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Review

Antibody-drug conjugates in precision oncology

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SUMMARY

Antibody-drug conjugates (ADCs) represent a growing therapeutic class in oncology marked by several transformative clinical successes. However, these exceptional outcomes remain restricted to a limited number of tumor types, and ADC development has been marked by frequent clinical setbacks, underscoring persistent challenges in optimal patient selection, biomarker assay standardization, chemical design, and the limited predictive value of existing preclinical models. Despite broader advances in precision oncology, ADC development has largely occurred without validated biomarkers. Emerging evidence indicates that ADC activity extends beyond target antigen expression alone, encompassing tumor-intrinsic features and tumor microenvironment-dependent processes. This challenges the view of ADCs as strictly targeted agents and supports their conceptualization as *tumor-ecosystem-targeting therapies* governed by multidimensional biological determinants. In this review, we link ADC successes and setbacks to mechanisms of efficacy, resistance, and toxicity, and discuss how biomarkers, ADC combinations, next-generation platforms, and curative-intent strategies should shape precision oncology frameworks.

INTRODUCTION

Antibody-drug conjugates (ADCs) are innovative and complex therapeutic entities that have transformed cancer treatment.[1,2] Initial clinical benefit was achieved in hematological malignancies, with gemtuzumab ozogamicin being the first ADC to receive Food and Drug Administration (FDA) accelerated approval in 2000 for adults with CD33-positive acute myeloid leukemia.[3] A decade later, the approval of trastuzumab emtansine (T-DM1) by the FDA for patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (BC) marked a milestone as the first ADC approved for solid tumors.[4] Building upon lessons learned from earlier generations, contemporary ADCs have undergone substantial optimization. Currently, 14 ADCs have been approved by the FDA, importantly, most within the past 5 years.[5] Additionally, five more ADCs have gained regulatory approval in China.[6–8] Structurally, ADCs are composed of three components: (1) the antibody, typically a fully human or humanized immunoglobulin G (IgG) monoclonal antibody; (2) the linker, classified as cleavable or non-cleavable; and (3) the payload, which for all clinically approved ADCs is a cytotoxic agent. Critical design parameters such as the drug-to-antibody ratio (DAR), defining the number of payload molecules attached per antibody, linker stability, conjugation chemistry, and pharmacokinetics (PK) are pivotal for balancing efficacy and safety.[9,10] The putative mechanism of action (MoA) described in the literature can be summarized in four major steps: (1) target recognition and ADC-target complex internalization, (2) intracellular trafficking of the internalized ADC-target complex to the lysosome, (3) linker cleavage, and (4) release of the payload resulting in apoptotic cell death. If the payload is bystander-active, meaning it can diffuse across cell membranes after release, neighboring antigen-negative cells may also be eliminated.[11,12] ADCs also modulate immune responses through both direct and indirect mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and immunogenic cell death (ICD).[13–15] ADCs now represent meaningful treatment options across several malignancies, including a tumor-agnostic indication for trastuzumab deruxtecan (T-DXd) in patients with HER2-expressing (immunohistochemistry [IHC] 3+) solid tumors.[16] Despite these advances, ADCs have produced durable, practice-changing benefits in only a limited subset of clinical contexts, and most patients eventually develop acquired resistance. This highlights the need for validated biomarkers to refine patient selection and to inform the development of next-generation ADCs and rational combination strategies, with the goal of bringing durable, transformative benefit to a broader population.[17,18] Moreover, the safety profile of ADCs takes its toll on patients' daily life, and the management of some toxicities remains a key clinical challenge, often requiring treatment discontinuation or dose reduction. Therefore, there is also a need for relevant biomarkers to identify patients at increased risk of toxicity, complementing

efficacy biomarkers in the shared goal of improving therapeutic precision.[19,20] Over the past decade, technological advances enabling increasingly detailed characterization of tumor biology have accelerated the transition toward precision medicine in oncology. These developments have led to remarkable improvements in outcomes for many cancers, thanks to the growing use of therapies tailored to patients whose individual and disease-specific characteristics predict the greatest likelihood of benefit.[21,22] While ADCs, by design and MoA, have the potential to function as targeted therapies, most ADC development has taken place in the absence of validated biomarkers capable of predicting efficacy or toxicity. This gap significantly limits our ability to fully realize the transformative potential of these compounds. In this review, we outline the critical gaps in ADC development that must be addressed to enable their integration into precision medicine strategies to optimize efficacy, minimize toxicity, and ultimately realize their transformative impact.

TRANSFORMATIVE SUCCESS STORIES

Like prior transformative cancer therapies, ADCs should be considered transformative for their ability to ensure: (1) a substantial and durable clinical benefit, reflected not only in survival endpoints but also in the depth and persistence of response; (2) preservation or improvement of quality of life, particularly in comparison with existing therapeutic options; (3) a manageable safety profile, including an acceptable balance between acute toxicities and the risk of long-term or cumulative adverse events; and (4) activity across disease settings, lines of therapy and populations with unmet medical needs. When examining the historical trajectory of ADC development in solid tumors, only a limited number of ADCs fulfill more than one of these criteria, and even fewer meet them comprehensively.

A notable example is T-DXd in HER2-positive BC. T-DXd first received accelerated FDA approval for heavily pretreated HER2-positive metastatic BC based on DESTINY-Breast01,[23] with subsequent phase III trials confirming its superiority over T-DM1 and standard chemotherapy + trastuzumab, thereby supporting its move into the second-line setting.[24,25] More recently, interim results from DESTINY-Breast09 led to its FDA approval in combination with pertuzumab as frontline therapy, further shifting T-DXd earlier in the treatment paradigm.[26] Beyond the magnitude of survival benefit, several additional dimensions support the transformative impact of T-DXd in HER2-positive BC. First, its safety profile is overall manageable, predominantly characterized by fatigue and gastrointestinal adverse events, with interstitial lung disease (ILD) occurring in a minority of patients and most frequently at grade 1–2, although requiring careful monitoring. Second, T-DXd achieves unprecedented depth and durability of response, with complete response rates more than doubled compared with standard-of-care regimens across randomized studies, and a median duration of response exceeding 3 years in trials such as DESTINY-Breast03 and -09.[24,26] These findings raise the provocative question of whether a subset of patients with HER2-positive metastatic BC may, in fact, be cured. Importantly, the transformative potential of T-DXd also extends beyond a single disease setting. The consistent activity observed across multiple HER2-expressing tumor types, with objective response rates exceeding 50% and durable responses approaching one year, supports its clinical relevance across a broad range of histologies.[27] Another transformative story, particularly because of its impact on the survival outcomes of a disease with poor prognosis and prior limited therapeutic options is the combination of enfortumab vedotin (EV) with pembrolizumab in the treatment of metastatic urothelial carcinoma. This regimen significantly improved progression-free survival (PFS) and overall survival (OS) as compared to platinum-based chemotherapy, with an acceptable safety profile, mostly characterized by peripheral neuropathy and cutaneous toxicity,[28] so leading to regulatory approvals from both the FDA and EMA.[29,30] Although EV monotherapy showed limited benefit in other tumor types,[31,32] its transformative impact in combination with pembrolizumab is also corroborated by substantial improvements in event-free survival (EFS) and OS in the perioperative setting in patients with muscle-invasive bladder cancer, regardless of cisplatin eligibility.[33,34]

T-DXd stories share a key biological foundation: HER2-positive BC is an oncogene-addicted disease.[35] This biological dependency may explain, at least in part, the exceptional efficacy of HER2-directed ADCs in this setting. In contrast, in HER2-low metastatic BC, T-DXd does not achieve the same level of clinical benefit, highlighting the importance of target dependency for ADC success.[17] Interestingly, despite the movement of T-DXd to earlier lines of therapy in the metastatic setting, the magnitude of benefit does not seem to increase. This observation raises critical biological and pharmacological questions. One possible explanation is the saturation of ADC activity once optimal target engagement is achieved.[36] Tumor biology may also profoundly influence ADC efficacy across tumor types. For instance, while T-DXd demonstrated clinical activity in HER2-positive metastatic gastric cancer, the outcomes are less impressive compared with those in BC.[37] This discrepancy may be attributed to the greater intratumoral heterogeneity of HER2 expression in gastric cancer, an inherent biological feature that limits homogeneous ADC binding and effective payload delivery.[38]

Turning to EV plus pembrolizumab, this combination leverages the immunomodulatory potential of ADCs, providing a strong rationale for combining with immuno-oncology (IO) agents. In preclinical models, ADCs have been shown to activate dendritic cells (DCs), macrophages, and natural killer (NK) cells, thereby promoting immune priming and enhancing anti-tumor responses.[39–41] In the DAISY trial, T-DXd did not decrease immune cell density, including $CD8^+$ T lymphocytes, in contrast to the lymphodepleting effects typically associated with cytotoxic chemotherapy.[42] Similarly, in the ICARUS-Breast01, patients responding to patritumab deruxtecan, an anti-human epidermal growth factor receptor 3 (HER3) ADC, exhibited upregulation of interferon signaling pathways, further reinforcing the link between ADC activity and immune activation.[43] Beyond these two paradigmatic examples, other ADCs have obtained regulatory approval in recent years by demonstrating clinically meaningful benefit in ''hard-to-treat'' malignancies that are often exhibiting primary resistance to cytotoxic chemotherapy. These include tisotumab vedotin, a tissue factor (TF)-targeting ADC conjugated with monomethyl auristatin E (MMAE) in patients with metastatic cervical cancer[44] and mirvetuximab

soravtansine (MIRV) in patients with platinum-resistant, folate receptor-α (FRα)-positive ovarian cancer.[45] However these "transformative stories," particularly those observed with T-DXd and EV plus pembrolizumab, raise critical questions as to why comparable benefits have not been achieved across other tumor types and which biological, pharmacological, and clinical factors underlie the exceptional efficacy observed in these settings and how these insights may pave the way for the development of novel ADC constructs (e.g., dual-payload or bispecific ADCs) and rational combination strategies such as with immune bispecific antibodies (e.g., PD-(L)1/TIGIT).

