Journal of Hematology & Oncology

REVIEW

Open Access

Evolving antibody-drug conjugates in breast cancer from precision delivery to tumor microenvironment reprogramming

Na Lu[1], Bin Yan[2], Yu-Qiang Li[1] and Jing-Lei Wan[2*]

Abstract

Antibody–drug conjugates (ADCs) have emerged as an important therapeutic strategy for breast cancer, particularly in the context of its molecular heterogeneity. Initially developed as targeted cytotoxic delivery systems, ADCs are increasingly being explored as multifunctional platforms that may also influence the tumor microenvironment (TME). The expansion of ADC targets beyond human epidermal growth factor receptor 2 (HER2) to include molecules such as trophoblast cell surface antigen 2 (TROP-2) and human epidermal growth factor receptor 3 (HER3) has broadened the therapeutic landscape, offering new options for subtypes with limited targeted therapies, including triple-negative breast cancer (TNBC).

Accumulating evidence suggests that the tumor microenvironment plays a critical role in modulating ADC efficacy and resistance. Physical barriers, immunosuppressive signaling, and stromal interactions may limit drug penetration and therapeutic response. In parallel, ADC-induced cytotoxicity has been associated with immunogenic cell death and potential remodeling of the tumor immune milieu. These insights have prompted the development of improved ADC designs, including environment-responsive linkers, optimized payloads, and rational combination strategies with immunotherapy.

In this review, we summarize the evolving landscape of ADC development in breast cancer, focusing on target expansion, structural optimization, resistance mechanisms, and interactions with the tumor microenvironment. We also discuss emerging strategies aimed at enhancing therapeutic efficacy and overcoming resistance, highlighting growing interest in integrating targeted cytotoxicity with modulation of the tumor microenvironment.

Keywords Breast cancer, Antibody–drug conjugates, Tumor microenvironment, Precision delivery, Resistance mechanisms, Immune reprogramming, Immunotherapy

*Correspondence:
Jing-Lei Wan
jlwan19@fudan.edu.cn
[1]Department of Pathology, Jinan People's Hospital Affiliated to Shandong First Medical University, Jinan 271199, Shandong, China
[2]Department of General Surgery, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080, China

Introduction

1. Biological heterogeneity and therapeutic landscape of breast cancer

Breast cancer remains the most frequently diagnosed malignancy and a leading cause of cancer-related mortality among women worldwide. Despite substantial advances in screening, molecular classification, and systemic therapy, it continues to impose a significant global health burden [1–3]. Over the past two decades, improvements in endocrine therapy, chemotherapy, and targeted treatments have significantly prolonged survival for many patients. Nevertheless, disease recurrence and therapeutic resistance remain common, particularly in advanced or metastatic settings. These persistent clinical challenges highlight the need for more effective therapeutic strategies capable of overcoming tumor heterogeneity and evolving resistance mechanisms [4].

Breast cancer is a biologically heterogeneous disease encompassing multiple molecular subtypes with distinct genomic landscapes, biological behaviors, and therapeutic vulnerabilities. The intrinsic subtypes—including hormone receptor–positive, HER2-positive, and triple-negative breast cancer (TNBC)—differ markedly in their biological behavior, therapeutic response, and clinical outcomes [5]. While endocrine therapies and HER2-targeted agents have transformed the management of hormone receptor–positive and HER2-amplified tumors, treatment options remain limited for other aggressive subtypes such as TNBC [6]. Moreover, even within individual subtypes, intratumoral heterogeneity and dynamic evolutionary changes during treatment contribute to variable therapeutic responses and eventual resistance. These complexities underscore the limitations of conventional cytotoxic therapies and emphasize the need for more precise and adaptable therapeutic strategies [7, 8].

The development of targeted therapies has substantially changed the treatment landscape of breast cancer by enabling selective inhibition of oncogenic drivers while minimizing systemic toxicity. Among these approaches, monoclonal antibodies such as trastuzumab and pertuzumab have demonstrated remarkable success and significantly improved survival outcomes, particularly in HER2-positive disease. However, despite these advances, a substantial proportion of patients eventually develop resistance, and many tumors lack sufficiently actionable targets. Consequently, increasing attention has been directed toward therapeutic platforms that combine the specificity of targeted antibodies with the potent cytotoxic activity of chemotherapy [9]. These clinical challenges—including heterogeneous tumor biology, evolving resistance, and limited efficacy of conventional targeted therapies—underscore the need for more precise and adaptable therapeutic strategies, motivating the development of antibody–drug conjugates (ADCs) as a promising approach.

2. Evolution of antibody–drug conjugates in breast cancer therapy

In this context, antibody–drug conjugates (ADCs) have emerged as an innovative class of targeted therapeutics designed to address these limitations. By chemically linking monoclonal antibodies to highly potent cytotoxic payloads through specialized linkers, ADCs enable selective delivery of chemotherapy directly to tumor cells expressing specific antigens. This design aims to maximize antitumor efficacy while potentially limiting off-target toxicity (Fig. 1) [10–15]. First-generation ADCs, represented by trastuzumab emtansine (T-DM1), employed non-cleavable linkers paired with microtubule inhibitors. These agents release cytotoxic metabolites following antibody internalization and lysosomal degradation, yielding significant clinical benefits in HER2-positive advanced breast cancer and establishing ADCs as a viable therapeutic platform [10, 14, 16, 17]. Next-generation ADCs, exemplified by trastuzumab deruxtecan (T-DXd), incorporate cleavable linkers and highly potent topoisomerase I inhibitor payloads, enabling a bystander effect that can overcome antigen heterogeneity. Clinical trials such as DESTINY-Breast04 have demonstrated significant survival benefits in patients with HER2-low metastatic breast cancer, substantially expanding the therapeutic scope of HER2-targeted therapy to include patients with HER2-low disease [13, 14].

3. Tumor microenvironmental determinants of ADC efficacy

However, despite the success of this precision delivery strategy, the tumor microenvironment (TME) represents a critical factor influencing ADC efficacy and driving acquired resistance [10, 18–21]. The TME—a complex ecosystem composed of immune cells, stromal components, and extracellular matrix—presents formidable physical and immunosuppressive barriers. Dense extracellular matrix structures can restrict deep drug penetration within tumors, while tumor-associated macrophages and inhibitory signaling pathways (e.g., TGF-β) create an immunosuppressive environment that attenuates ADC efficacy. Conversely, accumulating evidence suggests that the biological effects of ADCs extend beyond direct cytotoxicity; payload-mediated cytotoxicity has been reported to induce immunogenic cell death (ICD), thereby reshaping the tumor immune microenvironment [22–28]. Recognizing this intricate interplay has increasingly prompted researchers to explore whether ADCs

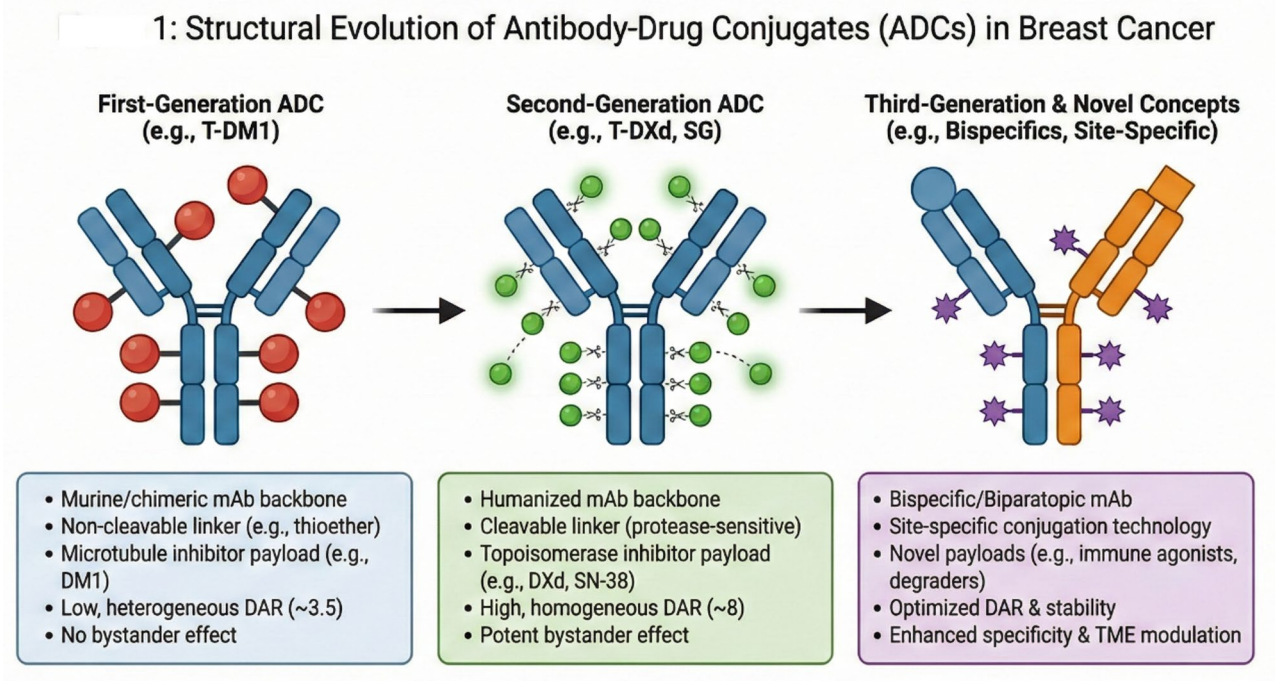

Fig. 1 Structural Evolution of ADC Drugs for Breast Cancer. The evolution from first-generation to next-generation ADCs is characterized by optimized drug-to-antibody ratios (DAR), the transition to tumor-selective cleavable linkers, and the integration of highly membrane-permeable payloads to enable bystander killing. Emerging third-generation constructs further utilize bispecific architectures and site-specific conjugation to enhance TME modulation

may influence not only tumor cells but also components of the tumor microenvironment [2, 29, 30]. Emerging strategies are being explored to address these challenges, including microenvironment-responsive linkers, immune-stimulating payloads, and rational combinations with immune checkpoint inhibitors [15, 31].

