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AN OVERVIEW OF ANTIBODY-DRUG CONJUGATES IN BREAST CANCER - NEOADJUVANT, ADJUVANT, AND METASTATIC DISEASE

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REVIEW BASED BOOK CHAPTER

AN OVERVIEW OF ANTIBODY-DRUG CONJUGATES IN BREAST CANCER - NEOADJUVANT, ADJUVANT, AND METASTATIC DISEASE

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Abstract

Antibody drug conjugates (ADCs) have transformed the therapeutic landscape of breast cancer by combining the specificity of monoclonal antibody targeting with the potency of cytotoxic chemotherapy. This chapter reviews the evolving role of ADCs across neoadjuvant, adjuvant, and metastatic breast cancer, beginning with the foundational principles of ADC design and payload structures. This chapter traces the evolution of trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd, sacituzumab govitecan (SG), and datopotamab deruxtecan (Dato-DXd), ADCs that have reshaped treatment strategies across HER2-positive, HER2-low, HER2-ultralow, and triple negative breast cancer. ADC specific toxicities are discussed, along with a practical framework for their management as these agents move into curative-intent settings. Mechanisms of ADC resistance, challenges in treatment sequencing, and emerging therapeutic directions, including new ADC targets, are also reviewed.

Keywords
Antibody Drug Conjugate, Breast Cancer, HER2-targeted Therapy, TROP2-targeted Therapy, Trastuzumab Deruxtecan, Sacituzumab Govitecan, Datopotamab Deruxtecan, Trastuzumab Emtansine

1. Introduction

Antibody drug conjugates (ADCs) have become an important therapeutic class in breast cancer. They combine the specificity of targeted therapy with the cytotoxic activity of chemotherapy. These agents use a monoclonal antibody to recognize a

surface antigen on the cancer cell and deliver a linked cytotoxic payload to the tumor. This allows highly potent therapy to be directed more selectively toward cancer cells, while limiting systemic exposure compared with administration of the cytotoxic drug alone [1].

The clinical development of ADCs in breast cancer began largely in HER2-positive disease. Trastuzumab emtansine (T-DM1) established that an antibody could be used not only to target HER2, but also to deliver chemotherapy directly to HER2-expressing tumor cells [2, 3]. Trastuzumab deruxtecan (T-DXd) later demonstrated activity across a broader range of HER2 expression and expanded the population of patients who could benefit from HER2- directed treatment [4, 5]. ADCs are now used across HER2-positive, HER2-low, and HER2-ultralow breast cancer, spanning treatment for all ranges of breast cancer subtypes including hormone receptor-positive, and triple negative breast cancer (TNBC), as well as both metastatic and early-stage disease [3, 6-8].

These advances have also changed the clinical significance of breast cancer biomarkers. Historically, HER2 testing was used primarily to identify tumors with HER2 overexpression or gene amplification that were likely to benefit from therapies directed against HER2 signaling. With T-DXd, lower levels of HER2 expression became clinically relevant because HER2 could also serve as a means of delivering a cytotoxic payload. This led to recognition of HER2-low and, more recently, HER2-ultralow disease, and placed greater emphasis on accurately assessing HER2 expression across the full range of immunohistochemical staining [4, 5].

The success of TROP2-directed ADCs has expanded this approach beyond HER2. TROP2 is a cell-surface protein expressed across all major subtypes of breast cancer, allowing agents such as sacituzumab govitecan (SG) and datopotamab deruxtecan (Dato-DXd) to use it as a target for delivery of a cytotoxic drug [7, 9].

The activity of an ADC also depends on its structure. Each ADC contains three main components: an antibody, a linker, and a cytotoxic payload. The antibody recognizes and binds the target antigen on the tumor cell. The linker connects the antibody to the payload and influences when and where the drug is released. The payload is the active cytotoxic agent responsible for tumor cell death. Additional features, including

drug to antibody ratio and the ability of the released payload to affect nearby tumor cells through the bystander effect, also contribute to efficacy and toxicity [1].

These structural differences help explain why ADCs directed against the same target can have different clinical activity. T-DM1 and T-DXd both target HER2, but differences in linker design, payload, drug to antibody ratio, and bystander activity result in important differences in their efficacy and the range of tumors they can treat [1, 10, 11]. Understanding these basic principles provides the foundation for interpreting the current ADC landscape in breast cancer and the expanding role of these agents across disease subtypes and treatment settings.

2. ADC Fundamentals

2.1. The Antibody

The antibody determines which antigen the ADC recognizes. Ideally, the selected antigen is present on the surface of tumor cells at a sufficient level to allow the ADC to bind and deliver its payload. HER2 and TROP2 are the two current important antigen targets in breast cancer that are clinically utilized [1].

After the antibody binds its target, the ADC may be internalized into the cancer cell and processed within intracellular compartments. This allows the cytotoxic payload to be released where it can exert its anticancer effect. The efficiency of binding, internalization, and processing can influence how much drug ultimately reaches the tumor cell [1].

2.2. The Linker

The linker connects the antibody to the cytotoxic payload. Its main role is to keep the ADC stable as it circulates in the bloodstream while allowing the payload to be released once the ADC reaches the tumor [1]. Linkers are generally classified as cleavable or noncleavable.

A noncleavable linker remains attached until the ADC is taken into the cancer cell and broken down. This tends to keep the cytotoxic effect more closely confined to the targeted cell. T-DM1 uses this type of linker [1, 12].

A cleavable linker is designed to release the payload after the ADC reaches the tumor. T-DXd and several newer ADCs use this type of linker. Once released, the payload may

also enter nearby cancer cells, including cells with lower levels of the target antigen [10, 11].

2.3. The Cytotoxic Payload

The payload is the cytotoxic drug responsible for killing the cancer cell. Because only a limited amount of drug can be carried by each antibody, ADC payloads are generally very potent [1]. The major payload classes currently used in breast cancer are microtubule inhibitors and topoisomerase I inhibitors.

T-DM1 contains emtansine (DM1), a microtubule inhibitor that interferes with normal microtubule function and prevents successful cell division [1, 12]. Several newer ADCs use topoisomerase I inhibitor payloads. T-DXd and Dato-DXd contain deruxtecan (DXd), while SG contains SN 38, which is the active metabolite of the chemotherapy drug irinotecan. These drugs interfere with the normal function of topoisomerase I, an enzyme involved in DNA replication, and the resulting DNA damage ultimately leads to tumor cell death [7, 9, 10].

The type of payload matters clinically because ADCs directed against different targets may still use similar cytotoxic drugs. As more ADCs become available, the payload may therefore become increasingly important when considering treatment sequencing, resistance, and toxicity [1].

2.4. Drug to Antibody Ratio

Another important feature of ADC design is the drug to antibody ratio (DAR). DAR refers to the average number of payload molecules attached to each antibody molecule. A higher DAR generally allows more cytotoxic drug to be carried by each antibody, but a higher DAR does not automatically make an ADC more effective [1].

For example, T-DM1 has an average DAR of approximately 3.5, whereas T-DXd has a DAR of approximately 8. SG carries approximately 7-8 molecules of SN 38, while Dato-DXd has a DAR of approximately 4. The optimal DAR depends on several factors, including drug stability, tumor penetration, and how effectively the payload can be released [7, 9, 10, 12].

2.5. The Bystander Effect

The bystander effect refers to the ability of a released payload to move from the targeted cancer cell into nearby tumor cells and kill them as well. This is particularly

important in breast cancer, because expression of targets such as HER2 may vary within the same tumor via tumor heterogeneity [1, 11].