LESSONS LEARNED FROM SETBACKS IN ADC DEVELOPMENT

The clinical development of ADCs has been marked by frequent setbacks over the past decade. These failures have raised fundamental questions regarding optimal patient selection, the biological determinants of ADC activity, and the extent to which preclinical models faithfully predict clinical efficacy, toxicity, and resistance. Lung cancer, the most commonly diagnosed malignancy worldwide and the leading cause of cancer-related mortality, has been one of the major focuses of ADC development.[46] Despite encouraging signals in early-phase trials, phase III studies evaluating ADCs such as sacituzumab govitecan (SG), tusamitamab ravtansine or datopotamab deruxtecan (Dato-DXd) in unselected, pre-treated patients with non-small cell lung cancer (NSCLC) failed to meet their primary endpoints[47,48] or showed only a modest benefit over docetaxel.[49] Notably, these studies consistently failed to demonstrate a PFS benefit with trophoblast cell-surface antigen 2 (TROP2)-directed ADCs in squamous cell carcinoma.[48,49] From a histological perspective, although no clinical evidence supports differential sensitivity to topoisomerase I (TOP1) inhibitors between squamous and non-squamous NSCLC,[50] differences in lysosomal protease expression, and drug efflux transporter activity have been suggested as potential factors contributing to the reduced activity of Dato-DXd in squamous tumors[51,52]; however, these hypotheses remain unconfirmed and require further validation. Pooled and randomized trial data also suggest that *EGFR*-mutant NSCLC is particularly sensitive to TROP2-directed ADCs, with consistent efficacy signals observed across agents in patients progressing after EGFR-tyrosine kinase inhibitors (TKIs). This supports the view that *EGFR*-mutant disease may define a clinically relevant subgroup for TROP2-ADC benefit, rather than the effect being limited to a single compound.[49,53,54] A potential mechanism for better outcomes with TROP2-directed ADCs in *EGFR*-mutant NSCLC can be related to the target internalization.[55] While membranous TROP2 expression has not reliably correlated with clinical benefit from TROP2-directed ADCs, antigen internalization appears to be a critical determinant of efficacy. Preclinical studies demonstrating marked variability in TROP2 internalization across cell lines led to the development of a computational pathology-based Quantitative Continuous Scoring (QCS) system, which measures the TROP2 normalized membrane ratio (NMR), reflecting the proportion of membrane-localized versus total cellular TROP2.[56] In TROPION-Lung01, patients with TROP2 QCS-NMR-positive tumors exhibited higher response rates and longer PFS with Dato-DXd than NMR-negative patients.[57] These findings are concordant with preclinical and clinical data showing greater internalization and activity of sac-TMT and Dato-DXd in the presence of *EGFR*-mutations.[55,58] Although the clinical relevance of TROP2 internalization remains to be assessed in lung cancer and in other tumor types, these data suggest that target internalization kinetics could be essential drivers of ADC efficacy, at least for TROP2-directed ADCs, reinforcing the need for clinically validated, functionally relevant biomarkers rather than reliance on conventional IHC alone.

Regarding target assessment by IHC, the association between target expression and efficacy appears strongest for TOP1–based HER2-directed ADCs, with higher HER2 levels, especially IHC 3+, consistently linked to greater benefit across tumor types, suggesting a potential class effect.[59] By contrast, although disitamab vedotin has shown activity correlated with HER2 expression in some settings, similar responses in HER2-positive and HER2-low disease suggest it may be less strictly dependent on target density, possibly due to payload-related differences.[60,61] All these examples highlight the critical importance of biomarker assay standardization and threshold definition and of tumor histology across different types of ADCs. A paradigmatic example of the consequences of suboptimal biomarker assessments comes from MIRV in ovarian cancer: The negative FORWARD I phase III trial was largely attributed to suboptimal, overly permissive FRα scoring,[62] whereas retrospective rescoring with a stricter method identified FRα-high expression as predictive of benefit and enabled subsequent successful biomarker-selected trials,[45] which ultimately led to regulatory approval. Similarly, with telisotuzumab vedotin (TV), an ADC targeting mesenchymal-epithelial transition factor (MET), efficacy was observed across c-MET expression levels in NSCLC but was more pronounced in patients with c-MET overexpression,[63] leading to FDA accelerated approval in this subgroup. These experiences further highlight the necessity of precise and reproducible thresholds for each biomarker to prevent the dilution of treatment effects and delays in drug development and approval.

With regard to the role of tumor histology and stromal architecture in ADC activity, pancreatic ductal adenocarcinoma (PDAC) provides a particularly striking example. Despite robust preclinical activity across multiple targets, including glypican-1,[64] MET,[65] uPAR,[66] mucin 1 C-terminal subunit (MUC1-C),[67] TROP2,[68] ephrin type-A receptor 2 (EphA2),[69] EGFR,[70] and others,[71–73] clinical translation has been hampered by intrinsic features of PDAC, such as low antigen density, inefficient ADC internalization, and dense desmoplastic stroma that limits intratumoral ADC penetration;-characteristics that are inadequately recapitulated by current preclinical models. Also, T-DXd has demonstrated among the lowest levels of activity in HER2-expressing PDAC when compared with other solid tumors.[16] Nevertheless, early-phase clinical trials have begun to report preliminary antitumor activity in patients with heavily pre-treated PDAC, particularly with ADC directed against Claudin 18 isoform 2 (CLDN18.2),[74] TF,[75] Carcinoembryonic antigen-related cell adhesion molecules 5/6 (CEACAM5/6)[76] and cMET.[77] Ongoing efforts are therefore focused on refining antigen selection, including stromal-modulating approaches, to overcome microenvironment-driven resistance.[68,78,79]

Finally, several ADC trials have failed to demonstrate superiority over standard chemotherapy, reflecting not only the lack of robust and standardized biomarkers but also limitations in study design, patient selection, and toxicity management. For instance, in the phase 3 TROPiCS-04 trial,[80] SG failed to improve PFS and OS in urothelial cancer, and early toxicity-related complications likely attenuated the treatment effect, as evidenced by higher rates of grade ≥3 adverse events and suboptimal use of prophylactic granulocyte colony-stimulating factor (G-CSF) in a high-risk population. More recently, the phase 3 ASCENT-07 trial in HR+/HER2− advanced BC failed to demonstrate superiority of SG over chemotherapy in the first-line setting,[81] against the initial assumption that earlier use of ADCs necessarily translates into greater clinical benefit. As is evident from these lessons, there is also a challenge in accurately modeling clinical responses and toxicities associated with ADCs. Indeed, preclinical studies with ADCs often show complete responses after repeated dosing, while rarely recapitulating acquired resistance or clinically relevant toxicities.

Although translational gaps between preclinical models and clinical outcomes are common across different modalities, ADCs pose unique challenges that should inform the design of future models and studies. First, the antibodies utilized often do not recognize murine counterpart antigens,[82–84] potentially exaggerating the antitumor effects and lack of on-target off-tumor disposition and toxicities. Second, the mechanisms for cleavage of the payload may involve tissue-specific enzymatic activities that are differentially represented in model systems.[85,86] Third, the dose-response relationships, including PK-PD, are often not clearly similar between human and mouse.[86–88] Fourth, preclinical models typically exhibit greater tolerance to cytotoxic drugs, allowing higher administered doses than in clinical settings. Meanwhile, *in vitro* types of assays do not recapitulate the potential for prolonged drug exposure or the unique effects of these drugs in the tumor microenvironment (TME). While there is no perfect model to date, studies that allow attention to these aspects will be invaluable going forward. These include humanizing murine models such that antibodies will recognize murine epitopes, use of immunocompetent models, development and use of bona-fide resistance models, and experimental systems designed to recapitulate human systemic payload exposure. Furthermore, tumor organoid co-cultures and organ-on-chip, which can model stromal or immune context, may help study ADC activity in a more physiological environment. Finally, refined assays are needed to quantify the disposition of distinct ADC components over time, including after repeated dosing, to better inform clinical translation. Such studies will be particularly important as ADC combinations and novel payloads advance in development.