Despite substantial progress in the development of antibody–drug conjugates (ADCs) for breast cancer, several important clinical and biological questions remain. It is not yet fully understood how successive generations of ADCs have reshaped therapeutic strategies in routine clinical practice, what mechanisms underlie primary and acquired resistance, and how features of the tumor microenvironment influence treatment response. In addition, emerging technologies such as artificial intelligence are increasingly being explored to facilitate ADC design and optimization. In this review, we synthesize current evidence on the clinical evolution of ADCs in breast cancer, summarize key mechanisms of resistance, and discuss the potential role of tumor microenvironment–associated factors in modulating ADC activity. We also highlight emerging strategies that may contribute to the development of more effective and individualized ADC-based therapies.

Evolution of ADC design elements: synergistic evolution of targets, linkers, and payloads

The evolution of ADCs in breast cancer is driven by the synergistic optimization of three core components: antibody/target selection, linker design, and the combined improvement of payload toxicity and function (Fig. 2) [16, 32, 33]. First-generation ADCs (represented by trastuzumab-based T-DM1) employed non-cleavable thioether linkers to conjugate the microtubule inhibitor DM1 to the antibody, with an average drug-to-antibody ratio (DAR) of approximately 3.5. While this design increased selectivity, the inability of the charged metabolites to penetrate cell membranes—due to the non-cleavable linker and payload properties—limited the bystander effect, thereby affecting the ability to overcome antigen expression heterogeneity. In the EMILIA randomized trial, T-DM1 significantly improved survival, but its activity in low-expressing tumors was limited [17, 34]. New-generation ADCs (exemplified by Trastuzumab deruxtecan, T-DXd/DS-8201) represent an important advancement in the field. These agents introduce tetrapeptide linkers (e.g., Gly-Gly-Phe-Gly) specifically cleavable by lysosomal enzymes (such as cathepsin B) and carry highly active topoisomerase I inhibitors (DXd) [14, 35]. This design offers three major advantages: first, it achieves a high, homogeneous DAR of 8, potentially improving delivery efficiency; second, the released payload possesses membrane permeability, generating

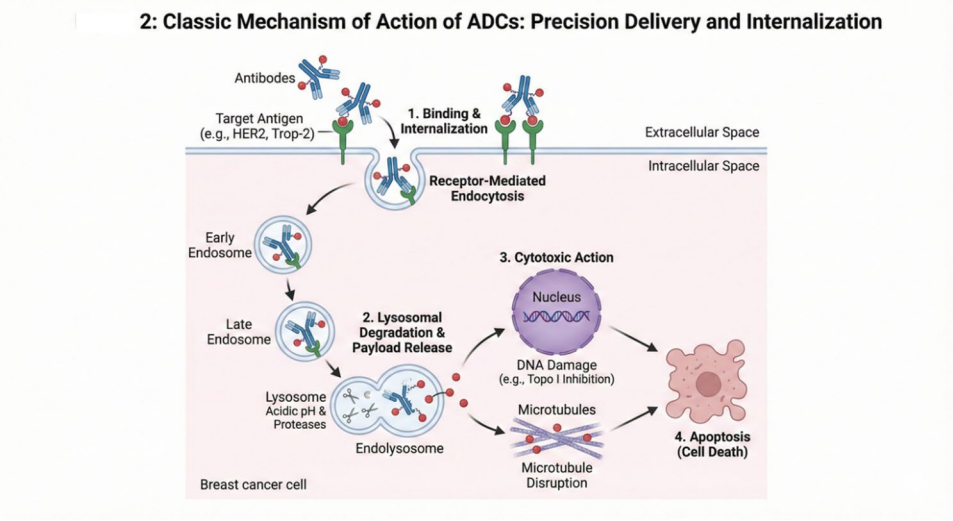

Fig. 2 Classic Mechanism of Action of ADCs: Precision Delivery and Internalization. Following antigen-specific binding and receptor-mediated endocytosis, ADCs undergo lysosomal degradation. The subsequently released cytotoxic payloads induce targeted tumor cell apoptosis by disrupting essential intracellular components, primarily through DNA damage or microtubule inhibition

a potent "bystander effect" to effectively kill surrounding antigen-negative tumor cells; third, certain payloads can induce ICD, activating anti-tumor immunity. Clinical benefit has been demonstrated in the DESTINY-Breast04 study (Table 1), supporting its therapeutic role in the HER2-low population [14, 36, 37]. Emerging third-generation concepts are advancing toward more precise regulation (Fig. 1), including the use of site-specific conjugation technologies to further improve homogeneity, and the engineering of bispecific ADCs (e.g., simultaneously targeting HER2/HER3) to augment tumor specificity and overcome resistance. With the integration of artificial intelligence-assisted design and multi-omics technologies, ADCs are being explored not only as cytotoxic delivery systems but also as more complex therapeutic platforms that may influence the tumor microenvironment [10, 16, 38, 39].

Target expansion (e.g., extending from HER2 to TROP-2, HER3, etc.) has indeed promoted the iteration of linker and payload technologies [16]. Taking the TROP-2-targeting sacituzumab govitecan (SG, Trodelvy) as an example, this drug uses a hydrolyzable/cleavable CL2A linker to conjugate SN-38 to the antibody (average DAR ~ 7–8), allowing SN-38 to be released within the TME and intracellularly, thereby achieving a bystander effect and clinical benefit in pretreated TNBC. However, the primary adverse events of SG include neutropenia and diarrhea. In the safety analysis of the Phase III ASCENT trial (Table 1), all-grade neutropenia was approximately 63% (Grade ≥ 3 approximately 51%), and all-grade diarrhea was approximately 59% (Grade ≥ 3 approximately 10%) [29, 40]. The new-generation TROP-2 ADC sacituzumab tirumotecan (SKB264) employs a CL2A-type cleavable linker. Through a dual response mechanism involving cathepsin B enzymatic cleavage and the acidic microenvironment, it precisely releases the topoisomerase I inhibitor T030 (KL610023) within tumor cells. Its optimized DAR (7.4) aims to improve the balance between the therapeutic window and safety [41].

The diversification of payload functions reflects an expansion of ADC design beyond direct cytotoxicity toward potential immunomodulatory effects. Traditional microtubule inhibitors/DNA damaging agents only achieve direct killing, whereas immune-agonist payloads (such as TLR8 agonist-ISACs) reshape the immune microenvironment by activating intratumoral dendritic cells and recruiting effector T cells. Although this strategy remains in early clinical development, it may offer a potential approach for tumors with limited baseline immune infiltration. In addition, dual-payload systems have initiated a new paradigm of synergistic toxicity. For example, the HER2-targeting SHR-A1811 carries a topoisomerase I inhibitor. Through dual mechanisms of the bystander effect and DNA damage, it has shown encouraging clinical activity in HER2-positive breast cancer (phase I objective response rate [ORR], 60.3%). Such designs suggest that future ADCs can achieve precision enhancement through payload combinations rather than simple toxicity superposition.

Rather than generic applications, artificial intelligence (AI) is increasingly being explored to support advancements in ADC engineering. For instance, deep learning frameworks and structural prediction models (e.g., AlphaFold-based iterations) are extensively utilized to optimize antibody-antigen binding affinities and design environment-responsive, structurally stable linkers, thereby minimizing off-target payload release [42]. Furthermore, AI-driven spatial multi-omics and digital

Table 1 Summary of Landmark Clinical Trials Evaluating ADCs in Breast Cancer

Trial Name (Phase)	Target & Drug	Study Population	Key Efficacy Outcomes
DESTINY-Breast04 (III)	HER2 (T-DXd)	HER2-low metastatic breast cancer	Median PFS: 9.9 vs. 5.1 months. Median OS: 23.4 vs. 16.8 months.
DESTINY-Breast03 (III)	HER2 (T-DXd)	HER2-positive breast cancer	Median PFS: 28.8 vs. 6.8 months (vs. T-DM1).
ASCENT (III)	TROP-2 (SG)	Pretreated metastatic TNBC	Median PFS: 5.6 vs. 1.7 months. ORR: ~35%.
OptiTROP-Breast01 (III)	TROP-2 (SKB264)	3 L TNBC	Median PFS: 5.7 vs. 2.3 months (HR = 0.31).
TROPiCS-02 (III)	TROP-2 (SG)	HR+/HER2- metastatic breast cancer	Median OS: 14.4 vs. 11.2 months.
TROPION-Breast01 (III)	TROP-2 (Dato-DXd)	HR+/HER2- advanced breast cancer	Median PFS: 6.9 vs. 4.9 months. OS non-significant (18.6 vs. 18.3 months).
ICARUS-BREAST01 (II)	HER3 (HER3-DXd)	HR+/HER2- advanced breast cancer	ORR: 53.5%. Median PFS: 9.4 months.
U31402-A-J101 (I/II)	HER3 (HER3-DXd)	Pretreated HER3-expressing breast cancer	Overall ORR: ~28–30%. HR+/HER2- ORR: ~30%; TNBC ORR: ~22%.

1. Clinical terms: PFS, progression-free survival; OS, overall survival; ORR, objective response rate; HR, hazard ratio; TNBC, triple-negative breast cancer; HR+/HER2-, hormone receptor–positive/HER2-negative

2. Drug abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; SG, sacituzumab govitecan; SKB264, sacituzumab tirumotecan; Dato-DXd, datopotamab deruxtecan; HER3-DXd, patritumab deruxtecan

3. Notes: Outcomes shown are representative primary or key secondary efficacy results reported in landmark clinical trials. Cross-trial comparisons should be interpreted with caution because of differences in study population, treatment line, trial design, and follow-up duration

pathology are being integrated to map complex TME architectures and may help identify patient subpopulations with specific immunosuppressive signatures who are most likely to benefit from immune-modulating payloads. With continuous optimization across multiple dimensions—such as target mining, responsive linker design, and payload function expansion—ADC configurations are extending beyond drug delivery efficiency toward possible modulation of the tumor microenvironment [43].

