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Review

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Antibody-drug Conjugates (ADCs) in Breast Cancer

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ABSTRACT

Breast cancer is the most common cancer in women worldwide and comprises numerous molecular subtypes. Antibody-drug conjugates (ADCs) are a new class of drugs that combine specific monoclonal antibodies with a cytotoxic drug and are also used in breast cancer treatment. This review discusses the ADCs ado-trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd), sacituzumab govitecan (SG), and datopotamab deruxtecan (Dato-DXd). These drugs have demonstrated significant benefits in overall survival in patients with human epidermal growth factor receptor 2 (HER2)-positive, HER2-low, hormone receptor-positive, and triple-negative breast cancer. T-DXd has extended the reach of HER2-targeted therapy to patients with HER2-low and HER2-ultralow disease; SG and Dato-DXd have emerged as effective options for patients with extensive prior treatment. In addition to therapeutic effectiveness, the individual adverse effect profiles of these medications must be carefully evaluated and managed. Important safety issues with these medications include thrombocytopenia and liver toxicity with T-DM1, interstitial lung disease/pneumonia with T-DXd, neutropenia and diarrhea with SG, and stomatitis and ocular damage with Dato-DXd. Ongoing clinical trials include investigations of early-stage therapies, new combination medicines, and next-generation research targeting resistance mechanisms associated with ADCs. As a result, ADCs have established a new standard in breast cancer treatment and play a vital role in personalized oncology.

Keywords: Antibody-drug conjugates, breast cancer, drug-related side effects and adverse reactions, molecular targeted therapy

Introduction

Accounting for 32% of all female cancer diagnoses, breast cancer is the most common cancer in the United States (US). Among women less than 50 years old, it is the top cancer killer; yet, when all age groups are taken into account collectively, it ranks second, after lung cancer [1]. Thanks to advances in the genomic era, breast cancer may now be classified into intrinsic molecular subgroups, which have improved our understanding of the disease's biological heterogeneity: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-positive, and basal-like/triple-negative. This classification has provided greater accuracy in predicting clinical course and treatment response [2,3]. Thanks to this molecular classification, endocrine therapy (ET) developed for hormone receptor (HR) positive disease [4] or anti-HER2 drugs used when HER2 amplification is available have significantly improved individual clinical survival [5]. However, in individuals with aggressive types of breast cancer, such as triple-negative breast cancer (TNBC), the effect of the medications used on survival has been significantly limited [6]. There is growing interest in developing more selective and effective therapeutic strategies for cases in which certain breast cancer subtypes are resistant to conventional treatments. In this framework, the paradigm of breast cancer treatment has changed substantially with the development of novel targeted agents in recent years [7].

The structure of antibody-drug conjugates (ADCs) comprises a monoclonal antibody targeting a tumor-associated antigen, a cytotoxic payload, and a chemical linker that connects them. The adverse effects of ADCs are caused by a number of factors, including the distribution of the target antigen, the payload, the linker, the conjugation process, the structure of the antibody, and its Fc receptor expression [8]. The ADCs ado-trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd), sacituzumab govitecan (SG), and datopotamab deruxtecan (Dato-DXd) have been approved by the US Food and Drug Administration (FDA) for the treatment of breast cancer and have entered practice (Table 1) [9]. These agents combine target specificity with strong cytotoxic activity and show promising results, especially in patient populations with drug resistance or limited treatment options.

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This review examines the growing importance of ADCs in breast cancer treatment and the research performed on them. It summarizes the most recent clinical data for all molecular subtypes and emphasizes their significance, especially for HER2-positive and TNBC subtypes. It also includes toxicity profiles and the management of side effects.

T-DM1

T-DM1 is an ADC created by conjugating trastuzumab, an HER2-targeted antibody, with DM1, a microtubule-inhibiting cytotoxic agent derived from maytansine [10]. The anticancer effects of trastuzumab are seen when T-DM1 binds to the HER2 receptor [11,12]. Following binding of the HER2-T-DM1 complex, it is taken up into the cell via endocytosis and lysosome fusion, and the breakdown of this intracellular complex releases the cytotoxic load known as DM1 [13]. In this way, T-DM1 causes cells to undergo apoptosis and mitotic breakdown [14].

In the first human study published in 2010, an intravenous (IV) dose regimen of 3.6 mg/kg every three weeks was determined for T-DM1 administration [15]. Trastuzumab in combination with docetaxel has long been recognized as an effective treatment for HER2-positive metastatic breast cancer (MBC). In the initial randomized phase II study, T-DM1 was compared with this treatment. In this context, T-DM1 has emerged as a highly effective treatment option for improving progression-free survival (PFS). The median PFS in the T-DM1 group was statistically significantly longer than in the trastuzumab plus docetaxel group [14.2 months vs. 9.2 months, hazard ratio (HR): 0.59, p=0.035]. Objective response rates (ORR) were similar (64.2% vs. 58.0). The tolerance profile was enhanced, and the number of adverse events graded 3 or higher decreased with T-DM1 [16].

The results of the phase II study served as the foundation for the EMILIA study. This phase III trial, which was randomized and open-label, investigated the safety and efficacy of T-DM1 in individuals with HER2-positive, locally advanced disease or MBC who had previously received trastuzumab and taxane therapy. In this study involving 991 patients, one group received oral lapatinib and capecitabine, while the other received T-DM1. T-DM1 demonstrated improvements in both PFS and overall survival (OS) compared with the other treatment. Increases of approximately 6 months in median OS and 3 months in median PFS were observed (OS: 25.1 vs. 30.9 months; PFS: 9.6 vs. 6.4 months). The T-DM1 group had a higher ORR (43.6% vs. 30.8%), and responses lasted longer (12.6 months). In terms of safety analyses, the T-DM1 group experienced fewer grade ≥3 adverse events (57% vs. 41%). The most prevalent adverse effects of T-DM1 were increased transaminases and thrombocytopenia, whereas the control group experienced diarrhea, palmar-plantar erythrodysesthesia, vomiting, and thrombocytopenia more frequently [10]. In 2013, the European Medicines Agency and the FDA approved the use of T-DM1, which was the first ADC to be used in the treatment of breast cancer [17]. In the most recent study, the median OS was 29.9 months in the T-DM1 group and 25.9 months in the control group. Additionally, the risk of mortality was reduced by 25% (HR: 0.75) [18]. Overall, T-DM1 has been shown to be a safe standard of care option for previously treated HER2-positive MBC. It not only increases the chances of survival, but it is also safe.