T-DXd provides an important example. After its payload is released, DXd can cross cell membranes and affect neighboring tumor cells, including cells with lower levels of HER2 expression. This helps explain why T-DXd can be effective in HER2-low/ultralow and heterogeneous tumors [4, 11].

T-DM1 has much less bystander activity. Its noncleavable linker and limited movement of the released payload mean that its cytotoxic effect remains more closely restricted to cells that directly internalize the ADC [11, 12].

3. The ADC Landscape in Breast Cancer

The breast cancer ADC landscape can be organized primarily according to the target antigen used for drug delivery. HER2 remains the most extensively developed target, with T-DM1 and T-DXd establishing successive generations of HER2-directed ADC therapy [3, 6]. TROP2 has become the second major target through SG and Dato-DXd [7, 8]. HER3 and several other cell-surface proteins are being investigated as targets for the next generation of ADCs [13].

ADCs directed against the same antigen should not be considered interchangeable. The antibodies, linkers, payloads, and drug-to-antibody ratios differ, and these differences influence how the drugs are processed, how much payload is delivered, whether neighboring tumor cells can be exposed to the released drug, and the resulting efficacy and toxicity profile (Table 1). T-DM1 and T-DXd provide the clearest example: both use trastuzumab to target HER2, yet they are pharmacologically distinct ADCs with substantially different clinical activity [1, 10, 11].

Table 1. ADCs in Breast Cancer: Targets, Payloads, Clinical Indications
Abbreviations: Hormone receptor = HR, Triple negative breast cancer = TNBC

Agent	Target / Antibody	Linker	Payload	Payload class	DAR	Breast cancer status
Trastuzumab emtansine (T-DM1)	HER2 / trastuzumab	Non-Cleavable	DM1	Microtubule inhibitor	~3.5	FDA approved in HER2-positive metastatic breast cancer after prior trastuzumab and taxane, and in HER2-positive early breast cancer with residual invasive disease after

						neoadjuvant therapy.
Trastuzumab deruxtecan (T-DXd)	HER2 / trastuzumab	Cleavable	DXd	Topoisomerase I inhibitor	~8	FDA approved in HER2-positive, HER2-low, and HER2-ultralow metastatic breast cancer. Approved for high risk HER2-positive early breast cancer in neoadjuvant and adjuvant setting if residual invasive disease
Sacituzumab govitecan (SG)	TROP-2 / sacituzumab	Cleavable	SN-38	Topoisomerase I inhibitor	~7–8	FDA approved in metastatic TNBC and HR-positive/HER2-negative metastatic breast cancer, with additional first-line TNBC indications
Datopotamab deruxtecan (Dato-DXd)	TROP-2 / datopotamab	Cleavable	DXd	Topoisomerase I inhibitor	~4	FDA approved in previously treated HR-positive/HER2-negative metastatic breast cancer and first-line for metastatic TNBC

4. Biomarkers and the Evolving Definition of HER2

ADCs have changed the clinical meaning of biomarker expression in breast cancer. Historically, HER2 testing was designed to identify tumors with HER2 overexpression or ERBB2 amplification that were likely to benefit from HER2-directed therapy. With T-DXd, lower and even minimal levels of HER2 expression have become clinically relevant because HER2 can serve as a target for delivery of a cytotoxic payload, and the bystander effect allows the cytotoxicity to extend to neighboring cancer cells that may lack HER2 expression [4, 5].

Importantly, HER2-low and HER2-ultralow are not replacements for the conventional HER2-positive and HER2-negative classification [14]. They are better understood as treatment-selection categories that identify additional patients who may benefit from specific HER2-directed ADC therapy.

4.1. Conventional HER2 Classification

HER2 status has been conventionally classified using a binary HER2-positive versus HER2-negative system. Tumors with immunohistochemistry (IHC) 3+ staining are classified as HER2-positive, whereas tumors with IHC 0 or 1+ staining are conventionally classified as HER2-negative. IHC 2+ results have been considered equivocal, requiring reflex in situ hybridization (ISH) testing to assess for ERBB2 gene amplification and determine the final HER2 status according to the ASCO/CAP algorithm [14]. Fluorescence in situ hybridization (FISH), a type of ISH, assesses ERBB2 gene amplification using the HER2/CEP17 ratio and average HER2 copy number. A FISH-positive result indicates ERBB2 amplification, with final interpretation incorporating concurrent IHC findings according to the ASCO/CAP algorithm [14].

This system was developed to identify tumors with HER2 overexpression or amplification and was not originally intended to distinguish among very low levels of HER2 expression [14]. historically, those distinctions had little therapeutic relevance because tumors below the threshold for HER2 positivity were treated as a single HER2-negative group.

4.2. HER2-Low

The development of T-DXd changed the significance of this lower range of HER2 expression. HER2-low refers to tumors with IHC 1+ or IHC 2+/ISH-negative disease [4]. Although these tumors remain HER2 negative according to the conventional ASCO/CAP classification, they may still express sufficient HER2 antigen on the tumor cell surface to allow for effective ADC binding and payload delivery [14].

DESTINY-Breast04 clinical trial established the clinical importance of the HER2-low category by demonstrating that T-DXd improved progression-free survival (PFS) and overall survival (OS) compared with chemotherapy in previously treated HER2-low metastatic breast cancer [4]. These findings showed that HER2 does not need to function as the dominant oncogenic driver for a HER2-directed ADC to be effective. Instead, HER2 can serve as a surface target through which the cytotoxic payload is delivered.

HER2-low is therefore best understood as a treatment-selection category rather than a distinct biological subtype.

4.3. HER2-Ultralow

The same concept was subsequently extended to tumors with even lower levels of HER2 expression. HER2-ultralow refers to IHC 0 tumors with minimally detectable membrane staining ≤10%, distinguishing them from IHC 0 tumors with no detectable membrane staining [5, 6].

DESTINY-Breast06 demonstrated benefit from T-DXd in hormone receptor-positive metastatic breast cancer with HER2-low or HER2-ultralow expression after progression on endocrine therapy [5]. These findings expanded the population in whom very low levels of HER2 expression may have therapeutic relevance and led to expansion of the T-DXd indication to include this population [6].

Like HER2-low, HER2-ultralow is best viewed as a treatment eligibility category rather than a separate molecular subtype [14]. Together; these categories have shifted attention from simply determining whether a tumor is HER2 positive to more precisely characterizing HER2 expression across the lower end of the spectrum.

4.4. Limitations of HER2 Testing

The expansion of T-DXd into HER2-low and HER2-ultralow disease has highlighted limitations of conventional HER2 testing. IHC assays were developed primarily to identify HER2 overexpression and are less reliable at distinguishing very low levels of expression.

The distinction between IHC 0 and IHC 1+ is particularly challenging, with one study reporting only 26% concordance among pathologists [15]. Results may also vary with tissue fixation, staining platform, antibody clone, interpretation, and intratumoral heterogeneity. These differences now matter clinically because they may affect eligibility for HER2-directed ADC therapy [14, 15]. Several new methods are in development to better identify HER2 expression, including quantitative immunofluorescence, HER2 RNA expression, mass spectrometry, and genomic assays, although additional validation is still needed before emerging into clinical practice [16].