HER2-targeting ADCs: clinical evolution and expansion into HER2-low disease

In the treatment of HER2-positive breast cancer, ADCs have significantly expanded the therapeutic landscape. Represented by Trastuzumab emtansine (T-DM1), these ADCs deliver the microtubule inhibitor DM1 to HER2-overexpressing tumors and have demonstrated clear clinical benefits in pretreated patients, such as significantly improving PFS and OS in pivotal Phase II/III studies [11, 44, 45]. Subsequently, the second-generation ADC trastuzumab deruxtecan (T-DXd) showed substantial clinical activity in patients with HER2-low (IHC 1 + or IHC 2+/ISH–) metastatic breast cancer. The DXd released by T-DXd induces immunogenic cell death in tumor cells and activates myeloid cells such as dendritic cells via the TLR4/STING pathway, enhancing antigen presentation and $CD8^+$ T cell effector function [13]. In the pivotal Phase III DESTINY-Breast04 trial (Table 1), T-DXd significantly improved PFS (median 9.9 vs. 5.1 months) and OS (median 23.4 vs. 16.8 months) compared with physician's choice chemotherapy, leading to its approval for HER2-low breast cancer [46]. Compared to the traditional HER2-ADC (T-DM1), T-DXd significantly increased HMGB1 (High-Mobility Group Box 1) release and calreticulin (CALR) exposure levels [47]. In the head-to-head DESTINY-Breast03 study (Table 1), T-DXd demonstrated a longer median PFS (28.8 vs. 6.8 months) and a favorable survival trend compared to T-DM1, supporting its role as a preferred second-line treatment option [48].

HER2-low breast cancer accounts for approximately 45–55% of all cases in multiple large-scale real-world cohorts and is considered to exist on a continuous spectrum of HER2 protein expression rather than as an independent molecular subtype. While predominantly overlapping with hormone receptor-positive disease, its prognostic significance remains inconsistent across studies [44, 48]. Leveraging the bystander effect of its lipophilic topoisomerase I inhibitor, T-DXd can generate broader cell killing within tumors with heterogeneous HER2 expression. In DESTINY-Breast04 (Table 1), T-DXd significantly improved the objective response rate in HER2-low patients (ORR > 50% in the HR+ subgroup), supporting its therapeutic role in this population. However, treatment strategies for HER2-low disease are still limited by fluctuations in target expression caused by spatiotemporal heterogeneity, as well as the impact of potential genomic events (such as PIK3CA mutations) on ADC efficacy. Therefore, further work is needed to evaluate circulating tumor DNA (ctDNA) and spatial omics approaches for dynamic biomarker monitoring.

Resistance has become a major bottleneck in clinical practice. While specific intracellular resistance paradigms are detailed in subsequent sections (Supplementary Figure S1), emerging engineering strategies are actively addressing these bottlenecks. Preclinical studies suggest that bispecific ADCs, by simultaneously targeting HER2 and compensatory antigens (such as HER3), can overcome resistance caused by the downregulation of a single HER2 antigen [49, 50]. Endocytic defects are related to dysregulation of the clathrin pathway, and basic research is exploring lysosome-targeting peptides

to enhance internalization efficiency. Cross-activation of signaling pathways occurs via HER2/EGFR dimerization or PI3K-AKT compensatory transduction; theoretical models demonstrate that pan-HER inhibitors may have the potential to overcome this. Immune microenvironment suppression involves the infiltration of tumor-associated macrophages and T cell exhaustion; early combination studies are exploring the value of PD-1/PD-L1 inhibitors. Future directions may involve exploring precise resistance reversal strategies through linker optimization and the integration of spatial multi-omics.

To further overcome mechanisms of resistance—such as aberrant endocytic trafficking and dynamic antigen downregulation—emerging biparatopic ADCs are reshaping HER2-targeted strategies [51]. By binding to two distinct, non-overlapping epitopes of HER2 (e.g., extracellular domains II and IV), these agents promote rapid receptor clustering, enhanced internalization, and improved lysosomal trafficking compared to traditional monospecific ADCs [52]. Notable examples include zanidatamab zovodotin (ZW49), which utilizes an auristatin-based payload and has shown the potential to induce immunogenic cell death and overcome trastuzumab resistance in early-phase studies [53]. Similarly, JSKN003, a biparatopic HER2-ADC utilizing a glycan-specific site-directed conjugation platform with a topoisomerase I inhibitor payload, has shown favorable serum stability and a bystander effect in early studies [54]. Recent pooled analyses of early-phase studies reported encouraging objective response rates in heavily pretreated HER2-positive breast cancer, supporting further evaluation of dual-epitope engagement [54].

Thus, HER2-targeted ADC therapy has evolved from T-DM1 to T-DXd and from HER2-high to HER2-low disease settings. This evolution has expanded the eligible patient population and broadened the clinical relevance of HER2 expression levels in treatment selection. Table 2 shows the currently approved HER2-targeting ADC drugs for breast cancer.

TROP-2–targeting ADCs in TNBC and HR+/HER2- negative breast cancer

TROP-2–targeting ADCs have emerged as important therapeutic options in advanced breast cancer and are influencing treatment strategies in selected refractory subgroups [55]. Sacituzumab tirumotecan (SKB264) was approved by the NMPA in China in 2024 for the third-line treatment of TNBC. Its Phase III study OptiTROP-Breast01 trial (Table 1) showed a median PFS of 5.7 months (a 148% improvement over chemotherapy) and a 69% reduction in the risk of disease progression [56]. The drug is also being expanded to HR+/HER2- breast cancer, with a single-agent ORR of 31.7% [56]. Sacituzumab govitecan (Trodelvy) became the first TROP-2 ADC to

Table 2 Approved HER2-Targeting ADC Drugs for Breast Cancer (as of November 2025)

Drug Name (Generic/Brand)	Target	Antibody Type	Linker Type	Cytotoxic Payload	Payload Mechanism of Action	US Approval & Indications	China Approval & Indications	Manufacturer	Key Notes
Trastuzumab Emtansine (T-DM1/Kadcyla)	HER2	Humanized IgG1 (Trastuzumab)	Non-cleavable thioether (MCC)	DM1 (Maytansinoid)	Microtubule inhibition → G2/M arrest	2013: HER2+ metastatic BC (≥2L therapy)	2020: Adjuvant therapy & metastatic 2L therapy	Roche	No bystander effect; adjuvant indication in NRDL
Fam-trastuzumab Deruxtecan (DS-8201/Enhertu)	HER2	Humanized IgG1 (Trastuzumab variant)	Cleavable tetrapeptide (Gly-Gly-Phe-Gly)	DXd (Topo I inhibitor)	DNA double-strand break induction	Dec 2019: HER2+ metastatic BC (≥3L); May 2022: HER2+ 2L therapy; Aug 2022: HER2-low (IHC 1+/2+); Jan 2025: HR+/HER2-ultralow (IHC 0)	2023: HER2+/low metastatic BC	AstraZeneca/Daiichi Sankyo	Bystander effect; ILD risk (Boxed Warning)

1. Clinical terms: PFS, progression-free survival; OS, overall survival; ORR, objective response rate; ILD, interstitial lung disease; TRAE, treatment-related adverse event; BC, breast cancer; TNBC, triple-negative breast cancer
2. Regulatory terms: AA, accelerated approval; FA, full approval; NRDL, National Reimbursement Drug List; IHC, immunohistochemistry
3. Mechanistic notes: DAR, drug-to-antibody ratio; bystander effect, diffusion of released payload into neighboring tumor cells, which may be relevant in tumors with heterogeneous antigen expression
4. Approval status and indications are summarized according to publicly available regulatory documents and major trial publications. Regulatory status may evolve over time and should be interpreted in the context of the approval date indicated in the table

cover the HR+/HER2- subtype. Its payload, SN-38, can induce immunogenic cell death in tumor cells, enhancing T cell infiltration into the tumor [57]. The Phase III TROPiCS-02 study (Table 1) extended the median OS of patients from 11.2 months to 14.4 months (reducing the risk of death by 21%) [55]. In 2025, Datopotamab deruxtecan (Dato-DXd) filed for approval in China based on TROPION-Breast01 study data (Table 1), which showed a 37% reduction in the risk of disease progression in HR+/HER2- patients (median PFS 6.9 vs. 4.9 months), with the incidence of Grade 3 adverse events being only half that of the chemotherapy group (21% vs. 45%) [58]. Combination strategies with immunotherapy are also being explored in multiple tumor types, providing a biological rationale for similar approaches in breast cancer. For example, SKB264 combined with a PD-L1 inhibitor showed encouraging PFS signals (approximately 15.4 months) in a small early cohort of NSCLC. This supports the biological rationale for exploring combination strategies in breast cancer and suggests potential synergy, although clinical benefit remains to be confirmed in randomized trials [56].

Beyond the established landscape of SG and Dato-DXd, a new wave of structurally optimized TROP-2 ADCs is entering preclinical and early clinical validation, with a strong focus on immunomodulation and overcoming multidrug resistance. For instance, OBI-992 targets a unique cysteine-rich domain (CRD) epitope of TROP-2 and utilizes a highly hydrophilic, enzyme-cleavable linker paired with exatecan. Preclinical data highlight its ability to bypass ATP-binding cassette (ABC) transporter-mediated efflux pumps (such as BCRP), showing synergistic efficacy when combined with PARP or immune checkpoint inhibitors [59]. Another innovative construct is hIMB1636-LDP-AE, which is engineered via molecular reconstitution incorporating lidamycin (LDM). This ADC exerts potent sub-nanomolar cytotoxicity and exhibits significantly lower myelotoxicity in moderate TROP-2 expressing models compared to SG [60]. Furthermore, the bispecific ADC BCG033, simultaneously targeting PTK7 and TROP-2, illustrates the next frontier in TNBC therapy. By utilizing a "low-affinity TROP-2 arm," BCG033 is designed to selectively accumulate in tumors co-expressing both antigens, thereby maximizing tumor-specific delivery while mitigating the classical TROP-2-related on-target off-tumor toxicities (e.g., skin rash) [61].