DECODING ADC MECHANISMS OF RESISTANCE

Investigations into mechanisms of resistance (MoR) to targeted therapies have deepened our understanding of both drug MoA and the oncogenic dependencies that drive specific cancer types.[89] For instance, resistance to T-DXd in *EGFR*-mutant NSCLC has been found to be due to the mutational reactivation of EGFR kinase activity as well as parallel activation of MET kinase.[90] This has reinforced the crucial role of receptor tyrosine kinase (RTK) activity in *EGFR*-mutant NSCLC and supported the development of next-generation EGFR inhibitors and EGFR-MET combination strategies.[91] Efforts to conduct analogous studies for conventional chemotherapy have been limited by the pleiotropic effects of these agents and by the difficulty of developing robust, non-genetic biomarkers of response and resistance. Given the design of current-generation ADCs, whether resistance studies will yield similarly actionable biological insights remains uncertain; however, emerging findings are beginning to provide important clues.

Target expression

As with numerous monoclonal antibodies and even cellular therapies, reduced or complete loss of target expression has been linked to resistance to ADCs. For HER2-directed ADCs, including T-DXd, complete loss of HER2 expression is a clinically meaningful biomarker, as none of these drugs are approved for HER2-negative tumors.[92–94] Preclinical studies further support that substantial reductions in HER2 expression can impair ADC efficacy.[93,95,96] In addition to reduced antigen expression, mutations affecting the antibody-binding epitope have also been observed, albeit uncommonly, and shown to mediate resistance.[93,97] These data together position complete loss of target as a bona fide mechanism of resistance. However, a major challenge is defining the quantitative threshold of HER2 loss required to compromise ADC activity, particularly for T-DXd. Quantitatively, there is no defined level of surface HER2 level that appears to be necessary to have a substantial antitumor benefit. However, this does not mean that the level of HER2 is irrelevant to both the depth and duration of response. In BC, while almost any level of HER2 expression can lead to T-DXd activity, the best activity is consistently observed in tumors with significantly high levels of HER2.[17,24,92] Such results are even more evident in other cancer types where T-DXd is only indicated for tumors with *ERBB2* amplifications.[37] A second challenge with ascertaining the role of target expression has been the semi- or non-quantitative nature of the biomarkers used, predominantly custom IHC assays. These assays have largely lacked rigor in reproducibly defining surface levels of the target molecules.[98–100] Moreover, it remains difficult to determine whether acquired reductions in target expression reflect isolated antigen loss or broader shifts in cell state, lineage identity, or clonal selection. For instance, losses of Nectin-4 may indeed contribute to resistance to EV or may merely accompany large-scale changes in lineage that may be confounding resistance.[101,102] Taken together, these data indicate that altered target expression or impaired antibody binding represent recurrent mechanisms by which some cancers evade efficient ADC internalization in the TME. However, defining the prevalence and clinical relevance of these mechanisms will require more robust diagnostic tools.

Altered cleavage

MoR attributed to linker cleavage have been observed only in preclinical models and are only hypothesized to contribute to clinical resistance. In particular, deregulation of lysosomal proteolytic activity was reported as a mechanism of T-DM1 resistance in cell line models.[103] Similarly, aberrant activity of V-ATPase in lysosomes has been shown *in vitro* to impair T-DM1 catabolism, resulting in the reduced formation of the

active T-DM1 metabolite.[104] However, it remains unclear whether these mechanisms are shared among other ADCs employing widely used cleavable linkers and whether they contribute to intrinsic or acquired resistance to ADCs in the clinical setting.

ADC internalization

For most clinically approved ADCs, payload release preferentially occurs in endosomal or lysosomal compartments, which have low pH and high expression of proteases that act on the payload-antibody linkers.[105] Accordingly, promoting efficient cancer cell internalization has been a central design objective for many antibodies used in ADCs. This dependence on internalization also creates a potential vulverability: Cellular adaptations that can block ADC uptake or trafficking have been conceived as additional potential modes of resistance. These range from tethering of the target antigen to the cell surface, enhanced recycling of intact antibody-ADC to the cell surface, or disruption of intracellular antibody trafficking.[106] For instance, overexpression of EGFR was found to suppress the internalization of HER2-TDXd in colorectal cancer due to heterodimer formation between EGFR and HER2.[107] A major challenge in establishing the clinical relevance of these mechanisms has been the lack of methods to map the *in vivo* disposition of ADCs or their individual components in patients, as well as the absence of tools capable of assessing their functional activity using conventional omics approaches, such as RNA or DNA sequencing. Readily accessible surrogate biomarkers obtained through serial, minimally invasive sampling are therefore critically needed to quantify these mechanisms and potential resistance pathways. For instance, trials such as NCT06222489 (Whole Body HER3 Quantification With Radiolabeled Patritumab Deruxtecan (HER3-DXd) positron emission tomography (PET) scan and a computed tomography (CT)) are leveraging immuno-PET imaging with radiolabeled ADCs to evaluate whole-body target expression and ADC biodistribution, providing non-invasive surrogate biomarkers of ADC pharmacology and efficacy.

Payload efficiency

Perhaps the most elusive mode of resistance is so-called payload resistance, which has broad parallels to widely recognized yet still poorly defined chemotherapy resistance in cancers. While the clinical phenomenon of chemotherapy resistance is well known, the actual means by which this occurs in solid tumors has been difficult to define and validate using clinical biomarkers.[108] For instance, despite decades of use, there are no robust methods for defining taxane, anthracycline, or platinum resistance. Consequently, for the common ADC payloads such as MMAE, SN38, or DXd, there is also a dearth of effective biomarkers. One notable exception has been the recent finding of a small set of patients with mutations in the *TOP1* gene. Functional studies have mapped a portion of these mutations to the drug binding site and helped to prove these to be true mediators of resistance, arguing for testing of payload switch strategies in these instances.[109] To the degree that such functional studies have been performed, mutations in *TOP1* likely represent a bona fide mechanism of resistance to TOP1 payload targeting ADCs. The prevalence of such mutations is unknown, but preliminary data suggest they are very uncommon.[109] Similarly, *Schlafen family member 11* (*SFLN11)* loss has also been described as MoR to T-DXd in patient-derived xenograft (PDX) models.[110] For the majority of cases where broad "chemo-resistance" is a consideration, a swath of enzymes involved in drug efflux and drug metabolism is likely to be germane.[111–113] Some clinical trials have reported the upregulation of ATP-binding cassette (ABC) transporters such as ABCB1 (P-glycoprotein), ABCC1 (MRP1), and ABCG2 (BCRP), as a mechanism underlying resistance to TOP1 inhibitor payloads.[111,113–115] Unfortunately, there is not yet a set of biomarkers or even assays where a defined expression level is known to correspond to drug resistance. In the absence of such assays, innovation beyond current ADCs, which largely relies on a limited set of payload classes, will risk becoming dependent on empirical, trial-and-error exploration of new agents. Finally, beyond the direct effect of the payload on its target, there are further possibilities for resistance in the execution of cell death pathways downstream of the target. This, in theory, spans broad pathways such as apoptosis, ferroptosis, senescence, and immune-mediated death. A recent preclinical report, for instance, revealed how expression of a truncated form of HER2, known as p95, could promote an immunosuppressive TME that prevented some of the major effects of T-DXd in model systems.[116]

DECODING ADC TOXICITY

Several mechanisms underlying ADC toxicity have been described: on-target off-tumor, off-target off-tumor, Fcγ receptor-mediated uptake, payload released in circulation, and albumin-conjugate disposition.[117,118] Off-target off-tumor toxicity is one of the most common mechanisms and explains many of the observed adverse events. ADCs can be uptaken by healthy cells through macropinocytosis or the payload can cross the cell membrane if sufficiently lipophilic once the ADC is cleaved in the bloodstream.[119,120] Linker stability is also critical and can have major implications for the toxicity profile of ADCs.

