficacy of cryoablation has been highlighted in a systematic review and meta-analysis of nine nonrandomized studies. The review provides further support for cryoablation as an effective option for symptom relief, with a high rate of nonprogressive disease (estimated pooled proportion of 85.8%).[48] Based on their analysis, cryoablation is a safe and well-tolerated procedure with low rates of major and minor complications (estimated pooled proportions of 4.2% and 10.2%, respectively).

As a result of these retrospective experiences, a prospective, nonrandomized, and noncomparative phase II study, CRYODESMO-01 (Evaluation of the Cryodestruction of Non-Abdominopelvic DTs in Patients Progressing Despite Medical Treatment) evaluated image-guided percutaneous cryoablation for DTs.[51] The study consisted of 50 patients and included those aged 18 years or older with extra-abdominopelvic DTs that progressed despite medical therapy (two or more treatment lines) or had functional symptoms or pain. Treated patients exhibited a nonprogression rate at

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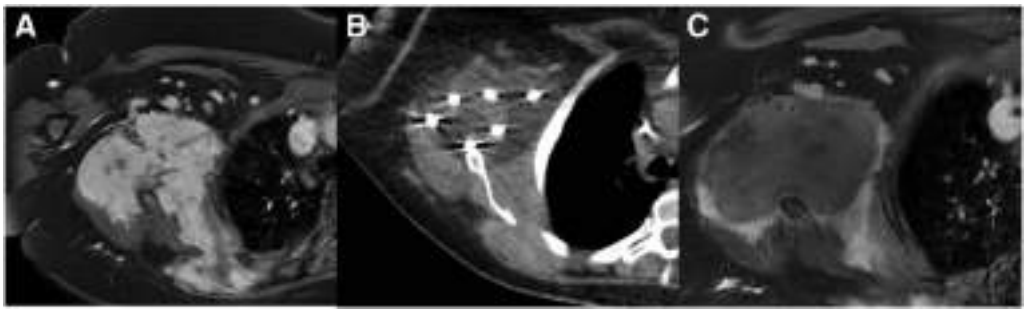

FIG 5. Twenty-year-old female patient with (A) an enlarging and painful biopsy-proven desmoid fibromatosis (axial postcontrast T1-weighted MRI with fat-suppression) centered between the right scapula and the right lateral chest wall. (B) Ultrasound- and CT-guided cryoablation was performed using six probes (ultrasound images not shown). (C) Three-month axial postcontrast T1 fat-suppressed MRI demonstrate postablation changes with decrease enhancement involving most of the mass and residual peripheral enhancing tumor. The patient reported improvement in pain. CT, computed tomography; MRI, magnetic resonance imaging.

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12 months of 86% (95% CI, 73 to 94) at 12 months. The study also found significant improvements in functional status and pain scores with cryoablation. However, in a multivariate analysis, tumor diameter was significantly correlated with lower treatment efficacy. Additionally, recurrences tend to occur at the tumor periphery rather than within the treated zone (Figs 5 and 6 for case examples). For larger tumors, a staged treatment approach is recommended to ensure adequate margins and reduce nodular margin recurrences.

Ongoing clinical trials are continuing to prospectively evaluate the role of percutaneous cryoablation. CRYODESMO-02 is an ongoing randomized trial comparing cryoablation to systemic therapy in DTs that progress after initial AS, which permits cross-over to cryoablation in the event of progression on systemic therapy (ClinicalTrials.gov identifier: NCT06081400). The results of the study will better delineate how cryoablation is best integrated with currently available medical therapy. Another study investigating this concept is a phase II study that administers three cycles of nirogacestat followed by cryoablation and another cycle of nirogacestat (ClinicalTrials.gov identifier: NCT05949099).

In addition to cryoablation, heat-based ablative therapies, such as radiofrequency and microwave ablation, have been used to induce coagulative necrosis in DT treatment. Although less widely used than cryoablation, multiple small studies suggest that these techniques can achieve meaningful reductions in tumor volume and symptomatic relief.[52,53] However, evidence of these thermal-ablative techniques is limited, and cryoablation remains the more established ablative technique.

High-Intensity Focused Ultrasound or MRI-Guided Focused Ultrasound

High-intensity focused ultrasound (HIFU) has been used for local control and symptom palliation in DTs. HIFU uses high-energy ultrasound waves to heat, ablate, and induce thermal coagulation necrosis while protecting the surrounding and overlying soft tissues.[54] Compared with thermal ablation, including cryoablation, it is relatively noninvasive and does not use ionizing radiation. HIFU can be performed under MRI guidance, particularly for small superficial DTs. HIFU can also be carried out under B-mode ultrasound or thermography. A recently published systematic review evaluated the role of HIFU in the treatment of both soft-tissue sarcomas and DTs.[54] Based on 27 studies, including 15 nonrandomized studies involving 417 patients with DTs, the authors concluded that HIFU has a favorable safety profile. In a representative prospective study using HIFU in 111 patients with DT, treating 145 tumors over 188 sessions, tumor volume was reduced by 36.1% at 3 months.[55]

In addition to focused ultrasound for thermal ablation, MRI-guided HIFU (MRgFUS) uses MRI for treatment planning and monitoring. In one retrospective study of 105 patients treated with extra-abdominal DTs, the median total tumor volume reduction was 34% (95% CI, 25 to 50), with 86% (95% CI, 75 to 93) achieving stable disease or better by RECIST, and a median PFS of 17 months.[56] The authors also found clinically significant improvement in pain scores (based on the Numerical Rating Scale) in 68% (95% CI, 52 to 82) and improvements in mental and physical health scores (based on the RAND 36-Item Health Survey). The decision to use MRgFUS for treatment in this cohort was based on multidisciplinary review as well as other factors, including risks from other treatments and progression despite chemotherapy and radiation.

A limiting factor for treatment with HIFU or MRgFUS is a poor acoustic window to the DTs, such as because of adjacent or overlying structures and close proximity to the skin.[56] Additional drawbacks include the need for longer or repeated treatments and tumors that are in close proximity to structures containing gas. Although promising as a noninvasive option in the MRI environment, HIFU can be time- and resource-intensive, limiting its widespread adoption.

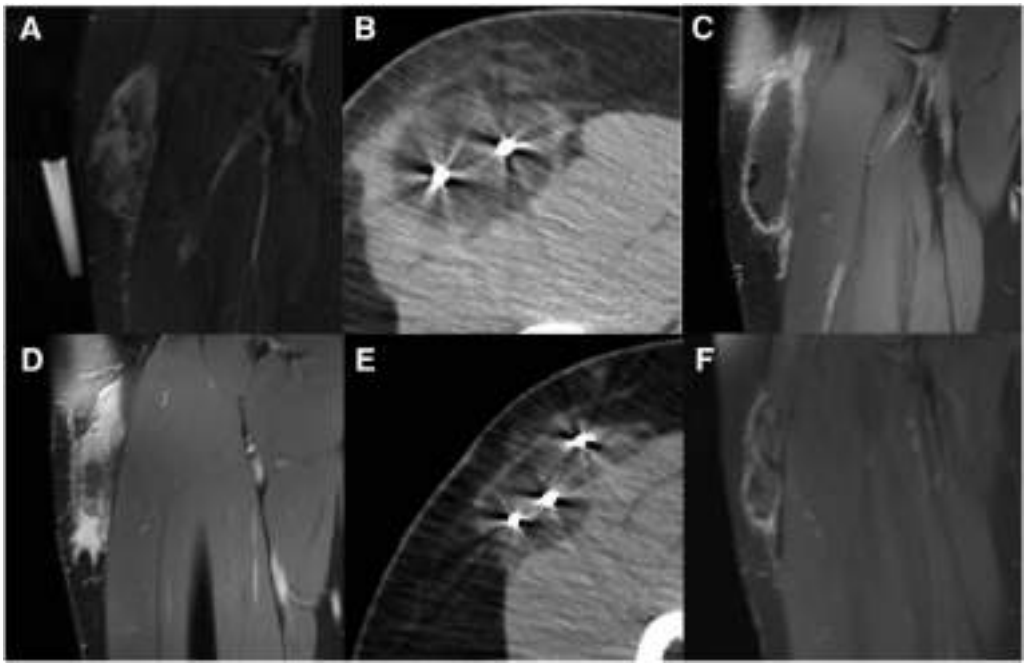

FIG 6. Twenty-year-old female patient with (A) a right thigh desmoid tumor status post prior excision (coronal T2-weighted STIR MRI; T1-weighted postcontrast MRI are unavailable) and (B) cryoablation with CT and ultrasound-guidance (ultrasound images not shown). (C) Six-month follow-up coronal T1-weighted fat-suppressed postcontrast MRI demonstrates postablation changes with a central nonenhancing and necrotic core. However, (D) there is a persistent peripheral nodular enhancing soft tissue, concerning for residual viable tumor. (E) Repeat cryoablation was performed with overlapping ablation zones to ensure complete coverage. (F) Final 6-month follow-up coronal T1-weighted fat-suppressed postcontrast MRI demonstrates interval decrease in tumor size and decreased peripheral nodular enhancement. The patient maintains full range of mobility and resolution of pain for extended periods. CT, computed tomography; MRI, magnetic resonance imaging.

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Emerging Strategies

Transarterial drug-eluting bead chemoembolization (DEB-TACE or DEB-DOX) has been evaluated in several small studies, although it is not currently considered the standard of care for DTs. The technique relies on the hypervascularity of DTs for the local transarterial delivery of chemotherapy drug-eluting microbeads. A systematic review of six studies (two case reports, three case series, and one observational study) with a total sample size of 43 patients found that DEB-TACE was commonly performed with doxorubicin and that postprocedure symptom improvement was reported in all 43 patients.[57] The largest included study comprised 24 patients treated over 52 sessions, with a median tumor volume reduction of 59% (IQR of 4%-71%). Partial response and stable disease were achieved in 39% and 52% according to RECIST, respectively.[58]

CONCLUSIONS

DTs demonstrate variable biologic behavior ranging from indolent tumors that can be followed on AS without ever requiring treatment to aggressive diseases that can threaten life and limb. Additionally, DTs have the potential to impart significant burden on quality of life for patients, not only physical symptoms but also emotional and psychologic distress. Fortunately, significant advances are being made in treatment options for patients, with approval of novel systemic therapies and emerging local treatment strategies such as cryoablation and HIFU. Optimal care for patients with DT requires multidisciplinary discussion, assessment of the individual patient's tumor biology and resulting symptoms and psychological impacts, and shared decision making with the patient to select the optimal management strategy.

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When Does Acceptable Become Unacceptable? Toxicities of Emerging Therapies

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OVERVIEW

Novel systemic anticancer therapies, including immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), bispecific antibodies, and next-generation targeted agents, have improved survival, expanded into earlier disease settings, and created a growing population of long-term survivors. However, these therapies introduce toxicity profiles that differ substantially from those of traditional cytotoxic chemotherapy, including differences in organs affected, timing of onset, management strategies, and long-term sequelae. Tailored approaches to monitoring, diagnosis, and treatment are therefore required, along with stronger evidence to guide strategies that reduce morbidity and mortality while maintaining antitumor efficacy. Importantly, patients' lived experiences of toxicity often do not align with clinician-graded Common Terminology Criteria for Adverse Events classifications. Nonobservable symptoms, daily functioning, and quality of life must also be taken into account. Here, ocular and cutaneous adverse events are used as illustrative examples of how toxicities that may appear mild can become unacceptable when they impair function, quality of life, or treatment sustainability. Interdisciplinary collaboration between oncologists and organ specialists is essential for optimal recognition and management. At the same time, the evidence base for toxicity risk and management must continue to evolve through registries such as Side Effect Registry Immuno-Oncology and prospective comparative studies. Better tailored treatment strategies, particularly for immune-related adverse events, are needed to preserve both tumor response and organ function while reducing reliance on corticosteroids and broad immunosuppression. Although these therapies are highly effective, their risks must be better understood and managed to maximize patient benefit.

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INTRODUCTION

Cancer therapy has entered an era in which increasingly effective systemic treatments are accompanied by increasingly complex toxicity profiles. Over the past decade, immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), bispecific antibodies, and next-generation targeted agents have become embedded across solid tumors and hematologic malignancies.[1] These therapies have improved survival and expanded into earlier disease stages, but they have also introduced toxicity profiles that differ fundamentally from those of traditional cytotoxic chemotherapy.[1] Immune-related and off-target adverse events can affect almost any organ system, emerge weeks to months after treatment initiation, and persist long after drug cessation, challenging traditional models of monitoring, management, and safety assessment within clinical studies.[2,3]

Persistent immune-related adverse events (irAEs) are increasingly recognized as an important part of the treatment experience and survivorship burden.[3,4] Patients with chronic irAEs report feeling less adequately informed about possible long-term toxicities compared with those without chronic toxicity.[3] These findings underscore that toxicity should be understood not only as an acute safety signal but also as a survivorship issue with durable physical, psychological, and functional consequences which have important implications for informed consent.