Resistance arises from the interplay of target heterogeneity, signaling compensation, and microenvironmental suppression. At the target level, TROP-2 expression is transcriptionally regulated, and chemotherapy-mediated epigenetic modifications may downregulate its expression. At the signaling level, the interaction between TROP-2 and IGF1R activates the AKT axis, while compensatory upregulation of PI3K-AKT/mTOR weakens ADC toxicity. At the microenvironment level, TROP-2 may indirectly promote the polarization of tumor-associated macrophages towards the M2 phenotype, contributing to an immunosuppressive microenvironment [62]. Baseline differences in TROP-2 expression across tumor types are significant, and the principles governing its dynamic changes during resistance remain to be elucidated. Table 3 shows the currently approved TROP-2-targeting ADC drugs for breast cancer.

HER3-targeting ADCs: emerging clinical evidence and current challenges

HER3 (ERBB3), as a member of the EGFR family, lacks intracellular kinase activity but fuels tumor proliferation, metastasis, and chemotherapy resistance by forming potent heterodimers with HER2, preferentially activating the PI3K-AKT pathway and synergistically stimulating MAPK/ERK signaling [63]. In breast cancer, HER3 expression is relatively common and associated with poor prognosis and endocrine resistance [64–66], yet traditional HER3 monoclonal antibodies have limited efficacy. New-generation HER3-ADCs, represented by patritumab deruxtecan (HER3-DXd), employ a design with a cleavable tetrapeptide linker conjugated to the topoisomerase I inhibitor DXd payload. They possess the potential for a bystander effect and have demonstrated considerable anti-tumor activity in early clinical trials and in vitro models [67, 68]. In a pooled analysis of the Phase I/II study U31402-A-J101 (NCT02980341) (Table 1), patritumab deruxtecan showed significant differences in ORR across different subgroups of pretreated HER3-expressing breast cancer patients (overall pooled ORR approximately 28–30%; HR+/HER2- cohort approximately 30%; TNBC cohort approximately 22%), and its efficacy requires further exploration in large-scale trials [69, 70]. Additionally, EGFR×HER3 bispecific ADCs are still in early clinical stages, and efficacy data are not yet mature [71, 72]. Currently, no HER3 ADC is approved for breast cancer indications, and all drugs rely on clinical trial exploration [69, 71].

Current major challenges include elucidating how HER3 expression and downstream signaling pathways evolve dynamically during treatment, and developing new strategies to overcome epigenetic/signaling compensation and microenvironment-related resistance. Literature suggests that compensatory activation among HER family members (including EGFR/HER3/HER4) may drive resistance, but systematic spatiotemporal evolution data are still lacking [63, 73]. Response strategies are still in the exploratory phase: some bispecific ADCs have entered late-stage trials in non-breast tumors, while combination strategies with PI3K-AKT pathway inhibitors are currently based mainly on preclinical evidence and

Table 3 Approved TROP-2-Targeting ADC Drugs for Breast Cancer (as of November 2025)

Drug Name (Generic/Brand)	Target	Antibody Type	Linker Type	Cytotoxic Payload	Payload Mechanism of Action	US Approval & Indications	China Approval & Indications	Manufacturer	Key Notes
Sacituzumab Govitecan (Trodelvy)	TROP-2	Humanized IgG1 (hRS7)	Cleavable hydrazone (CL2A)	SN-38 (Topo I inhibitor)	Topo I inhibition → DNA replication block	Apr 2020 (AA): TNBC 3L; Apr 2021 (FA); Feb 2023: HR+/HER2- BC	Jun 2022: TNBC 3L; Mar 2023: HR+/HER2- BC	Gilead (ex-Immunomedics)	Hematologic toxicity (neutropenia 31%)
Datopotamab Deruxtecan (Dato-DXd/Datroway)	TROP-2	Humanized IgG1	Cleavable β-glucuronide linker	DXd (Topo I inhibitor)	DNA damage induction	Jan 17, 2025: HR+/HER2- advanced BC (post-ET/CT)	Expected 2025 Q3 (under review)	AstraZeneca/Daiichi Sankyo	OS non-significant (18.6 vs 18.3 mo; HR=1.01); Lower rate of grade ≥3 TRAEs than chemotherapy
Sacituzumab Tirumotecan (SKB264/Jiatekai)	TROP-2	Humanized IgG1	Modified CL2A linker	KL610023 (Topo I inhibitor)	DNA integrity disruption	Not approved	Nov 2024: TNBC 3L; May 2025: HR+/HER2- indication under review	Kelun-Biotech	First domestic TROP-2 ADC; phase III PFS 5.7 vs. 2.3 months in TNBC (HR=0.31)

1. Clinical terms: PFS, progression-free survival; OS, overall survival; ORR, objective response rate; ILD, interstitial lung disease; TRAE, treatment-related adverse event; BC, breast cancer; TNBC, triple-negative breast cancer

2. Regulatory terms: AA, accelerated approval; FA, full approval; NRDL, National Reimbursement Drug List

3. Mechanistic notes: DAR, drug-to-antibody ratio; bystander effect, diffusion of released payload into neighboring tumor cells, which may contribute to activity in antigen-heterogeneous tumors

4. Approval status and indications are summarized according to publicly available regulatory documents and major clinical trial reports. For agents under regulatory review, descriptions refer to the status at the time of manuscript preparation

require verification of safety and potentiation through clinical trials [74]. Table 4 shows HER3-targeting ADC drugs currently in clinical trials specifically for breast cancer. Supplementary Table S1 shows HER3-targeting ADCs in clinical trials that include breast cancer exploration but are not exclusive to it.

Target-specific and payload-mediated resistance mechanisms

To fully unlock the potential of next-generation ADCs, it is critical to delineate the intricate target-specific and payload-mediated resistance mechanisms. For TROP-2-targeted ADCs, recent genomic profiling has revealed that acquired resistance often involves parallel genomic alterations. Specifically, a novel TACSTD2/TROP-2 T256R missense mutation has been shown to confer resistance to sacituzumab govitecan (SG) by causing defective plasma membrane localization and reduced cell-surface binding of the antibody, operating alongside canonical TOP1 payload-resistance mutations (e.g., E418K) [75]. Payload-driven resistance may have important clinical implications; a large-scale real-world study recently demonstrated that prior treatment with SG is associated with significantly inferior outcomes upon subsequent trastuzumab deruxtecan (T-DXd) therapy, strongly suggesting cross-resistance mediated by their shared topoisomerase I inhibitor payloads [76].

In the context of HER2-targeted ADCs, mechanisms of resistance extend far beyond simple antigen downregulation, involving dynamic spatial redistribution and intricate compensatory signaling. Recent mechanistic studies highlight that upregulation of PAK5 kinase promotes resistance by driving the nuclear accumulation of HER2 (N-HER2), effectively sequestering the target away from the cell surface and reducing ADC accessibility [77]. Furthermore, the HER family exhibits profound network plasticity. The compensatory activation of ERBB3 (HER3) and intricate signal crosstalk frequently emerge under sustained HER2 blockade [78]. This cross-compensation is tightly regulated by cellular phosphatases; for instance, the loss of the phosphatase PTPRO leads to the hyperactivation of ERBB3 and downstream SRC pathways, identifying PTPRO as a critical node whose upregulation can counteract trastuzumab-based resistance [79].

Moreover, the distinct payload classes dictate disparate resistance profiles among HER2 ADCs. Resistance to the earlier-generation T-DM1 is frequently driven by MDR1/ABCB1-mediated drug efflux and impaired lysosomal degradation (e.g., SLC46A3 downregulation). In contrast, the topoisomerase I inhibitor payload in T-DXd is a poor substrate for MDR1, enabling it to bypass these classical efflux pumps. Instead, T-DXd resistance predominantly shifts toward SLX4-driven DNA repair alterations and TOP1 integrity, highlighting the necessity of tailoring

Table 4 Clinical Trial List of HER3-Targeting ADC Drugs for Breast Cancer (Focus on Breast Cancer Indications)

Drug Name	Sponsor	Target Structure	Breast Cancer-Specific Trial	Key Breast Cancer Data	Development Stage
Patritumab deruxtecan (HER3-DXd)	Daiichi Sankyo	Anti-HER3 mAb	ICARUS-BREAST01 Phase II (NCT04699630) • Population: HR+/HER2- advanced breast cancer (≥2 prior therapies)	• ORR=53.5% (95%CI: 43.7–63.1) • Median PFS=9.4 months • TRAE-related discontinuation: 9.6% • ILD incidence: 5.8% (Grade ≥3: 1.9%)	Phase III advancing
Iza-bren (BL-B01D1)	SystImmune (Baili)	EGFR×HER3 bispecific	IZABRIGHT-Breast01 Phase II/III (NCT06392770) • Population: PD-(L)1 ineligible TNBC (vs. chemotherapy)	• Phase I TNBC subgroup: ORR=59.5% • Disease control rate DCR=91.7% (ASCO 2023) • Grade ≥3 TRAE: Neutropenia (45.8%)	Phase III ongoing
U3-1402	Daiichi Sankyo	Anti-HER3 mAb	Pan-tumor Phase I/II (NCT03260491) • Breast cancer subgroup: HER2+ (n=28) & HER2-low (n=18)	• HER2+ group ORR=42.9% • Median PFS=11.0 months • No strong HER3 expression-efficacy correlation	Phase III (lung focus)

1. Clinical terms: ORR, objective response rate; PFS, progression-free survival; DCR, disease control rate; TRAE, treatment-related adverse event; ILD, interstitial lung disease; TNBC, triple-negative breast cancer; HR+/HER2-, hormone receptor–positive/HER2-negative

2. This table summarizes HER3-targeting ADCs in clinical development with breast cancer–specific data or dedicated breast cancer cohorts. Reported outcomes

sequential ADC therapies based on specific acquired resistance profiles.