The TH3RESA trial demonstrated that T-DM1 was effective in treating HER2-positive MBC in patients who had previously received other treatments without success. In patients treated with trastuzumab, lapatinib, and a taxane, T-DM1 added 2.9 months to PFS compared to physician-choice chemotherapeutic regimens (HR: 0.52, p<0.0001). A considerable improvement in OS (HR: 0.55) was observed as well. The T-DM1 group had a higher incidence of grade 3 or higher adverse events (43% vs. 32%). In the T-DM1 group, thrombocytopenia was the most common serious adverse event [19]. Patients who have previously received trastuzumab and lapatinib for HER2-positive MBC may find T-DM1 a more acceptable alternative because of its lower toxicity profile.

The MARIANNE trial investigated the efficacy of T-DM1 as a first-line treatment for HER2-positive MBC. Patients were divided into three groups and received trastuzumab plus a taxane, T-DM1, or T-DM1 plus pertuzumab. T-DM1 was as effective for PFS and OS as the standard trastuzumab-taxane combination. The frequency of adverse events of grade 3 and above was lower in the T-DM1 group. In the control group, alopecia, peripheral neuropathy, and gastroenteritis occurred more frequently. Conversely, T-DM1-containing regimens were more frequently associated with thrombocytopenia and increased hepatic toxicity [20]. These data suggest that although T-DM1 does not show superiority to standard therapy in the first-line setting, it may be a better-tolerated alternative.

The KAMILLA study evaluated the clinical benefit of T-DM1 in breast cancer with HER2-positive brain metastases. Furthermore, an ORR of 21.4% in patients with brain metastases and a 42.9% response rate (defined as >30% reduction in intracranial lesions) demonstrated that T-DM1

Table 1. Structural and functional characteristics of ADCs used in breast cancer

ADC	Target antigen	Cytotoxic payload	Linker type	DAR	Bystander effect
T-DM1	HER2	DM1 (microtubule inhibitor)	Non-cleavable	~3.5	No
T-DXd	HER2	DXd (topoisomerase I inhibitor)	Cleavable	~8	Yes
SG	Trop-2	SN-38 (topoisomerase I inhibitor)	CL2A (cleavable)	~8	Yes
Dato-DXd	Trop-2	DXd (topoisomerase I inhibitor)	Cleavable	~4	Yes

ADC: Antibody-drug conjugate, DAR: Drug-to-antibody ratio, Dato-DXd: Datopotamab deruxtecan, HER2: Human epidermal growth factor receptor 2, HR: Hormone receptor, T-DM1: Trastuzumab emtansine, T-DXd: Trastuzumab deruxtecan, SG: Sacituzumab govitecan, TNBC: Triple-negative breast cancer

can also exhibit clinical activity in central nervous system (CNS) metastases. The preponderance of the adverse events was hematologic and hepatic in nature, and the most common events were thrombocytopenia and elevated liver function tests. The low treatment discontinuation rate (5.7%) supports the manageability of the toxicity profile [21]. The incorporation of atezolizumab into T-DM1 therapy did not improve PFS in the overall HER2-positive MBC population in the KATE2 study. However, a signal of enhanced clinical activity was observed in the programmed death-ligand 1 (PD-L1)-positive subgroup [22].

T-DM1 has been studied in early-stage HER2-positive breast cancer and in disseminated disease. The pathological complete response (pCR) rate for T-DM1 plus pertuzumab in the neoadjuvant phase of the KRISTINE study was 55.7%, which was higher than the 44.4% observed with the standard chemotherapy strategy of trastuzumab plus carboplatin plus pertuzumab. The patients' quality of life was preserved because there were a lot fewer grade 3 or higher adverse events in the T-DM1+P group (31.8% vs. 67.7%) [23].

The KATHERINE study is an adjuvant TDM-1 study of early-stage HER2-positive breast cancer patients who underwent surgery after trastuzumab and taxane-based chemotherapy and who experienced persistent invasive disease. Adjuvant T-DM1 demonstrated a significant improvement in invasive disease-free survival (iDFS) compared with adjuvant trastuzumab. T-DM1 significantly increased the 3-year iDFS rate (88.3% vs. 77.0%). It also reduced the rate of distant metastasis (10.5% vs. 15.9%). The rate of discontinuation due to grade 3 or higher adverse events was higher in the T-DM1 group (15.4% and 2.1% vs. 25.7% and 18.0%) [24]. Based on the results of the final long-term analysis of a 7-year follow-up, T-DM1 increased the iDFS rate to 80.8%, representing an absolute gain of 13.7 percentage points, compared with trastuzumab; it also increased the OS rate to 89.1%, representing an absolute improvement of 4.7 percentage points [25]. Therefore, 14 cycles of T-DM1 are now considered the established standard of care for patients with persistent HER2-positive disease after neoadjuvant treatment.

The T-DM1+P combination did not exhibit superiority over the conventional regimen of taxane + trastuzumab + P (THP) in terms of iDFS in the KAITLIN trial, which evaluated adjuvant therapy in patients with high-risk HER2-positive early-stage breast cancer [26]. Nevertheless, the ATEMPT study, which investigated the efficacy of adjuvant T-DM1 in patients with stage I HER2-positive breast cancer, compared it with the conventional regimen of paclitaxel and trastuzumab. A three-year iDFS rate of 97.8% was achieved after one year of adjuvant T-DM1 therapy [27].