4.5. TROP-2 Expressions as a Biomarker

TROP-2 provides a contrast to HER2. TROP-2 is a cell-surface transmembrane glycoprotein found across multiple solid tumors that activates oncogenic signaling pathways through cell proliferation, invasion, and survival when overexpressed [17]. Reported TROP-2 expression varies according to the assay and cutoff used. One review

reported TROP-2 overexpression in approximately 80% of breast cancers and 88% of TNBCs, while a separate hormone receptor-positive/HER2-negative cohort identified high TROP-2 expression in approximately 31% of tumors [18, 19]. SG and Dato-DXd both target TROP-2, but treatment does not currently require a specific expression threshold [7, 8].

In ASCENT, SG improved outcomes across TROP-2 expression groups, although the benefit appeared greater with higher expression [20]. TROP-2 expression may therefore influence activity, but it has not been validated as a binary biomarker for treatment selection. In an exploratory analysis of ASCENT-04 evaluating SG plus pembrolizumab for first-line treatment of metastatic TNBC, higher levels of TROP-2 expression had a greater treatment benefit; however, median PFS favored SG plus pembrolizumab across all levels of TROP-2 expression, including the lowest quartile [21].

4.6. Beyond Antigen Expression

ADC activity depends on more than antigen expression alone. Target density and heterogeneity, internalization, trafficking, linker processing, payload release, bystander activity, and sensitivity to the payload can all influence response [1].

IHC therefore provides only part of the picture. In the ADC era, the question is not only whether a tumor is driven by a target such as HER2, but whether enough accessible antigens are present to permit effective payload delivery [1, 14].

5. ADCs in Metastatic Disease

ADCs used to treat breast cancer first demonstrated clinical efficacy in the metastatic setting and have since become a cornerstone of treatment for advanced stage breast cancer across multiple subtypes. The clinical development of ADCs has progressively expanded into earlier lines of therapy, advancing to first line metastatic disease and into the perioperative setting with curative intent.

5.1. HER2-Positive Metastatic Disease

Trastuzumab emtansine (T-DM1)

T-DM1 was the first ADC to outperform conventional HER2-directed monoclonal antibody therapy in HER2-positive metastatic breast cancer. In EMILIA (2012), T-DM1 significantly improved median PFS (9.6 vs 6.4 months; HR 0.65; $p<0.001$) and OS (30.9 vs 25.1 months; HR 0.68; $p<0.001$) compared to lapatinib plus capecitabine in pretreated

advanced stage HER2-positive breast cancer [2]. TH3RESA (2014) later established T-DM1 efficacy over physician's choice in heavily pretreated patients [22] (Table 2). Both trials established T-DM1 as standard second-line therapy for HER2-positive metastatic breast cancer for nearly a decade. This decade long standard would soon be redefined by T-DXd, whose distinct molecular design led to a transformative shift in clinical practice.

Trastuzumab deruxtecan (T-DXd)

T-DXd was introduced following the results of DESTINY-Breast01 (2019) and has since changed the treatment paradigm not once but repeatedly, with each successive trial expanding on its potential benefits [23]. In DESTINY-Breast01, a single-arm study in heavily pretreated HER2-positive metastatic breast cancer (including prior T-DM1 use), T-DXd demonstrated an impressive objective response rate (ORR) of 62%, median PFS of 19.4 months, and median OS 29.1 months [23] (Table 2). These unprecedented results lead to accelerated approval and marked the beginning of shift in treatment in HER2-positive metastatic breast cancer.

T-DXd established superiority over T-DM1 in the second line setting for HER2-positive metastatic breast cancer patients in the pivotal phase 3 trial DESTINY-Breast03 (2022) [24]. At long term follow up, T-DXd demonstrated improved median PFS (29.0 vs 7.2 months; HR 0.30), median OS (52.6 vs 42.7 months; HR 0.73), and 36-month PFS (45.7% vs 12.4%) compared to T-DM1, albeit with higher incidence of interstitial lung disease (ILD) or pneumonitis (16.7% vs 3.4%), with no fatal (grade 5) events reported [24] (Table 2). The magnitude of PFS benefit was remarkable, with T-DXd reducing the risk of disease progression or death by approximately 70%, solidifying T-DXd as the preferred second-line treatment over T-DM1[24]. In practice, this relegated T-DM1 to later-lines of therapy and made ILD surveillance a routine part of clinical practice, reflecting a trade-off between greater efficacy and increased treatment-related toxicity, including ILD/pneumonitis, cytopenias, nausea, alopecia, and fatigue.

T-DXd also demonstrated substantial therapeutic benefit after prior T-DM1 exposure. In DESTINY-Breast02 (2023), T-DXd had superior median PFS (17.8 vs 6.9 months; HR 0.36; $p<0.0001$) and OS (39.2 vs 26.5 months; HR 0.66; $p=0.0021$) compared to treatment of physician's choice in advanced stage HER2-positive patients who progressed on T-DM1

[25] (Table 2). This trial confirmed that T-DXd retained efficacy after T-DM1 resistance, and that sequential HER2-directed ADCs can be effective.

As T-DXd continued to demonstrate remarkable efficacy across multiple trials, T-DXd progressively moved earlier in the treatment paradigm reaching the first-line setting in 2025 following DESTINY-Breast09 [26]. For more than a decade, a taxane with trastuzumab and pertuzumab (THP) was the first-line standard of care for HER2-positive metastatic breast cancer patients following CLEOPATRA (2012) [27]. In DESTINY-Breast09 (2025), T-DXd plus pertuzumab established superiority to THP in the first-line setting, demonstrating significantly improved median PFS (40.7 vs 26.9 months; HR 0.56; $p<0.00001$), ORR (85.1% vs 78.6%), complete responses (15.1% vs 8.5%), and median duration of response (DOR) (39.2 vs 26.4 months) [26]. DESTINY-Breast09 also included a T-DXd monotherapy arm; however, data remains blinded and final PFS analysis has not been reported yet (Table 2). T-DXd plus pertuzumab and THP during induction therapy had similar grade $\geq$3 adverse events (63.5% vs 62.5%) with differing toxicity profiles. Notably, T-DXd plus pertuzumab had increased ILD or pneumonitis (12.1% vs 1.0%) with 2 fatal events (grade 5) compared to THP [26]. T-DXd plus pertuzumab represents the first successful challenge to THP in over a decade and has since established itself as an important first-line treatment option for HER2-positive metastatic breast cancer, although vigilance for ILD/pneumonitis and other toxicities remains essential.

Since T-DXd plus pertuzumab was continued until disease progression or intolerable toxicity in DESTINY-Breast09, questions arose regarding optimal duration of therapy and if transitioning to a less toxic maintenance regimen is appropriate to reduce treatment-related toxicity. While T-DXd plus pertuzumab had similar grade $\geq$3 toxicities to THP during its six-cycle induction phase, this contrasts with the THP maintenance phase, where treatment is de-escalated to trastuzumab and pertuzumab (HP) maintenance therapy and is generally well tolerated [26, 27]. An exploratory analysis of DESTINY-Breast09 (2026) found median treatment durations of 28.0 months among patients achieving a durable complete response and 22.2 months among those achieving a deep partial response; the corresponding 24-month PFS rates were 85.1% and 80.0%, respectively [28]. This is relevant because clinicians may want to consider less toxic maintenance strategies for patients with deep responses, such as HP plus tucatinib or

palbociclib with endocrine therapy, although these strategies require further study [29, 30].