The role of the tumor microenvironment in ADC efficacy and reprogramming strategies

The TME may present multiple barriers to ADC efficacy: physical barriers and immunosuppression conspire to attenuate drug potency [16]. The dense extracellular matrix (ECM) and high interstitial pressure significantly limit the uniform penetration of ADCs in tumor tissue, leading to insufficient drug concentration and incomplete killing in the tumor core [80]. Simultaneously, immunosuppressive cells in the TME (such as tumor-associated macrophages, TAMs) inhibit T cell function by secreting factors like TGF-β and IL-10 and expressing "don't eat me" signals (CD47/SIRPα axis). This contributes to an immunosuppressive microenvironment that may attenuate ADC activity [80]. Collectively, preclinical models support a mechanistic contribution of these TME features to restricted ADC penetration and activity; however, their relative causal weight in patients is context dependent and should be interpreted as one of several converging determinants of ADC response [81]. Furthermore, this dense stroma creates a "binding-site barrier," prematurely sequestering ADCs at the tumor periphery and shielding the hypoxic core from cytotoxic payloads [50, 82]. Furthermore, non-specific linker cleavage, target heterogeneity, and signaling compensation further exacerbate resistance, making it difficult for ADC monotherapy to break through the efficacy bottleneck [30, 83, 84].

Strategies to reprogram the TME are advancing along two parallel tracks: linker optimization and immune combinations. New-generation ADCs employ controlled-release linkers to improve tumor specificity. For example, Datopotamab deruxtecan (Dato-DXd) uses a GGFG tetrapeptide linker cleavable by intracellular lysosomal proteases (e.g., cathepsins) in tumor cells. This design allows precise drug release only within target cells, thereby enhancing intratumoral concentration and reducing peripheral toxicity [85]. In immune combination strategies, reversing the "immune desert" involves inhibiting immune checkpoints and clearing immunosuppressive cells. CD47 blockers and PD-1 inhibitors have shown synergistic potential in early studies; by clearing M2-type TAMs and restoring T cell function, they may reverse the immunosuppressive microenvironment [80, 86]. Frontier directions cover oncolytic viruses to disrupt matrix barriers and AI-assisted design to predict drug distribution, but most are still in preclinical stages [87, 88]. Notably, these strategies need to integrate dynamic biomarker monitoring, such as spatial transcriptomics to resolve TME heterogeneity, to guide personalized medication [89].

Future research may benefit from moving beyond barrier penetration alone toward broader modulation of the tumor microenvironment. Further improvements in efficacy will likely require ADC design strategies that integrate drug delivery, immune regulation, and biomarker-guided patient selection. Although TME reprogramming holds broad prospects, clinical translation still faces challenges in mechanistic complexity and technological maturity. Through interdisciplinary collaboration, combining computational simulation with experimental validation, and continuously refining ADC design and personalized treatment regimens, the TME may become a therapeutically tractable component that can be modulated to improve ADC efficacy, although this concept still requires substantial clinical validation (Fig. 3).

Emerging delivery systems for more precise TME regulation

Nanotechnology and biomimetic strategies, including stimuli-responsive systems and cell-membrane coating approaches, are expanding ADC delivery concepts beyond passive targeting toward more context-dependent interaction with the tumor microenvironment [90, 91]. Stimuli-responsive nanosystems achieve spatiotemporally precise drug release by sensing TME-specific signals;

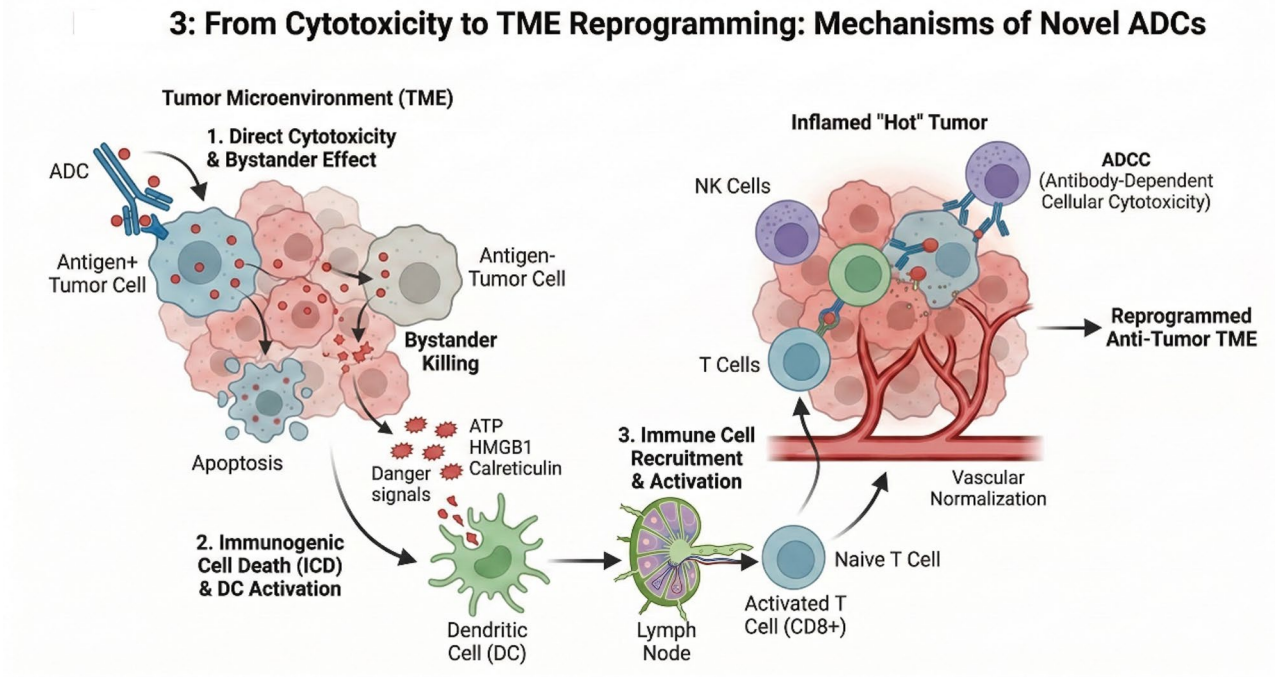

Fig. 3 ADC-mediated reprogramming of the tumor microenvironment (TME). The schematic illustrates a transition from a restrictive, immunosuppressive TME (left) to a more immunologically active microenvironment (right). This remodeling is driven by next-generation strategies, particularly payload-induced immunogenic cell death (ICD) and subsequent recruitment of effector T cells

pH-sensitive and enzyme-cleavable dual-response strategies can enhance drug release efficiency in the acidic tumor microenvironment and reduce peripheral toxicity [90, 92]. For instance, the cleavable tetrapeptide linker (GGFG) relies on cathepsin B for intracellular specific release, a design that successfully reduced the risk of disease progression by 37% in patients with HR+/HER2- breast cancer in the Phase III study of Dato-DXd [58, 93, 94]. Biomimetic technologies, such as macrophage membrane-coated nanocarriers, utilize surface CD47 proteins to transmit "don't eat me" signals to extend circulation half-life; preclinical models show a 2–3 fold increase in tumor accumulation [91, 95].

Multimodal strategies and intelligent design may help address barriers imposed by the TME. Oncolytic viruses, by disrupting matrix barriers and releasing danger signals, theoretically can synergize with ADCs to enhance drug penetration and immune activation, but indications for breast cancer are still in the preclinical exploration stage [96]. AI-assisted design platforms, such as Schrödinger's LiveDesign system, can optimize carrier structures by predicting drug-matrix interactions, yet their clinical translational value requires validation in Phase I trials [90]. Overall, these advances suggest that ADC delivery strategies are evolving toward more precise spatial and temporal control, but translation of promising preclinical findings into confirmed clinical benefit still requires rigorous toxicology, pharmacokinetic studies, controlled clinical trials, and validation using dynamic biomarkers and spatial omics.

Integration of artificial intelligence and digital twin modeling in ADC optimization

To support the transition from precision delivery to microenvironmental modulation, artificial intelligence (AI) and digital twin (DT) technologies are increasingly being explored. Rather than relying on empirical trial-and-error, AI-based approaches—particularly deep learning models for protein structure prediction (e.g., AlphaFold-based iterations) and molecular docking—are increasingly being applied to the early screening of novel payloads and to the design of conditionally cleavable linkers tailored to specific TME enzymes (such as legumain or cathepsins) [97, 98]. Furthermore, machine learning models utilizing spatial transcriptomics and multiplex immunofluorescence (mIF) data may help predict the "bystander effect" radius of different ADCs, thereby matching the optimal linker-payload combination to the specific spatial heterogeneity of a patient's TME [99, 100].