Real-world registries have begun to characterize the breadth and severity of these toxicities in routine practice. The Side Effect Registry Immuno-Oncology (SERIO)[5] has highlighted the diversity, persistence, and clinical impact of irAEs across multiple organ systems.[2] Half of all recorded irAEs in SERIO were grade 3 or higher, 23% required second-line immunosuppression for steroid-refractory or steroid-dependent toxicity, and a subset were fatal, particularly neurologic and cardiac events.[2,6,7] Ocular and cutaneous irAEs appear prominently in these data sets, reflecting both their frequency and tendency to require dermatologic and ophthalmologic expertise for optimal management.[2,8,9]

At the same time, it is increasingly clear that traditional clinician-graded toxicity scales inadequately capture the

PRACTICAL APPLICATIONS

- Morbidity and mortality from treatment-related toxicities can be reduced through timely recognition, diagnosis, and management.
- Management of treatment-related toxicities requires close interdisciplinary collaboration between oncologists and organ-specific specialists.
- Patient-reported symptoms must be adequately assessed and addressed to preserve quality of life and daily functioning.
- A stronger evidence base for toxicity management is needed, including registries and prospective comparative trials.
- Regulatory frameworks should encourage generation of longer-term and more comprehensive toxicity data during drug development and approval trials.

patient experience. Studies comparing clinician-rated adverse events (AEs) with patient-reported outcomes (PROs) show systematic under-recognition of subjective symptoms such as fatigue, pain, appetite loss, photosensitivity, and low-grade skin and eye irritation, even when these symptoms substantially impair daily functioning.[10,11] Qualitative studies and patient narratives similarly emphasize that toxicity becomes unacceptable not at a particular Common Terminology Criteria for Adverse Events (CTCAE) grade, but when it disrupts independence, work, family roles, identity, or the ability to participate in life in meaningful ways.[12] Fear that reporting these symptoms will jeopardize access to effective cancer treatment can drive underreporting and silent nonadherence, further widening the gap between what clinicians document and what patients experience.[12,13] Notably, the same symptoms were treated less aggressively when attributed to cancer immunotherapy compared with symptoms caused by spontaneous autoimmune disease.[3]

Although this chapter focuses on ocular and cutaneous toxicities as illustrative examples, the underlying principle—that toxicity becomes clinically meaningful when it disrupts patient function and treatment sustainability—applies broadly across organ systems and emerging cancer therapies. In this chapter, we first examine acceptable versus unacceptable toxicity from the patient perspective and its implications for communication, adherence, and shared decision making. We then review ophthalmic and cutaneous toxicities associated with emerging systemic therapies, with attention to practical recognition, early management, referral, and coordinated care aimed at preserving both quality of life and the benefit of effective anticancer therapy.

WHEN DOES ACCEPTABLE BECOME UNACCEPTABLE?

Clinicians Grade Toxicity; Patients Live It

As an oncology hospitalist during the pandemic, I admitted patients with treatment-related complications: sepsis from febrile neutropenia, dehydration from uncontrolled mucositis, and respiratory compromise. These events were categorized by CTCAE grade and managed according to established algorithms. At the bedside, they were people whose lives had narrowed until a symptom crossed from manageable to unacceptable.

I was diagnosed with stage IV lung cancer in 2017, during residency. My first tyrosine kinase inhibitor came with warnings: nausea, diarrhea, and visual symptoms. I experienced diarrhea and painless flashing lights, but I had also been told what to expect, which symptoms required urgent evaluation, and which were likely to improve with time. That anticipatory guidance gave me a framework. It reduced uncertainty, helped me interpret what I was experiencing, and made those toxicities feel manageable.

From the patient perspective, toxicity becomes unacceptable not simply when it reaches a certain grade, but when it disrupts daily function, creates persistent uncertainty, or forces trade-offs that are difficult to sustain. Whether a symptom feels tolerable depends not only on severity but also on predictability, duration, reversibility, cumulative burden, and the extent to which it interferes with work, reading, sleep, driving, caregiving, or meaningful participation in daily life. This distinction matters because treatment decisions are often made not only on the basis of efficacy but also on the basis of what a patient feels able to keep carrying.

How Patients Experience Toxicities

Qualitative studies suggest that patients experience treatment-related toxicity through four primary lenses: disruption of daily life, the hidden work of self-managing symptoms, emotional distress, and uncertainty about meaning and duration.[14,16] From the patient perspective, these dimensions often determine whether toxicity remains tolerable or becomes unacceptable. One patient wrote: *“Life was not being lived… I was existing.”*[15] A symptom may appear limited in severity from the outside while exerting a disproportionate effect on the inside of a person’s life.

Fatigue, diarrhea, and skin changes may threaten work, caregiving, and social roles.[17] Ocular symptoms are not just eye issues; they may impair reading, driving, screen use, and with that, independence and employment. Cutaneous toxicities, often labeled as mild, can nevertheless be stigmatizing, sleep disrupting, and socially isolating, particularly when visible or persistent.[8,14]

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In checkpoint inhibitor-treated patients, long-term irAEs lasting ≥12 months are increasingly recognized and are associated with clinically significant reductions in health-related quality of life, as well as patients feeling less adequately informed about potential long-term sequelae.[3]

Acceptability becomes a moving threshold shaped by functional interference, duration, predictability, cumulative burden, perceived benefit, and fear of treatment loss.

The Measurement Gap

A central challenge in the management of treatment-related toxicity is that clinician-assessed toxicity and patient-experienced toxicity are related but not interchangeable. Standardized clinician grading remains essential for safety reporting, trial conduct, and treatment decisions, but it does not necessarily capture the full burden of symptoms as they are lived day to day.[10,11] Clinician-rated CTCAE and patient-reported symptoms reflect overlapping but distinct dimensions of toxicity: Clinician assessment may better identify some medically significant events, whereas PROs more directly capture daily symptom burden and functional status. Together, these findings suggest that clinician grading remains necessary but is insufficient on its own to characterize the full impact of treatment-related toxicity, particularly when symptoms are subjective, function limiting, or only partially visible on examination. In addition, commonly used reporting approaches, such as grouping grade 1 and 2 toxicities or describing effects as acceptable or manageable, may further obscure the cumulative burden of chronic, low-grade symptoms over time.[19,20]

From the hospital side, I saw this gap's clinical expression. Many admitted patients had endured worsening symptoms for days to weeks. About half recalled mentioning them but downplayed severity or framed it as expected. The note might read grade 1 mucositis; tolerating PO. The patient in the bed was unable to eat or drink. What appeared mild in documentation had already become functionally significant.

When Acceptable Becomes Unacceptable

Patients constantly make trade-offs among efficacy, organ toxicity, time toxicity, and other costs.[18] Stated-preference studies show that many accept substantial toxicity for a meaningful benefit,[21] but thresholds vary widely based on prognosis, role responsibilities, and values.[22] When that threshold is crossed, three patterns emerge: full reporting and request for help; partial reporting with minimization (hoping to preserve dose intensity); or silent nonadherence, skipped doses, self-reduction, and altered timing, without informing clinicians.[23,24]

Reviews of oral anticancer agents show nonadherence rates of 20%-50%, with adverse effects and symptom burden as major drivers.[23,24] Fear-based minimization is documented: Patients hesitate to disclose symptoms fearing dose reduction, trial removal, or being perceived as unable to tolerate therapy.[12] Management of side effects can itself be challenging, with about 10% of checkpoint inhibitor-induced irAEs requiring second-line therapy because they may be steroid refractory or steroid dependent.[25] However, the optimal second-line treatment remains uncertain,[26] and prospective data are limited.[27,28]

Why Patients Do Not Report—Implications for Ocular and Skin Toxicities

Qualitative work identifies why patients underreport: fear that reporting leads to dose reduction of effective therapy, belief that side effects are part of treatment, previous experiences of dismissal, and uncertainty about which symptoms are serious.[14,15] When treatment is seen as precious or high stakes, some patients may consciously or unconsciously edit what they disclose in an effort to preserve it. This can create a pattern in which symptoms are mentioned only after they have become much harder to ignore or much more disruptive to daily life. In many cases, patients are not ignoring symptoms; they are interpreting them through a framework of endurance, uncertainty, and perceived necessity.

For ocular toxicities from ADCs and targeted agents, patients often report early symptoms such as dryness, grittiness, and blurred vision at night as nuisances and may blame screen time or fatigue. Only when reading, driving, or work become unsafe do they feel justified raising the issue. Yet, ophthalmology data show that many ADC-related ocular events are more reversible when identified and managed early, with prophylactic measures and dose adjustments.[9]

Similarly, patients may see rash and pruritus as cosmetic and avoid reporting for fear of seeming vain, particularly if told serious events involve organs rather than skin. One patient described: *"Photosensitivity was significantly downplayed... the severity was validated only later by a dermatologist specializing in oncology-related skin conditions."*[15] Dermatology literature emphasizes that visible and symptomatic skin AEs erode sleep, social participation, and dignity and are closely tied to adherence.[8,14] Also, initially discrete symptoms may, in some cases, precede more serious toxicity, including severe cutaneous adverse reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis (SJS/TEN), reinforcing the need for early recognition and careful clinical assessment.[29]

OPHTHALMIC TOXICITIES

Ocular AEs can significantly impact quality of life.[30-33] A wide range of anticancer therapies are associated with ocular toxicities affecting the eye and surrounding tissues,[31,34,35] and this section focuses on clinically important and emerging patterns by drug class. Ocular symptoms are uniquely disruptive for patients because even subtle changes can quickly impair function and independence. At the same time, several emerging systemic therapies, including ADCs,

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ICIs, and targeted agents, are associated with ocular adverse events that may begin mildly and progress if not recognized early. Because early detection can preserve vision, quality of life, and treatment continuity, the discussion below highlights practical approaches to recognition, initial management, and referral.

Antibody-Drug Conjugates

ADCs provide targeted delivery of a cytotoxic payload by linking the toxic compound to an antibody upregulated on cancer cells.[36] However, ocular surface AEs, including dry eye, conjunctivitis, and keratopathy, are frequent, especially with ADCs that use a microtubule-inhibitor payload.[37-41] Examples of drugs with reported ocular AEs include belantamab mafodotin, mirvetuximab soravtansine, and tisotumab vedotin.[42] Corneal pseudomicrocysts, located in the superficial epithelial layer of the cornea, affect more than half of patients in some series (Fig 1). These lesions most often involve both eyes and begin in a ring around the peripheral cornea, called the limbus, before migrating centrally.[42] Some patients have mild involvement with no symptoms, but others experience blurry vision, photophobia, irritation, pain, and tearing that can reduce quality of life.

Corneal pseudomicrocysts caused by ADCs are often managed conservatively with topical artificial tears and topical corticosteroids, which can improve symptoms but may not improve the pseudomicrocysts.[42] For more persistent discomfort and blurry vision, scleral contact lenses can be fit to help retain an extra layer of moisture in front of the eye. In cases of severe corneal side effects, dose reductions, delays, or ADC discontinuation may be required, which warrants careful discussion between the ophthalmologist and oncologist to balance the benefits of potentially life-saving ADC therapy with quality of life-affecting ocular AEs.[42]

Targeted Therapies

Inhibitors of the mitogen-activated protein kinase (MAPK) pathway, including FGFR, MEK, and ERK inhibitors (eg, erdafitinib and trametinib), have characteristic ophthalmic AEs.[43-45] MEK inhibitor-associated retinopathy (MEKAR) is characterized by pockets of fluid detaching focal areas of the neurosensory retina and may affect nearly 80% of patients.[43,46] MEKAR is most often bilateral, with multifocal fluid foci, and at least one fluid focus often involving the fovea, which can cause blurry or distorted vision.[43] Findings are typically self-limited, with resolution over time or after stopping medication, and patients rarely have permanent vision deficits after the fluid resolves.[43,47] A comparison of MEKAR in patients exposed to FGFR, MEK, and ERK inhibitors found that drugs working on downstream targets (MEK and ERK inhibitors) were associated with more frequent and more severe retinopathy than drugs working further upstream (FGFR inhibitors).[48] Retinal vein occlusion is a more serious side effect of MEK inhibitors, which affects 1% or fewer patients and requires permanent drug discontinuation.[31]

Other targeted agents, including BRAF inhibitors, such as vemurafenib or dabrafenib, may cause inflammatory uveitis, dry eye, or conjunctivitis.[31,48-51] Topical or periocular corticosteroids may help resolve symptoms without disruption to cancer treatment. More serious ocular inflammatory syndromes, including Vogt-Koyanagi-Harada (VKH)–like uveitis or ischemic retinal vasculitis, may warrant interruption or discontinuation of therapy.[31,49,50]

Checkpoint Inhibitors

ICIs activate the immune system, improving antitumor response while also breaking immune tolerance.[35] These agents include CTLA-4, PD-1/PD-L1, and LAG-3 inhibitors such as ipilimumab, pembrolizumab, and nivolumab. As ICIs activate the immune system, autoimmune adverse events may occur. Mostly, they occur within the first several weeks but can occur much later and even after cessation of the drugs.[52-56] Although other systemic side effects are more common, 1%-3% of patients experience ophthalmic AEs requiring specialist evaluation.[57,58] Ophthalmic AEs may be less common because of the eye's relative immune privilege, but the risk may increase with the use of combination therapies, such as ipilimumab plus nivolumab (Fig 2).[59] Myositis and neuritis may also impair visual function.[60]

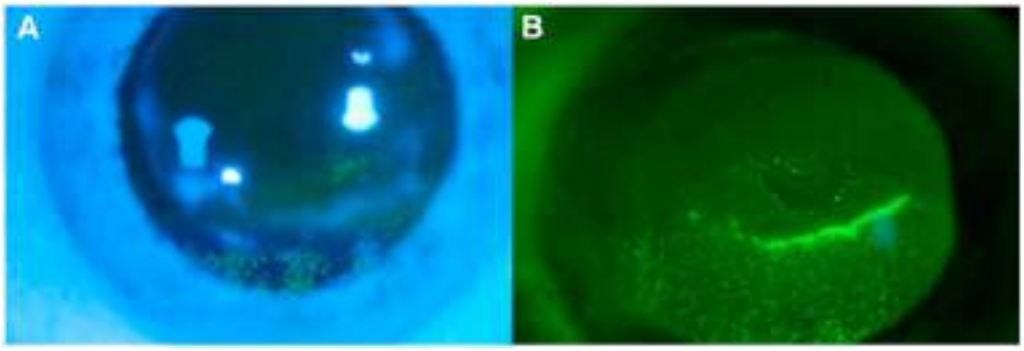

FIG 1. Corneal side effects from antibody-drug conjugate exposure. Corneal pseudomicrocysts are highlighted with green fluorescein staining and start (A) in the peripheral cornea with (B) migration to the central cornea.