5.2. HER2-Low and HER2-Ultralow Metastatic Disease

The indications for T-DXd subsequently expanded to hormone receptor-positive metastatic breast cancer with HER2-low and HER2-ultra low disease, a population traditionally considered HER2-negative and not eligible for HER2-directed therapy. In DESTINY-Breast04 (2022), T-DXd first demonstrated significant benefit in HER2-low (IHC 1+ or IHC 2+/ negative ISH) metastatic breast cancer after 1-2 lines of prior therapy, including hormone receptor-positive disease [31]. T-DXd significantly improved median PFS (9.9 vs 5.1 months; HR 0.50; p<0.001) in all patients compared to physician's choice of therapy, and improved median OS in the overall population (22.9 vs 16.8 months; HR 0.69) and hormone receptor-positive cohort (23.9 vs 17.6 months; HR 0.69) at long term follow up [4, 31] (Table 2). This established T-DXd as a standard treatment for HER2-low metastatic breast cancer after prior chemotherapy.

DESTINY-Breast06 (2024) advanced T-DXd into earlier lines of treatment and broadened its eligibility by including hormone receptor-positive metastatic breast cancer with HER2-low and HER2-ultralow (IHC 0 with minimal membrane staining) after progression on endocrine therapy and no prior chemotherapy use [5]. T-DXd significantly improved median PFS compared with physician's choice of chemotherapy in both the HER2-low (13.2 vs 8.1 months; HR 0.62; p<0.001) and HER2-ultralow subgroups (13.2 vs 8.3 months; HR 0.78) and also improved ORR in both populations (HER2-low: 56.5% vs 32.2%; HER2-ultralow: 61.8% vs 26.3%) [5] (Table 2). Together, DESTINY-Breast04 & DESTINY-Breast06 redefined the traditional framework for HER2 classification as a continuum and substantially expanded the population of patients who may benefit from T-DXd.

Table 2. HER2-directed ADCs for Metastatic Breast Cancer
Abbreviations: 1L = First line; 2L = Second line

Trial	Agent	Population	Comparator	PFS	OS
EMILIA (2012)	T-DM1	2L HER2-positive metastatic breast cancer after progression on trastuzumab and taxane	Lapatinib + capecitabine	9.6 vs 6.4 months; HR 0.65 (p<0.001)	30.9 vs 25.1 months; HR 0.68 (p<0.001)
DESTINY-Breast03 (2022)	T-DXd	2L HER2-positive metastatic breast cancer after progression on trastuzumab and taxane	T-DM1	29.0 vs 7.2 months; HR 0.30	52.6 vs 42.7 months; HR 0.73
DESTINY-Breast04 (2022)	T-DXd	2L HER2-low metastatic breast cancer after progression on chemotherapy; included HR+	Physician's choice	9.9 vs 5.1 months; HR 0.50 (p<0.001)	All: 22.9 vs 16.8 months; HR 0.69 HR+: 23.9 vs 17.6 months; HR 0.69
DESTINY-Breast02 (2023)	T-DXd	2L HER2-positive metastatic breast cancer after progression of T-DM1	Physician's choice	17.8 vs 6.9 months; HR 0.36 (p<0.0001)	39.2 vs 26.5 months; HR 0.66 (p=0.0021)
DESTINY-Breast06 (2024)	T-DXd	2L HER2-low & HER2-ultralow HR+ metastatic breast cancer after progression on endocrine therapy and no prior chemotherapy	Physician's choice	HER2-low: 13.2 vs 8.1 months; HR 0.62 (p<0.001) HER2-ultralow: 13.2 vs 8.3 months; HR 0.78	Immature
DESTINY-Breast12 (2024)	T-DXd	HER2-positive advanced/ metastatic breast cancer after prior anti-HER2-based therapy with stable or active brain metastases and without brain metastases	No comparator arm	Brain metastasis cohort: 12-month intracranial PFS 58.9%	-

DESTINY-Breast09 (2025)	T-DXd ± pertuzumab	1L HER2-positive metastatic breast cancer	THP	T-DXd + pertuzumab: 40.7 vs 26.9 months; HR 0.56 (p<0.00001) T-DXd monotherapy: pending	Immature

5.3. T-DXd Central Nervous System Activity

Historically, metastatic breast cancer with central nervous system (CNS) involvement had limited responses to systemic therapy; however, T-DXd has since emerged as an effective treatment option. In DESTINY-Breast12 (2024), T-DXd demonstrated durable intracranial activity in HER2-positive metastatic patients with brain metastases with a 12-month intracranial PFS 58.9% and CNS ORR 71.7% [32]. The intracranial response rates of T-DXd were further supported by TUXEDO-1 (2022) with intracranial ORR 73.3% in HER2-positive breast cancer, and by DEBBRAH (2023) which demonstrated intracranial responses in hormone receptor-positive, HER2-low patients (intracranial ORR 50.0% in asymptomatic untreated brain metastasis and 44.4% in progressing brain metastasis) [33, 34]. CNS involvement is now an important consideration in treatment selection with T-DXd, although it does not replace local therapies if indicated.

5.4. TROP2-Directed ADCs

Sacituzumab govitecan (SG)

SG was the first TROP2-directed ADC to demonstrate superior efficacy over chemotherapy in triple-negative breast cancer (TNBC). In ASCENT (2021), SG significantly improved median PFS (4.8 vs 1.7 months; HR 0.41; p<0.001) and OS (11.8 vs 6.9 months; HR 0.51; p<0.001) compared to physician's choice of chemotherapy in metastatic TNBC after 2 lines of prior therapy, establishing this as an effective treatment option for previously treated patients [35]. Notably, ASCENT demonstrated that TROP2-directed ADC was effective without requiring a specific threshold for TROP2 IHC expression [35].

SG has since moved into the front-line setting for metastatic TNBC following ASCENT-03 (2025) for SG monotherapy and ASCENT-04/KEYNOTE-D19 (2026) for SG with pembrolizumab in PD-L1 positive (CPS ≥10) patients [36, 37]. In ASCENT-03, SG monotherapy outperformed chemotherapy as first-line treatment in patients ineligible for PD-1/PD-L1 inhibitors, demonstrating significantly improved median PFS (9.7 vs 6.9 months; HR 0.62; p<0.001) and median DOR (12.2 vs 7.2 months) [36]. SG had slightly higher grade ≥3 adverse events compared to chemotherapy (66% vs 62%), with most common toxicities including neutropenia, diarrhea, and leukopenia. Despite this, SG had a lower incidence of discontinuation due to adverse events (4% vs 12%) [36]. In ASCENT-04/KEYNOTE-D19, SG plus pembrolizumab was superior to chemotherapy plus pembrolizumab as first-line treatment in PD-L1-positive metastatic TNBC, demonstrating significantly improved median PFS (11.2 vs 7.8 months; HR 0.65; p<0.001), ORR (60% vs 53%), and median DOR (16.5 vs 9.2 months) with lower discontinuation rates (12% vs 31%) [37]. These trials reshaped the front-line management of TNBC, although OS data remains immature (Table 3).

In hormone receptor-positive, HER2-negative metastatic breast cancer, SG demonstrated clinical benefit in the second-line setting, expanding its role beyond TNBC. In TROPiCS-02 (2022), SG significantly improved median PFS (5.5 vs 4.0 months; HR 0.66; p=0.0003), OS (14.4 vs 11.2 months; HR 0.79; p=0.020), and ORR (21% vs 14%) compared to treatment of physician's choice in endocrine-resistant patients after 2 lines of prior therapy [38]. This established SG as a preferred second-line treatment for hormone receptor-positive, HER2-negative metastatic breast cancer patients.