In the clinical translation phase, digital twin modeling represents a potentially useful conceptual framework. An oncological DT creates a dynamic, multi-scale computational replica of a patient's tumor and its immune microenvironment, continuously updated with real-world clinical and multi-omic data [101, 102]. By simulating the spatiotemporal pharmacokinetics (PK) and pharmacodynamics (PD) of ADCs within this virtual TME, DT

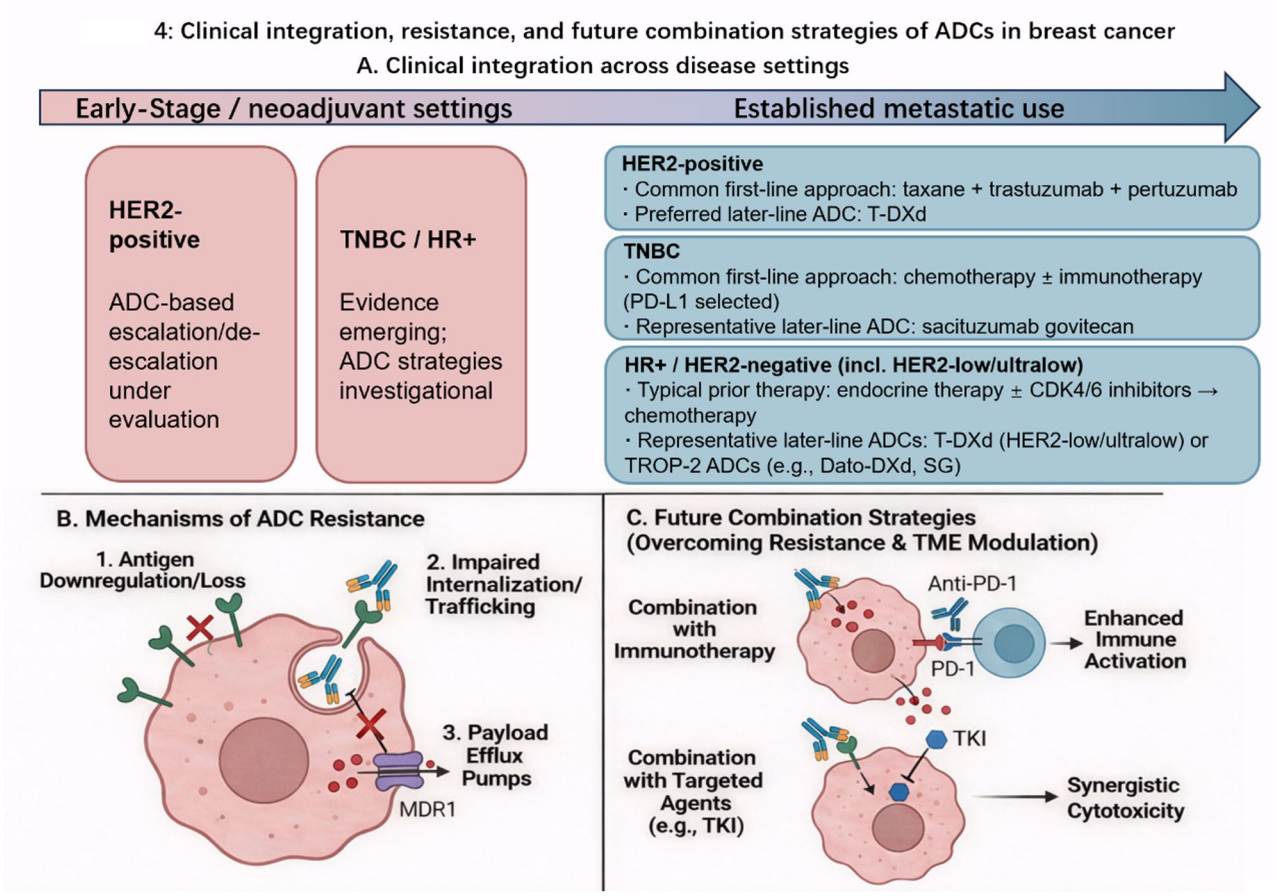

Fig. 4 Clinical integration, resistance mechanisms, and emerging combination strategies of antibody–drug conjugates in breast cancer. (**A**) Clinical integration across disease settings. Panel A summarizes the current clinical landscape of ADC use across disease settings, including investigational exploration in earlier-stage and neoadjuvant settings and established use in metastatic disease. In earlier-stage disease, ADC-containing strategies remain investigational, and the maturity of evidence differs across breast cancer subtypes. In metastatic disease, representative subtype-specific treatment patterns are shown for HER2-positive, TNBC, and HR+/HER2-negative disease, including HER2-low/ultralow tumors. (**B**) Resistance mechanisms. Panel B illustrates key mechanisms that may limit sustained ADC efficacy, including antigen downregulation or loss, impaired internalization or intracellular trafficking, and active payload efflux. (**C**) Emerging combination strategies. Panel C summarizes rational therapeutic combinations being explored to enhance ADC efficacy and overcome resistance, including immune checkpoint blockade and tyrosine kinase inhibitors (TKIs). Together, these panels provide an integrated overview of the clinical integration, resistance mechanisms, and emerging therapeutic strategies of ADCs in breast cancer

models can predict interstitial fluid pressure barriers and optimal dosing schedules. In principle, such computational modeling could support virtual evaluation of synergistic combinations—such as ADCs with immune checkpoint inhibitors or anti-angiogenic agents—to help identify regimens that may improve tumor penetration and immunogenic cell death while mitigating cumulative toxicities [103, 104].

Clinical integration, resistance mechanisms, and future combination strategies of ADCs in breast cancer

ADC development is moving beyond single-target cytotoxic delivery toward more integrated strategies that combine controlled drug release with modulation of the tumor microenvironment (TME). As summarized in Fig. 4, current ADC development in breast cancer spans three closely related dimensions: clinical integration across disease settings, emerging mechanisms of resistance that limit durable benefit, and rational combination strategies designed to enhance efficacy.

Clinically, ADCs are increasingly being evaluated in earlier lines of therapy, moving beyond late-line settings. As illustrated in Fig. 4A, their integration into neoadjuvant and adjuvant treatment strategies remains largely investigational, with ongoing studies exploring their potential to improve pathological response and long-term outcomes. Nevertheless, the level of evidence supporting this transition varies across tumor subtypes and disease stages. In the metastatic setting, ADCs have already become important components of treatment across multiple subtypes, including HER2-positive, TROP-2–expressing, and HER2-low/ultralow disease settings [58].

However, broader clinical integration also requires a clearer understanding of the biological barriers that may constrain sustained benefit. As summarized in Fig. 4B, resistance to ADCs may arise from multiple mechanisms, including antigen downregulation or loss, impaired internalization or intracellular trafficking, and active payload efflux [50, 105]. These resistance processes, together with tumor microenvironment–associated barriers, may contribute to heterogeneous treatment responses across clinical settings and may ultimately influence the effectiveness of ADC sequencing and combination strategies [106, 107].

In this context, current therapeutic development increasingly includes rational combination strategies aimed at overcoming these barriers. As outlined in Fig. 4C, combinations with immune checkpoint inhibitors, tyrosine kinase inhibitors (TKIs), and other targeted or microenvironment-directed agents are being explored to enhance ADC efficacy. These approaches are supported by mechanistic rationale and early-phase evidence, particularly in settings where immune suppression, stromal restriction, or adaptive signaling may attenuate ADC activity. However, their clinical benefit and optimal positioning remain to be confirmed in randomized trials [98, 108].

A central requirement for successful clinical translation is the establishment of a robust evidentiary framework together with biomarker-driven patient selection. Computational approaches, including artificial intelligence and multi-omics integration, may facilitate the identification of optimal targets and ADC components. Dynamic biomarkers, including spatial transcriptomics and circulating tumor DNA (ctDNA), may further help refine patient stratification and treatment sequencing. Nonetheless, prospective studies guiding ADC selection, switching, and combination use remain limited. Overall, future progress in ADC development will depend on integrating rational drug design, resistance-informed therapeutic strategies, and high-quality clinical evidence to achieve consistent and clinically meaningful benefit across patient populations.

Conclusion

In summary, antibody–drug conjugates have expanded the therapeutic landscape of breast cancer and continue to evolve through advances in target selection, linker chemistry, and payload design [47, 109]. At the same time, accumulating evidence indicates that the tumor microenvironment plays an important role in shaping treatment response and resistance, supporting further evaluation of combination strategies and next-generation ADC development [110]. This review has several limitations. As a narrative synthesis, it is inherently influenced by heterogeneity across study designs, patient populations, treatment lines, and follow-up duration, and does not provide the methodological rigor of a formal systematic review or meta-analysis. In addition, several emerging themes discussed here—including AI-assisted ADC design, digital twin modeling, and TME-directed combination strategies—are supported predominantly by preclinical findings, early-phase clinical trials, retrospective analyses, or subgroup studies and therefore should be interpreted cautiously. Further prospective and well-controlled investigations are needed to validate these findings and to better define the optimal integration of ADCs across different clinical settings. Continued efforts to refine patient selection and to understand resistance mechanisms will be essential for maximizing the clinical benefit of ADC-based therapies.

Abbreviations

ADC	Antibody–Drug Conjugate
ADCC	Antibody-Dependent Cellular Cytotoxicity
AI	Artificial Intelligence
CALR	Calreticulin
CL2A	Cleavable Linker Type
DAR	Drug-to-Antibody Ratio
Dato-DXd	Datopotamab Deruxtecan
DCR	Disease Control Rate
DT	Digital Twin
DXd	Topoisomerase I Inhibitor Payload
EGFR	Epidermal Growth Factor Receptor
HER2	Human Epidermal Growth Factor Receptor 2
HER3	Human Epidermal Growth Factor Receptor 3
HMGB1	High-Mobility Group Box 1
HR+	Hormone Receptor–Positive
ICD	Immunogenic Cell Death
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
mAb	Monoclonal Antibody
mIF	Multiplex Immunofluorescence
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PI3K	Phosphatidylinositol 3-Kinase
SG	Sacituzumab Govitecan
SKB264	Sacituzumab Tirumotecan
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TKIs	Tyrosine Kinase Inhibitors
TLR	Toll-Like Receptor
TME	Tumor Microenvironment
TNBC	Triple-Negative Breast Cancer
TROP-2	Trophoblast cell surface antigen 2

Acknowledgements

Not applicable.

Author contributions

J.L.W. conceptualized and designed the study. N.L. and B.Y. performed the literature search and wrote the main manuscript text. Y.Q.L. assisted in the preparation of figures and tables. J.L.W. critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable. This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability
Not applicable. No datasets were generated or analyzed during the current study. All information included in this review is derived from previously published literature.

Declarations

Ethics approval and consent to participate
Not applicable. This manuscript is a review article and does not involve any original studies with human participants or animals performed by any of the authors.

Consent for publication
Not applicable. This review contains no individual patient data, images, or identifying information.

Competing interests
The authors declare no competing interests.