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The most common ocular AE associated with checkpoint inhibitors is dry eye, affecting about one quarter of patients.[57] Dry eye can often be managed with topical lubricating eye drops with or without punctal occlusion to reduce tear drainage, although rare cases of corneal ulcers or perforation have been reported.[35,59] Inflammatory uveitis affects about 1% of patients and may present with photophobia and blurry vision.[35,51,57] Mild cases may respond to topical or periocular corticosteroids, whereas vision-threatening events such as retinal vasculitis or VKH-like syndrome may require systemic corticosteroids and interruption or discontinuation of checkpoint inhibitor therapy.[35] Severe ocular side effects requiring permanent checkpoint inhibitor discontinuation are rare,[57] but caution is required in patients with a known history of uveitis.[31,35]

Neuro-ophthalmic side effects may be the third most common type of ocular AE and include cranial nerve disorders or myasthenia gravis-like syndrome.[61] These should be considered in patients receiving ICIs who present with new diplopia or blepharoptosis. Associated respiratory depression can be fatal, and cessation of ICI therapy may be required.[31,35] Importantly, myasthenia gravis-like syndrome can be part of the triple M overlap syndrome, along with myocarditis and myositis.[62] Prompt recognition is critical, particularly because myocarditis carries a high mortality rate.[6]

In addition to dry eye, blurry vision, photophobia, and diplopia, patients may present with a wide array of other symptoms, including changes in color vision, visual field defects, blind spots, distortion, eye redness, pain, tenderness, periorbital edema, or proptosis, and these AEs often occur concurrently with other systemic irAEs. ASCO published guidelines for management of checkpoint inhibitor-associated uveitis and episcleritis, including criteria for grading severity and recommendations for when to discontinue treatment.[63] As emphasized in these guidelines, collaboration with an ophthalmologist is essential. Grading of ocular AEs has been evolving, and recent consensus disease definitions for ophthalmic irAEs may help better guide future trials and clinical decision making.[64]

For oncology teams, the practical issue is not only to master every ophthalmic detail, but also to recognize when symptoms may signal more than routine irritation and warrant timely specialist evaluation. Initial management should therefore be guided by clinical concern and functional impact, with mild symptoms managed supportively while expedited referral is arranged and more concerning features prompting urgent ophthalmologic input. Decisions about treatment continuation, interruption, or modification are best made collaboratively, with attention to both the severity of the ocular event and the oncologic importance of the therapy.

Many of these same principles—early recognition, pattern identification, and timely specialist involvement—apply across organ systems and are equally relevant to cutaneous toxicities.

CUTANEOUS TOXICITIES

Many cutaneous toxicities in clinical studies are reported simply as rash. However, this term encompasses a wide range of dermatologic phenotypes with different pathomechanisms, severities, chronicity, and management approaches.

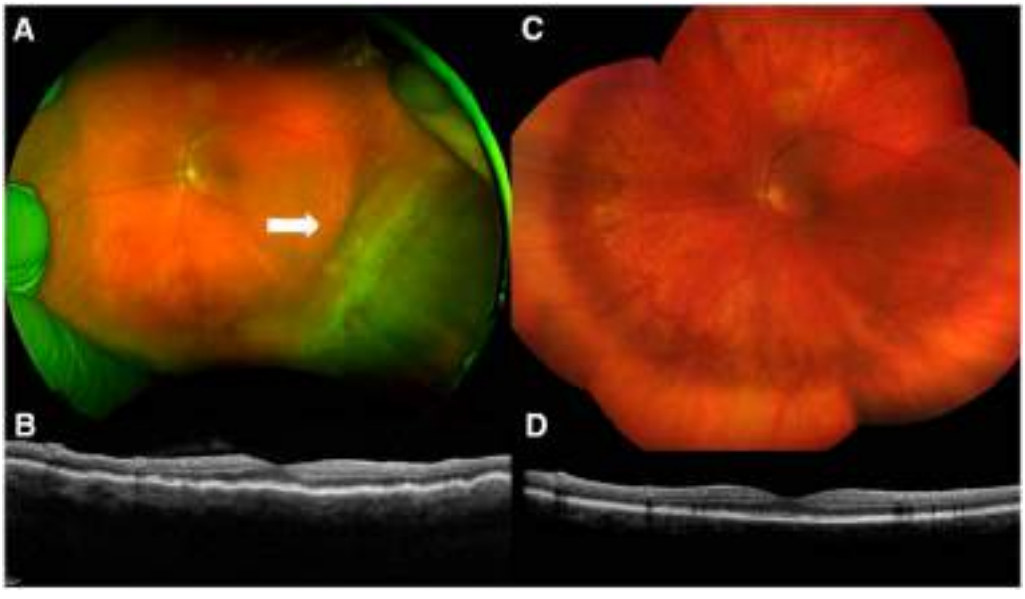

FIG 2. Intraocular side effects from checkpoint inhibitor exposure. Checkpoint inhibitors can cause immune-related inflammatory side effects. In this case, combination treatment with ipilimumab and nivolumab was associated with (A) serous retinal detachment (arrow) and (B) choroidal folds, having a lumpy bumpy appearance on optical coherence tomography. Therapy was stopped because of systemic side effects and the (C) serous retinal detachment resolved along with (D) disappearance of the choroidal folds.

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Different therapy modalities each have their own characteristic side effect profile, including differences in timing of onset and preferred therapeutic strategies (Table 1). A thorough drug history is essential because cutaneous adverse events may also be caused by concomitant medications or infections.

Cutaneous toxicity matters not only because some reactions can become severe but also because many low-grade skin toxicities carry substantial functional and psychosocial burden. Persistent pruritus can significantly impair sleep, visible eruptions may alter social participation and self-image, and mucosal involvement can reduce oral intake and lead to weight loss. For this reason, cutaneous toxicities are a useful example of the broader principle that symptoms described as mild in documentation may still become unacceptable in lived experience.

Early recognition of severe cutaneous adverse reactions such as SJS/TEN is critical. Concerning features include violaceous or dusky skin lesions, blistering or epidermal detachment, mucosal involvement, pain out of proportion to examination, systemic symptoms, and conjunctivitis. Suspicion should prompt urgent evaluation, including dermatologic consultation and appropriate laboratory assessment. Management requires immediate discontinuation of the culprit agent(s) and supportive care, often in an intensive or burn unit, with attention to fluid, electrolyte, and temperature management, wound care, and infection surveillance. Systemic immunomodulation, including high-dose corticosteroids, intravenous immunoglobulin, cyclosporine, and in selected cases TNF-alpha inhibitors or JAK inhibitors may be required.

Importantly, some cutaneous presentations may be the first clue to broader immune-mediated or systemic toxicity. For example, immune-related dermatomyositis may initially present with characteristic skin findings but can be associated with more serious systemic involvement, underscoring the need for careful assessment when cutaneous symptoms are accompanied by weakness or other systemic features.[6,65]

Immune Checkpoint Inhibitors

Cutaneous toxicities are among the most frequent side effects induced by checkpoint inhibitors. They occur in 70%-90% of patients and commonly manifest as pruritus and eczematous eruptions. However, lichenoid reactions, bullous reactions and, rarely, severe cutaneous adverse reactions such as SJS/TEN may occur. Although often not life-threatening, they may become chronic, difficult to treat, and function limiting.

Immune-related bullous pemphigoid, which manifests in 0.3% of patients treated with ICIs, is an example of a chronic persistent cutaneous irAE that may require long-term treatment and can complicate continuation of anticancer therapy.[66] In addition to topical therapy, more targeted approaches, including IL-4/IL-13 inhibition with dupilumab, may offer benefit in selected cases.[67-70] Pruritus itself may also require escalation beyond supportive skin care, with systemic approaches such as omalizumab explored in refractory settings.[71]

Immunotherapy-induced lichen planus is another clinically important example. It may be more disseminated and erosive than spontaneous lichen planus and, in refractory cases, may require more than topical therapy alone.[72] Although no comparative studies are available, retinoids, cyclosporine, and methotrexate have been used with benefit on a case-by-case basis.[73] Importantly, newer options for therapy-refractory disease, including extracorporeal photopheresis and dupilumab, have been explored.[74-76]

Although topical corticosteroids and antihistamines are often still the first line of therapy in conjunction with emollients, systemic steroids may be necessary. However, emerging evidence suggests that corticosteroid therapy impairs ICI efficacy,[77] and long-term systemic corticosteroid use carries well-known risks. Management of cutaneous irAEs has therefore moved toward more tailored, phenotype-directed approaches incorporating biologics and steroid-sparing regimens.

Bispecifics and ADCs

Bispecific antibodies and ADCs add further complexity to the dermatologic toxicity landscape. Tebentafusp, a bispecific antibody approved for the treatment of metastatic uveal melanoma in HLA-A*02:01–positive patients, is frequently associated with pruritic and inflammatory skin reactions. Most patients experience a transient cytokine release syndrome early in treatment, and cutaneous toxicity is common, observed in 91% of patients and often including pruritus. These reactions may present as symmetrical erythematous patches, hemorrhagic macules, urticarial lesions, bullous lesions, or skin and hair depigmentation. Although many of these reactions are manageable with supportive measures, their frequency reinforces the need for early recognition, anticipatory counseling, and clear pathways for symptom management.

Mogamulizumab, a CCR4 antibody approved for the treatment of cutaneous T-cell lymphoma (Mycosis fungoides) and Sézary syndrome, induces cutaneous eruptions in 25% of patients. Mogamulizumab-associated rash (MAR) presents a different clinical challenge, as it can be difficult to distinguish from the underlying disease itself, yet may also be associated with better response to therapy. Detailed instructions have been developed to assist health care providers in identifying and managing MAR.[78] This is a useful reminder that dermatologic assessment is valuable not only for severity grading but also for diagnosis and treatment direction.

ADCs such as brentuximab-vedotin or enfortumab-vedotin may also produce cutaneous toxicities including pruritus,

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TABLE 1. Cutaneous Side Effects From Selected Tumor Therapies

Drug/Agent	Type of Therapy	Target	Tumor Entity	Combined With	Types of Cutaneous Side Effects and Frequency	Dermatology Details	Main Challenges	Treatment of cAE	References
Tebentafusp	Bispecific T-cell engager (TCR–anti-CD3; ImmTAC)	gp100 (peptide presented by HLA-A*02:01)	Metastatic/advanced uveal melanoma (HLA-A*02:01+)	NA (monotherapy)	Skin reactions: 91% (any CTCAE grade); CTCAE grade 2: 44% CTCAE grade 3: 21% Components: Rash 83%, pruritus 69%, erythema 25%	Often symmetrical erythematous patches, hemorrhagic macules, urticarial lesions, bullous lesions, and skin/hair depigmentation; histopathology: Focal lymphocytic interface dermatitis with epidermal $CD8^+$ lymphocyte infiltration	Very early onset (median 1 day) and high frequency; can overlap with cytokine release syndrome	Monitor for skin reactions; treat with antihistamines and topical or systemic corticosteroids according to persistence/severity; withhold or permanently discontinue based on severity	FDA United States Prescribing Information KIMMTRAK (tebentafusp), 2022
Mogamulizumab	Monoclonal antibody (humanized IgG1)	CCR4	Cutaneous T-cell lymphoma: Mycosis fungoides/Sézary syndrome	NA (monotherapy)	Rash/cutaneous drug eruption: 25% (any CTCAE grade); CTCAE grade 3: 18%	Mogamulizumab-associated rash—typically folliculotropic MF-like scalp plaques with alopecia; papules and/or plaques; photoaccentuated dermatitis; and morbilliform or erythrodermic dermatitis. Histology may show spongiotic/psoriasiform dermatitis, interface dermatitis, and/or granulomatous dermatitis	Potential for severe/life-threatening reactions (SJS/TEN); variable and often delayed onset (median 15 weeks; 25% after 31 weeks), may mimic lymphoma progression	Monitor throughout therapy; manage with topical corticosteroids; interrupt or permanently discontinue depending on severity; consider skin biopsy to distinguish drug eruption from disease progression. Permanently discontinue for SJS/TEN or grade 4 (life-threatening) reactions; for suspected SJS/TEN, interrupt and do not restart unless ruled out and resolved to ≤grade 1	FDA United States Prescribing Information POTELIGEO (mogamulizumab), 2018

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TABLE 1. Cutaneous Side Effects From Selected Tumor Therapies (continued)

Drug/Agent	Type of Therapy	Target	Tumor Entity	Combined With	Types of Cutaneous Side Effects and Frequency	Dermatology Details	Main Challenges	Treatment of cAE	References
Brentuximab vedotin	Antibody-drug conjugate (anti-CD30 mAb + microtubule inhibitor)	CD30	$CD30^+$ lymphomas	Monotherapy or combined with chemotherapy (indication-dependent; eg, doxorubicin, vinblastin and dacarbazin for advanced Hodgkin lymphoma)	Relapsed systemic ALCL (pivotal phase II trial): Rash 31% (any CTCAE grade), pruritus 19% (any grade). Serious dermatologic reactions (SJS/TEN) reported	Morbilliform/maculopapular rash; histology: Predominantly spongiotic dermatitis, often with eosinophils, sometimes with mild interface changes	Spectrum ranges from common rash to rare but potentially fatal SJS/TEN; need prompt recognition of severe mucocutaneous involvement and differentiation from infections/other drug rashes	If SJS or TEN occurs: Discontinue brentuximab vedotin and administer appropriate medical therapy	FDA United States Prescribing Information, ADCETRIS (brentuximab vedotin), rev 02/2025
Enfortumab vedotin	Antibody-drug conjugate (anti–nectin-4 mAb + microtubule inhibitor)	Nectin-4	Locally advanced/metastatic urothelial carcinoma	Monotherapy or combined with pembrolizumab	Skin reactions: 58% (all grades) as single agent; maculopapular rash 23%, pruritus 34%; grade 3 to 4 skin reactions 14%. In combination with pembrolizumab: Skin reactions 70% (all grades); grade 3 to 4 17% (grade 4 1%); SJS/TEN can occur	Maculopapular/exanthematous rash, SDRIFE-like intertriginous dermatitis, rare SJS/TEN; histology: Interface dermatitis with keratinocyte apoptosis/necrosis (on-target toxicity)	Risk of severe/fatal cutaneous adverse reactions incl. SJS/TEN (often early, first cycle); higher incidence/severity with pembrolizumab combination; recurrence possible on rechallenge	Closely monitor; consider topical corticosteroids and antihistamines as clinically indicated. Dose modify: For persistent/recurrent CTCAE grade 2, consider withholding until ≤CTCAE grade 1 then resume (same dose or dose-reduce); for CTCAE grade 3 withhold until ≤CTCAE grade 1 then resume (same dose or dose-reduce). For suspected SJS/TEN: Immediately withhold and consult specialist; permanently discontinue for confirmed SJS/TEN, CTCAE grade 4, or recurrent CTCAE grade 3 skin reactions	FDA United States Prescribing Information PADCEV (enfortumab vedotin), rev 02/2025

Abbreviations: ALCL, anaplastic large cell lymphoma; cAE, cutaneous adverse event; CCR4, C-C chemokine receptor 4; CTCAE, Common Terminology Criteria for Adverse Events; FDA, US Food and Drug Administration; HLA, human leukocyte antigen; IgG1, immunoglobulin G1; ImmTAC, immune-mobilizing monoclonal T-cell receptors against cancer; mAb, monoclonal antibody; NA, not applicable; SJS, Stevens-Johnson syndrome; TCR, T-cell receptor; TEN, toxic epidermal necrolysis.

maculopapular eruptions, palmar-plantar erythrodysesthesia, and drug reactions with eosinophilia and systemic symptoms, and some agents have been associated with an increased risk of severe cutaneous adverse reactions such as SJS/TEN.[79] These examples reinforce a broader point: Different drug classes may produce distinct dermatologic phenotypes, and careful characterization often helps guide more effective and less toxic management.