ADC disposition and linker stability

ADCs, like other antibody-based therapeutics, are eliminated predominantly through intracellular catabolism. Uptake may occur through target engagement as well as through non-specific pathways in both malignant and normal tissues. Consistent with this, clinical studies have shown that only a small proportion of the administered dose of antibodies and ADCs, frequently estimated at less than 1%, accumulates within tumors.[121] For ADCs bearing hydrophobic drug-linkers, clearance is often DAR-dependent, with higher-DAR and more hydrophobic constructs exhibiting more rapid elimination.[122]

Linkers are broadly categorized as cleavable or non-cleavable.[121] Both cleavable and non-cleavable linkers can exhibit intrinsic linker instability in circulation, defined as spontaneous chemical transformations outside the intended cleavage process. The majority of FDA-approved ADCs contain at least one instability that is distinct from the intended payload-release mechanism.[121] Notably, non-cleavable linkers are not necessarily stable. For example, T-DM1 partially deconjugates the DM1 payload over time[123,124] and belantamab mafodotin deconjugates the whole MC-MMAF drug-linker over time,[125] despite both ADCs being categorized as non-cleavable. Efforts to

engineer increasingly stable linkers have dominated ADC technology development for more than a decade. Many approaches, spanning site-specific conjugation, novel maleimide and non-maleimide chemistries, cysteine-bridging platforms, and enzymatic ligations, were designed with the expectation that greater stability in circulation would translate directly into improved safety and efficacy.[126] However, clinical evidence, particularly from comparisons of ADCs that share the same antibody and payload but differ in linker stability, has demonstrated that more stable linkers do not necessarily yield a better safety-efficacy profile.[88,121] This can be understood in the context of ADC disposition: because uptake into normal tissues often dominates overall disposition, ADCs with more stable linkers may produce higher and more prolonged normal tissue exposure than less stable counterparts, potentially leading to a less favorable profile.[127,128] Despite these complexities, emerging linker technologies remain important tools for modulating non-specific uptake, ADC clearance, and the spatial and temporal control of payload release.[129]

Fc-gamma interaction and toxicity

An additional contributor to ADC toxicity is the potential fragment crystallizable region (Fc)-mediated engagement with the immune system. Interactions between the Fc domain and Fcγ receptors on immune cells may drive uptake of ADCs into non-target cells, promoting intracellular payload release and off-target toxicity. Fc engagement may also trigger effector functions such as ADCC or phagocytosis, further contributing to tissue-specific adverse events. The extent of these effects depends on antibody isotype, Fc engineering, and receptor expression in normal tissues, highlighting another layer of complexity in ADC safety that extends beyond antigen targeting and payload biology. For example, thrombocytopenia associated with T-DM1 has been postulated to be linked to the inhibition of megakaryocyte differentiation, which in turn impairs platelet production, in a FcγRIIa-dependent, HER2-independent manner.[130] In the context of T-DXd, ILD is hypothesized to arise from Fc-FcγR interactions with perivascular alveolar macrophages.[131,132] However, other studies have shown that ADC uptake in differentiating megakaryocytes is mediated by macropinocytosis and is independent of FcγRIIa.[133] Moreover, although all approved ADCs and most ADCs in clinical development retain Fc-competent backbones, only a subset are associated with ILD. In addition, studies correlating ADC or payload uptake at a cellular level in specific cell types with toxicity in humans are lacking. Together, these observations point to an incomplete understanding of the relationship between FcγR engagement and specific toxicities in patients. Nevertheless, an increasing number of ADCs are being engineered to reduce or eliminate Fc receptor interactions, with the aim of limiting uptake in FcγR-expressing cells and potentially mitigating certain adverse events.[134,135] Given this uncertainty, the potential advantages and disadvantages of Fc silencing, preservation, or enhancement should be carefully considered when designing structural modifications that might alter Fc functionality, such as Fc region mutations, site-specific conjugation, or glycoengineering.[136] In some cases, preserving or enhancing Fc-mediated interactions through antibody backbone design may be desirable to optimize therapeutic activity.

Exposure-relationship analysis for ADCs

The pharmacokinetic behavior of ADCs is intrinsically multifaceted, with distinct routes of distribution, catabolism, and elimination of the different ADC components and dynamic changes in DAR for ADCs with unstable linkers. This complexity has driven the development of different pharmacometric frameworks to better define ADC disposition. Examples include physiologically based, semi-mechanistic, and population PK models.[137] These models commonly employ the intact conjugate and released drug to characterize exposure-response, exposure-toxicity relationships, and guide dose optimization. Both early (cycle 1) and steady-state exposure metrics have been used to characterize exposure-response relationships for ADCs. Steady-state metrics are often more informative, as they capture time-dependent changes in clearance and the impact of dose modifications over repeated cycles. Given the intrinsic complexity of ADCs, including differences in linker stability, DAR, heterogeneity, and the formation of multiple circulating catabolites, careful selection of analytes is essential for robust exposure-response analyses. Commonly used exposure parameters include area under the curve (AUC), maximum concentration (Cmax), and trough concentrations (Cmin/Ctrough/Ctau), each capturing distinct aspects of systemic exposure. Exposure metrics derived from total antibody, conjugated antibody, antibody-conjugated drug, and released payload have all been evaluated, reflecting the potential contribution of each component to efficacy and toxicity. Across the 14 FDA-approved ADCs, no single analyte consistently predicts exposure-response relationships, with correlations variably observed for conjugated antibody, total antibody, or released payload depending on the molecule and endpoint. Exposure-response modeling for ADCs faces several challenges. A major limitation is the scarcity of well-designed dose-ranging studies, which constrains the ability to define robust exposure-response relationships. Analyses based on single-dose regimens limit the exploration of variability in both exposure and clinical outcomes, although recent regulatory initiatives aimed at dose optimization, such as FDA Project Optimus, are beginning to address this gap.[138] Population PK analyses have identified multiple covariates influencing both ADC and payload exposure, including body weight, albumin levels, tumor burden, antigen expression, and the development of anti-drug antibodies. These factors can meaningfully impact systemic exposure and, consequently, safety and efficacy. To account for this variability, several ADCs incorporate dosing strategies tailored to patient characteristics, including capping the ADC dose above a certain body weight, dose calculated based on each patient's adjusted ideal body weight (AIBW), or dose by body surface area instead of by body weight. These observations highlight that ADC safety cannot be predicted solely from antibody dose. In March 2024, the FDA issued specific guidance for ADC drug development, recommending the use of exposure-response analyses for both the intact conjugate and its components to support dose selection and optimization.[139] Similar guidance was released by the China Center for Drug Evaluation (CDE) and the National Medical Products Administration (NMPA) in September 2025.[140]These regulatory frameworks highlight a growing consensus that dose optimization for ADCs cannot rely solely on maximum tolerated dose paradigms, but instead requires a quantitative understanding of the relationships between exposure, efficacy, and toxicity across multiple analytes.

A further promising refinement for ADC development is the use of ctDNA kinetics as an early on-treatment biomarker of response. Across solid tumors, early ctDNA decline or clearance can anticipate radiographic benefit, and preliminary ADC data also support this concept: in an early-phase study of the HER2-directed ADC SHR-A1811, on-treatment changes in ctDNA correlated with tumor shrinkage.[141] Prospective early-phase studies should therefore incorporate serial ctDNA sampling alongside PK, efficacy, and toxicity assessments to determine whether ctDNA can serve as a robust intermediate biomarker for ADC dose optimization. In the near future, a comprehensive precision medicine strategy for ADCs must incorporate pharmacokinetic and pharmacogenomics profiling, together with the development of biomarkers predictive of toxicity, to optimize dosing, patient selection, and long-term tolerability.

TOWARD A PRECISION ONCOLOGY FRAMEWORK FOR ADCs

Over the past two decades, advances in molecular and genomic characterization have enabled the selection of the right treatment for the right patient at the right time, giving rise to precision medicine. Its most tangible clinical realization has been the successful development and implementation of targeted therapies.[22,142,143] Unlike chemotherapy, which exerts non-specific cytotoxic effects on rapidly proliferating cells, targeted therapies selectively inhibit key molecular drivers of tumor growth in biomarker-defined patient populations, resulting in improved efficacy, tolerability, and a direct correlation between target engagement and drug activity. Within this conceptual framework, the classification of ADCs remains nuanced. At present, only a limited number of biomarkers can be regarded as clinically validated for ADCs, including HER2 expression and activating mutations for HER2-directed ADCs,[17,25,37] FRα expression for MIRV[144] in ovarian cancer using the FDA-approved VENTANA FOLR1 assay, c-MET overexpression for TV, and *EGFR-mut* in NSCLC for TROP2-directed ADCs. By contrast, biomarkers, such as TROP2 internalization, HER3 expression, TOP1 mutations, SLFN11 loss, and ABC transporter overexpression, have thus far been identified only in exploratory retrospective studies and await prospective validation, while biomarkers related to ADC internalization and lysosomal processing remain largely preclinical.