Received: 13 December 2025 / Accepted: 8 April 2026
Published online: 27 April 2026

References

1. Bray F, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49.
3. Fang F, Zhang X, Li J. Personalized Trastuzumab-Induced Cardiac Dysfunction Risk Stratification and Surveillance. JACC CardioOncol. 2025;7(3):216–8.
4. Harbeck N, et al. Breast cancer. Nat Rev Dis Primers. 2019;5(1):66.
5. Lee JS, et al. CDK4/6 Inhibitor Resistance in Hormone Receptor-Positive Metastatic Breast Cancer: Translational Research, Clinical Trials, and Future Directions. Int J Mol Sci. 2023;24(14):11791.
6. Vernieri C, et al. Resistance mechanisms to anti-HER2 therapies in HER2-positive breast cancer: Current knowledge, new research directions and therapeutic perspectives. Crit Rev Oncol Hematol. 2019;139:53–66.
7. Wang X, et al. Effect of Capecitabine Maintenance Therapy Using Lower Dosage and Higher Frequency vs Observation on Disease-Free Survival Among Patients With Early-Stage Triple-Negative Breast Cancer Who Had Received Standard Treatment: The SYSUCC-001 Randomized Clinical Trial. JAMA. 2021;325(1):50–8.
8. Bianchini G, et al. Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. Nat Rev Clin Oncol. 2022;19(2):91–113.
9. Chang HL, Schwettmann B, McArthur HL, Chan IS. Antibody-drug conjugates in breast cancer: overcoming resistance and boosting immune response. J Clin Invest. 2023;133(18):e172156.
10. Dumontet C, et al. Antibody-drug conjugates come of age in oncology. Nat Rev Drug Discov. 2023;22(8):641–61.
11. Tarantino P, et al. Antibody-drug conjugates: Smart chemotherapy delivery across tumor histologies. CA Cancer J Clin. 2022;72(2):165–82.
12. Conilh L, et al. Payload diversification: a key step in the development of antibody-drug conjugates. J Hematol Oncol. 2023;16(1):3.
13. Tsao LC, et al. Effective extracellular payload release and immunomodulatory interactions govern the therapeutic effect of trastuzumab deruxtecan (T-DXd). Nat Commun. 2025;16(1):3167.
14. Modi S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022;387(1):9–20.
15. Kumari S, Raj S, Babu MA, Bhatti GK, Bhatti JS. Antibody-drug conjugates in cancer therapy: innovations, challenges, and future directions. Arch Pharm Res. 2024;47(1):40–65.
16. Tsuchikama K, et al. Exploring the next generation of antibody-drug conjugates. Nat Rev Clin Oncol. 2024;21(3):203–23.
17. Verma S, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783–91.
18. Wang S, et al. Development of a prosaposin-derived therapeutic cyclic peptide that targets ovarian cancer via the tumor microenvironment. Sci Transl Med. 2016;8(329):329ra34.
19. Liu M, et al. Metabolic rewiring of macrophages by CpG potentiates clearance of cancer cells and overcomes tumor-expressed CD47-mediated 'don't-eat-me' signal. Nat Immunol. 2019;20(3):265–75.
20. Fernandes RA, et al. Immune receptor inhibition through enforced phosphatase recruitment. Nature. 2020;586(7831):779–84.
21. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med. 2013;19(11):1423–37.
22. Wang B, et al. Potent and Prolonged Innate Immune Activation by Enzyme-Responsive Imidazoquinoline TLR7/8 Agonist Prodrug Vesicles. J Am Chem Soc. 2020;142(28):12133–9.
23. Burnouf PA, et al. Reversible glycosidic switch for secure delivery of molecular nanocargos. Nat Commun. 2018;9(1):1843.
24. Kadiyala P, et al. High-Density Lipoprotein-Mimicking Nanodiscs for Chemo-immunotherapy against Glioblastoma Multiforme. ACS Nano. 2019;13(2):1365–84.
25. Torrejon DY, et al. Overcoming Genetically Based Resistance Mechanisms to PD-1 Blockade. Cancer Discov. 2020;10(8):1140–57.
26. Zhao P, et al. Depletion of PD-1-positive cells ameliorates autoimmune disease. Nat Biomed Eng. 2019;3(4):292–305.
27. Maiti R, et al. Antibody drug conjugates as targeted cancer therapy: past development, present challenges and future opportunities. Arch Pharm Res. 2023;46(5):361–88.
28. Dongye Z, Li J, Wu Y. Toll-like receptor 9 agonists and combination therapies: strategies to modulate the tumour immune microenvironment for systemic anti-tumour immunity. Br J Cancer. 2022;127(9):1584–94.
29. Bardia A, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021;384(16):1529–41.
30. Bardia A, et al. Final Results From the Randomized Phase III ASCENT Clinical Trial in Metastatic Triple-Negative Breast Cancer and Association of Outcomes by Human Epidermal Growth Factor Receptor 2 and Trophoblast Cell Surface Antigen 2 Expression. J Clin Oncol. 2024;42(15):1738–44.
31. Hou J, Greten TF, Xia Q. Immunosuppressive cell death in cancer. Nat Rev Immunol. 2017;17(6):401.
32. Chen YF, et al. SNX10 deficiency impairs sensitivity to anti-HER2 antibody-drug conjugates via altering HER2 trafficking in HER2-positive breast cancer. Proc Natl Acad Sci U S A. 2025;122(16):e2417586122.
33. Wang R, et al. Antibody–Drug Conjugates (ADCs): current and future biopharmaceuticals. J Hematol Oncol. 2025;18(1):51.
34. Qi X, et al. Research Trend of Publications Concerning Antibody-Drug Conjugate in Solid Cancer: A Bibliometric Study. Front Pharmacol. 2022;13:921385.
35. Hunter FW, et al. Mechanisms of resistance to trastuzumab emtansine (T-DM1) in HER2-positive breast cancer. Br J Cancer. 2020;122(5):603–12.
36. Makhlin I, DeMichele A. Trastuzumab deruxtecan: An antibody-drug conjugate embracing its destiny in breast cancer. Cell Rep Med. 2022;3(6):100668.
37. Khatri VM, et al. Multi-institutional report of trastuzumab deruxtecan and stereotactic radiosurgery for HER2 positive and HER2-low breast cancer brain metastases. NPJ Breast Cancer. 2024;10(1):100.
38. Zong HF, et al. A novel bispecific antibody drug conjugate targeting HER2 and HER3 with potent therapeutic efficacy against breast cancer. Acta Pharmacol Sin. 2024;45(8):1727–39.
39. Wang Y, Guo C, Li W. Artificial intelligence in antibody-drug conjugate development. Trends Pharmacol Sci; 2025.
40. Zhang F, Li S. Antibody-drug conjugates as game changers in bladder cancer: current progress and future directions. Front Immunol. 2025;16:1591191.
41. Wang J, et al. Novel TROP2 antibody-drug conjugates for treatment of HER2-negative metastatic breast cancer patients with brain metastases: a promising option. ESMO Open. 2025;10(5):105059.
42. Croitoru A, Orr AA, MacKerell AD Jr. Harnessing computational technologies to facilitate antibody-drug conjugate development. Nat Chem Biol. 2025;21(8):1138–47.
43. Gupta N, et al. Development of a facile antibody-drug conjugate platform for increased stability and homogeneity. Chem Sci. 2017;8(3):2387–95.
44. Ogitani Y, et al. DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. Clin Cancer Res. 2016;22(20):5097–108.
45. Modi S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med. 2020;382(7):610–21.
46. Modi S, Jacot W, Iwata H, et al. Trastuzumab deruxtecan in HER2-low metastatic breast cancer: long-term survival analysis of the randomized, phase 3 DESTINY-Breast04 trial. Nat Med. 2025;31:4205–4213.
47. Valle I, et al. Antibody–drug conjugates in breast cancer: mechanisms of resistance and future therapeutic perspectives. npj Breast Cancer. 2025;11(1):102.