T-DM1: Toxicity and Management

The safety profile of T-DM1 treatment has been comprehensively evaluated for hematologic, hepatic, neurological, pulmonary, and cardiac toxicities. With a frequency of 12.9% in the EMILIA study, 5% in the TH3RESA trial, and 5.7% in the adjuvant KATHERINE trial, thrombocytopenia was the most commonly reported grade ≥3 adverse event in clinical studies [10,19,24]. Thrombocytopenia is generally observed during the initial two treatment cycles and is believed to be the result of the suppression of megakaryocyte differentiation [22]. The KAMILLA study, however, demonstrated that severe thrombocytopenia is rarely associated with clinically significant bleeding events [21]. In the context of clinical management, it is advisable to maintain the current dose of treatment for patients with grade 1-2 thrombocytopenia. In the event of grade 3 thrombocytopenia, treatment should be discontinued until the platelet count reaches grade 1 or lower, at which point it should be resumed at the same dose. For patients developing thrombocytopenia grade 4, treatment should be interrupted and resumed at a reduced dose level after hematological recovery [28].

Hepatotoxicity is a characteristic toxicity of T-DM1, most often presenting as asymptomatic transaminase elevations. In the EMILIA trial, grade 3 or higher increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were reported in 4.3% and 2.9% of patients, respectively. In the KATHERINE study, the rates of AST and ALT elevations at all grades were 28.4% and 23.1%, respectively [24]. Nodular regenerative hyperplasia, an uncommon yet serious complication, has been reported, especially in the KATHERINE and KAITLIN studies [24,26]. If hepatotoxicity is grade ≥3, temporary suspension of treatment is recommended. If there is significant elevation of bilirubin: permanent discontinuation of treatment is recommended [10].

Compared with conventional taxane-based therapies, which are associated with neurological toxicity, T-DM1 has been linked to a lower incidence of peripheral neuropathy. In the KATHERINE study, the rate of peripheral neuropathy of all grades was 18.6%, while grade ≥3 neuropathy was reported in only 1.4% of patients [24]. In the KRISTINE study, the rate of grade 3 or higher peripheral neuropathy was found to be 3.1% [23]. In patients who develop severe neuropathy, it is recommended to interrupt treatment until symptoms resolve and to reduce the dose as necessary.

Pulmonary toxicities, particularly pneumonitis and interstitial lung disease (ILD), are uncommon but potentially life-threatening complications. While the incidence of pneumonitis was reported as 2.6% in the KATHERINE study [24], the incidence of radiation-associated pneumonia was reported as 2.3% in the KAITLIN study [26]. Therefore, permanent discontinuation of T-DM1 therapy is recommended when pneumonitis or ILD is suspected [20,22].

Clinically substantial reductions in left ventricular ejection fraction with T-DM1 are uncommon when cardiac safety is assessed. In the EMILIA trial, 1.7% of patients experienced a reduction to less than 50%, and the left ventricular ejection fraction decreased by over 15% from baseline [10]. In the KATHERINE study, the rate of cardiac events was found to be quite low (0.1%) [24]. However, in line with the general safety approach for HER2-targeted therapies, regular cardiac monitoring is recommended.

The cornerstones of toxicity management in T-DM1 therapy are dose delay and dose reduction. The standard regimen is

an IV dose of 3.6 mg/kg every 21 days; if toxicity develops, the dose can be reduced to 3.0 mg/kg and then to 2.4 mg/kg, respectively [10,22]. Treatment may be delayed for up to 42 days until toxicity resolves; however, discontinuation of treatment is recommended if tolerance cannot be achieved even at lower doses [22]. In adjuvant studies, allowing patients who could not continue T-DM1 due to toxicity to complete their treatment with trastuzumab has been considered an important approach for maintaining treatment continuity [26]. Additionally, in a study evaluating the real-world analysis of adjuvant T-DM1, it demonstrated a manageable toxicity profile [29].

T-DXd

T-DXd, the next-generation ADC, is composed of a humanized anti-HER2 immunoglobulin G1 monoclonal antibody, a cleavable tetrapeptide binder, and a topoisomerase I inhibitor payload (DXd) [30]. T-DXd has a superior drug-to-antibody ratio compared to T-DM1 (approximately 8 vs. approximately 3.5) [30-32]. The bystander effect is a mechanism by which the released lethal payload can affect nearby cells to eradicate cancer by more easily passing through their membranes [33]. T-DXd employs a tumor-agnostic approach targeting HER2 expression, with HER2 expression determined by central/local evaluation as immunohistochemistry (IHC) 3+ or 2+ using the DAKO HER2 HercepTest [34].

Participants with HER2-positive MBC who had already received extensive therapy, including T-DM1, were evaluated for T-DXd in the Phase II DESTINY-Breast01 trial. The OS was 62% after an average of 26.5 months of follow-up, with the shortest PFS and OS at 19.4 and 29.1 months, respectively. Patients were most severely affected by ILD/pneumonitis, which occurred in 15.8% of cases and was associated with a 2.7% mortality rate [35].

DESTINY-Breast03 was a study designed to evaluate the efficacy of T-DXd versus T-DM1 in HER2-positive MBC patients who had previously received trastuzumab and taxane [36]. T-DXd provided a 20-month advantage in PFS and a 36% reduction in overall mortality risk (HR: 0.64). In the T-DXd arm, ILD/pneumonitis cases were low-grade, with an incidence of 15.2%; no fatal cases occurred. This demonstrates that toxicity can be managed with appropriate monitoring. These results strengthen the status of T-DXd as a standard second-line treatment for HER2-positive MBC [37].