By design, ADCs constitute a form of targeted therapy, as the monoclonal antibody component enables preferential tumor accumulation and enhanced activity in the presence of high target antigen expression. Consistent with this rationale, preclinical studies have demonstrated a strong association between target expression or amplification and ADC activity. For example, as mentioned above, T-DXd exhibits HER2 expression-dependent growth inhibition,[145] EV shows enhanced efficacy in tumors with high Nectin-4 amplification,[146] and SG displays lower IC_{50} ratios relative to free SN-38 in TROP2-high cells.[147] Similarly, Dato-DXd demonstrates increased antitumor activity in PDX models and isogenic cell lines with elevated TROP2 expression.[148] Across clinical trials, however, the predictive value of target expression varies among ADCs, with an unclear relationship, for instance, for agents targeting TROP2,[149,150] Nectin-4,[151] HER3[43,152] or TF.[153] For most ADCs, their activity is influenced by tumor type, histology, and co-existing oncogenic pathways. For instance, it has been shown that elevated EGFR expression may promote EGFR-HER2 heterodimerization, reducing T-DXd internalization and efficacy.[107] Histology-specific molecular contexts also modulate ADC activity, as exemplified by the heightened efficacy of TROP2-directed ADCs in *EGFR*-mutant NSCLC.[53,54]

Beyond target abundance, additional determinants include TME-dependent factors governing linker cleavage, payload release, and immune modulation.[39,43,154,155] Consequently, tumor response to ADCs reflects the integration of multiple biological processes, rather than target expression alone. Taken together, these observations challenge the classification of ADCs as targeted therapies *stricto sensu.* Instead, ADCs may be more accurately conceptualized as *tumor-ecosystem-targeting therapies*, for which predictive biomarkers encompass a multidimensional landscape influencing ADC distribution, antigen binding and internalization, linker cleavage, payload fate, and immune engagement (Figure 1) at the tumor site and in normal tissues. The interplay among these factors ultimately defines the balance between efficacy and tolerability. By virtue of their MoA and biomarker dependence, ADCs align with the principles of precision oncology, which integrates molecular, genomic, and clinical data to optimize treatment selection. However, it is important to acknowledge that most evidence informing ADC pharmacology within the tumors and the TME, such as intratumoral distribution, antigen internalization kinetics (QCS), and payload release, derives from retrospective, exploratory analyses based on limited sample sizes. These studies are hypothesis-generating, but largely lack prospective validation. Therefore, many proposed multidimensional biomarker strategies remain largely conceptual and not yet scalable for routine clinical use. At present, only a limited number of prospectively validated and clinically deployable biomarkers are available, and these still rely on target expression assessed by IHC (e.g., HER2, FRα, and cMET).

As summarized in Table 1, the implementation of a precision medicine framework for ADCs is constrained by a hierarchy of interrelated barriers. The first three priorities represent foundational challenges that must be addressed to enable subsequent advances. Specifically, incomplete characterization of antigen expression with reliable quantitative assays, and antigen spatial heterogeneity (priority 1); limited understanding of ADC pharmacology within tumors and the TME (priority 2), and insufficient clinical characterization of resistance mechanisms (priority 3) collectively impair our ability to define the biological determinants of ADC activity and resistance. These upstream limitations directly hinder progress in downstream translational applications. In particular, they preclude the development of robust predictive composite biomarkers integrating multi-omics data by leveraging deep learning models and the validation of standardized companion diagnostics, applicable on a large scale, which are essential for clinical implementation. Therefore, translating the tumor ecosystem-targeting paradigm into clinical practice requires a fundamental shift toward integrated, biomarker-driven frameworks that redefine both trial design and therapeutic decision-making (Figure 1). This transformation rests on three converging pillars. First, early-phase trials must evolve into

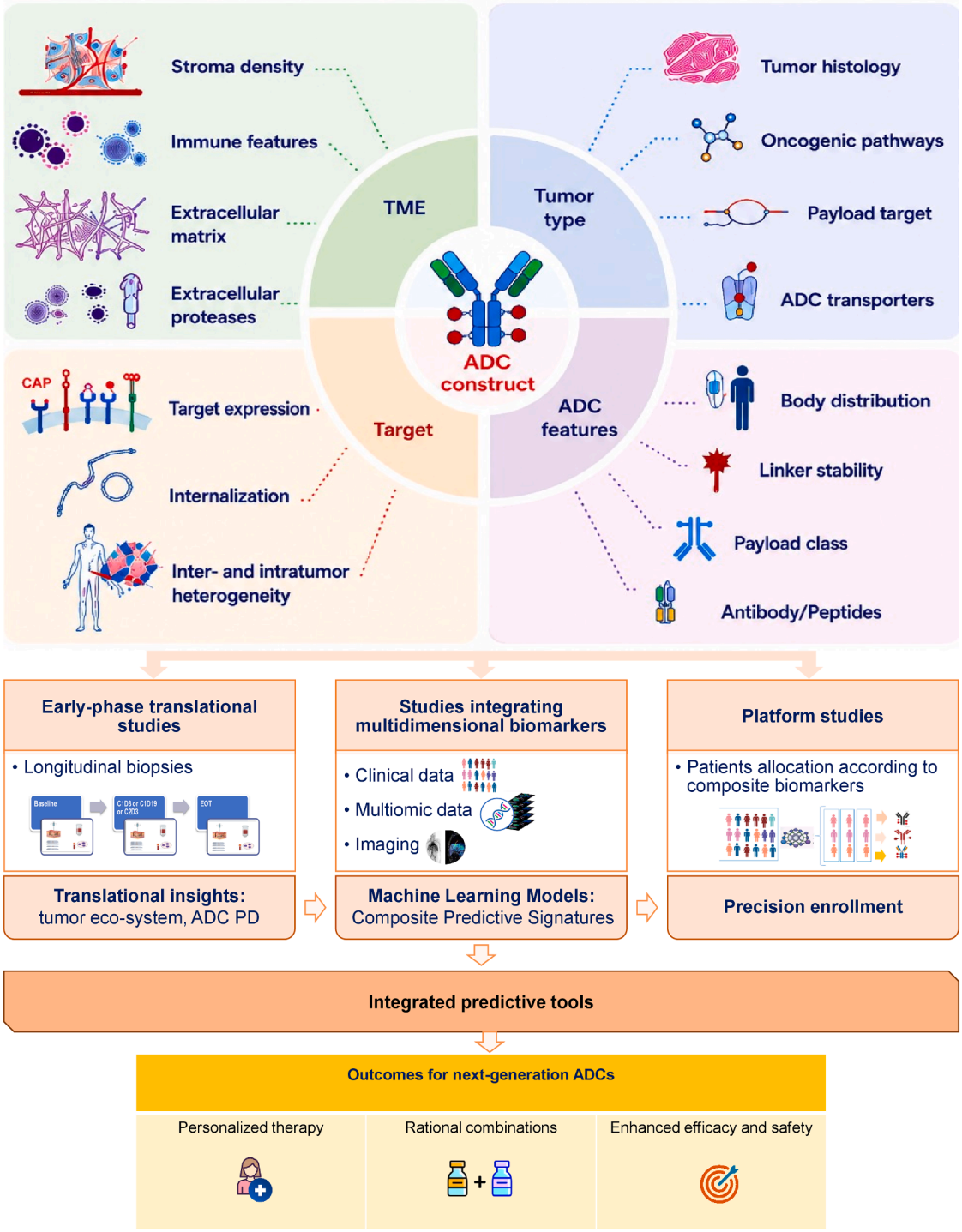


Figure 1. ADCs as tumor-ecosystem-targeting therapies requiring the development and validation of multidimensional biomarkers

Tumor response to ADCs is determined by the integration of multiple biological processes extending beyond target antigen abundance. In addition to antigen expression, tumor and TME-dependent factors critically influence ADC intratumoral distribution, antigen binding and internalization, linker cleavage, payload release and fate, and downstream immune modulation. This multidimensional dependency challenges the classification of ADCs as strictly targeted therapies and supports their reconceptualization as tumor-ecosystem-targeting agents. Translating tumor ecosystem-targeting strategies into clinical practice requires dedicated study designs: (1) translational early-phase trials with longitudinal tumor and blood sampling to define ADC pharmacology *in vivo*; (2) development of composite, prospectively validated biomarkers integrating clinical, molecular, spatial, and imaging features through computational modeling; and (3) biomarker-enriched platform studies assigning patients according to composite tumor features. Together, these strategies aim to support more precise patient selection and accelerate the clinical implementation of next-generation ADCs.

Table 1. Key gaps to fill in to support ADCs' development as Precision Medicine

Priority	Challenge/Gap	Why It Matters	Current Limitation	Potential Directions
1	**Antigen expression and intratumoral and intertumoral heterogeneity**	a minimum target threshold necessary to have some antitumor benefit is not defined for the majority of ADCs Spatial and temporal heterogeneity reduces effective target engagement	IHC-based assays do not provide a quantitative target assessment and intra- and intertumoral variability	fully quantitative methods for target assessment on histology slides; spatial biology tools (multiplex imaging, digital pathology); immuno-PET imaging to assess whole-body target heterogeneity and longitudinal assessment of antigen expression
2	**ADC pharmacology in tumors and TME**	ADC activity depends on: 1. the tumor: antigen internalization kinetics, intracellular trafficking, and payload release 2. the TME that influences ADC penetration, payload diffusion, and immune modulation	IHC does not capture spatial heterogeneity or internalization; limited tools to assess ADC distribution, intracellular processing, payload release, and immune effects within tumors	assays capturing cytoplasmic/internalized targets On-treatment biopsies with spatial transcriptomics/proteomics to map intratumoral distribution; integration of immune profiling
3	**Resistance mechanisms**	resistance limits the durability of response and long-term clinical benefit	limited clinical data; lack of longitudinal sampling and validated resistance biomarkers	longitudinal tumor and liquid biopsies; identification of resistance pathways; develop strategies to overcome resistance (e.g., novel payload classes and efflux pump inhibitors)
4	**Biomarker selection**	target expression alone is insufficient to predict ADC response and the durability of benefit	most approved ADCs lack validated predictive biomarkers; reliance on IHC with limited biological resolution	develop composite biomarkers integrating quantitative and spatial target expression, genomics, proteomics, and immune contexture; leverage deep learning to integrate multi-omics data
5	**Validation of standardized biomarker assays**	reproducible diagnostics are essential for clinical implementation and regulatory approval	lack of harmonized companion diagnostics and standardized thresholds across trials	validate assay-specific CDx platforms with reproducible scoring systems and clinically meaningful cutoffs across clinical trials with ADC
6	**Patient selection strategies**	optimal benefit requires integrating multiple biological determinants	most trials rely on single biomarkers and do not incorporate multidimensional tumor features	implement in clinics composite selection scores integrating antigen expression, internalization, genomics, and TME features to select optimal ADC for each patient and fulfill a precision medicine development of ADCs
7	**Design of new ADCs**	improve efficacy and reduce toxicity through optimized selection of the antibody, linker-cleavage technology, and payload	suboptimal patient selection, inconsistent efficacy signals, and avoidable toxicity	design of next-generation ADCs through the selection of antibodies, linker-cleavage technologies, and payloads based on multidimensional biomarkers