Datopotamab deruxtecan (Dato-DXd)

Dato-DXd emerged as the second TROP2-directed ADC to expand treatment options for metastatic breast cancer. In hormone receptor-positive, HER2-negative previously treated metastatic breast cancer, Dato-DXd demonstrated significantly improved median PFS (6.9 vs 4.9 months; HR 0.63; p<0.0001), ORR (36% vs 23%), and DOR (6.7 vs 5.7 months) with lower grade ≥3 adverse events compared to therapy of physician's choice in TROPION-Breast01 (2025) [39]. Despite the improvement in PFS, the final OS analysis did not reach statistical significance (18.6 vs 18.3 months; HR 1.01; p=0.9445)

[39]. Dato-DXd was approved for the second-line setting for metastatic hormone receptor-positive, HER2-negative breast cancer; however, SG and T-DXd are preferred due to OS benefit.

Dato-DXd clinical benefit is most clearly established in metastatic TNBC in the first-line setting. In TROPION-Breast02 (2026), Dato-DXd significantly improved PFS (10.8 vs 5.6 months; HR 0.57; p<0.0001) and OS (23.7 vs 18.7 months; HR 0.79; p=0.029) compared to physician's choice of therapy in untreated advanced TNBC ineligible for immunotherapy (IO) [40]. Dato-DXd had slightly higher ≥3 adverse events compared to chemotherapy (33% vs 29%), with most common toxicities including stomatitis, nausea, alopecia, constipation, fatigue, and keratitis/dry eyes. Despite this, Dato-DXd had a lower incidence of discontinuation due to adverse events (4% vs 7%) [40] (Table 3). This trial established Dato-DXd as a first-line treatment option for metastatic TNBC ineligible for immunotherapy. Dato-DXd plus durvalumab is being investigated for first line therapy in PD-L1 positive (CPS ≥10) metastatic TNBC in the phase 3 TROPION-Breast05 trial, with results pending [41].

5.5. SG versus Dato-DXd for First Line Metastatic TNBC

With both SG and Dato-DXd now approved in the front-line setting for metastatic TNBC, selection of the appropriate TROP2-directed ADC should be guided by efficacy, toxicity, and treatment schedule with consideration of patient-specific history and preferences. SG is given on days 1 and 8 of a 21-day cycle, and has most common side effects of neutropenia, nausea, diarrhea, anemia, and fatigue [36]. Dato-DXd is given every 21 days, offering a more convenient therapy schedule, and has distinct side effects including stomatitis, ocular toxicities, ILD/pneumonitis [40]. In practice, the decision often hinges on patient's comorbidities and lifestyle (Table 3).

Table 3. TROP2-directed ADC for First-line Treatment of Metastatic TNBC

	SG	SG + Pembrolizumab	Dato-DXd
Trial	ASCENT-03 (2025)	ASCENT-04/KEYNOTE-D19 (2026)	TROPION-Breast02 (2026)
Population	1L metastatic TNBC ineligible for immunotherapy	1L metastatic TNBC PD-L1 positive (CPS ≥10)	1L metastatic TNBC ineligible for immunotherapy
PFS	9.7 vs 6.9 months; HR 0.62 (p<0.001)	11.2 vs 7.8 months; HR 0.65 (p<0.001)	10.8 vs 5.6 months; HR 0.57 (p<0.0001)
OS	Immature	Immature	23.7 vs 18.7 months; HR 0.79 (p=0.029)
Key Toxicities	Neutropenia, nausea, diarrhea	SG side effects + immune-related adverse events	Stomatitis, ocular toxicity, nausea, constipation, ILD/pneumonitis
Scheduling	10 mg/kg IV D1 & D8 every 21 days	SG: 10 mg/kg IV D1 & D8 every 21 days Pembrolizumab: 200 mg IV every 21 days	6 mg/kg IV every 21 days

6. ADCs in the Adjuvant Setting for Early-Stage Breast Cancer

In HER2-positive early-stage breast cancer, adjuvant ADC therapy has been the backbone to response-adapted escalated therapy for patients who did not obtain a pathological complete response (pCR) after neoadjuvant therapy. KATHERINE (2018) is the landmark trial that established the benefit of intensified adjuvant treatment, demonstrating adjuvant T-DM1 reduced the risk of invasive disease recurrence by 46% at long term follow up (7-year IDFS 80.8% vs 67.1%; HR 0.54) and improved 7-year OS (89.1% vs 84.4%; HR 0.66; p=0.003) when compared to trastuzumab monotherapy for patients with residual disease after neoadjuvant therapy [42] (Table 4). T-DM1 then became the first adjuvant ADC and standard of care for residual disease post-neoadjuvant therapy HER2-positive disease.

Building on the success in the metastatic setting, T-DXd is now redefining the adjuvant treatment for high-risk early-stage HER2-positive breast cancer. In DESTINY-Breast05 (2026), adjuvant T-DXd was superior to T-DM1 in high-risk patients with either inoperable

or residual nodal disease after neoadjuvant therapy, demonstrating a reduction in the risk of invasive disease recurrence or death by 53% (3-year IDFS 92.4% vs 83.7%; HR 0.47; p<0.001) [43]. High-risk was defined as inoperable disease at presentation (cT4 N0-3 M0 or cT1-3 cN2-3 M0) or operable disease at presentation with (cT1-3 N0-1 M0) with axillary-node positive disease after neoadjuvant therapy (ypN1-3) [43] (Table 4). This established T-DXd as the new standard of care for residual disease in these high-risk patients. The decision to escalate to T-DXd should be individualized, weighing the risk of ILD and current immaturity of OS data.

Table 4. Adjuvant ADC in HER2-positive Early-stage Breast Cancer

	T-DM1	**T-DXd**
Trial	KATHERINE (2018)	DESTINY-Breast05 (2026)
Comparator	T-DM1 vs trastuzumab	T-DXd vs T-DM1
Indication	HER2-positive breast cancer with residual disease after neoadjuvant therapy	High risk HER2-positive breast cancer with residual disease after neoadjuvant therapy - Inoperable at diagnosis: cT4 N0-3 M0 or cT1-3 cN2-3 M0 - Operable (cT1-3 N0-1 M0) with axillary lymph node residual disease after neoadjuvant therapy (ypN1-3)
IDFS	7-year IDFS: 80.8% vs 67.1%; HR 0.54	3-year IDFS 92.4% vs 83.7%; HR 0.47 (p<0.001)
OS	7-year OS: 89.1% vs 84.4% (p=0.003)	Immature
Key Toxicities	Nausea, thrombocytopenia, transaminitis, peripheral neuropathy, fatigue, ILD/pneumonitis (1.6%)	Nausea/vomiting, constipation, neutropenia, anemia, fatigue, ILD/pneumonitis (9.6%)
Scheduling	3.6 mg/kg IV every 3 weeks x 14 cycles	5.4 mg/kg every 3 weeks x 14 cycles

7. ADCs in the Neoadjuvant Setting

T-DXd has now extended into the neoadjuvant setting. In DESTINY-Breast11 (2026), neoadjuvant T-DXd followed by THP significantly improved pCR rates (67.3% vs 56.3%) with less toxicity compared to dose-dense doxorubicin and cyclophosphamide

followed by THP (ddAC-THP) in high-risk HER2-positive early-stage breast cancer [44]. T-DXd followed by THP improved pCR in both HR-positive (61.4% vs 52.3%) and HR-negative (83.1 vs 67.1%) subgroups. High risk was defined as ≥cT3 N0 or cT0-4 N1-3 [44]. Preliminary data showed a trend toward improved event-free survival (HR 0.56), although longer follow-up is needed to confirm. T-DXd is now approved for high-risk HER2-positive early-stage breast cancer patients.