Just as some breast cancers lack HER2 amplification, overexpression, or both, a large proportion exhibit low but treatable levels of HER2 expression. In these patients with "HER2-low" cancer, current HER2-targeted therapies have been ineffective. HER2-low expression is indicated by IHC findings of 1^+ or 2^+ and by negative *in situ* hybridization (ISH) results. In DESTINY-Breast04, patients with HER2-low MBC who had already received one or two rounds of chemotherapy were compared in two groups: those who received T-DXd and those who received chemotherapy given at the discretion of the clinician. Whether evaluated in the overall patient group or in the HR-positive arm, T-DXd demonstrated a substantial clinical advantage. The ORR was substantially higher with T-DXd than with chemotherapy (52.3% vs. 16.3%), and the risk of mortality with T-DXd was 36% lower. In safety analyses, although grade ≥3 adverse events were observed at a lower rate compared to chemotherapy, ILD/pneumonia (0.8% fatal) developing in 12.1% of patients emerged as the primary toxicity requiring attention. Subgroup analyses showing similar efficacy in HER2 IHC 1^+ and HER2 IHC 2^+/ISH-negative patients support that T-DXd provides broad clinical benefit in the HER2-low disease group [38].

Patients with HER2-ultralow expression were included in the clinical use of T-DXd in the DESTINY-Breast06 study, which followed the DESTINY-Breast04 study. We included patients with HR-positive MBC who had not undergone chemotherapy for metastatic disease and whose disease had progressed after at least one ET session. Patients were considered to have HER2-low expression if their IHC scores were 1^+ or 2^+/ISH-negative, and HER2-ultra-low expression if their IHC scores were 0 with mild membrane staining. T-DXd was compared with investigator-selected single-agent chemotherapy. T-DXd improved PFS in both the HER2-low and HER2-ultralow groups (HRs: 0.62 and 0.78, respectively). This demonstrates that T-DXd is effective across a broader spectrum of HER2 expression [39]. Based on these results, T-DXd appears to be a viable alternative to other ET for patients with HR-positive, HER2-low, or ultra-low MBC [40].

The DAISY study is another trial evaluating the efficacy of T-DXd in patients with HER2-overexpressing, HER2-low, and HER2-negative MBC. The ORR was 70.6%, 37.5%, and 29.7%, respectively. These results indicate that clinical responses observed in HER2-negative patients, the bystander effect, and alternative biological mechanisms may play a role in treatment response [41].

The DESTINY-Breast02 study compared T-DXd to the physician's recommended treatment for individuals with HER2-positive MBC whose disease had progressed on T-DM1. T-DXd demonstrated a significant advantage in terms of PFS, OS, and ORR (70% vs. 29%). ILD/pneumonia, observed in 10% of patients, emerged as the primary toxicity of concern [42]. These results provided the first randomized evidence suggesting that resistance developed against one ADC can be overcome by another ADC.

The DESTINY-Breast12 trial evaluated the effectiveness of T-DXd in patients with brain metastases. Participants were patients with HER2-positive MBC who had previously received anti-HER2 treatment; the trial was a phase 3b/4 study. Among patients with brain metastases, T-DXd demonstrated a 71.7% CNS response rate and a 61.6% PFS rate at 12 months. The ORR was 62.7% in patients who did not have brain metastases [43]. Even in cases where brain metastases are present, our data show that T-DXd is an effective therapeutic option.

Patients with HER2-positive advanced-stage disease or MBC were enrolled in the DESTINY-Breast09 trial, a first-line study that assessed the effectiveness of T-DXd + P. T-DXd+P outperformed the gold-standard regimen of THP, achieving a median increase in PFS of 44% (40.7 months vs. 26.9 months).

The T-DXd+P group had a higher ORR (87% vs. 81%) [44]. Even at the outset of therapy, these results support the proposition that T-DXd may be an appropriate therapeutic option. Thanks to NCT04784715, we can still obtain OS data and conduct long-term follow-up. In the DESTINY-Breast05 study, researchers evaluated T-DXd and T-DM1 in women with high-risk HER2-positive breast cancer who had residual disease after neoadjuvant therapy. T-DXd showed superior 3-year iDFS compared with T-DM1 (92.4% vs. 83.7%; HR: 0.47). The decreased risk of distant recurrence in the T-DXd arm provides additional evidence that the medicine has the ability to be an effective post-neoadjuvant therapy for early-stage HER2-positive cancer (NCT04622319) [45].

T-DXd: Toxicity and Management

Although the safety profile of T-DXd therapy is generally manageable, it is characterized by gastrointestinal and hematologic toxicities, as well as adverse events such as ILD and pneumonia, which require close monitoring [35].

Nausea, vomiting, fatigue, alopecia, and constipation were the most frequently reported adverse effects in clinical trials [42]. Nausea, in particular, is observed in the majority of patients and is more pronounced during the early stages of treatment [35]. Given that the drug is classified as having a high emetogenic risk, appropriate prophylactic antiemetic measures is important. For primary prophylaxis before treatment, a triple antiemetic regimen of dexamethasone, a 5-hydroxytryptamine receptor antagonist, and a neurokinin-1 receptor antagonist is suggested [46].

Neutropenia, anemia, and leukopenia are the major hematologic toxicities, and regular monitoring of complete blood count and dose adjustment as required is recommended [37].

ILD/pneumonitis is the most serious and potentially fatal toxicity associated with T-DXd, with an incidence of approximately 10-15.8%. Therefore, patients should be carefully evaluated for symptoms such as cough, dyspnea, and fever [35]. In the case of suspected ILD/pneumonitis, T-DXd treatment should be held, and the patient should be clinically, radiologically, and, if needed, pulmonologically assessed.

In grade 1 (asymptomatic) cases, treatment should be stopped until the radiological findings have completely resolved and regressed to grade 0, with close monitoring of symptoms and oxygen saturation for 2-7 days; a follow-up chest computed tomography scan should be performed within 1-2 weeks. During this period, systemic corticosteroid therapy with prednisone or equivalent at a dose of at least 0.5 mg/kg/day should be considered. After clinical recovery, the dose should be gradually reduced over at least 4 weeks. T-DXd can be resumed at the same dose if ILD/pneumonitis has fully resolved within 28 days of onset; if resolution occurs later than 28 days after onset, treatment should be resumed at a reduced dose level. Conversely, if the condition has not completely resolved within 49 days, T-DXd treatment should be permanently discontinued.