Together, these examples underscore why cutaneous toxicity management cannot rely on the label rash alone, but instead requires attention to morphology, severity, pace of progression, and functional impact. Many lower-grade toxicities can be approached with supportive skin care, emollients, topical corticosteroids, antihistamines, and close follow-up, whereas painful, blistering, mucosal, atypical, or rapidly progressive eruptions warrant urgent dermatologic input. In persistent, atypical, or steroid-refractory cases, dermatology involvement is valuable not only for diagnosis but also for identifying more tailored therapies that may better control symptoms while minimizing compromise of anticancer treatment. As with ocular toxicities, the practical issue is not to master every dermatologic detail, but to recognize when symptoms may represent more than routine irritation and require timely specialist assessment.

CROSS-SYSTEM LESSONS AND COLLABORATION

Novel systemic therapies are producing novel toxicities, and many toxicities—particularly those affecting the skin, eyes, and other specialized organ systems—require expertise that extends beyond the scope of a single clinician. Although referral to subspecialists is standard practice, this approach is often fragmented, delayed, and inconsistent. A more structured model is needed to support timely, coordinated decision making. Multidisciplinary toxicity boards, or toxboards, offer one such framework.

Interdisciplinary toxboards operationalize this approach. They do two high-yield things: (1) They formalize a center's toxicity expertise by identifying organ-based specialists who can be contacted quickly, and (2) they provide a consistent forum where oncologists can receive real-time guidance on complex or therapy-refractory toxicities. This model is especially valuable for rare presentations and for high-risk populations, such as patients with preexisting autoimmune disease or transplant recipients, where evidence is limited and the margin for error is small. In practice, a toxboard may include medical oncology, specialized oncology nursing, pharmacy, and relevant organ specialists such as dermatology and ophthalmology, with input from palliative care, social work, or other disciplines as needed. Such discussions are particularly valuable when decisions about treatment interruption, rechallenge, or escalation of supportive care are uncertain because they can reduce variability in care and help avoid unnecessary interruption of effective therapy. Cases may be identified through routine clinic assessment, patient-reported symptoms, nurse triage, or expedited referral pathways, with more complex cases reviewed through structured multidisciplinary discussion. Not every patient requires formal board review, but timely access to coordinated expertise can help distinguish toxicities that require urgent escalation from those that can be managed supportively while preserving effective treatment.

Because uncommon toxicities will remain uncommon at any single institution, multicenter registries and consortia are essential for learning at scale. International efforts such as the immune-oncology SERIO registry[5] aggregate cases across centers to build cohorts large enough for meaningful analyses, while also advancing education through tools like case-based teaching and ongoing project dissemination. In parallel, the Alliance for Support and Prevention of Immune-Related Events, a multi-stakeholder consortium spanning academic, nonprofit, and industry partners, focuses on disseminating best practices and addressing persistent gaps in prevention, recognition, and management of irAEs. Together, these initiatives convert isolated clinical surprises into shared, actionable knowledge.

Across organ systems, ocular and cutaneous adverse events illustrate a set of practical, patient-centered principles that generalize to emerging therapies:

- Lead with function, not grade. Ask not only what the symptom is, but what is it preventing. A low-grade toxicity can still be unacceptable if it erodes independence, adherence, or quality of life.
- Make reporting accessible and safe. Patients delay reporting when they fear discontinuation or when they cannot access timely, reliable advice.[14] Clear anticipatory guidance about expected symptoms, red flags, and when to contact the team can reduce uncertainty and encourage earlier reporting.
- Build reliable care pathways. Define who triages, build networks of organ specialists, and clarify how quickly patients should be evaluated, particularly for potentially vision-threatening or progressive complaints. Clear pathways should also specify how decisions about side-effect management and oncologic therapy are communicated, including through interdisciplinary toxboards.
- Balance disease control with quality of life. When symptoms threaten safety or adherence, coordinated supportive care, paired with drug interruption or modification when needed, can prevent irreversible harm while preserving treatment benefit.
- Generate prospective data on toxicity risk, monitoring, and side-effect management. A stronger evidence base is needed to guide how adverse events can be treated effectively while preserving tumor response and organ function.

In short, collaboration is not simply referral. It is a repeatable pathway: patients are taught what matters, symptoms are recognized earlier, specialty teams are engaged quickly, and treatment decisions are made jointly with a clear view of both

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disease control and quality of life. This is how centers move from reactive toxicity management to proactive, multidisciplinary safety, across therapies, across organs, and across the full trajectory of cancer care. As a community, we must continue to generate more prospective and comparative data on toxicity recognition, monitoring, and management so that these pathways are guided not only by experience, but by stronger evidence.

CHAPTER CONCLUSION

Our aim must be to prevent mortality from treatment-related toxicity and reduce morbidity. Toxicity from novel anticancer agents becomes unacceptable when it disrupts function, creates uncertainty, or forces trade-offs patients cannot sustain. Early symptom assessment, paired with timely referral pathways and coordinated multidisciplinary care, can prevent avoidable morbidity, preserve quality of life, and help patients remain safely on life-prolonging therapy.

To advance the field, toxicity management must be treated as both a clinical priority and a research mandate. First, we must shorten the time from symptom onset to diagnosis by equipping oncologists, generalists, and frontline teams with clear recognition frameworks, referral triggers, and practical management pathways for organ-specific toxicities. Second, we must accelerate research in treatment-related toxicities, particularly for rare presentations and high-risk populations, through shared registries, interdisciplinary case review, and multicenter collaboration. Prospective clinical studies should include longer-term toxicity follow-up, and comparative trials of adverse event management strategies are needed. Third, we must strengthen patient education and involvement, empowering patients to recognize life- or function-threatening symptoms early, report them without fear of automatic discontinuation, and participate in shared decision making.

Achieving these goals will require dedicated investment in toxicity prevention and management research, not only for new drugs but also for supportive care strategies that help patients remain on therapy safely when appropriate. Finally, clinical trials must routinely incorporate PROs and side effect end points alongside traditional efficacy measures, so that the field measures what patients actually experience and designs therapies and care models that improve not only survival, but the quality of that survival.

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Translating Innovation Into Practice: Dissemination of Immune Checkpoint Inhibitors and Their Toxicity Management Across the Globe

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OVERVIEW

Immune checkpoint inhibitors (ICIs) have redefined the therapeutic landscape of oncology, producing durable responses across multiple tumor types and treatment settings. However, widespread adoption of ICIs has introduced challenges related to cost, optimal dosing, treatment duration, and immune-related toxicities, particularly in low- and middle-income countries (LMICs), where resource constraints have driven pragmatic innovations in delivery. This review summarizes exposure optimization strategies, including low-dose regimens, extended-interval dosing, fixed-duration therapy, and biomarker-guided patient selection supported by pharmacokinetic and pharmacodynamic data showing near-maximal PD-1 receptor occupancy at lower doses. Clinical evidence from randomized trials and real-world studies across tumor types suggest that these approaches may preserve efficacy in selected settings while improving affordability and feasibility. These LMIC-driven adaptations in treatment delivery, toxicity surveillance, and health-system design offer practical insights that may be applicable to high-resource settings facing sustainability challenges. Importantly, exposure optimization strategies have direct implications for toxicity burden, particularly immune-related adverse events (irAEs), hence the manuscript also reviews key organ-specific irAEs, with a focus on cardiovascular and gastrointestinal toxicities, emphasizing early detection, multidisciplinary management, and the relationship between treatment intensity and toxicity burden. Together, these approaches represent an attempt to improve the scalability of immunotherapy while balancing effectiveness, safety, and cost across different health care settings.

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INTRODUCTION

Major advances in oncology have often come in waves, with each new therapeutic paradigm improving survival while introducing new clinical and administrative challenges. The introduction of combination chemotherapy improved cure rates but necessitated the development of supportive care systems to manage treatment-related toxicity. Targeted therapies subsequently transformed outcomes in biomarker-driven cancers but introduced new challenges, including prolonged daily administration with compliance concerns, clinically significant drug-drug interactions, dependence on reliable molecular diagnostic infrastructure, acquired resistance, and distinct toxicities.

Immune checkpoint inhibitors (ICIs) represent the most recent paradigm shift. By restoring antitumor immunity through inhibition of the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and PD-1 and PD-L1 pathway, ICIs have produced durable responses across multiple malignancies.[1-3]

The use of ICIs has expanded from the advanced palliative setting to adjuvant and neoadjuvant settings and, in some tumor types, ICIs have indeed redefined established treatment algorithms. In select patients with localized mismatch repair-deficient (dMMR) rectal cancer, immunotherapy has even challenged traditional surgery-first paradigms and introduced the possibility of nonoperative management.[4,5] This evolution illustrates how each clinical paradigm shift delivers therapeutic gains while generating new structural and safety demands. The central question is no longer whether ICIs are effective, but how much immune activation is required, for what duration, and within what monitoring framework to ensure safe and sustainable care.

ICIs are now administered to broader patient populations, often for longer durations and in combination with other systemic therapies. Although policy initiatives, including inclusion of ICIs in the WHO Essential Medicines List, acknowledge their clinical importance, implementation in low- and middle-income countries (LMICs) remains constrained

PRACTICAL APPLICATIONS

- Clinicians may consider low-dose and extended-interval immunotherapy in selected patients to reduce cost and treatment burden, although there are no randomized comparative data with standard dosing, and equivalence in efficacy has not been established. Fixed-duration treatment can be used in patients with sustained response, with close follow-up and to restart therapy, if needed.
- Biomarker-based selection, especially in microsatellite instability-high or mismatch repair-deficient tumors, can help identify patients who may benefit from lower-intensity treatment.
- Early and structured monitoring is important for timely detection and management of immune-related toxicities.
- Health systems can explore dose optimized delivery models to improve access and sustainability of immunotherapy in both resource-constrained and high-resource settings.

by affordability and health-system capacity.[6] In advanced or metastatic settings, treatment continues for up to two years or until disease progression, and combination regimens further intensify immune activation.[7-12] Although these practices have improved outcomes for many patients, they have also increased cumulative immune exposure, treatment-related toxicity, and overall cost, in LMICs as well as in high-resource settings.[13-17] These trends highlight the need to rationalize treatment duration and intensity across health systems.[18,19]

In resource-constrained settings, challenges with implementation of ICIs in clinical practice were encountered early, often at the time of the initial regulatory approval.[20-23] This necessitated careful reconsideration of conventional dosing and treatment duration.[24-28] The concept of whether reduced dosing and extended dosing intervals could maintain therapeutic efficacy while improving affordability and feasibility was explored. These strategies are based on strong pharmacokinetic and pharmacodynamic data demonstrating adequate receptor engagement at lower exposures, along with clinical evidence from real-world studies and systematic reviews.[27,29,30]

Despite the transformative impact of immunotherapy in oncology, the immune-related toxicities that accompany these agents present important toxicities that must be proactively managed. Immune-related adverse events (irAEs) occur due to activation of the immune system. Toxicities may involve the skin, endocrine glands, lungs, gastrointestinal tract, hepatic, cardiac, and nervous system. Although the majority of irAEs are low grade and manageable with appropriate intervention, a subset may present with delayed onset, unpredictable clinical trajectories, multisystem involvement, and potentially life-threatening complications.[31] The incidence, timing, and severity of irAEs are closely associated with treatment intensity, use of combination regimens, and cumulative immune activation.[1,2,32] Among this spectrum, gastrointestinal and cardiovascular toxicities are among the most critical dimensions of immunotherapy-related risk.[33-37] Cardiovascular toxicities, although less common, are associated with substantial morbidity and mortality.[38]

Hence, strategies that optimize immune exposure influence not only access and cost but also the timing and severity of irAEs. This manuscript examines these issues in three sections. The first explores the dissemination of ICIs and highlights strategies developed in resource-constrained settings that may inform sustainable practice in high-resource systems. Subsequent sections review cardiac and gastrointestinal toxicities, focusing on timing, severity assessment, and evidence-based management. By integrating global experience with established principles of toxicity management, we aim to provide a framework for translating immunotherapy innovation into safe and equitable clinical practice worldwide.

DISSEMINATION OF ICIs: WHAT HIGH-RESOURCE SETTINGS CAN ADOPT FROM GLOBAL PARTNERS

Randomized clinical trials have demonstrated that ICIs improve overall survival (OS) and produce durable responses across multiple tumor types, with median survival gains of 6-12 months in advanced disease and increasing benefit in curative settings.[1-3,7-10,39-43]

However, these benefits are not consistently seen in real-world practice, especially in LMICs. Delayed access, early treatment discontinuation, and financial toxicity often limit sustained immunotherapy exposure in these settings.[44] Cross-national analyses show wide variation in ICI availability, reimbursement, and out-of-pocket costs. In many LMICs, high drug prices and limited public funding result in substantial patient cost-sharing.[20,21] Real-world data from India indicate that ICIs are administered to only 15%-25% of eligible patients in tertiary care centers, largely due to affordability constraints and limited reimbursement. In addition, only 40%-50% of patients considered for ICIs undergo recommended biomarker testing, reflecting the cumulative impact of drug acquisition and diagnostic costs on access in LMIC settings.[23] Cost-related barriers are not confined to LMICs. In high-income countries, prolonged immunotherapy use contributes to financial toxicity and reduced adherence. Annual per-patient costs often exceed $100,000 US dollars.[13-17] As ICIs become the standard of care, high-resource health systems are also facing sustainability

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concerns. In several countries, ICIs account for approximately 30%-50% of total oncology drug expenditure, where prolonged treatment duration is a major driver of these costs.[13-15]

Within this shared context, pragmatic strategies developed in resource-constrained settings to optimize dose, interval, duration, and delivery of immunotherapy offer important lessons for value-based cancer care.