deeply translational platforms, systematically incorporating longitudinal tumor and blood sampling to interrogate ADC pharmacology *in vivo*, capturing intratumoral distribution, antigen internalization, payload release, and resistance dynamics. Studies such as DAISY,[92] ICARUS-BREAST01,[43] ICARUS-LUNG01,[58] and FASCINATE-N[156] illustrate the power of this approach, revealing that ADC response is governed by a complex interplay of spatial target distribution, tumor genomics, and immune contexture. Second, these multidimensional insights must be translated into composite, prospectively validated biomarkers. Emerging evidence supports the feasibility of integrating clinical, molecular, spatial, and imaging data into predictive models using advanced computational approaches. The multimodal framework developed in FASCINATE-N, alongside ongoing initiatives such as ADC-Match [NCT06311214] and OASIS [NCT07259226], are some examples. Such approaches have the potential to move the field beyond static, single-parameter biomarkers toward dynamic, multidimensional signatures capable of predicting both efficacy and toxicity. Third, clinical trial design must be reimagined to operationalize these biomarkers. Future studies should move beyond target expression-based enrollment toward adaptive, biomarker-enriched, and mainly platform-based designs that allocate patients according to composite tumor features, including antigen heterogeneity, TME characteristics, and genomic dependencies. Established frameworks such as I-SPY[157] and NCI-MATCH[158] demonstrate the feasibility of these studies and can pave the way for ADC-specific applications. Ultimately, as the ADC landscape expands, N-of-1 trial designs with algorithmic matching scores may enable real-time matching of patients to the most appropriate ADC or ADC combination.[159] This path would mark a shift from a population-based to a highly personalized, data-driven ADC-development, supported by robust data infrastructures capable of offering real-time multiomic analysis and cross-institutional data sharing.

MAXIMIZING ADC EFFICACY

Combination strategies

A growing number of studies are evaluating ADC combinations to optimize ADC efficacy through enhancing internalization, improving intracellular payload delivery, and promoting cytotoxic or immunologic synergy. Several studies have already reported meaningful activity of ADCs in combination with immune checkpoint inhibitors (ICIs), particularly in triple-negative breast cancer (TNBC)[160,161] and NSCLC,[162] with an efficacy that appears to extend beyond classical PD-L1 expression-based stratification, suggesting the involvement of distinct or complementary immunologic mechanisms.[28,163] The use of ADCs to debulk disease, followed by immunotherapy to maintain response, could also be an attractive therapeutic strategy, as ADCs may rapidly reduce tumor burden while also enhancing immune priming through antigen release and remodeling of the TME. However, clinical examples of this approach remain limited and are mostly explored in the curative setting (NCT06055465, NCT06112379). Optimal scheduling will need to be defined through prospective trials directly comparing sequential versus concurrent strategies, ideally incorporating translational endpoints. Dynamic biomarkers such as ctDNA clearance, immune-cell infiltration, and markers of ICD may help determine the most effective timing for transition from ADC-based debulking to immunotherapy maintenance.

Strategies to enhance ADC internalization have shown promising activity in HER2-positive metastatic BC, with tucatinib improving outcomes when added to T-DM1 and ongoing trials evaluating T-DXd-based combinations such as T-DXd plus neratinib.[164–166] Similarly, the superior efficacy of T-DXd plus pertuzumab in DESTINY-Breast09 may partly reflect pertuzumab-mediated increases in HER2 internalization and downstream pathway inhibition.[26,167] Several combination strategies are exploiting synthetic lethality by pairing TOP1 inhibitor-based ADCs with agents targeting the DNA damage response (DDR), mostly PARP and ATR inhibitors. Although the first clinical trials combining PARP inhibitors with TOP1-targeting ADCs were discontinued due to overlapping hematologic toxicity, subsequent studies using reduced PARP inhibitor dosing and staggered schedules have shown promising clinical outcomes with acceptable safety.[168] Ongoing trials are also evaluating selective PARP1 inhibitors in combination with Dato-DXd or T-DXd; however, it remains unclear whether these combinations expand ADC efficacy or can also overcome resistance driven by DDR pathway activation.[58] Given that replication stress can be induced by TOP1-targeting ADCs, concomitant ATR inhibition represents a rational strategy to exploit replication stress-induced vulnerability and enhance tumor cell lethality.[169,170]

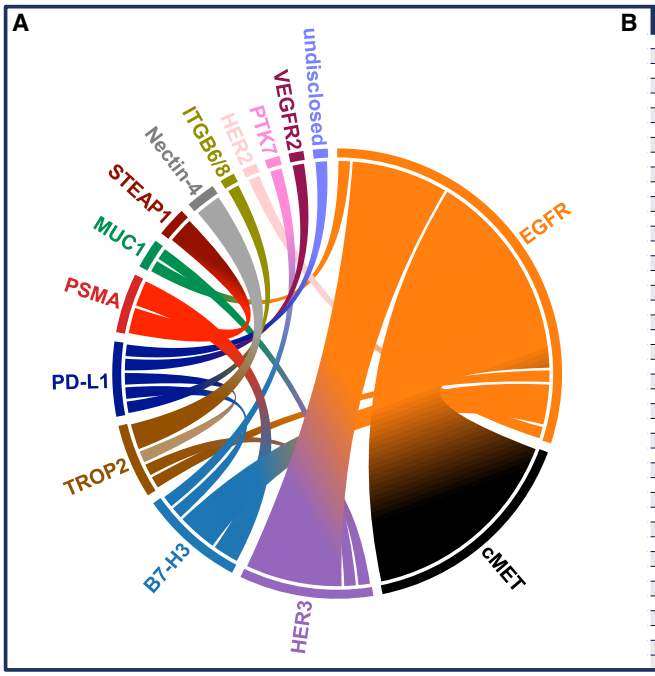
Other strategies include ADC-ADC combinations. Notably, the combination of SG and EV was developed to exploit dual targeting of TROP-2 and Nectin-4 with mechanistically distinct payloads and partially non-overlapping toxicities. Early efficacy from the phase I DAD trial appears clinically promising, with an ORR of 70% (95% CI 47-87) and a median PFS of 8.9 months (95% CI 4.8-11.8) in patients with metastatic urothelial carcinoma.[171] However, the small non-randomized dataset requires confirmation in ongoing phase II expansion cohorts and in the DAD-IO program, which will clarify durability, patient selection, and the role of this strategy relative to current standards (NCT04724018).

Finally, combination approaches based on identified resistance mechanisms are also being explored. For example, *MET* amplification or overexpression can drive the HER3-dependent activation of the PI3K signaling pathway as a mechanism of resistance to TKIs,[172,173] providing the biological rationale for combining MET or HER3-targeting ADCs with TKIs. However, clinical experience with TV plus TKIs has been limited by unacceptable toxicity, leading to the discontinuation of some development programs. Several clinical trials are currently evaluating numerous ADC-TKI combinations (NCT04676477, NCT06895928, NCT06350097, NCT06670196, NCT06417814), with a particularly large number of ongoing studies focusing on combinations with osimertinib.