Symptomatic grade 2 ILD/pneumonitis represents a clinically significant toxicity requiring definitive discontinuation of T-DXd and prompt administration of systemic corticosteroids at therapeutic doses. Steroid medication must be maintained for a minimum of 14 days or until clinical and radiological abnormalities have fully resolved, followed by a progressive dosage reduction over at least four weeks. If clinical improvement is not evident within the initial five days, it is advisable to either escalate the steroid dosage to 2 mg/kg/day or to transition to IV corticosteroid therapy.

Grade 3 or grade 4 ILD/pneumonitis is a serious clinical condition requiring urgent and aggressive treatment. In these patients, T-DXd therapy should be permanently discontinued, and the patients should be hospitalized. Treatment should be initiated immediately with high-dose IV methylprednisolone (typically 500-1000 mg/day for three days), followed by at least 1 mg/kg/day of oral prednisone or an equivalent. After 14 days of corticosteroid treatment, or earlier if radiological and clinical improvements are seen, the dosage should be gradually reduced over four weeks. In cases where a clinical response is not achieved within 3-5 days despite steroid therapy, additional immunosuppressive agents, such as infliximab or mycophenolate mofetil, should be considered.

Patients at all stages should be closely monitored until clinical symptoms and radiological findings have completely resolved, even if T-DXd treatment has been discontinued. Additionally, the increased risk of opportunistic infections in patients using prednisone or equivalent corticosteroids at doses higher than 20 mg daily should be considered, and appropriate prophylactic treatments, particularly for Pneumocystis jirovecii pneumonia, should be evaluated [47].

Furthermore, it is necessary to conduct routine assessments of cardiac function both prior to and during treatment, as there is a low incidence of decreased left ventricular ejection fraction with other HER2-targeted agents [35].

In general, the majority of adverse events can be effectively managed through treatment interruptions, dose reductions, and supportive care approaches [44].

SG

Targeting trophoblast cell-surface antigen-2 (Trop-2), SG is an ADC composed of an anti-Trop-2 monoclonal antibody conjugated to an SN-38 payload via a hydrolyzable CL2A linker. Owing to its high drug-to-antibody ratio (~8:1) and efficient cellular internalization, SG exhibits selective cytotoxic effects on tumor cells expressing Trop-2. The released SN-38 inhibits cell proliferation by causing deoxyribonucleic acid (DNA) damage and inducing apoptosis. Additionally, free SN-38, which can diffuse into the tumor microenvironment, exerts a cytotoxic effect on neighboring cells, contributing to the "bystander effect" mechanism [48].

SG has become an important part of the Phase 1/2 IMMU-132-01 project to demonstrate the efficacy of the ADC method in treating metastatic TNBC. It demonstrated a 33.3% ORR in individuals with advanced TNBC who had previously undergone extensive treatment. Neutropenia and anemia occurred frequently as grade 3 side effects; 3% of people stopped their medication. Overall, SG demonstrated a manageable

safety profile [49]. SG and physician-selected chemotherapy were evaluated in the phase 3 ASCENT trial in patients with metastatic TNBC who had previously undergone two or more lines of treatment or who had relapsed. The OS was 12.1 months, the median PFS was 5.6 months, and the ORR was 35% in patients without brain metastases, compared with 5% in those with brain metastases. Diarrhea and myelosuppression were more common side effects of SG therapy [50]. These findings further establish SG as the treatment of choice for patients with metastatic TNBC who have undergone two or more prior treatments. Furthermore, since SG demonstrated a PFS advantage over chemotherapy across all Trop-2 expression levels, its efficacy was shown to persist across a broad biological spectrum, suggesting that routine pre-treatment Trop-2 assessment may not be mandatory [51].

Particularly in HR^+/HER2-MBC, SG showed encouraging effectiveness in the Phase I/II IMMU-132-01 basket trial [49]. In endocrine-resistant, previously treated patients with HR^+/HER2-negative MBC, the TROPiCS-02 trial compared SG with physician-selected chemotherapy. SG enhanced ORR (21% vs. 14%) and increased median PFS (from 4 months to 5.5 months; HR: 0.66) [52]. Initial results showed a numerical advantage in OS; however, after adjusting for confounding factors, the SG group had a higher median OS (14.4 vs. 11.2 months; HR: 0.79). A survival advantage was observed regardless of the level of Trop-2 expression. The occurrence of diarrhea was 10% greater with SG treatment compared to chemotherapy (1% lower), and grade ≥3 neutropenia was 51% higher (compared to 39%). No instances of treatment-associated pneumonitis were seen in the SG group [53]. The results support SG's status as the first approved ADC for HR^+/HER2-negative MBC in patients with a history of ET, taxanes, and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors who have completed 2-4 cycles of chemotherapy for metastatic disease.

Patients with HER2-negative breast cancer who are at high risk of recurrence and have residual disease after neoadjuvant chemotherapy are being studied in the SASCIA phase 3 trial to determine the safety and effectiveness of SG. According to an interim safety analysis, The adverse events, such as nausea, vomiting, diarrhea, alopecia, and hematologic toxicities, were more prevalent in the SG group. The SG group also had a higher rate of grade ≥3 adverse events than the physician's choice group (66.7% vs. 20.9%). No new safety signals were found. Although dose delays were more common with SG therapy, the rates of dose decrease were equal in both arms. The data support the notion that ADCs might be useful in treating early-stage breast cancer and demonstrate that SG has an acceptable safety profile despite its increased toxicity burden [54]. The study has reported only interim safety analyses, and primary efficacy results are not yet mature (NCT04595565). The NeoSTAR study is a phase 2 trial evaluating neoadjuvant SG in early-stage TNBC in combination with pembrolizumab. In this study, a pCR was achieved in 34% of patients. The most frequently reported events in patients were hair loss, fatigue, and diarrhea. While these results indicate that the combination of SG and pembrolizumab demonstrates promising antitumor activity in early-stage TNBC, they also indicate a need for further studies to determine the optimal treatment duration and sequence [55].