8. Toxicity Management Across ADC Class

ADCs have distinct safety profiles determined by target biology, linker characteristics, payload class, pharmacokinetics, and off-target exposure [1]. Recognizing these agent-specific toxicities is increasingly important as ADCs move into earlier lines of therapy and curative-intent settings. Below are some of the most clinically significant adverse events by ADC.

8.1. Trastuzumab deruxtecan: Interstitial Lung Disease and Pneumonitis

ILD and pneumonitis are the defining, potentially fatal toxicities of T-DXd. All-grade incidence across breast cancer trials has been approximately 10%-15%, with most events being grade 1-2. Fatal events are uncommon but remain an important treatment-related risk. In DESTINY-Breast03, ILD/pneumonitis occurred in 16.7% of patients receiving T-DXd versus 3.4% with T-DM1 [24]. Onset of ILD/pneumonitis is usually within the first several months of therapy but may occur at any time. Reported risk factors include renal impairment and pre-existing pulmonary disease, supporting continued vigilance and imaging throughout treatment [6, 45].

Because radiographic findings are nonspecific, alternate diagnoses such as infection, tumor progression, radiation pneumonitis, and cardiogenic pulmonary edema should be considered before confirming drug-related ILD. Management of T-DXd related ILD/pneumonitis is grade-driven, with a particular emphasis that asymptomatic grade 1 events require treatment interruption and consideration of corticosteroids, whereas symptomatic grade ≥2 ILD mandates permanent discontinuation of T-DXd and prompt corticosteroid therapy [6, 45] (Table 5).

Therapy rechallenge after complete resolution of grade 1 ILD remains an area of clinical nuance. In a pooled analysis of nine T-DXd trials, approximately 9% of patients had a first grade 1 event; of the 23.3% that were subsequently retreated, 33.3%

developed recurrent ILD (all grade 1-2) [46]. These data support carefully selected rechallenge after complete resolution, while emphasizing the substantial risk of recurrence. The clinical implications are particularly important as T-DXd is increasingly being used in curative intent settings.

8.2. Trastuzumab emtansine: Thrombocytopenia and Hepatotoxicity

T-DM1 has distinct toxicities driven by its DM1 payload and noncleavable linker, particularly thrombocytopenia and hepatotoxicity. Thrombocytopenia is more frequent and severe in patients of Asian descent and warrants caution with concurrent anticoagulation.[12] Hepatotoxicity is a boxed warning for T-DM1 [12]. It's most distinctive and under-recognized hepatic complication, nodular regenerative hyperplasia, is a rare cause of noncirrhotic portal hypertension that can occur despite normal transaminases. It should be suspected when signs of portal hypertension or a cirrhosis-like hepatic contour appears without another explanation; diagnosis is confirmed histologically and mandates permanent discontinuation [12].

8.3. Cardiac Monitoring with HER2-directed ADCs

Because both HER2-directed ADCs (T-DXd and T-DM1) share the trastuzumab backbone, both can reduce left ventricular ejection fraction. While symptomatic heart failure is uncommon, subclinical decline is not; therefore cardiac surveillance imaging applies to both ADCs [6, 12].

8.4. Sacituzumab govitecan: Diarrhea and Neutropenia

Diarrhea and neutropenia are two boxed warning toxicities for SG, both reflecting the irinotecan-like biology of its SN-38 payload [7]. Management of toxicities is based on the nadir of neutropenia and temporal onset of diarrhea (acute vs late-onset) (Table 5). Pharmacogenomics is clinically relevant: patients homozygous for the reduced-function UGT1A1*28 allele have reduced UGT1A1-mediated SN-38 metabolism and higher rates of grade 4 neutropenia, febrile neutropenia, anemia, and diarrhea. Although genotyping is not mandated, a UGT1A1*28 poor-metabolizer status should lower the threshold for growth-factor support and dose modification [7].

8.5. Datopotamab deruxtecan: Stomatitis and Ocular Toxicity

Stomatitis and ocular toxicity (dry eyes, keratitis) are among the most common toxicities with Dato-DXd, although both are largely preventable with proactive oral and ocular

care [8] (Table 5). Ophthalmologic examination is required at baseline and periodically with treatment [8]. Dato-DXd is defined less by pulmonary toxicity, though ILD/pneumonitis remains a recognized toxicity of deruxtecan-containing ADCs.

8.6. Nausea and Antiemetic Prophylaxis with Highly Emetogenic ADCs

Nausea and vomiting are common but rarely severe with the ADCs. The NCCN antiemesis guidelines classify T-DXd, Dato-DXd, and SG as high emetic-risk agents, for which guideline-concordant prophylaxis typically includes a neurokinin-1 antagonist, a 5-HT3 antagonist, and dexamethasone rather than a single agent antiemetic [47]. Low-grade nausea with T-DXd often persists beyond the acute window and may require continued oral antiemetics between cycles [6, 8].

Table 5. Hallmark Toxicities and Management by ADC

ADC	Hallmark Toxicities	Prevention / Monitoring	Key Management	Permanent-discontinuation Triggers
T-DXd	ILD / pneumonitis, nausea, vomiting, fatigue, myelosuppression, LVEF decline	Periodic CT chest monitoring Educate to report respiratory symptoms High-emetic-risk antiemetic prophylaxis Periodic LVEF monitoring CBC monitoring	ILD / pneumonitis Grade 1 (asymptomatic, radiographic findings only): hold, consider prednisone ≥0.5 mg/kg/day, resume same dose if resolved ≤28 days, otherwise reduce one dose level Grade ≥2 (symptomatic): permanently discontinue and promptly start prednisone ≥1 mg/kg/day	Grade ≥2 (symptomatic) ILD / pneumonitis; severe hypersensitivity
T-DM1	Thrombocytopenia, hepatotoxicity	CBC (platelets), AST/ALT, and bilirubin monitoring Periodic LVEF monitoring Caution with anticoagulation	Increased transaminases (AST/ALT) Grade 2 (>2.5 to ≤5 x ULN): treat at same dose level Grade 3 (>5 to ≤20 x ULN): hold until grade 2, then reduce one dose level Grade 4 (>20 x ULN): permanently discontinue Hyperbilirubinemia Grade 2 (>1.5 to ≤3 x ULN): hold until grade ≤1, then resume at same dose level Grade 3 (>3 to ≤10 x ULN):	Nodular regenerative hyperplasia (histologic); grade 4 hepatotoxicity; symptomatic congestive heart failure; LVEF <40% that does not recover after holding for 3 weeks or decreased LVEF ≥10% from baseline that doesn't recover within 10% from baseline after holding for 3 weeks; life-threatening infusion-related reaction

ADC	Hallmark Toxicities	Prevention / Monitoring	Key Management	Permanent-discontinuation Triggers
			hold until grade ≤1, then reduce one dose level Grade 4 (>10 x ULN): permanently discontinue Thrombocytopenia Grade 3 (platelets 25,000 to <50,000/mm³): hold until recovers to grade ≤1 (≥75,000/mm³), then treat at same dose level Grade 4 (platelets <25,000/mm³): hold until recovers to grade ≤1 (≥75,000/mm³), then reduce one dose level	
SG	Neutropenia, diarrhea (both boxed warnings)	CBC (ANC) monitoring Avoid UGT1A1 inhibitors / inducers and consider UGT1A1 status G-CSF primary prophylaxis if UGT1A1 poor metabolizer High-emetic-risk antiemetic prophylaxis	Neutropenia Withhold treatment if grade 2 (ANC <1,500/mm³) on day 1, grade 3 (ANC <1,000/mm³) on day 8, grade 4 (ANC <500/mm³), or neutropenic fever Dose reduce 25% for grade 4 neutropenia ≥7 days, grade 3 febrile neutropenia, or each episode of prolonged grade 3-4 neutropenia Diarrhea Withhold treatment for grade 3 (>7 stools/day over baseline or hospitalization) or grade 4 (life-threatening) 25% dose reduction grade 3-4 not controlled with anti-diarrheal medications Atropine for early cholinergic diarrhea. Loperamide for late-onset diarrhea episodes (maximum 16 mg/day) after infection is excluded; fluids and electrolytes	Grade 3-4 neutropenia or non-neutropenic toxicity that delays dosing by 3 weeks for recovery to grade ≤1; recurrent toxicity after maximal dose reduction (per label); life-threatening hypersensitivity / infusion reaction