Emerging platforms and other targeting strategies

ADC development is rapidly evolving toward more tumor-specific antigen selection, incorporation of novel payloads, and the design of next-generation constructs, such as dual-payload platforms, bispecific or biparatopic antibodies, immune-stimulating ADCs, and protein degrader conjugates. These approaches aim to improve intratumoral drug delivery, address

Target pairs used in bispecific ADCs



Bispecific ADCs that have entered clinical development

B

ADC	Year entering the clinic	Target 1	Target 2	Payload class	Drug status
M1231	2021	EGFR	MUC1	Hemiasterlin	Discontinued
Iza-bren	2022	EGFR	HER3	Camptothecin	In clinical development
AZD9592	2022	EGFR	cMET	Camptothecin	In clinical development
ABBV-969	2024	PSMA	STEAP1	Camptothecin	In clinical development
JSKN016	2024	TROP2	HER3	Camptothecin	In clinical development
IBI3001	2024	EGFR	B7-H3	Camptothecin	In clinical development
IBI3005	2024	EGFR	HER3	Camptothecin	In clinical development
BL-B16D1	2024	EGFR	HER3	Auristatin	In clinical development
DM001	2024	EGFR	TROP2	Camptothecin	In clinical development
DB-1419	2024	B7-H3	PD-L1	Camptothecin	In clinical development
DM005	2024	EGFR	cMET	Camptothecin	In clinical development
MK-2750	2024	EGFR	cMET	Camptothecin	In clinical development
ALK202	2024	EGFR	cMET	Camptothecin	In clinical development
GEN1286	2024	EGFR	cMET	Camptothecin	Discontinued
FH-006	2025	EGFR	B7-H3	*Undisclosed*	In clinical development
DM002	2025	MUC1	HER3	Camptothecin	In clinical development
DXC008	2025	PSMA	STEAP1	Camptothecin	In clinical development
HS-20122	2025	EGFR	cMET	Camptothecin	In clinical development
TQB6411	2025	EGFR	cMET	Camptothecin	In clinical development
AK146D1	2025	TROP2	Nectin-4	Camptothecin	In clinical development
KY-0301	2025	EGFR	cMET	Auristatin	In clinical development
JNJ-95437446	2025	EGFR	cMET	Camptothecin	In clinical development
JS212	2025	EGFR	HER3	Camptothecin	In clinical development
AVZO-1418	2025	EGFR	HER3	Camptothecin	In clinical development
IBI3014	2025	TROP2	PD-L1	Camptothecin	In clinical development
JSKN022	2025	ITGB6/8	PD-L1	Camptothecin	In clinical development
TJ101	2025	EGFR	B7-H3	Camptothecin	In clinical development
AVZO-103	2025	TROP2	Nectin-4	Camptothecin	In clinical development
BNT3212	2025	EGFR	HER3	Camptothecin	In clinical development
BG-C0902	2025	EGFR	cMET	Camptothecin	In clinical development
Gensci139	2025	EGFR	HER2	Camptothecin	In clinical development
GenSci143	2025	PSMA	B7-H3	Camptothecin	In clinical development
VBC101	2025	EGFR	cMET	Camptothecin	In clinical development
SIM0610	2026	EGFR	cMET	Camptothecin	In clinical development
IDE034	2026	B7-H3	PTK7	Camptothecin	In clinical development
DXC014	2026	PSMA	B7-H3	Camptothecin	In clinical development
IBI3028	2026	EGFR	cMET	Dual payload	In clinical development
HDM2024	2026	EGFR	HER3	Camptothecin	In clinical development
QLS5316	2026	EGFR	cMET	Camptothecin	In clinical development *
JSKN027	2026	PD-L1	VEGFR2	Camptothecin	In clinical development *
SKB103	2026	PD-L1	undisclosed	Camptothecin	In clinical development *
HLX48	2026	EGFR	cMET	Camptothecin	In clinical development *
HDM2024	2026	EGFR	HER3	Camptothecin	In clinical development *

* not yet enrolling

Figure 2. Bispecific ADCs in clinical development and associated target pairs

(A) Most frequent target pairs currently used in bispecific ADCs under clinical development; (B) list of bispecific ADCs that entered clinical development as of April 25th, 2026.

target heterogeneity, and expand activity beyond the limitations of current ADC designs. By aligning target selection and drug design with tumor biology and its microenvironment, these advances could enable more precise matching of ADCs to patient- and tumor-specific features, provided that comprehensive biomarker strategies are implemented from early-phase development, including longitudinal tumor and blood sampling to support multi-omic analyses. However, most studies remain limited to target expression assessment and do not incorporate multidimensional tumor characteristics.

The targeting landscape is being enriched with novel antigens, including immune checkpoint-related targets such as Programmed death ligand 1 (PD-L1), B7 homolog 3 (B7-H3) and B7-H4, as well as tumor-specific antigens such as SEZ6 and DLL3[174] and a wide range of cadherins (CDH3, CDH6, CDH17), claudins (CLDN6, CLDN1, CLDN18.2) and integrins (ITGB6, ITGA2).[175–177,174] TME-directed ADCs represent a strategy to expand efficacy by engaging stromal, vascular, and immunosuppressive compartments that are less prone to somatic mutation and more consistently represented across different tumor types.[178,179] A major advance in ADC engineering is the development of biparatopic and bispecific constructs. Biparatopic ADCs recognize two non-overlapping epitopes on a single antigen, resulting in increased binding avidity, enhanced receptor clustering, and more efficient internalization.[180–182] Bispecific ADCs can simultaneously engage two distinct surface antigens (Figure 2A), either broadening patient eligibility and addressing intratumoral heterogeneity or enhancing specificity by requiring co-expression of both targets, thereby potentially sparing normal tissues. In the recent years, more than 40 bispecific ADCs have entered clinical development (Figure 2B). Given that HER3 appears as a mechanism of resistance to EGFR TKIs, several bispecific ADCs targeting EGFR and HER3 with TOP1 inhibitor payloads are currently under development.[183,184] BL-B01D1 (izalontamab brengitecan)[185] is a bispecific ADC targeting both EGFR and HER3 and conjugated to a TOP1 inhibitor. Early-phase studies have demonstrated substantial antitumor activity across several solid tumors,[184] including BC[186] and lung cancer,[187] leading to multiple ongoing phase II/III trials. Similarly, co-targeting EGFR and cMET has emerged as a popular bispecific ADC strategy, building on the clinical success of the bispecific antibody amivantamab. Conditionally activated ADCs constitute another innovative class, designed to be selectively activated within the TME in response to acidic pH, enzymatic activity, or redox conditions. To further improve intratumoral distribution, small-format conjugates such as peptide-based drug conjugates and small-molecule drug conjugates (SMDCs) are being actively explored.[188] However, smaller formats are typically associated with rapid clearance, making dose and schedule critical variables to maximize efficacy while maintaining a manageable safety profile.

Payload diversification represents a further axis of innovation. Non-cytotoxic payloads, particularly immune-stimulating agents, are being explored to induce durable antitumor immunity by activating DCs and macrophages and promoting T cell recruitment. ISACs typically couple tumor-targeting antibodies to Toll-like receptor (TLR) or STING agonists, which are delivered to antigen-presenting cells via Fcγ receptor-mediated uptake, triggering

innate immune activation and potentially enhancing immunologic memory. However, the clinical development of ISACs remains challenging, as early studies have been limited by unacceptable systemic toxicities, which highlight the need for improved therapeutic indices. A distinct strategy involves degrader antibody conjugates (DACs), which incorporate proteolysis-targeting chimeras (PROTACs) or molecular glue as payloads to induce the selective degradation of intracellular proteins. Also in this case, recent clinical discontinuations of both a molecular glue-based DAC (ORM-5029) and a bifunctional PROTAC-based DAC (ABBV-787) highlight the need to better understand the determinants of intracellular delivery, target engagement, and degradation efficiency required to achieve efficacy at a tolerated dose (i.e., to achieve a meaningful therapeutic window). Finally, dual-payload ADCs represent a promising approach to address tumor heterogeneity and resistance by simultaneously delivering two or more cytotoxic or immunomodulatory agents. Several dual-payload ADCs have entered early-phase clinical development, for instance combining a TOP1 inhibitor with agents such as an RNA polymerase II inhibitor, a microtubule inhibitor, an ATR inhibitor, or an STING agonist.[189,190] ADCs incorporating innovative payloads remain scarce. However, constructs with diversified payload classes have recently entered clinical development, including compounds carrying PI3K/PIKK inhibitor[191] or ecteinascidin payload,[192] and more recently, the Investigational New Drug (IND) application for GFS784,[193] carrying a RAS inhibitor, has been accepted by the National Medical Products Administration (NMPA) in China.

New ADC platforms bring new opportunities but also important challenges. For immune-stimulating antibody conjugates (ISACs), the main issue is defining the optimal balance between antibody dose and PRR agonist payload exposure to achieve intratumoral immune activation without excessive systemic immune toxicity, including cytokine-related adverse events. For DACs and dual-payload ADCs, a major limitation is the need for a high DAR to deliver enough active drug, which increases hydrophobicity, complicates formulation, and may worsen toxicity; in dual-payload constructs, payload selection is also critical and requires combining agents with complementary mechanisms and balanced potency. For bispecific ADCs, careful selection of targets and epitopes is essential to maximize tumor selectivity and internalization while limiting toxicity.[194] Furthermore, the clinical potential of these increasingly sophisticated agents risks being diluted by suboptimal patient selection, inconsistent efficacy signals, and avoidable toxicity. There still remains an imbalance between ADC therapeutic innovation and biomarker development and implementation. Filling this gap is now urgent, as the future impact of next-generation ADCs will depend not only on continued engineering advances but on the parallel development of robust, multidimensional biomarkers capable of guiding precise patient selection and ultimately optimizing clinical benefit.