SG: Toxicity and Management

Hematologic and gastrointestinal adverse events are the most prevalent, and the toxicity profile of SG treatment is essentially consistent with the known effects of SN-38.

The most frequent side effect of grade 3 or higher was neutropenia. The ASCENT and TROPiCS-02 studies reported an incidence of approximately 51% for grade ≥3 neutropenia [50,52]. The approach for neutropenia includes dose skipping, dose reduction as needed, and granulocyte-colony stimulating factor (G-CSF) supplementation [49,50]. Clinical studies have shown that approximately 49-54% of patients require G-CSF support, and dose modifications can be applied in 25-50% of cases involving recurrent severe hematologic toxicity [49,50,52].

Gastrointestinal toxicities are also a notable component of SG therapy [49,50]. In particular, diarrhea is observed to some degree in approximately 59-62% of patients, while the rate of grade ≥3 diarrhea is approximately 10%. Therefore, the early initiation of anti-motility agents, such as loperamide, and the implementation of supportive care measures are important. Common side effects include nausea in 59% of cases and vomiting in 29% [50]; therefore, prophylactic antiemetic therapy is recommended as an important part of clinical practice [49]. Alopecia is observed in approximately 46-48% of patients and is considered an expected side effect related to the cytotoxic burden of SG [50].

Peripheral neuropathy should be considered, and, in particular, ILD/pneumonia is significantly lower with SG than with other ADCs [50]. Furthermore, the uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) *28/*28 genotype, which affects SN-38 metabolism, has been linked to an elevated risk of hematologic toxicity. Although neutropenia and anemia may be observed more frequently in these patients, current data do not support routine UGT1A1 screening prior to SG treatment; instead, close clinical monitoring is recommended. It is evident that SG toxicities may be effectively treated with proactive supportive techniques and appropriate dosage changes, since the treatment discontinuation rates owing to adverse events remain low (5-6%) [52].

Dato-DXd

One ADC that stands out is Dato-DXd. Combines a conjugated humanized anti-Trop-2 antibody with the powerful topoisomerase I inhibitor DXd [56]. The half-life of Dato-DXd is greater than that of SG [57]. Patients with solid tumors who had previously received therapy were assessed for safety and effectiveness of Dato-DXd in the TROPION-PanTumor01 phase 1 study. Remarkably, the TNBC subgroup achieved an ORR of 31.8% and a median PFS of 4.4 months [58]. Participants in the TROPION-Breast01 trial's third phase were patients with HR^+/HER2-negative inoperable disease or MBC who were receiving investigational treatment, had previously undergone

one or two cycles of chemotherapy in a metastatic setting, and were resistant to or not eligible for ET; they were compared with investigator-selected single-agent chemotherapy for safety and efficacy. Compared with chemotherapy, Dato-DXd demonstrated a considerable improvement in PFS, with a 37% lower likelihood of death or progression. Final OS analysis did not reveal any statistically significant differences between Dato-DXd and chemotherapy after controlling for variables such as median follow-up time (22.8 months vs. 18.3 months; HR: 1.01). On the other hand, Dato-DXd outperformed the other treatments secondary outcomes such as time to second advancement, duration of reaction, and ORR. Mild nausea and stomatitis were the most often reported toxicities, and treatment-related adverse events grade ≥3 occurred far less frequently in the Dato-DXd group than in the chemotherapy group (45.6% vs. 22.2%) [59]. Adults who have already received endocrine-based treatment or chemotherapy and have HR^+ but HER2-negative breast cancer (IHC: 0, IHC: 1^+, or IHC $2^+/ISH^-$) are eligible for treatment with Dato-DXd according to the TROPION-Breast01 investigation.

The BEGONIA study examined the efficacy and tolerability of Dato-DXd with durvalumab in previously untreated individuals with advanced or metastatic TNBC. A full recovery was noted in 10% of patients, contributing to an ORR of 79%. The treatment response was shown to be independent of PD-L1 expression levels, and the median PFS was reported to be 13.8 months. According to the safety studies, 65% of patients had nausea and stomatitis as adverse events, while 57% of patients reported adverse events of grade ≥3. ILD/pneumonitis occurred in 5% of patients, and no fatalities were reported as a result of therapy. These results provide credence to the idea that Dato-DXd and durvalumab should be the subject of additional clinical trials [60].

The effectiveness of neoadjuvant Dato-DXd in treating early-stage breast cancer was assessed in the I-SPY2.2 study. Although 30% of patients in the other group achieved pCR using Dato-DXd, only 6% of patients with $HR^+/HER2^-$ and TNBC did so. The pCR incidence was particularly high (41% in this category) among patients who tested negative for HR, HER2, immune status, and DNA repair deficiency. Based on these results, it seems that selecting patients based on their molecular traits is crucial for maximizing Dato-DXd therapy efficacy [61].

Dato-DXd: Toxicity and Management

The Dato-DXd group had a better tolerability profile, as evidenced by a reduced frequency of grade ≥3 treatment-related side events (45% vs. 21-22%) in clinical studies compared to the investigator-selected chemotherapy regimen [59].

The most commonly observed adverse events include stomatitis, nausea, vomiting, fatigue, skin rash, decreased appetite, and alopecia. Stomatitis is a characteristic toxicity of Dato-DXd therapy; it was reported in 72-83% of patients in the studies and was predominantly mild to moderate (Grade 1-2). Dexamethasone-containing mouthwashes are recommended to reduce the risk of stomatitis [58,61]. Additionally, ocular toxicities such as dry eyes, keratitis, and blurred vision have been observed in approximately 38-44% of patients [61]. The use of lubricating eye drops is emphasized for the management of ocular toxicities.

As with other ADCs containing T-DXd, ILD/pneumonitis is a clinically significant adverse event with an incidence ranging from approximately 2% to 4%; most cases are mild [53,54]. Dose delays or dose reductions are implemented as needed, and close clinical monitoring of patients is recommended, particularly for those with ILD.