ADC	Hallmark Toxicities	Prevention / Monitoring	Key Management	Permanent-discontinuation Triggers
Dato-DXd	Stomatitis / oral mucositis, ocular surface toxicity, ILD/ pneumonitis	Dexamethasone mouthwash, oral cryotherapy during infusion Lubricant eye drops, avoid contact lenses, periodic eye exams Chest CT monitoring for ILD Antiemetic prophylaxis	ILD / Pneumonitis Grade 1 (asymptomatic, radiographic findings only): hold, consider prednisone ≥0.5 mg/kg/day, resume at same dose if resolved <28 days, otherwise reduce one dose level Grade 2 (symptomatic): permanently discontinue and promptly start prednisone ≥1 mg/kg/day Ocular Toxicity Ophthalmology referral and dose modification for ocular events per label Stomatitis Grade 2 (moderate pain/ulcers not interfering with oral intake): hold until resolves to grade ≤1 Grade 3 (severe pain limiting oral intake): hold until resolves to grade ≤1, then reduce one dose level Intensify mouthwash and topical care for stomatitis	Grade ≥2 ILD / pneumonitis; corneal perforation; severe hypersensitivity

9. Resistance, Sequencing, and Future Directions

Resistance to ADC therapy is common in the metastatic setting, and it can occur during antigen binding, internalization, intracellular trafficking, payload release, and payload action (Table 6). Notably, ADC resistance presents a challenge to optimal ADC sequencing. Understanding where in this sequence resistance arises clarifies why some strategies to overcome it succeed and others fail [1, 48, 49].

9.1. Antigen Loss and Heterogeneity

The most common mechanism of resistance is loss or downregulation of the target antigen. HER2 expression can decrease overtime under therapeutic pressure. TROP2 expression may show substantial spatial and temporal heterogeneity across metastatic sites, so a biopsy at progression may not reflect the full antigen landscape. Complete

antigen loss is uncommon; partial loss and spatial heterogeneity are more typical and may blunt rather than abolish activity, highlighting the importance of the bystander effect for agents with cleavable linkers [1, 48] (Table 6).

9.2. Intracellular Processing and Payload-Level Resistance

Because an ADC must be internalized, trafficked to the lysosome, and processed to liberate its payload, defects or alterations at any of these steps can confer resistance even when the surface antigen is preserved. Altered receptor internalization or recycling, disrupted endosomal-lysosomal trafficking, and deficient lysosomal proteolysis or linker cleavage can each reduce the intracellular concentration of active payload [1]. These mechanisms are difficult to detect with routine clinical assays and are largely inferred from preclinical models, which limits their present role in treatment selection [48].

Once released, the payload is subject to the same resistance biology as conventional cytotoxics. Upregulation of ATP-binding cassette efflux transporters, such as Multi-Drug Resistance 1 (MDR1)- mediated efflux, can reduce intracellular exposure to ADC payloads, including both maytansinoids like DM1 and topoisomerase-I inhibitors like DXd and SN-38 [48]. Alterations in the payload target, such as microtubule dynamics or topoisomerase-I levels, can reduce the efficacy of the respective payload. Payload-specific resistance is central to the ADC sequencing problem, since different ADCs may have differing receptor antigen targets, but many share the same payload [50] (Table 6). A systematic review of real-world outcomes and cross-resistance of sequential ADCs in HER2-low and TNBC revealed that approximately 53% of patients had cross-resistance and approximately 75% of patients had shorter real-world PFS with second ADC use [51].

For HER2-positive disease, sequential HER2-directed ADC therapy is supported by prospective data: DESTINY-Breast02 demonstrated that T-DXd retains meaningful activity after progression on T-DM1, establishing that sequential ADCs directed against the same target can be effective when the two agents differ substantially in linker, payload, bystander effect, and drug-to-antibody ratio [20]. For HER2-negative disease, the evidence for sequencing the topoisomerase-I ADCs (T-DXd, SG, and Dato-DXd) is retrospective. Multicenter cohort studies of patients treated sequentially with T-DXd and

SG (in either order) for HER2-low metastatic disease have a shorter median time to treatment failure with the second ADC, although some patients still derive meaningful benefit [52].

Because T-DXd, Dato-DXd, and SG all deliver topoisomerase-I inhibitor payloads, payload-level resistance is a plausible mechanism of cross-resistance even when the antibody target changes from HER2 to TROP2. Acquired TOP1 mutations have been identified at progression after topoisomerase-I ADC exposure and were associated with resistance to subsequent ADCs carrying the same payload class [50]. This suggests that switching the surface target alone (HER2 to TROP2) or between TROP2 agents may be insufficient to overcome resistance when the payload class is unchanged, and that the payload, not only the antigen, should inform selection of a subsequent ADC. This reasoning has prompted interest in evaluating agents with non–topoisomerase-I payloads after failure of a topoisomerase-I ADC, although this remains a hypothesis rather than an established strategy [1, 50, 52].The sequencing literature is almost entirely retrospective, subject to selection bias and confounding, and the pivotal randomized trials largely excluded patients with prior ADC exposure. No randomized trial has yet defined the optimal order of ADCs in HER2-negative disease. Predictors of second-ADC benefit identified retrospectively, such as longer benefit from the first ADC and differing payloads, require prospective validation [49, 52]. Retrospective signals also suggest that ADCs deliver more benefit earlier in the treatment course, before extensive clonal diversification [1, 52].

Several prospective studies are currently investigating optimal ADC sequencing. TRADE-DXd is a randomized phase 2 trial evaluating Dato-DXd followed by T-DXd versus T-DXd followed by Dato-DXd [53]. SERIES is a prospective phase 2 study evaluating SG after prior T-DXd, while ENCORE is a prospective registry examining sequential ADC use in HER2-negative metastatic breast cancer [52]. Re-biopsy at progression may be considered to reassess tumor biology; however, its role in guiding ADC selection remains unproven. Its clinical usefulness is limited by spatial tumor heterogeneity, the activity of T-DXd in HER2-low and HER2-ultralow disease, and the fact that TROP-2 testing is not routinely required. No prospective evidence currently demonstrates that biopsy-guided ADC selection improves outcomes [54].

9.3. Tumor Microenvironment and Clonal Evolution

Resistance also emerges at the level of the tumor as a system. Selection under treatment pressure enriches for resistant tumor clones, as well as resistance from the tumor microenvironment, including stromal barriers to ADC penetration [48]. These processes make resistance dynamic and complex rather than a single switch, and they help explain why the benefit from a sequential ADC is often shorter than from the first [52] (Table 6).