Low-Dose Immunotherapy

One of the most prominent innovations emerging from LMIC oncology practice is the use of low-dose ICIs, driven by the need to improve affordability while preserving clinical benefit. Pharmacokinetic and pharmacodynamic studies of nivolumab and pembrolizumab have demonstrated that >80%-90% PD-1 receptor occupancy and downstream immune activation are achieved at doses as low as 0.3-1 mg/kg every 2 weeks with minimal incremental biological effect observed at higher conventionally approved doses (nivolumab 3 mg/kg or fixed dosing of 240 mg every 2 weeks, 480 mg every 4 weeks), providing a strong rationale for dose-attenuation strategies.[8,27]

Evidence in Advanced and Palliative Settings

Multiple studies have evaluated reduced-dose ICIs across tumor types in the palliative setting. Gandhi et al[27] demonstrated that meaningful antitumor activity can be achieved at doses substantially lower than conventionally approved regimens, with acceptable safety and response rates.

A randomized phase III study from India showed that nivolumab 20 mg administered intravenously once every 3 weeks, combined with metronomic chemotherapy (continuous low-dose cytotoxic therapy without prolonged drug-free intervals), resulted in superior OS compared with physician's-choice chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma (HNSCC; median OS = 10.6 *v* 6.9 months; hazard ratio [HR], 0.63; $P = .004$).[24]

Real-world cohorts from Singapore and Korea reported comparable response rates and survival outcomes in patients with advanced non–small cell lung cancer (NSCLC) treated with reduced-dose pembrolizumab (100 mg once every 3 weeks) compared with conventional dose (200 mg once every 3 weeks) or reduced-dose nivolumab (20-40 mg once every 2-4 weeks) compared with standard dosing (3 mg/kg once every 2 weeks).[25,26]

In patients with previously treated NSCLC, the comparative NVALT-30 study showed that reduced-dose nivolumab (100 mg once every 3 weeks or 300 mg once every 6 weeks) resulted in no statistically significant difference in progression-free survival (PFS) compared with standard dosing (HR for PFS approximately equal to 0.86, $P > .05$).[45]

At the 2025 annual ASCO meeting, Noronha et al[46] reported that low-dose ICIs across multiple solid tumors were associated with a modest but statistically significant improvement in OS compared with physician's-choice therapy in second-line and later settings (median OS 5.88 *v* 4.70 months; HR, 0.80; $P = .022$), with grade ≥3 immune-related toxicity <15% and improved patient-reported quality of life.

In advanced renal cell carcinoma, the addition of low-dose nivolumab to tyrosine kinase inhibitors (TKIs) was associated with higher response rates than TKI alone, particularly in clear cell disease (objective response rate 68% *v* 50%) and non–clear cell histology (50% *v* 0%), with no significant increase in toxicity.[47]

In a real-world audit of patients with advanced solid tumors treated with low-dose nivolumab, responders (28%) demonstrated significantly higher 6-month PFS (100% *v* 8.7%; HR, 0.05; $P = .003$) and OS (100% *v* 29.7%; HR, 0.03; $P = .047$) compared with nonresponders, with manageable toxicity, supporting the clinical feasibility of reduced-dose immunotherapy in resource-constrained settings.[28]

Evidence in Curative-Intent Settings

Low-dose immunotherapy has also shown activity in the curative setting. In the phase II PLANeT (Pembrolizumab Low dose in Addition to Neoadjuvant Therapy in Triple-Negative Breast Cancer) trial from the All India Institute of Medical Sciences (AIIMS) New Delhi, pembrolizumab 50 mg once every 6 weeks (three doses) added to neoadjuvant chemotherapy in patients with stages II to III triple-negative breast cancer improved pathologic complete response rates (pCR) from 40.5% (from neoadjuvant chemotherapy alone, in the control arm) to 53.8% ($P = .047$) without increasing grade ≥3 toxicity (59.5% in the control arm *v* 50.0% in the low-dose pembrolizumab arm).[48]

However, the chemotherapy backbone in PLANeT did not include carboplatin, limiting direct comparison with KEYNOTE-522,[42] where higher pCR rates were achieved with a carboplatin-containing regimen. The relatively lower pCR rates in the control arm of PLANeT also suggest that outcomes may not reflect those seen with contemporary optimized chemotherapy. Randomized data from Tata Memorial Centre evaluating the addition of carboplatin to neoadjuvant chemotherapy demonstrated improvements not only in pCR but also in long-term outcomes, with 5-year event-free survival of 70.7% versus 64.1% (HR, 0.80) and OS of 74.4% versus 66.8% (HR, 0.74), with the greatest benefit observed in premenopausal patients.[49] In addition, data from the PEARLY trial further support the role of carboplatin in improving pCR rates in triple-negative breast cancer, reinforcing the importance of an optimized chemotherapy backbone. These findings highlight the impact of optimizing the chemotherapy backbone.[48] Taken together, these data raise an important question regarding the relative contribution of chemotherapy optimization

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versus immunotherapy intensification. Given the low cost and established efficacy of carboplatin, it remains uncertain whether the benefits observed in PLANeT reflect the addition of immunotherapy or the absence of an optimized chemotherapy backbone.

In a single-institution ambispective study of patients with locally advanced, unresectable or borderline resectable HNSCC, the addition of low-dose nivolumab to induction chemotherapy achieved an ORR of 75.3% and a pCR of 32%. It enabled surgical resection in 31.6% of patients with oral cavity tumors, illustrating treatment-intent conversion in a resource-constrained setting.[50]

Similarly, a multicenter retrospective cohort in patients with resectable NSCLC showed that low-dose PD-1 blockade combined with neoadjuvant chemotherapy produced major pathologic response rates of 30%-40%, without increased perioperative morbidity.[51]

In locally advanced HNSCC, a single-center observational study of neoadjuvant paclitaxel and carboplatin with triple oral metronomic chemotherapy and low-dose nivolumab (20-40 mg once every 3 weeks) reported an ORR of 65%. Among patients who underwent surgery, a major pathologic response was seen in 50% and a pCR in 12.5%. Importantly, 51% of patients with initially unresectable or borderline-resectable disease were able to proceed to surgery, with no grade ≥3 irAEs observed and median OS not reached at a short follow-up of 7.0 months (95% CI, 6.0 to 7.9).[52]

Parallel principles have been explored in hematologic malignancies. In a retrospective cohort of 18 children with high-risk relapsed/refractory classical Hodgkin lymphoma, fixed low-dose nivolumab (40 mg once every 2 weeks) plus bendamustine achieved a complete response rate of 88%, with 1-year PFS of 88.2% and OS of 94.4%, demonstrating robust activity of reduced-dose ICIs.[53] A phase II trial of low-dose nivolumab (40 mg once every 2 weeks) plus lenalidomide in relapsed/refractory classical Hodgkin lymphoma demonstrated a 90% ORR with 60% complete responses and 83.5% PFS at approximately 15 months (and 92.9% relapse-free survival post-transplant), supporting the activity of low-dose ICI combinations in this setting.[54]

Collectively, evidence from breast cancer, HNSCC, NSCLC, and lymphoma supports further exploration of low-dose immunotherapy as a clinically feasible, biologically sound strategy in both the curative and palliative settings.

Ongoing and Emerging Studies

In addition to published phase II to III studies, multiple investigator-initiated trials across India are currently evaluating low-dose ICIs in both solid and hematologic malignancies, spanning palliative, neoadjuvant, and curative-intent settings (Table 1).

Extended-Interval and Fixed-Duration Strategies

Dose optimization, interval extension, and planned treatment duration represent complementary strategies to reduce cumulative drug exposure and treatment burden while preserving efficacy. Extended-interval dosing is supported by pharmacokinetic and exposure-response analyses demonstrating sustained PD-1 receptor occupancy beyond conventional schedules, which led to regulatory approval of pembrolizumab administration once every 6 weeks.[29] In resource-constrained settings, interval extension has been used to improve access and reduce visit and cost burden. The PLANeT trial used low-dose pembrolizumab once every 6 weeks in combination with chemotherapy, integrating the dual concepts of interval extension with reduced dosing.[55]

Beyond dose and interval, the optimal duration of immunotherapy has emerged as a key question, particularly among patients with durable responses. Fixed-duration immunotherapy, defined as planned treatment cessation after a predefined period or upon achieving a predefined depth of response, aligns with randomized evidence in LMIC practice. Randomized data from CheckMate-153 and multiple KEYNOTE trials demonstrate durable disease control after stopping therapy in selected patients with NSCLC, with preserved sensitivity to rechallenge.[7-10] In melanoma, long-term follow-up from KEYNOTE-001 and KEYNOTE-006 shows disease-free survival exceeding 80%-90% among patients who discontinued therapy after achieving a complete response or completing two years of treatment.[11,12] Real-world Asian cohorts and microsatellite instability-high (MSI-H) colorectal cancer series further support planned discontinuation strategies in carefully selected responders.[56] Collectively, these data support fixed-duration frameworks with structured surveillance and retreatment pathways as a means to reduce toxicity, cost, and treatment burden without compromising long-term outcomes.

Combination Strategies to Enhance Immunotherapy Efficiency

In resource-constrained settings, combination strategies have been used not to intensify treatment, but to improve immunotherapy efficiency, enhance durability of response, and enable dose or duration optimization. Metronomic chemotherapy has been preferentially combined with ICIs because of its immunomodulatory effects, including reduction of regulatory T cells and myeloid-derived suppressor cells, improved antigen presentation, and modulation of the tumor microenvironment, while limiting additional toxicity and cost (Figs 1A and 1B). Multitumor clinical experiences and translational studies suggest that metronomic chemotherapy can enhance immune responsiveness across solid tumors through schedule-dependent synergy with PD-1/PD-L1 blockade.[57,58]

Clinical evidence for this approach has largely emerged from LMICs. In recurrent or metastatic HNSCC, a randomized

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TABLE 1. Ongoing Interventional Clinical Trials of Low-Dose Immune Checkpoint Inhibitors in India

Disease/Tumor Type	Study Type	Title	Planned Sample Size	Intervention	Treatment Setting	Primary End Point	Institution	CTRI Number
(A) Solid tumors: Resectable/locally advanced setting								
Oral squamous cell carcinoma	Phase III randomized study	A multicenter randomized study of neoadjuvant systemic therapy in oral cavity cancer	348	Nivolumab 40 mg IV once every 3 weeks × 3 + OMCT followed by surgery *v* upfront surgery	T3 N1/N2/N3 or T4 HNSCC of the oral cavity	DFS	Tata Memorial Centre, India	2024/04/065574
Oral SCC	Phase II single-arm study	Neoadjuvant chemo-immunotherapy using carboplatin, paclitaxel, oral metronomic chemotherapy and low-dose nivolumab for locally advanced borderline resectable oral cavity squamous cell carcinoma—A prospective study	31	Neoadjuvant carboplatin AUC 5 + nab-paclitaxel 175 mg/m^2 IV + nivolumab 20 mg (<65 kg)/40 mg (≥65 kg) IV once every 3 weeks × 2 + OMCT	Stage III to IVB deemed borderline resectable in MDT	R0 resection rate	CMC Vellore, Tamil Nadu, India	2023/04/051617
Oral cavity SCC	Phase II, randomized, multicenter study	A prospective, open labeled, randomized, multicenter, investigator initiative study to evaluate the efficacy, safety, low-dose nivolumab along with neoadjuvant chemotherapy with TPF regimen in subjects with locally advanced stage IVA/B squamous cell carcinoma of buccal mucosa	50	Nivolumab 40 mg IV D1,15,29 + docetaxel 75 mg/m^2 IV D1,22,43 + cisplatin 75 mg/m^2 IV D1,22,43 + 5-FU 750 mg/m^2 IV D1-5,22-26,43-47 *v* chemotherapy alone	Locally advanced—Stage IVA/IVB	ORR	HCG Enterprises, India	2024/02/062244
Oral Cavity SCC	Phase II, randomized study	A phase II randomized trial of neoadjuvant carboplatin, paclitaxel, low-dose nivolumab and metronomic therapy compared to standard chemotherapy in technically unresectable oral cavity squamous cancer	106	Carboplatin AUC 5 IV + paclitaxel 175 mg/m^2 IV + nivolumab 0.3 mg/kg IV once every 3 weeks × 4 *v* physician's choice chemotherapy	Technically unresectable locally advanced SCC of the oral cavity	R0 resection rate	CMC Vellore, Tamil Nadu, India	2024/08/072823
Cervical cancer	Phase II study	Low-dose nivolumab in combination with neoadjuvant chemotherapy followed by concurrent chemoradiation in advanced carcinoma cervix: A phase II study	28	Nivolumab 20 mg IV once every 3 weeks × 2 + weekly carboplatin AUC 2 IV + paclitaxel 60 mg/m^2 IV × 6 weeks → followed by concurrent chemoradiation with weekly cisplatin 40 mg/m^2 IV + EBRT 50.4 Gy/25 fractions over 5 weeks	FIGO stage IIIC to IVa squamous, adeno, or adenosquamous carcinoma of the cervix	ORR to neoadjuvant chemoimmunotherapy	AIIMS New Delhi, India	2024/07/071051
Triple-negative breast cancer	Phase II, randomized study	A phase II randomized controlled trial of low-dose pembrolizumab in addition to standard neoadjuvant chemotherapy in patients with triple-negative breast cancer	154	Standard NACT (anthracycline × 4 → Taxane × 4) + pembrolizumab 50 mg IV once every 6 weeks *v* chemotherapy alone	Triple-negative breast cancer	pCR	AIIMS New Delhi, India	2023/12/060529