Infusion-related reactions have been reported in approximately 18-20% of cases. Dato-DXd's lower rates of neutropenia and diarrhea compared to other Trop-2-targeted ADCs are attributed to its linker structure, which is more stable in plasma and thus contributes significantly to the drug's safety profile.

Table 2 provides a comprehensive comparative overview of clinical indications, efficacy outcomes from landmark trials, characteristic toxicity profiles, and clinical management strategies for the evaluated ADCs.

Future Perspectives

As part of research into ADCs, current agents are used in the early stages of treatment, and next-generation ADCs and novel combination strategies are being developed. In this context, studies are being conducted to assess the appropriate use of T-DXd in metastatic and early-stage HER2-positive breast cancer and to redefine its role in current treatment algorithms. Additionally, the Phase III DESTINY-Breast11 trial showed higher pCR rates with neoadjuvant T-DXd followed by THP than with dose-dense anthracycline-based chemotherapy followed by THP in patients with high-risk HER2-positive early breast cancer. Although longer follow-up is needed to clarify event-free and OS outcomes, these results may support the incorporation of T-DXd-based, anthracycline-free strategies into future treatment algorithms [62]. Furthermore, the potential synergistic antitumor benefits and the ability to overcome resistance mechanisms achieved by combining ADCs with immune checkpoint inhibitors, tyrosine kinase inhibitors, CDK4/6 inhibitors, and other targeted therapies are under intensive investigation.

Furthermore, supportive therapies such as bispecific ADCs, dual-loaded ADCs, probody-drug conjugates, and immune-activated ADC platforms aim to overcome current limitations such as tumor heterogeneity, treatment resistance, and off-target toxicities [9]. The results of these ongoing trials are expected to significantly improve the therapeutic index of ADCs and set new standards in breast cancer treatment.

Table 2. Comparative clinical summary of ADCs in breast cancer: current indications, landmark efficacy outcomes, and toxicity profiles

Ado-trastuzumab emtansine (T-DM1)	**HER2**	• **Adjuvant eBC:** residual invasive HER2-positive eBC after neoadjuvant taxane- and trastuzumab-based therapy. • **mBC:** previously treated unresectable locally advanced or metastatic HER2-positive breast cancer.	• **EMILIA** • **TH3RESA** • **KATHERINE** • **KAMILLA**	• **Residual eBC (KATHERINE):** at 8.4 yrs follow-up, 7-yr iDFS was 80.8% vs. 67.1% with trastuzumab (HR: 0.54); 7-yr OS was 89.1% vs 84.4% (HR: 0.66). • **Prior mBC (EMILIA):** mPFS 9.6 vs. 6.4 months; mOS 30.9 vs. 25.1 months compared with lapatinib + capecitabine. • **Brain metastases (KAMILLA):** intracranial ORR ~21% in patients with measurable brain metastases.	• Thrombocytopenia (inc. grade ≥3) • Hepatotoxicity/ transaminase elevation • Peripheral neuropathy • Fatigue & nausea • Left ventricular dysfunction • Rare ILD/ pneumonitis • Nodular regenerative hyperplasia	• Established standard of care for residual HER2-positive disease after neoadjuvant therapy; future treatment algorithms may evolve with emerging comparative evidence. • Monitor CBC and LFTs prior to each dose. • Withhold or reduce dose for clinically significant thrombocytopenia or transaminitis. • Discontinue permanently for nodular regenerative hyperplasia, severe DILI, or clinically significant ILD/ pneumonitis. • Monitor LVEF at baseline and periodically.
Trastuzumab deruxtecan (T-DXd)	**HER2**	• **Neoadjuvant eBC:** T-DXd → THP (Stage II-III HER2+). • **Adjuvant eBC:** residual invasive HER2+ eBC post-neoadjuvant trastuzumab/ taxane therapy. • **1L mBC:** T-DXd + pertuzumab for unresectable/metastatic HER2+. • **Previously treated mBC:** unresectable/metastatic HER2+. • **HER2-low mBC:** unresectable/ metastatic after prior chemo in metastatic setting or early relapse. • **HR+/HER2-low or ultralow:** unresectable/metastatic post-≥1 ET.	• DESTINY-Breast01/02/03 • DESTINY-Breast04 • DESTINY-Breast05 • DESTINY-Breast06 • DESTINY-Breast09 • DESTINY-Breast11 • DESTINY-Breast12	• **Neoadjuvant eBC (DB-11):** pCR 67.3% (T-DXd→THP) vs. 56.3% (ddAC→THP). • **Residual eBC (DB-05):** 3-yr iDFS 92.4% vs. 83.7% with T-DM1 (HR: 0.47). • **1L mBC (DB-09):** T-DXd + pertuzumab mPFS 40.7 vs. 26.9 months (HR: 0.56); ORR 87% vs. 81%. • **Prior mBC (DB-03):** Sustained PFS & OS superiority over T-DM1. • **HER2-low mBC (DB-04):** mPFS 9.9 vs. 5.1 months (HR: 0.50); mOS 23.4 vs. 16.8 months; ORR 52.3% vs. 16.3%. • **HR$^+$/HER2-low/ultralow (DB-06):** mPFS 13.2 vs. 8.1 months (HR: 0.64). • **Brain metastases (DB-12):** CNS ORR 71.7% in patients with active or stable brain metastases; 12-month PFS 61.6%	• ILD/pneumonitis (potentially fatal) • Nausea & vomiting • Neutropenia, anemia, thrombocytopenia • Fatigue & alopecia • Left ventricular dysfunction • Infusion-related reactions	• Educate patients to report new respiratory symptoms immediately. • Obtain prompt chest CT and specialist evaluation on ILD suspicion. • Grade 1 ILD: hold T-DXd until resolution; consider systemic corticosteroids (prednisone ≥0.5 mg/ kg/day). • Grade ≥2 ILD: discontinue permanently; promptly initiate systemic corticosteroids (prednisone ≥1 mg/kg/day with prolonged taper). • Require 3-drug antiemetic prophylaxis. • Monitor CBC and LVEF baseline and periodically.