9.4. Rational Combinations

Combination strategies aim to prevent or delay resistance. The most mature combination is the addition of immune checkpoint inhibition to a TROP2-directed ADC in TNBC, where SG plus pembrolizumab improved outcomes in the first-line PD-L1-positive metastatic setting compared to conventional chemo-immunotherapy [37]. Dato-DXd plus durvalumab is currently being investigated for first-line treatment in PD-L1-positive metastatic TNBC [41].

In HER2-positive disease, T-DXd with pertuzumab improved outcomes in the first-line metastatic setting compared with THP [26]. Combinations of T-DXd with HER2 small molecule inhibitors, such as tucatinib, remain investigational. Other rational combinations under investigation include endocrine therapy and biomarker-matched targeted agents, such as poly (ADP-ribose) polymerase (PARP) inhibitors and PI3K/AKT-pathway inhibitors [55, 56]. The unifying principle is pairing the ADC with an agent that addresses a complementary vulnerability, while balancing the potential for overlapping toxicity [1].

Table 6. ADC Resistance Mechanisms, Clinical Consequences, and Potential Strategies

Resistance mechanism	Clinical consequence	Potential strategy
Antigen loss or downregulation	Reduced binding and payload delivery; partial loss may still respond via bystander effect	Switching target or payload; favor cleavable-linker, bystander-capable agents
Antigen heterogeneity (intra- and inter-tumoral)	Variable, incomplete response across lesions	Bystander-active ADCs; combination approaches
Impaired internalization, trafficking, or lysosomal processing	Less payload liberated despite antigen presence	Switch payload class or delivery mechanism (largely preclinical basis)

Resistance mechanism	Clinical consequence	Potential strategy
Deficient linker cleavage or payload release	Subtherapeutic intracellular payload	Switch to an ADC with a different linker chemistry and release mechanism
Drug efflux (ABC transporters, e.g., P-glycoprotein)	Payload extruded; cross-resistance across payloads that are transporter substrates	Switch payload class; efflux-independent payloads (investigational)
Payload-target alteration: Acquired TOP1 mutation for DXd/SN-38; altered microtubule dynamics for DM1	Cross-resistance among ADCs sharing a payload class	Change the payload class, not only the antigen target
Clonal evolution and tumor microenvironment	Dynamic, polyclonal resistance; shorter benefit from later ADC	Rational combinations; earlier ADC use before extensive clonal diversification is under study

10. Future Directions

The pace of ADC development suggests that the current landscape represents an early stage rather than a mature one. Progress is proceeding along several axes: new targets, improved engineering, more informative biomarkers (e.g., circulating tumor DNA), and investigation of TROP2-directed ADCs into curative intent therapy. For example, ASCENT-05/ OptimICE-RD are currently evaluating SG plus pembrolizumab for early-stage TNBC with residual disease after neoadjuvant therapy [57].

10.1. New Targets, including HER3

The target repertoire is expanding beyond HER2 and TROP2. HER3 is the most advanced new target: patritumab deruxtecan (HER3-DXd), which pairs a HER3-directed antibody with the DXd payload and showed meaningful activity (ORR 53.5%) in heavily pretreated hormone receptor-positive/HER2-negative metastatic breast cancer in the phase 2 ICARUS-BREAST01 [13, 58]. HER3 is attractive because it is broadly expressed in hormone receptor-positive disease, and contributes to endocrine and targeted therapy resistance, potentially addressing a population with limited therapeutic options after CDK4/6-inhibitor failure [58]. Patritumab deruxtecan remains investigational in breast cancer, with a phase 3 trial now underway in hormone receptor-positive/HER2-negative metastatic disease after endocrine therapy with a CDK4/6-inhibitor. Due to its payload of DXd, cross-resistance and sequencing considerations like those discussed above will need to be defined prospectively.

10.2. Improved Linker Chemistry, DAR Optimization, and Payload Diversification

A second axis of innovation is the ADC platform itself: linker refinements to improve plasma stability and control payload release, DAR optimization to balance potency and tolerability, and payload diversification to address cross-resistance. Non-topoisomerase-I payloads including next-generation microtubule inhibitors and novel DNA-damaging or immune-activating warheads are being investigated. Most of these approaches remain in preclinical or early-phase development, and no practice-changing randomized breast cancer trial has yet established the clinical benefit of DAR optimization or novel payload design [1, 48].

10.3. Bispecific, Biparatopic, and Dual-Payload ADCs

Structural innovation extends to the antibody and payload architecture. Biparatopic antibodies that bind two epitopes of the same antigen can enhance receptor clustering and internalization. Bispecific ADCs targeting two antigens aim to address the antigen heterogeneity that limits single-target agents [48]. Dual-payload ADCs that carry two mechanistically distinct cytotoxics on a single antibody are being explored to pre-empt payload resistance. For example, BL-B01D1 (izalontamab brengitecan) is a bispecific ADC targeting EGFR and HER3 that is currently being investigated for advanced stage TNBC in IZABRIGHT-Brest01 [59]. Each of these designs attempts to engineer around a specific resistance mechanism, but all remain investigational in breast cancer [48].

10.4. Biomarkers Beyond Immunohistochemistry: ctDNA and Molecular Residual Disease

The limitations of IHC have driven a search for better predictive biomarkers. Dynamic functional or genomic markers may predict benefit more accurately than a static IHC score because ADC activity depends on antigen density and heterogeneity, internalization, trafficking, and payload sensitivity [1, 14].

Circulating tumor DNA (ctDNA) is being investigated both to detect molecular residual disease (MRD) after curative-intent therapy in the early-stage setting, and to monitor clonal evolution and resistance-associated alterations during treatment of metastatic disease. If validated, ctDNA-based MRD could guide treatment escalation or de-escalation in the early-stage setting and could inform decisions on treatment

adaptation in the metastatic setting, including timing of ADC switching. These approaches are exploratory and are not yet standard for treatment decisions [60, 61].

10.5. Escalation and De-escalation, and the Move into Curative-Intent Disease

Response-adapted escalation in early-stage breast cancer is already established in the adjuvant HER2-positive setting, and future strategies aim to use pathologic response, MRD status, and ctDNA to escalate therapy for the highest-risk patients while de-escalating for those with an excellent prognosis, to limit cumulative toxicity without sacrificing cure [43, 44].

There is continued movement of ADCs into curative-intent disease. DESTINY-Breast05 established adjuvant T-DXd as superior to T-DM1 for high-risk HER2-positive residual disease, and DESTINY-Breast11 established T-DXd followed by THP improved pCR in the neoadjuvant setting [43, 44]. These results raise an important question regarding the sequencing of DESTINY-Breast05 after DESTINY-Breast11; further data are needed to address optimal sequencing.

11. Conclusion

ADCs have moved from a promising concept to one of the central therapeutic platforms in breast cancer, reshaping the treatment paradigm across every major breast cancer subtype and transforming HER2 from a binary biomarker into a continuum that now includes HER2-low and HER2-ultralow disease. The trajectory of these agents from later lines of metastatic therapy to the first line setting and, most recently, into the adjuvant and neoadjuvant treatment of early-stage disease reflects a broader shift from palliation toward cure. Toxicity remains agent-specific and should be carefully considered when selecting an ADC and monitored while on therapy, particularly in the curative-intent setting. Sequencing decisions are, for now, guided largely by retrospective data and expert judgment rather than by randomized evidence.

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Conceptualization, literature review and analysis, writing – original draft preparation [AK, VVQ, SA]; writing – review and editing [AK, SA]; supervision and critical revision of manuscript [AE, AH]. All authors have read and agreed to publish version of the manuscript.

Conflicts of interest

The authors do not have conflict of interest.

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