MOVING ADCs INTO CURATIVE SETTINGS

The remarkable efficacy achieved by several ADCs in the metastatic setting has naturally prompted their evaluation in early-stage disease, where systemic therapies, often combined with local treatment, are administered with curative intent. The rationale for earlier ADC use is compelling. First, intervention at this stage allows molecular vulnerabilities to be targeted before the emergence of extensive genomic complexity and resistance mechanisms. Second, the capacity of ADCs to modulate the TME provides a strong biological basis for combination strategies with ICIs, particularly in early disease, where antitumor immune responses may be more robust. Third, ADC-based strategies could potentially reduce long-term and sometimes irreversible toxicities associated with chemotherapy, including taxane-related neurotoxicity, anthracycline-related cardiotoxicity, and impairment of fertility, outcomes of particular importance in long-term survivors. These concepts have translated into a rapidly expanding portfolio of clinical trials investigating ADCs in neoadjuvant, adjuvant, and post-neoadjuvant settings across multiple tumor types. In early BC, the approval of T-DM1 based on the KATHERINE trial established the first proof of principle for ADCs in the curative setting.[195] More recently, the DESTINY-Breast05[196] and DESTINY-Breast11[197] trials have demonstrated that T-DXd-based regimens can significantly improve iDFS and pCR rates compared with established standards. In the neoadjuvant setting, however, important limitations have emerged. Several studies have shown that short-duration neoadjuvant treatment with ADCs as single agents is insufficient to achieve a meaningful increase in pCR rates and cannot replace standard, longer chemotherapy regimens, as exemplified by the NEOSTAR A1/A2 cohorts[198,199] in TNBC and the I-SPY 2.2 platform.[157,200] Conversely, accumulating evidence suggests that the efficacy of ADCs in the neoadjuvant context may be maximized by administering longer treatment courses, approaching the duration of conventional multi-cycle chemotherapy, or by strategically replacing selected components of standard chemotherapy with ADCs rather than omitting chemotherapy altogether.[197,201] Beyond BC, encouraging signals are emerging in other tumor types. In resectable NSCLC, early neoadjuvant studies suggest that the addition of Dato-DXd to durvalumab can enhance pCR without substantially increasing toxicity.[202] Similarly, perioperative strategies combining EV with pembrolizumab have produced unprecedented pCR rates and survival benefits in muscle-invasive bladder cancer,[33] reinforcing the potential of ADC-immunotherapy combinations in early disease. Despite these advances, several critical challenges remain (Figure 3). First, the optimal integration of ADCs into curative-intent treatment paradigms, such as sequencing, duration, and combination strategies, has yet to be defined. Second, and more importantly, patient selection remains insufficiently precise. As ADC use expands into early-stage disease, there is an urgent need for robust biomarkers to guide ADC choice, treatment intensity, and avoid overtreatment. Treatment decisions must balance toxicity against the absolute benefit for each individual. ADCs should therefore be restricted to patient populations and disease stages in which a clear reduction in recurrence risk has been demonstrated. The DESTINY-Breast05 trial illustrates this paradigm. In high-risk HER2-positive early BC with residual disease, T-DXd significantly reduced the risk of recurrence or death compared with T-DM1 (HR 0.47). The absolute benefit (~8.7%) translates into treating approximately 11 patients to prevent one recurrence, while exposing all to increased toxicity, including a 9.6% rate of ILD in a curative setting. Emerging strategies such as ctDNA-based minimal residual disease (MRD)

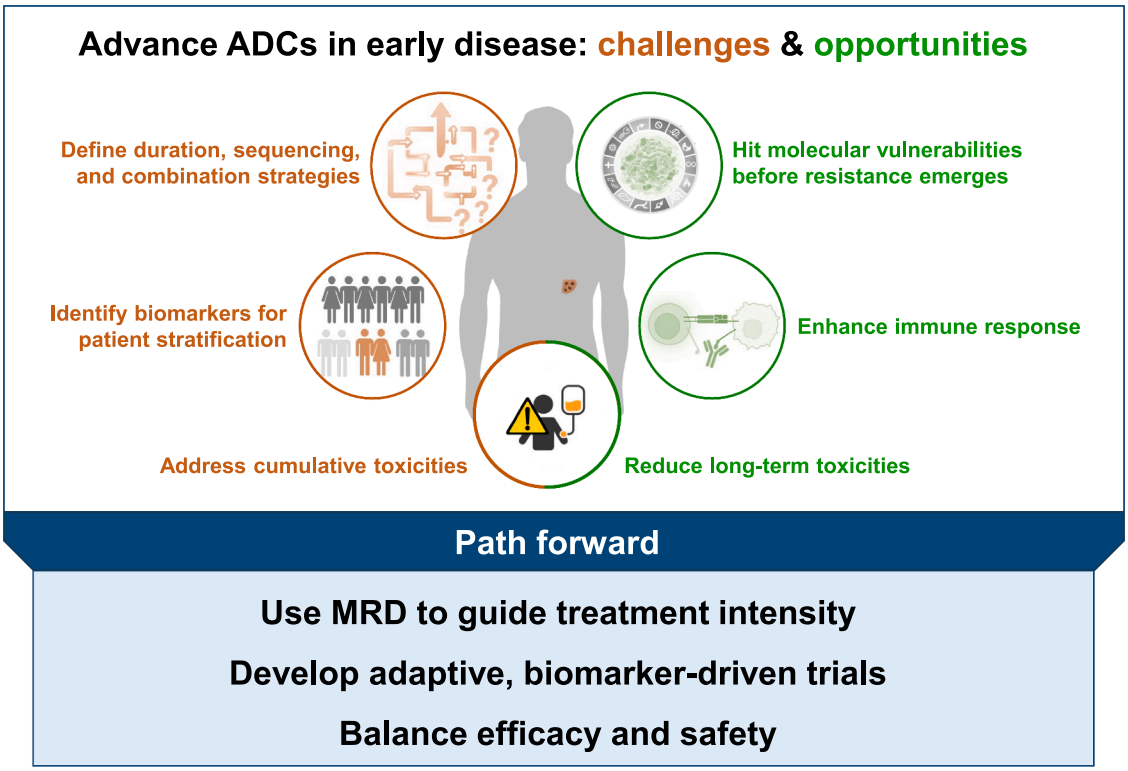


Figure 3. Incorporating ADCs in Curative Setting: Opportunities and Challenges
Clinical use of ADCs in early-stage cancer should be guided by a careful balance between toxicity and absolute benefit, restricting treatment to settings in which a clear reduction in recurrence risk has been demonstrated. Key unresolved issues include optimal schedules, patient selection and whether ADC-based regimens reduce late and irreversible toxicities compared with conventional chemotherapy, as long-term follow-up is still needed.

assessment and adaptive, biomarker-driven trial designs[157,200] may offer a path toward more personalized and shorter treatment courses, sparing unnecessary toxicities. Finally, whether ADC-based regimens ultimately translate into a meaningful reduction in late and irreversible toxicities compared with conventional chemotherapy remains an open question that will require long-term follow-up. Peripheral neuropathy illustrates this uncertainty. While persistent neuropathy has been reported after conventional taxane therapy, affecting nearly half of patients at 2–3 years,[203] the extent to which MMAE-containing ADCs are associated with long-term peripheral neuropathy remains unclear.[29] Furthermore, pyrrolobenzodiazepine (PBD)-containing ADCs raise significant genotoxicity concerns, reflecting their MoA as covalent DNA minor groove cross-linking agents, with confirmed genotoxicity in preclinical studies.[204] Addressing these unmet needs will be essential to ensure that the promise of ADCs in early-stage cancer is realized without compromising survivorship and quality of life.

CONCLUSION AND FUTURE DIRECTIONS

ADCs have delivered truly transformative benefits in selected clinical contexts, yet their overall impact remains uneven and far from fully realized. Although ADCs are designed as targeted therapies, their development and clinical implementation have largely proceeded without the rigorous biomarker integration and patient stratification frameworks that define modern precision oncology. As a result, ADC efficacy is often unpredictable, toxicity remains difficult to anticipate, and resistance frequently appears, limiting durable benefit. A central lesson from clinical and translational studies is that target antigen expression alone is insufficient to explain or predict ADC activity. Instead, ADC response likely reflects the integration of multiple layers, including tumor cell-intrinsic features, stromal architecture, immune contexture, and pharmacologic properties of the linker-payload. This complexity challenges the classification of ADCs as strictly targeted agents. Rather, ADCs may be more accurately viewed as *tumor-ecosystem-targeting therapies* whose success depends on multidimensional biological and pharmacological determinants. Several critical gaps must be addressed to enable the integration of ADCs into precision medicine frameworks. These include, (1) the lack of validated biomarker assays, as the majority of evidence come from retrospective analysis on limited samples size and, as such, lack any prospective validation, (2) the limited tools to assess ADC intratumoral distribution, internalization, and immune engagement, (3) the incomplete understanding of clinically relevant resistance mechanisms, and (4) the inadequate patient selection strategies. Moving toward true precision ADCs will require composite biomarkers that integrate spatial antigen distribution, internalization capacity, tumor genetics, and TME features. Equally important will be the harmonization and validation of companion diagnostics with clearly defined thresholds to ensure reproducibility and clinical utility. Only through such an integrated approach can ADCs move

beyond limited success stories and become broadly transformative therapies for a wider patient population.

AUTHOR CONTRIBUTIONS

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