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TABLE 1. Ongoing Interventional Clinical Trials of Low-Dose Immune Checkpoint Inhibitors in India (continued)

Disease/Tumor Type	Study Type	Title	Planned Sample Size	Intervention	Treatment Setting	Primary End Point	Institution	CTRI Number
NSCLC	Phase II single-arm study	Neoadjuvant chemotherapy with low-dose immunotherapy in resectable non–small cell lung cancer—A phase II open-label single-arm study	53	Neoadjuvant pemetrexed 500 mg/m^2 IV or paclitaxel 175 mg/m^2 IV + cisplatin 75 mg/m^2 IV or carboplatin AUC 5 IV + nivolumab 40 mg IV once every 3 weeks × 3 → response assessment → surgery	Stage IIA ≥ 4 cm 2B 3A 3B N2 NSCLC (EGFR/ALK-negative)	pCR	Tata Memorial Hospital, Mumbai, India	2025/02/081029
NSCLC	Phase II randomized study	Evaluation of low-dose nivolumab with neoadjuvant chemotherapy in non–small cell lung cancer	50	Nivolumab 40 mg IV once every 3 weeks (Day 1) + paclitaxel 80 mg/m^2 IV (Days 1, 8, 15) once every 3 weeks + carboplatin AUC 6 IV (Day 1) once every 3 weeks *v* chemotherapy alone	Stage IIB or IIIA NSCLC (EGFR/ALK/ROS-negative)	Major pathologic response rates	AIIMS New Delhi, India	2023/02/050126
Penile squamous cell carcinoma	Phase II randomized study	A phase II randomized trial of neoadjuvant chemotherapy with or without triple oral metronomic chemotherapy and low-dose immunotherapy in resectable locally advanced penile squamous cell carcinoma	100	Weekly paclitaxel 80 mg/m^2 IV + weekly carboplatin AUC 2 IV + OMCT + nivolumab 40 mg IV once every 3 weeks (3-4 cycles) × 8-12 weeks *v* IV chemotherapy alone	Surgically resectable penile squamous cell carcinoma	pCR	Tata Memorial Hospital, Mumbai, India	2025/11/097637
Esophageal squamous cell carcinoma	Phase III randomized study (NEO-I)	Phase III RCT comparing triplet neoadjuvant chemotherapy with triplet neoadjuvant chemoimmunotherapy in patients with locally advanced resectable esophageal squamous carcinoma	362	5-FU 750 mg/m^2 CI D1-5, cisplatin 75 mg/m^2 IV D1 or carboplatin AUC 5-6 IV D1, docetaxel 75 mg/m^2 IV D, capecitabine 650 mg/m^2 PO twice a day (continuous, once every 3 weeks), nivolumab 40 mg IV once every 3 weeks *v* chemotherapy alone	Squamous cell carcinoma of the esophagus or esophagogastric junction cT2-4a, N0-3, M0	3-year EFS	Tata Memorial Hospital, Mumbai, India	2025/02/080989
Esophageal squamous cell carcinoma	Phase III randomized study (NEO-X)	Phase III RCT comparing triplet neoadjuvant chemotherapy with neoadjuvant chemoradiation in patients with locally advanced resectable esophageal squamous carcinoma	404	Docetaxel 75 mg/m^2 IV + cisplatin 75 mg/m^2 IV or carboplatin AUC 5-6 IV + 5-FU 750 mg/m^2 CI D1-5 or capecitabine 650 mg/m^2 PO twice a day + nivolumab 40 mg IV once every 3 weeks × 3-4 cycles → surgery *v* concurrent chemoradiation: carboplatin AUC 2 IV weekly + paclitaxel 50 mg/m^2 IV weekly with RT 41.4 Gy in 23 fractions (1.8 Gy/fraction) → surgery (4-6 weeks post-CRT)	Resectable squamous cell carcinoma of the esophagus or esophagogastric junction Pre-treatment stage cT24a, N0-3, M0	OS	Tata Memorial Hospital, Mumbai Sher i kashmir Institute of Medical Sciences, Kashmir Thangam Hospital, Tamil Nadu, India	2024/11/076896
(B) Solid tumors: Advanced/metastatic disease								
HNSCC	Phase III randomized study	A phase III, randomized controlled study comparing triple oral metronomic chemotherapy with low-dose immunotherapy to intravenous chemotherapy in patients with advanced platinum-sensitive head and neck squamous cell carcinoma in first-line palliative setting	422	OMCT + nivolumab 20 mg IV once every 3 weeks until progression *v* cisplatin 75 mg/m^2 IV (Day 1) or carboplatin AUC 6 IV (Day 1) + paclitaxel 175 mg/m^2 IV (Day 1, 3-hour infusion) once every 3 weeks until progression	Platinum-sensitive recurrent/metastatic	Noninferior OS	Tata Memorial Hospital, Mumbai, India	2024/01/061661

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TABLE 1. Ongoing Interventional Clinical Trials of Low-Dose Immune Checkpoint Inhibitors in India (continued)

Disease/Tumor Type	Study Type	Title	Planned Sample Size	Intervention	Treatment Setting	Primary End Point	Institution	CTRI Number
HNSCC		Triple oral metronomic chemotherapy with paclitaxel and carboplatin plus low-dose nivolumab: first-line immunotherapy and repurposed-drug combination—A Phase III randomized controlled trial in platinum-sensitive recurrent or metastatic head and neck squamous cell carcinoma	436	Weekly paclitaxel 80 mg/m^2 IV + weekly carboplatin AUC 2 IV + OMCT+ nivolumab 40 mg IV once every 3 weeks; after approximately 4 months (approximately equal to 4-6 once every 3 weeks cycles), weekly paclitaxel/carboplatin may be discontinued at physician discretion with continuation of OMCT ± nivolumab until progression or unacceptable toxicity *v* IV chemotherapy alone	Squamous cell carcinoma of the head and neck oral cavity, oropharynx, larynx, hypopharynx, carcinoma of unknown primary in cervical lymph nodes	OS	Tata Memorial Hospital, Mumbai, India	2026/02/105089
NSCLC	Phase III randomized study	Phase III randomized study for evaluation of addition of pembrolizumab to palliative therapy in NSCLC	380	Paclitaxel (175 mg/m^2) with platinum (cisplatin-75 mg/m^2 or carboplatin AUC-5) OR pemetrexed (500 mg/m^2) with platinum (cisplatin-75 mg/m^2 or carboplatin AUC-5) plus pembrolizumab 50 mg 3 weekly	Advanced metastatic	OS	Tata Memorial Hospital, Mumbai, India	2023/08/056715
NSCLC		An open-label phase-II randomized clinical trial to evaluate the efficacy and safety of low-dose nivolumab and low-dose chemotherapy in patients of advanced NSCLC with poor PS	70	Nivolumab 20 mg IV once every 3 weeks + paclitaxel 60 mg/m^2 IV weekly × 6 weeks → if PS ≤ 2: paclitaxel 60 mg/m^2 IV (Days 1, 8, 15) + carboplatin AUC 2 IV once every 3 weeks × up to 4 cycles → maintenance nivolumab 20 mg IV once every 3 weeks until progression/toxicity; nonsquamous histology with nonprogressive disease may receive pemetrexed maintenance + nivolumab; if no PS improvement after 6 weeks, option for single-agent chemotherapy + nivolumab *v* low-dose chemotherapy: paclitaxel 60 mg/m^2 IV weekly × 6 weeks → paclitaxel 60 mg/m^2 IV (Days 1, 8, 15) + carboplatin AUC 2 IV once every 3 weeks	Locally advanced/metastatic NSCLC	6-month PFS	Tata Memorial Hospital, Mumbai AIIMS New Delhi, India	2025/03/082809
Esophageal squamous cell carcinoma	Phase III randomized study (NICE)	Phase III RCT comparing chemotherapy to chemotherapy plus immunotherapy in patients with advanced esophageal squamous cell cancer receiving first-line palliative-intent systemic therapy (NICE Study)	320	Paclitaxel 175 mg/m^2 IV once every 3 weeks or 80 mg/m^2 IV weekly → carboplatin AUC 5-6 IV once every 3 weeks + nivolumab 40 mg IV once every 3 weeks until progression/toxicity *v* physician's choice chemotherapy alone	Advanced metastatic	OS	Tata Memorial Hospital, Mumbai, India	2024/03/064939

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TABLE 1. Ongoing Interventional Clinical Trials of Low-Dose Immune Checkpoint Inhibitors in India (continued)

Disease/Tumor Type	Study Type	Title	Planned Sample Size	Intervention	Treatment Setting	Primary End Point	Institution	CTRI Number
Colorectal cancer	Phase II single-arm study	A single-arm phase II prospective open-label interventional study in 1st-line therapy for patients with metastatic colorectal cancer (MSI-H) with low-dose nivolumab (CLOuD)	52	Nivolumab 40 mg IV once every 3 weeks × 6 months → once every 6 weeks × 6 months (total 12 months or until progression, whichever earlier)	First-line metastatic (MSI-H)	PFS	Tata Memorial Hospital, Mumbai, India	2024/01/061681
Advanced solid tumors	Phase II single-arm study	A phase II single-arm study evaluating the safety and efficacy of fixed low-dose nivolumab in advanced malignancy	141	Nivolumab 40 mg IV once every 3 weeks	Multiple metastatic disease	ORR	Ramaiah Medical College, Bengaluru, India	2022/05/042895
(C) Hematologic malignancies								
Hodgkin lymphoma	Phase II single-arm study	Efficacy of low-dose nivolumab as remission-induction therapy in primary progressive and relapsed Hodgkin lymphoma	20	Transplant-eligible: nivolumab 40 mg IV once every 3 weeks × 4 → response assessment → autologous stem-cell transplant Transplant-ineligible: nivolumab 40 mg IV once every 3 weeks → lenalidomide maintenance × 2 years	Primary progressive/relapsed HL	2-year relapse-free survival	CMC Vellore, Tamil Nadu, India	2022/04/042179
Hodgkin lymphoma	Phase III, randomized study	A phase III RCT comparing AVD+ low-dose nivolumab versus ABVD using a risk-adapted strategy in newly diagnosed advanced stage classical Hodgkin lymphoma	280	Nivolumab 40 mg IV once every 3 weeks × 4 + doxorubicin 25 mg/m^2 IV + vinblastine 6 mg/m^2 IV) + dacarbazine 375 mg/m^2 IV (Days 1, 15) *v* nivolumab 40 mg IV once every 3 weeks × 4 + doxorubicin 25 mg/m^2 IV + bleomycin 10 U/m^2 IV + vinblastine 6 mg/m^2 IV + dacarbazine 375 mg/m^2 IV (Days 1, 15)	Newly diagnosed, advanced-stage HL	Early treatment failure (iPET2 with Deauville score above 3), disease progression, relapse, or death at any time point	CMC Vellore, Tamil Nadu Tata Memorial Hospital, Mumbai, India	2024/03/063942
Pediatric Hodgkin lymphoma	Phase II/III, randomized, multicenter study	Efficacy and safety of substitution of bleomycin by low-dose nivolumab in ABVD (doxorubicin plus bleomycin plus vinblastine plus dacarbazine) backbone chemotherapy in newly diagnosed advanced-stage pediatric Hodgkin lymphoma	169	Nivolumab 0.75 mg/kg IV once every 2 weeks × 12 + doxorubicin 25 mg/m^2 IV once every 2 weeks × 12 + vinblastine 6 mg/m^2 IV once every 2 weeks × 12 + dacarbazine 375 mg/m^2 IV once every 2 weeks × 12 *v* bleomycin 10 U/m^2 IV once every 2 weeks × 12 + doxorubicin 25 mg/m^2 IV once every 2 weeks × 12 + vinblastine 6 mg/m^2 IV once every 2 weeks × 12 + dacarbazine 375 mg/m^2 IV once every 2 weeks × 12	Newly diagnosed, advanced stage	CMR rates	AIIMS Bhubaneswar, Orissa, India	2025/03/082456

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AIIMS, All India Institute of Medical Sciences; AVD, doxorubicin, vinblastine, dacarbazine; BID, twice daily; CI, continuous infusion; CMC, Christian Medical College; CMR, complete metabolic remission; CTRI, Clinical Trials Registry of India; D, day; DFS, disease-free survival; EBRT, external beam radiotherapy; EFS, event-free survival; HNSCC, head and neck squamous cell carcinoma; iPET2, interim positron emission tomography; IV, intravenous; MDT, multidisciplinary team; MSI-H, microsatellite instability–high; NACT, neoadjuvant chemotherapy; NSCLC, non–small cell lung cancer; OD, once daily; OMCT, oral metronomic chemotherapy (erlotinib 100-150 mg daily, celecoxib 200 mg twice daily, methotrexate 9 mg/m^2 weekly); ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PET, positron emission tomography; PFS, progression-free survival; PO, oral; PS, performance status; SCC, squamous cell carcinoma; TPF, docetaxel, cisplatin, and 5-fluorouracil.