48. Hurvitz SA, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet. 2023;401(10371):105–17.
49. DiPeri TP, et al. Co-clinical Trial of Novel Bispecific Anti-HER2 Antibody Zanidatamab in Patient-Derived Xenografts. Cancer Discov. 2024;14(5):828–45.
50. Khoury R, Saleh K, Khalife N, Saleh M, Chahine C, Ibrahim R, et al. Mechanisms of Resistance to Antibody-Drug Conjugates. Int J Mol Sci. 2023;24(11):9674.
51. Ji X, et al. Recent advances in bispecific antibody-drug conjugates for breast cancer therapy. Cancer Chemother Pharmacol. 2026;96(1):15.
52. Cheng J, Liang M, Carvalho MF, Tigue N, Faggioni R, Roskos LK, et al. Molecular mechanism of HER2 rapid internalization and redirected trafficking induced by anti-HER2 biparatopic antibody. Antibodies (Basel). 2020;9(3):49.
53. Mercogliano MF, Bruni S, Mauro FL, Schillaci R, Elizalde PV, De Martino M. Emerging targeted therapies for HER2-positive breast cancer. Cancers (Basel). 2023;15(7):1987.
54. Xue Q, et al. A biparatopic HER2-targeting ADC constructed via site-specific glycan conjugation exhibits superior stability, safety, and efficacy. RSC Chem Biol. 2025;6(8):1284–96.
55. Rugo HS, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023;402(10411):1423–33.
56. Xu B et al. *Sacituzumab tirumotecan (SKB264/MK-2870) in patients (pts) with previously treated locally recurrent or metastatic triple-negative breast cancer (TNBC): results from the phase III OptiTROP-Breast01 study*. 2024, American Society of Clinical Oncology.
57. Jiang L, et al. The efficacy and safety of sacituzumab govitecan in the treatment of breast cancer: a systemic review and meta-analysis of emerging clinical data. Front Immunol. 2025;16:1683594.
58. Bardia A, et al. Datopotamab Deruxtecan Versus Chemotherapy in Previously Treated Inoperable/Metastatic Hormone Receptor-Positive Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer: Primary Results From TROPION-Breast01. J Clin Oncol. 2025;43(3):285–96.
59. Li WF, et al. OBI-992, a Novel TROP2-Targeted Antibody-Drug Conjugate, Demonstrates Antitumor Activity in Multiple Cancer Models. Mol Cancer Ther. 2025;24(2):163–75.
60. Zhou DD, et al. A new TROP2-targeting antibody-drug conjugate shows potent antitumor efficacy in breast and lung cancers. NPJ Precis Oncol. 2024;8(1):94.
61. Yao S, et al. Abstract 2616: BCG033, a novel bispecific antibody-drug conjugate targeting PTK7 and TROP2, demonstrates preclinical efficacy against triple-negative breast cancer and other solid tumor xenografts. Cancer Res. 2024;84(6Supplement):2616–2616.
62. Yüceer RO, et al. Exploring the Prognostic Role of Trop-2, CD47, and CD163 Expression Levels on Survival Outcomes in Patients with Triple-Negative Breast Cancer. Diagnostics. 2025;15(2):232.
63. Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. Nat Rev Cancer. 2005;5(5):341–54.
64. Li X, et al. Posttranscriptional upregulation of HER3 by HER2 mRNA induces trastuzumab resistance in breast cancer. Mol Cancer. 2018;17(1):113.
65. Mark C, Lee JS, Cui X, Yuan Y. Antibody-Drug Conjugates in Breast Cancer: Current Status and Future Directions. Int J Mol Sci. 2023;24(18):13726.
66. Sinevici N, et al. A prospective study of HER3 expression pre and post neoadjuvant therapy of different breast cancer subtypes: implications for HER3 imaging therapy guidance. Breast Cancer Res. 2024;26(1):107.
67. Liu X, et al. The clinical development of antibody-drug conjugates for non-small cell lung cancer therapy. Front Immunol. 2023;14:1335252.
68. Li L, et al. Exposure-Response Relationships in Patients with Non-Small-Cell Lung Cancer and Other Solid Tumors Treated with Patritumab Deruxtecan (HER3-DXd). Clin Pharmacol Ther. 2025;118(2):408–17.
69. Krop IE, et al. Patritumab Deruxtecan (HER3-DXd), a Human Epidermal Growth Factor Receptor 3-Directed Antibody-Drug Conjugate, in Patients With Previously Treated Human Epidermal Growth Factor Receptor 3-Expressing Metastatic Breast Cancer: A Multicenter, Phase I/II Trial. J Clin Oncol. 2023;41(36):5550–60.
70. D'Arienzo A, et al. Toxicity profile of antibody-drug conjugates in breast cancer: practical considerations. EClinicalMedicine. 2023;62:102113.
71. Nix MA, et al. Identifying optimal tumor-associated antigen combinations with single-cell genomics to enable multi-targeting therapies. Front Immunol. 2024;15:1492782.
72. Xu L, et al. A comprehensive single-cell breast tumor atlas defines epithelial and immune heterogeneity and interactions predicting anti-PD-1 therapy response. Cell Rep Med. 2024;5(5):101511.
73. Watanabe S, et al. Targeting of the HER2/HER3 signaling axis overcomes ligand-mediated resistance to trastuzumab in HER2-positive breast cancer. Cancer Med. 2019;8(3):1258–68.
74. Tao JJ, et al. Antagonism of EGFR and HER3 enhances the response to inhibitors of the PI3K-Akt pathway in triple-negative breast cancer. Sci Signal. 2014;7(318):ra29.
75. Coates JT, et al. Parallel Genomic Alterations of Antigen and Payload Targets Mediate Polyclonal Acquired Clinical Resistance to Sacituzumab Govitecan in Triple-Negative Breast Cancer. Cancer Discov. 2021;11(10):2436–45.
76. Tarantino P, et al. Outcomes with trastuzumab deruxtecan by biomarker status, line of treatment and prior receipt of sacituzumab govitecan in a large real-world database of patients with metastatic breast cancer. ESMO Open. 2025;10(7):105330.
77. Zhao X, et al. PAK5 promotes the trastuzumab resistance by increasing HER2 nuclear accumulation in HER2-positive breast cancer. Cell Death Dis. 2025;16(1):323.
78. Chen Y, et al. ERBB3 targeting: A promising approach to overcoming cancer therapeutic resistance. Cancer Lett. 2024;599:217146.
79. Wang L, et al. Targeting undruggable phosphatase overcomes trastuzumab resistance by inhibiting multi-oncogenic kinases. Drug Resist Updat. 2024;76:101118.
80. Zhou K, Liu X, Zhu H. Overcoming resistance to antibody-drug conjugates: from mechanistic insights to cutting-edge strategies. J Hematol Oncol. 2025;18(1):96.
81. Jain RK. Delivery of molecular and cellular medicine to solid tumors. Adv Drug Deliv Rev. 2012;64(Suppl):353–65.
82. Li F, et al. Tumor-Associated Macrophages Can Contribute to Antitumor Activity through FcγR-Mediated Processing of Antibody-Drug Conjugates. Mol Cancer Ther. 2017;16(7):1347–54.
83. Nanda R, et al. Effectiveness of sacituzumab govitecan and management of neutropenia in patients with metastatic triple-negative breast cancer treated in real-world settings in the United States. ESMO Open. 2025;10(6):105308.
84. García-Estévez L, et al. The association of high body mass index with the safety and efficacy of sacituzumab govitecan in patients with metastatic triple-negative breast cancer from the ASCENT study. ESMO Open. 2025;10(6):105294.
85. Jang JY, Kim SG, Choi JS, Park SH, Kim JH. Antibody-Drug conjugates powered by deruxtecan: Innovations and Challenges in oncology. Int J Mol Sci. 2025;26(13):6523.
86. Yang C, et al. IMM2520, a novel anti-CD47/PD-L1 bispecific antibody for cancer immune therapy. Heliyon. 2024;10(21):e39858.
87. Mai Z, et al. Modulating extracellular matrix stiffness: a strategic approach to boost cancer immunotherapy. Cell Death Dis. 2024;15(5):307.
88. Lu Y, et al. Leveraging artificial intelligence in antibody-drug conjugate development: from target identification to clinical translation in oncology. npj Precision Oncol. 2025;9(1):374.
89. Wang X, et al. Spatial transcriptomics reveals substantial heterogeneity in triple-negative breast cancer with potential clinical implications. Nat Commun. 2024;15(1):10232.
90. Yan Y, Ding H. pH-Responsive nanoparticles for cancer immunotherapy. Nanomaterials (Basel). 2020;10(8):1613.
91. Zeng S, et al. Cell membrane-coated nanomaterials for cancer therapy. Mater Today Bio. 2023;20:100633.
92. He S, et al. Dual-responsive supramolecular photodynamic nanomedicine with activatable immunomodulation for enhanced antitumor therapy. Acta Pharm Sin B. 2024;14(2):765–80.
93. Lei L, Dai W, Zhao J, Jiang A, Peng H, Jin Q, et al. A pH-Sensitive nano-sized Covalent-Organic polymer for enhanced tumor photodynamic immunotherapy by hypoxia relief and stat3 inhibition. Adv Sci (Weinh). 2025;12(29):e04860.
94. Balamkundu S, Liu CF. Lysosomal-cleavable peptide linkers in antibody–drug conjugates. Biomedicines. 2023;11(11):3080.
95. Zhang F, et al. Coordination and Redox Dual-Responsive Mesoporous Organosilica Nanoparticles Amplify Immunogenic Cell Death for Cancer Chemoimmunotherapy. Small. 2021;17(26):e2100006.
96. Bazan-Peregrino M, et al. VCN-01 disrupts pancreatic cancer stroma and exerts antitumor effects. J Immunother Cancer. 2021;9(11):e003254.
97. Jumper J, et al. Highly accurate protein structure prediction with AlphaFold. Nature. 2021;596(7873):583–9.

98. Lu Y, et al. Leveraging artificial intelligence in antibody-drug conjugate development: from target identification to clinical translation in oncology. NPJ Precis Oncol. 2025;9(1):374.
99. Marx V. Method of the Year: spatially resolved transcriptomics. Nat Methods. 2021;18(1):9–14.
100. Wang N, et al. Next-generation spatial transcriptomics: unleashing the power to gear up translational oncology. MedComm. 2020;5(10):e765. 2024.
101. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44–56.
102. Shen S, et al. From virtual to reality: innovative practices of digital twins in tumor therapy. J Transl Med. 2025;23(1):348.
103. Beck A, et al. Strategies and challenges for the next generation of antibody-drug conjugates. Nat Rev Drug Discov. 2017;16(5):315–37.
104. Wang Y, Guo C, Li W. Artificial intelligence in antibody-drug conjugate development. Trends Pharmacol Sci. 2025;46(12):1209–23.
105. Chen YF, et al. Resistance to antibody-drug conjugates in breast cancer: mechanisms and solutions. Cancer Commun (Lond). 2023;43(3):297–337.
106. Kai M, et al. A phase II study of talimogene laherparepvec for patients with inoperable locoregional recurrence of breast cancer. Sci Rep. 2021;11(1):22242.
107. Huppert LA, et al. Phase Ib study of intratumoral talimogene laherparepvec (T-VEC) in combination with chemotherapy or endocrine therapy in patients with advanced HER2-negative breast cancer. NPJ Breast Cancer. 2025;11(1):130.
108. Bartolomucci A, et al. Circulating tumor DNA to monitor treatment response in solid tumors and advance precision oncology. NPJ Precis Oncol. 2025;9(1):84.
109. Yao X, et al. Antibody-drug conjugates (ADCs): Smart Missiles targeting cancer therapy. Colloids Surf B. 2026;257:115161.
110. Sun L, et al. Unveiling the future of breast cancer therapy: Cutting-edge antibody-drug conjugate strategies and clinical outcomes. Breast. 2024;78:103830.

Publisher's note