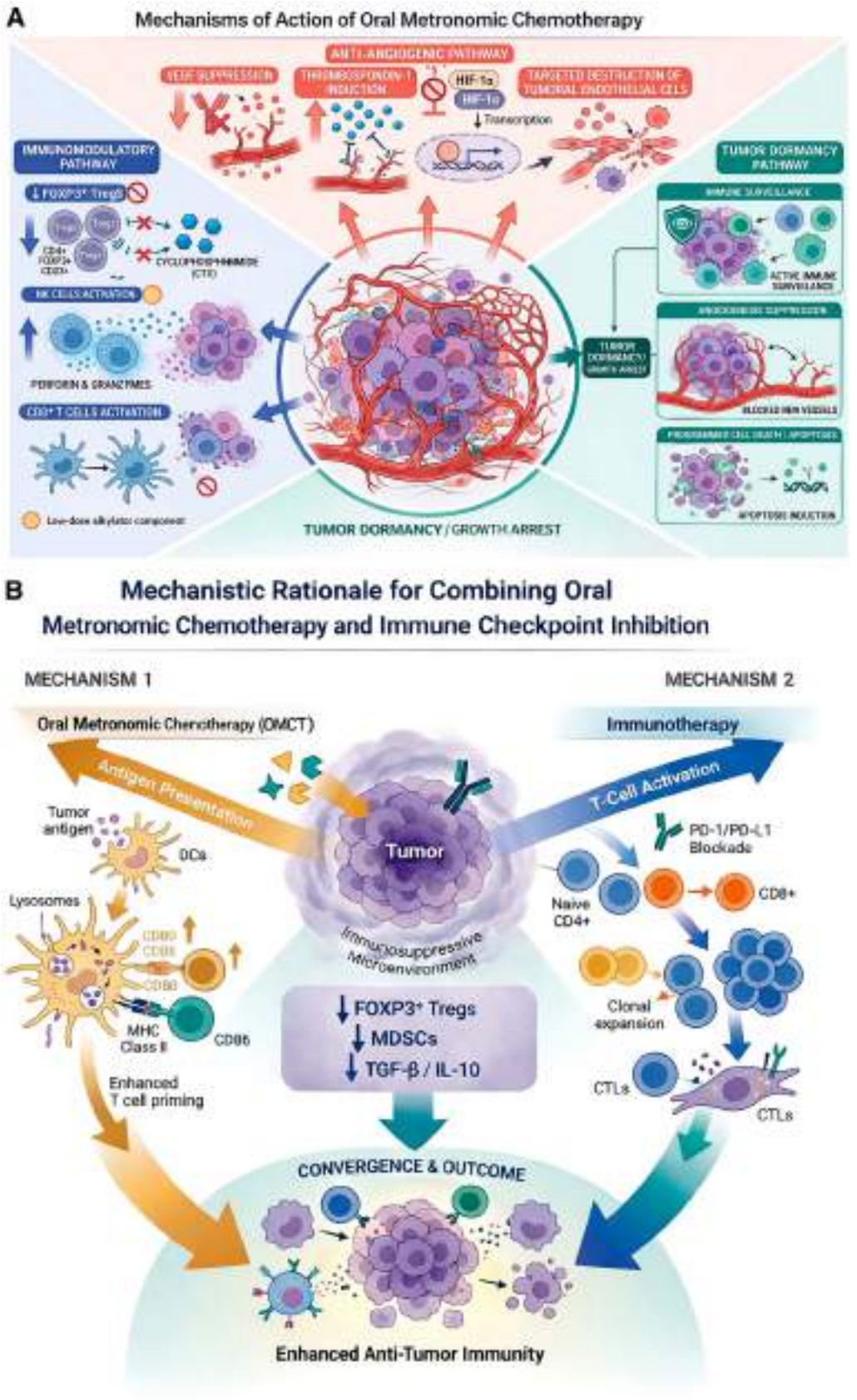

FIG 1. (A) Mechanisms of action of oral metronomic chemotherapy. (B) Biological basis for combining oral metronomic chemotherapy with immune checkpoint. The images for this Figure were generated using biorender.com.

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phase III study demonstrated that low-dose nivolumab combined with oral metronomic chemotherapy (a combination of celecoxib, erlotinib, and methotrexate) improved PFS and OS compared with standard therapy, with acceptable toxicity.[24]

A retrospective study from Tata Memorial Hospital showed that adding axitinib to triple oral metronomic chemotherapy and low-dose nivolumab in advanced HNSCC did not improve OS (median OS 7 months) and was associated with higher grade ≥3 toxicities, highlighting the need for careful selection of combination strategies.[59]

Biomarker-Guided Optimization of Immunotherapy

Appropriate biomarker selection is central to immunotherapy efficacy, as only a subset of patients derives durable benefit. MSI-H/dMMR status represents the most robust predictive biomarker, with landmark trials demonstrating high and durable responses to PD-1 blockade across tumor types.[4,5] In biologically favorable subgroups, pharmacokinetic and pharmacodynamic analyses show early PD-1 receptor saturation and immune activation at relatively low drug exposures, indicating that clinical benefit is driven primarily by tumor immunogenicity and patient selection rather than maximal dosing.[27]

In this context, the CLouD-High study, a real-world analysis of patients with MSI-H metastatic colorectal cancer treated with low-dose nivolumab (20-40 mg once every 3 weeks), reported an ORR of 47%, with PFS and durability of response comparable with standard dosing and no increase in immune-related toxicity.[56] These findings reinforce the principle that biomarker-guided patient selection can enable effective dose-attenuated immunotherapy in highly immunogenic tumors.

Toxicity Surveillance

Proactive toxicity surveillance is essential for the safe implementation of systemic therapy, including immunotherapy. Nurse-led symptom monitoring, grading of toxicity, and defined escalation pathways facilitate early detection of irAEs.[23] The Chemo Care Unit at Tata Memorial Center exemplifies a centralized model for early toxicity triage and symptom management in patients receiving systemic anticancer therapy. Although originally developed for cytotoxic chemotherapy, its core principles are directly applicable to immunotherapy, supporting safe decentralization of ICI delivery in high-resource health systems.

Health-System and Economic Considerations

Health-system and economic frameworks are critical to the scalable adoption of immunotherapy innovations. Modeling analyses suggest that price negotiations, tiered pricing strategies, and treatment optimization could substantially reduce the budgetary impact of ICIs, particularly in high-incidence cancers such as advanced NSCLC.[18] Cost-effectiveness studies further identify treatment duration and dose intensity as key drivers of value, reinforcing the importance of exposure-optimized strategies.[19] In parallel, expansion of public insurance coverage and risk-pooling mechanisms has been associated with improved access to high-cost cancer medicines, highlighting the close interplay between financing structures and sustainable treatment delivery.[20]

Experience from LMICs highlights several transferable strategies that may inform more sustainable and equitable implementation of immunotherapy in high-resource health systems:

1. Regulatory alignment and reliance pathways: Reliance or mutual recognition pathways reduce duplication in regulatory review and enable faster access to therapies with established efficacy and safety.
2. Equity-oriented clinical trial ecosystems: Investment in clinical trial infrastructure in LMICs facilitates the generation of context-specific evidence, enables earlier patient access through trials, and strengthens the global evidence base for treatment strategies.
3. Adaptive dosing and value-based frameworks: Systematic evaluation of dose optimization, fixed-duration therapy, and exposure-response relationships, integrated with health-economic analyses, can help align clinical benefit with long-term affordability.
4. Shared diagnostic and toxicity-management infrastructure: Coordinated approaches to biomarker testing, toxicity surveillance, and workforce training improve consistency of care while reducing inefficiencies across health systems.
5. Financial risk-sharing and pricing models: Structured engagement between payers, providers, and manufacturers, including tiered pricing and outcome-linked reimbursement, can align commercial incentives with public health goals and improve access.

irAES: ORGAN-SPECIFIC CONSIDERATIONS

The advent of ICIs has led to unprecedented survival benefits across a broad spectrum of malignancies. However, this progress is tempered by the emergence of irAEs, which can affect nearly every organ system. Gastrointestinal toxicities are among the most commonly encountered complications in clinical practice.[34] By contrast, cardiovascular toxicities are less frequent but are associated with significant morbidity and mortality.[36,37] Careful recognition, timely diagnosis, and appropriate management are therefore essential to maintain the safety of immunotherapy as its use continues to expand.

ICI-Associated Cardiovascular Toxicity

ICIs are associated with a broad spectrum of irAEs, including the cardiovascular system. We review the epidemiology, risk

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factors, diagnostic approaches, and management strategies for ICI-associated cardiovascular toxicities with an emphasis on myocarditis—a rare but potentially fatal complication. Recent guidelines and clinical data emphasize the need for multidisciplinary care, early intervention, and ongoing research to manage this potentially fatal complication.

Epidemiology

Cardiovascular toxicities, while comprising only 1.14%-5% of all irAEs, stand out as particularly insidious due to their potential for rapid progression and high mortality.[60] ICI-associated cardiovascular toxicities encompass a heterogeneous array of conditions, including myocarditis, acute coronary syndrome, vasculitis, atrioventricular (AV) block, supraventricular and ventricular arrhythmias, sudden death, Takotsubo syndrome, noninflammatory left ventricular dysfunction, pericarditis, pericardial effusion, dyslipidemia, and ischemic stroke.[36,37]

The prevalence of arrhythmias, such as atrial fibrillation and conduction disturbances, is 0.7%-4%, pericardial disease 0.3%-1.4%, and acute coronary syndromes 0.5%-2%.[37,61-64] Real-world data suggest the prevalence of ICI induced cardiotoxicities may be underestimated, with some studies indicating cumulative rates as high as 12.5% at 12 months after treatment initiation.[32,62] Vasculitis and thromboembolism have also been reported in patients treated with ICIs but estimates of risk are not well defined.[65]

Myocarditis

Among cardiac ICI irAEs, myocarditis emerges as the most severe and often fatal manifestation, with an incidence ranging from 0.04% to 1.14%[38,66] among patients receiving ICI treatment, with higher rates observed with combination therapy (approximately 1%-2%) compared with single agent (approximately 0.75%),[65] and mortality rates of 38%-50%.[67-69] Determining the true incidence remains challenging due to diagnostic complexities and variable detection across studies. Meta-analyses of clinical trials report all-grade myocarditis in approximately 0.57% of patients receiving ICIs, with grade 3 to 4 myocarditis occurring in 0.35%.[67] Hospital registry data report similar rates, with an incidence of approximately 0.36% among patients treated with ICIs.[69]

Combination therapies, such as anti–CTLA-4 with PD-1/PD-L1 inhibitors or PD-1 with anti–lymphocyte activation gene 3, confer a 2- to 4.5-fold increased risk compared with monotherapy,[68,70-72] although recent meta-analyses show no difference in high-grade events. Additional risk factors include preexisting cardiovascular disease, older age (age 75 years and older), female sex, history of myasthenia gravis, and autoimmune diseases and specific malignancies such as lung cancer and melanoma.[68] Myocarditis is disproportionately common in patients with melanoma,[69] and preexisting conditions such as hypertension, prior myocardial infarction, or heart failure further increase susceptibility.[68,69] Notably, overlap syndromes where myocarditis is seen with myositis and myasthenia gravis (the so-called triple-M phenomenon) are frequent, complicating management.[37] Individuals with thymic epithelial tumors are at the highest risk of developing ICI myocarditis (10- to 30-fold higher than other cancers) and adverse outcomes.[65]

Clinical features. Myocarditis usually manifests within the first 12 weeks of ICI therapy, although delayed cases beyond 20 weeks are recognized,[36,62] the median onset is around 30 days based on systematic reviews and large case series.[37,67] Myocarditis severity can range from smoldering to fulminant forms. Most patients present with mild symptoms such as chest pain, fatigue, dyspnea, and palpitations, often with preserved left ventricular ejection fraction (LVEF). Identifying overlapping syndromes such as hepatitis, myositis, or myasthenia gravis syndromes is critical. In the setting of ICI therapy, myocarditis should be considered in patients with muscle weakness, myalgia, ptosis, diplopia, or blurred vision. Conduction abnormalities such as AV block or arrythmias (atrial fibrillation/flutter) or ventricular tachycardia may occur.[65]

Diagnosis. The diagnosis of ICI myocarditis requires clinical suspicion and careful clinical assessment with multimodality testing, including cardiac biomarkers, electrocardiography, echocardiography, cardiac magnetic resonance imaging (MRI), cardiac computed tomography, and, when the diagnosis is unclear, myocardial biopsy. Evaluation must rule out alternative etiologies such as acute coronary syndrome.

Key diagnostic tools include:

- Cardiac biomarkers: High-sensitivity troponin T/I (hs-TnT/I) elevation is sensitive for diagnosis and prognosis[65,73]
- ECG: Detects AV blocks, arrhythmias, or conduction delays.[65]
- Echocardiography: Assesses global longitudinal strain (global longotudinal strain <16% predicts major adverse cardiovascular events even with preserved left ventricular ejection fraction).[65,73] LVEF may be normal in myocarditis
- Cardiac MRI: Identifies delayed enhancement, T1/T2 mapping for edema/fibrosis.[65,73] Higher yield if performed within 4 days of hospital admission.

It is crucial to recognize that no single clinical or imaging finding is specific to ICI myocarditis; diagnosis requires the correct clinical scenario. An endomyocardial biopsy can be helpful if the diagnosis remains unclear. A proposed diagnostic framework (Fig 2) classifies myocarditis as definite (biopsy-proven), probable (major criterion such as complete metabolic remission meeting modified Lake Louise—imaging protocol for evaluating cardiac tissues for suspected myocarditis—criteria plus one minor), or possible (major criterion alone or three minors).[74] Minor criteria include

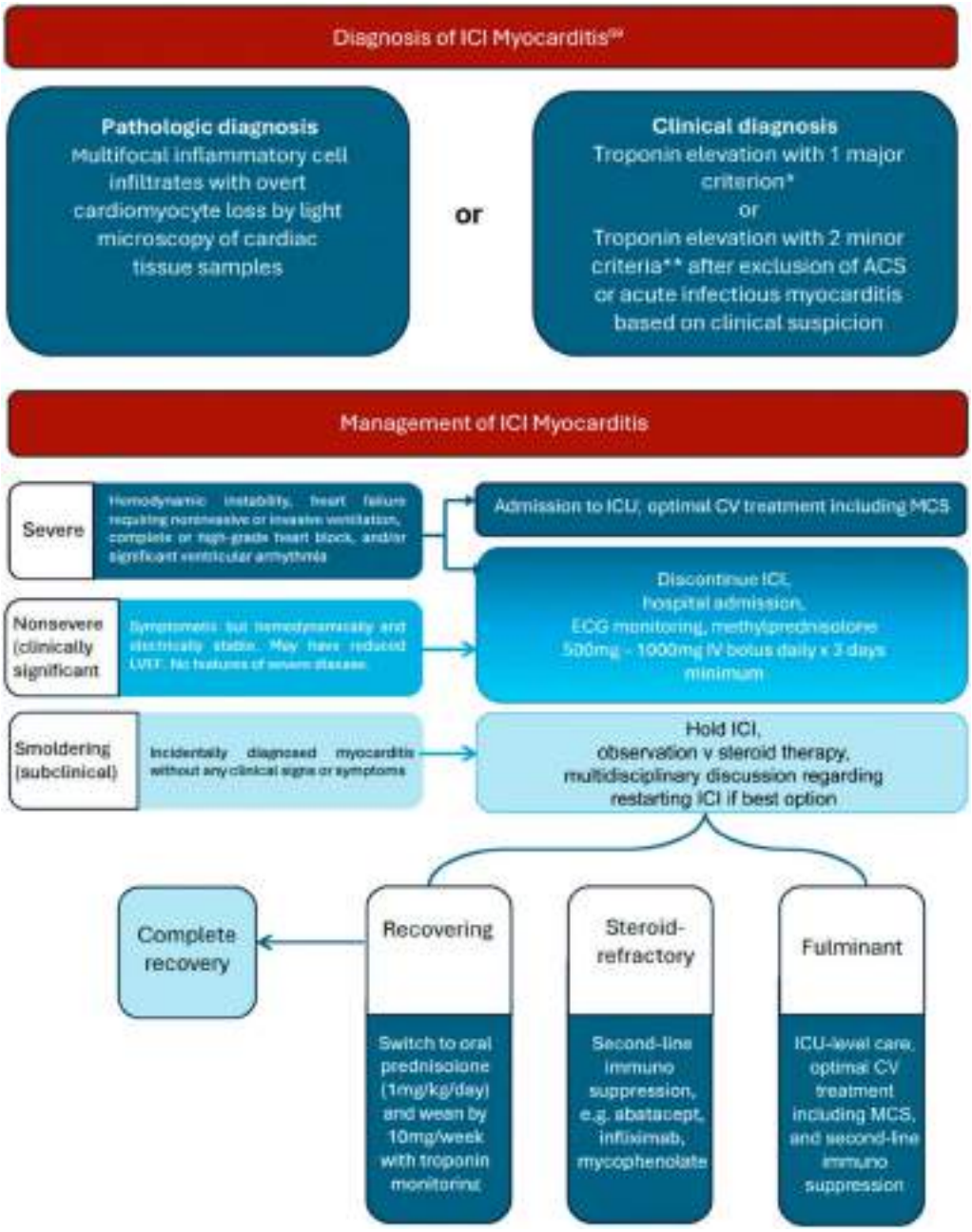

FIG 2. Diagnosis and management of ICI myocarditis (adapted from consensus statements). *Major criterion: cardiac magnetic resonance (CMR) diagnostic for acute myocarditis (modified Lake Louise criteria), **Minor criteria: clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock); Ventricular arrhythmia and/or new conduction system disease; Decline in cardiac (systolic) function, with or without regional WMA in a non-Takotsubo pattern; Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis; Suggestive CMR (meeting some but not all of the modified Lake Louise criteria. ACS, acute coronary syndrome; CV, cardiovascular; ICI, immune checkpoint inhibitor; ICU, intensive care unit; IV, intravenous; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support.

clinical syndromes, arrhythmias, functional decline, or concurrent irAEs.[74]

Screening and surveillance. Identifying patients at high risk for ICI-associated cardiotoxicity, particularly myocarditis, is crucial, yet guidelines vary in their recommendations for baseline and surveillance cardiac evaluations. The 2021 ASCO guideline found insufficient evidence to endorse routine baseline or serial ECGs or troponin measurements.[61] By contrast, the 2022 European Society of Cardiology (ESC) guideline, developed in collaboration with the International Cardio-Oncology Society (IC-OS), advocate for baseline echocardiography and biomarkers (troponin and

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N-terminal pro-B-type natriuretic peptide) in all patients initiating ICIs (Class I, Level of Evidence C), with weaker support for ongoing surveillance.[36]

The 2025 American College of Cardiology consensus, however, cautions against routine baseline testing, citing limited evidence from a single study on the utility of troponin measurement.[75] The cost-effectiveness of routine cardiac surveillance during ICI treatment remains undefined, although early detection in those at highest risk may be considered.[74]

Management. Prompt recognition and multidisciplinary intervention are critical, as untreated myocarditis carries a mortality rate of 30%-50%.[60,61,69] All major guidelines, including ASCO (2021), ESC (2025), and IC-OS (2026), recommend immediate ICI discontinuation for any grade of cardiovascular toxicity, particularly myocarditis.[64,65]

For grades ≥2 (symptomatic with abnormal biomarkers or conduction issues), initiate high-dose corticosteroids (1-2 mg/kg/d prednisone equivalent, intravenously or oral) within 24 hours for 3-5 days.[61,62] Admission for prompt cardiology evaluation, heart failure management, and potential cardiac care unit transfer are advised if hemodynamic instability or significant conduction abnormalities arise.[61,64] Monitoring involves serial troponin, ECG, and echocardiography; a >50% troponin reduction within 72 hours signals an appropriate response, permitting oral tapering over weeks.[69,73]

For refractory cases (persistent troponin elevations after 3 days), escalating to second-line agents such as mycophenolate mofetil, antithymocyte globulin, intravenous immunoglobulin (IVIG), Janus Kinas inhibitors (ruxolitinib/tofacitinib), interleukin-6 inhibitors (tocilizumab), alemtuzumab, or abatacept is often required.[37,61,75] Combinations such as ruxolitinib-abatacept have reduced mortality to approximately 3% in patients who are severely affected including those needing mechanical ventilation.[69,76] In fulminant cases with hemodynamic compromise, care in the intensive care unit, mechanical support (microaxial pumps/extracorporeal membrane oxygenation), IVIG, and plasmapheresis can be lifesaving.[62,64]

Supportive therapies include guideline-directed medical therapy for heart failure (beta-blockers, renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter 2 [SGLT2] inhibitors, mineralocorticoid antagonists), pacemakers for blocks (up to 25% of cases), and antiarrhythmics.[61,64]

Overlap syndromes require tailored approaches, such as plasmapheresis/rituximab for cases involving the triple-M phenomenon.[77] Rechallenge is rarely advised but feasible if benefits clearly outweigh risks and an intensified monitoring strategy is pursued.[60,66]

In 2026, the landscape favors steroid-sparing regimens to avert long-term, adverse corticosteroid sequelae. The ATRIUM trial (NIH-NCT05335928) is evaluating abatacept (in addition to steroids) versus placebo for reduction of major adverse cardiac events in individuals hospitalized with ICI-induced mycoarditis,[73] while prospective registries aim to enhance risk stratification via novel biomarkers.[73,77]

ICI-Associated Gastrointestinal Toxicity

These GI toxicities can involve the upper GI tract, leading to esophagitis, gastritis, or duodenitis; lower GI tract, causing diarrhea/colitis; and the hepatobiliary system, leading to elevated levels of ALT, AST, and alkaline phosphatase (ALP). They can also result in pancreatic toxicities, including elevated lipase levels and acute pancreatitis. Of these, ICI colitis and hepatotoxicity are the most common and will be described here. Early detection, with severity graded using the Common Terminology Criteria for Adverse Events system, and prompt management, with multidisciplinary collaboration with gastroenterologists, are essential to prevent serious complications while maintaining the therapeutic benefits of immunotherapy.

Diarrhea/Colitis

Approximately 8%-27% of patients receiving ICI develop diarrhea/colitis, with higher rates reported in those treated with combination therapy.[33,61] In patients receiving anti–CTLA-4 or combination therapy, colitis was the most common fatal adverse event in the WHO international database.[33]

Definition

ICI-related diarrhea is typically defined as an increase in stool frequency above a patient's baseline, whereas colitis, often confirmed on endoscopy or imaging, implies inflammation of the colon with diarrhea often accompanied by inflammatory symptoms such as abdominal pain, hematochezia, mucus in stools, fever, or other systemic symptoms. ICI-induced colitis typically presents around 6-8 weeks after treatment initiation, although onset can vary, with delayed-onset cases >2 years after the discontinuation of immunotherapy reported in the literature.[78]

Evaluation

Before attributing symptoms to ICIs, infectious etiologies must be excluded through comprehensive testing. The evaluation should include stool cultures, Clostridioides difficile testing, nucleic acid amplification tests for GI pathogens, and abdominal imaging. Given the concomitant administration of immunotherapy with chemotherapy, it is often challenging to ascertain the causative agent to help guide management.

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If the severity of symptoms is grade 2 or higher, defined as more than four bowel movements daily above baseline, or in select patients with grade 1 diarrhea with high suspicion, obtaining stool inflammatory markers such as fecal lactoferrin and calprotectin can help risk-stratify patients for endoscopic evaluation.[34] Endoscopic confirmation with biopsy should be strongly considered, especially when immunotherapy is given in combination with cytotoxic chemotherapy known to cause diarrhea, before initiating high-dose systemic glucocorticoids, as it helps confirm the diagnosis and exclude alternative causes.[61,78]

Management

Management is grade-dependent. For grade 1 diarrhea, ICIs can be continued in most cases with close monitoring and symptomatic management with fluids and antidiarrheals.[35,61] Grade 2 colitis warrants holding immunotherapy until symptoms improve to baseline or grade 1 as well as the initiation of corticosteroids (prednisone 1 mg/kg/d or equivalent).[35] Steroids are continued until symptoms improve to grade 1 or to baseline and subsequently tapered over 4-6 weeks. If anti–CTLA-4 agents were involved, permanent discontinuation should be considered. However, anti–PD-1 and anti–PD-L1 agents may be cautiously restarted after recovery. Grade 3 or higher colitis requires hospitalization, permanent discontinuation of ICIs, and administration of high-dose steroids intravenously.[34,35,61] If patients fail to respond within 2-5 days of steroids, biologic therapy should be initiated with either infliximab or vedolizumab. Patients who fail to respond to initial biologic therapy can switch to the alternative class or use other agents such as tofacitinib or ustekinumab.[34,35,61] Although there is some retrospective evidence that budesonide may help in the management of microscopic colitis, prophylactic use studied in a randomized controlled trial showed no therapeutic benefit.[79,80]

Hepatitis

ICI hepatotoxicity occurs at a lower rate than luminal GI toxicities with an incidence of up to 9% and 2% in patients receiving anti–CTLA-4 and anti–PD-1/PD-L1, respectively.[81] The rate is higher among those receiving combination therapy, approaching 29%. Similar to ICI colitis, hepatotoxicity can occur early (5-6 weeks from the start of treatment) or can be delayed in onset occurring months after discontinuation of therapy.[81] ICI-induced hepatitis is often asymptomatic and detected through routine laboratory monitoring, although patients can present with jaundice, fevers, or malaise. While on therapy, all patients must receive baseline evaluation of liver chemistries including AST, ALT, ALP, total bilirubin, with repeat testing before each cycle of therapy.[34] Hepatotoxicity is graded by the degree of transaminase and bilirubin elevation.

KEY TAKEAWAYS

- Immune checkpoint inhibitors require dose, duration, and interval optimization to improve sustainability.
- Low-dose and fixed-duration strategies are biologically plausible and clinically proven in randomized trials across tumor types and settings of treatment.
- Gastrointestinal toxicities are common and require structured grading and early intervention.
- Myocarditis, although rare, carries high mortality and mandates urgent multidisciplinary care.
- Sustainable immunotherapy demands integration of pharmacologic, economic, and health-system frameworks.

Evaluation

Initial evaluation requires the exclusion of alternative causes such as viral hepatitis, disease progression, biliary obstruction, thromboembolic disease, or damage from hepatotoxic medications. Extensive evaluation for alternative etiologies is recommended and includes serologic testing for viruses (hepatitis A/B/C/E virus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus), other acute hepatitis laboratory tests (iron profile, ferritin level, antinuclear antibodies, smooth muscle antibody, liver/kidney microsome type 1 antibody, immunoglobulin levels, and tissue transglutaminase antibody), and abdominal imaging (ultrasound and computed tomography scan).

Management

Management is grade-dependent. Grade 1 hepatitis allows for continuation of therapy with intensified monitoring. Liver function tests can be repeated 1-2 times per week. For grade 2 hepatitis or greater, ICIs must be held until liver chemistries improve to grade 1 or baseline; if there is no improvement after 1 week of observation, steroids can be started at a dose of 0.5-1 mg/kg/d of prednisone. In grade 3 or higher elevations, ICIs should be permanently discontinued, and higher dose of steroids (1-2 mg/kg/d of prednisone) should be started and should be tapered over 4-6 weeks after improvement. In these patients, and especially those who are refractory to steroids, liver biopsy should be obtained to confirm diagnosis.[82] If patients do not respond to steroids within 48-72 hours (drop in transaminases of at least 50%), mycophenolate mofetil is the preferred second-line agent with azathioprine (after thiopurine methyltransferase

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testing) or tacrolimus as alternative options.[34,35,61,82] Of note, if patients present with a cholestatic pattern, prescribing ursodeoxycholic acid along with steroids, especially in grade 2 or higher patients, has clinical benefit.[35,83]

CONCLUSION

ICIs have reshaped the therapeutic landscape of oncology, offering durable responses across tumor types and treatment settings. However, their expanding use has introduced new challenges related to affordability, optimal dosing, treatment duration, and immune-related toxicity. Experience from LMICs demonstrates that pragmatic dose optimization, interval extension, biomarker-guided selection, and structured toxicity surveillance can preserve clinical efficacy while improving access and sustainability. These strategies are rational, biologically grounded adaptations that will allow patients to benefit across diverse health care settings globally. In resource-constrained settings, these strategies may improve access and outcomes; however, in the absence of direct comparisons with phase III randomized trials, they should be considered alternatives rather than equivalent standards.

With the widespread use of immunotherapy drugs, oncologists must be prepared to manage the increasingly broad spectrum of immune-related toxicities. Organ-specific complications such as myocarditis and colitis highlight the importance of early recognition, timely intervention, and coordinated multidisciplinary care. Rare but high-fatality events demand vigilance, structured monitoring pathways, and prompt escalation of immunosuppression.

As immunotherapy transitions from innovation to the global standard of care, the next phase of progress includes refining how existing agents can be delivered. Sustainable oncology requires harmonizing efficacy, safety, and affordability. By integrating global experience with clinical evidence, we can ensure that immunotherapy remains both transformative and responsibly deployed across health systems worldwide.

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