Table 2. Continued

Sacituzumab govitecan (SG)	**Trop-2**	• **1L mTNBC:** monotherapy for patients not candidates for PD-1/PD-L1 inhibitors. • **1L PD-L1⁺ mTNBC:** SG + pembrolizumab (CPS ≥10). • **Prior mTNBC:** unresectable/ metastatic after ≥2 prior therapies (≥1 for mBC). • **HR⁺/HER2- mBC:** post-ET and ≥2 chemo regimens in mBC setting.	• **IMMU-132-01** • **ASCENT** • **TROPiCS-02** • **ASCENT-03** • **ASCENT-04 / KEYNOTE-D19** • **SASCIA**	• **1L TNBC (ASCENT-03):** mPFS 9.7 vs. 6.9 months (HR: 0.62); ORR 50% vs 47%. • **1L PD-L1⁺ TNBC (ASCENT-04):** SG + pembro mPFS 11.2 vs. 7.8 months (HR: 0.65); ORR 61% vs 55%. • **Prior mTNBC (ASCENT):** mPFS 5.6 vs 1.7 months; mOS 12.1 vs 6.7 months; ORR 35% vs. 5%. • **HR⁺/HER2- mBC (TROPiCS-02):** mPFS 5.5 vs 4.0 months; mOS 14.4 vs 11.2 months. • Efficacy observed regardless of Trop-2 expression; routine testing not required.	• Neutropenia (inc. grade ≥3 & febrile neutropenia) • Diarrhea (inc. severe) • Nausea & vomiting • Alopecia & fatigue • Anemia • Infusion/ hypersensitivity reactions • Increased toxicity risk in UGT1A1-deficient patients	• Severe or life-threatening neutropenia and diarrhea. • Monitor CBC before dosing and during treatment. • Consider primary G-CSF prophylaxis in high-risk patients; use secondary prophylaxis post-neutropenic events. • Initiate loperamide promptly at onset of uncomplicated diarrhea. • Close monitoring for patients homozygous for UGT1A1*28.
Datopotamab deruxtecan (Dato-DXd)	**Trop-2**	• **HR+/HER2- mBC:** Post-ET and chemotherapy in metastatic setting. • **1L mTNBC:** Unresectable/ metastatic in patients not candidates for PD-1/PD-L1 inhibitors. • Additional early-stage and combination strategies remain under clinical investigation	• TROPION-PanTumor01 • TROPION-Breast01 • TROPION-Breast02 • BEGONIA • I-SPY2.2	• **HR⁺/HER2- mBC (TROPION-Breast01):** mPFS 6.9 vs. 4.9 months (HR: 0.63); ORR 36% vs. 23%; mOS 18.6 vs. 18.3 months (HR: 1.01). • **1L mTNBC (TROPION-Breast02):** mPFS 10.8 vs. 5.6 months (HR: 0.57); mOS 23.7 vs. 18.7 months (HR: 0.79); ORR 64% vs. 30%. • **BEGONIA:** ORR 79%; mPFS 13.8 months with Dato-DXd + durvalumab in 1L TNBC (exploratory).	• Stomatitis/ oral mucositis (predominantly Gr 1-2) • Ocular toxicities (dry eye, keratitis, blepharitis, blurred vision) • Nausea & vomiting • Fatigue • ILD/pneumonitis • Anemia & neutropenia (generally lower vs. SG)	• High incidence of stomatitis; prophylactic dexamethasone oral rinse (swish-and-spit) is strongly recommended from cycle 1 to prevent oral mucositis. • Recommend preservative-free eye drops; avoid contact lenses. • Perform baseline and periodic ophthalmologic examinations. • Hold for suspected ILD; permanently discontinue for Grade ≥2 ILD.

Current indications are summarized based on the United States Food and Drug Administration approvals as of July 2026. Regulatory approvals, treatment sequencing, reimbursement, and availability may differ across countries and regions. The DESTINY-Breast05, DESTINY-Breast11, ASCENT-03/04, and TROPION-Breast02 trials have recently reported primary Phase III results. Although these findings have led to regulatory approvals in selected settings, incorporation into regional clinical practice guidelines (including ESMO and NCCN) may vary according to the timing of guideline updates.
ADC: Antibody-drug conjugate, BC: Breast cancer, CBC: Complete blood count, CPS: Combined positive score, ddAC: Dose-dense doxorubicin and cyclophosphamide, DILI: Drug-induced liver injury, eBC: Early breast cancer, ESMO: European Society for Medical Oncology, ET: Endocrine therapy, G-CSF: Granulocyte-colony stimulating factor, HER2: Human epidermal growth factor receptor 2, HR+: Hormone receptor, HR: Hazard ratio, iDFS: Invasive disease-free survival, ILD: İnterstitial lung disease, LFT: Liver function test, LVEF: Left ventricular ejection fraction, mBC: Metastatic breast cancer, mOS: Median overall survival, mPFS: Median progression-free survival, mTNBC: Metastatic triple-negative breast cancer, NCCN: National Comprehensive Cancer Network, ORR: Objective response rate, OS: Overall survival, pCR: Pathological complete response, PD-1: Programmed cell death protein 1, PD-L1: Programmed death-ligand 1, THP: Taxane, trastuzumab, and pertuzumab, TNBC: Triple-negative breast cancer, Trop-2: Trophoblast cell-surface antigen 2, UGT1A1: Uridine diphosphate glucuronosyltransferase 1A1

Conclusion

The efficacy and safety profiles of ADCs make them novel therapeutic modalities in cancer therapy. T-DM1, T-DXd, SG, and Dato-DXd are approved for breast cancer, have shown efficacy in relevant clinical studies, and are currently in use. Moreover, the existence of many agents in late-phase clinical development is a positive development for breast cancer treatment. A better understanding of ADCs through clinical practice will foster rational decision-making as well as planning for effective research. Analyses of toxicity and management issues arising during ADC use in the real world will further advance our understanding. This will facilitate the development of superior next-generation ADCs with more reliable and better-characterized toxicity profiles.

Footnotes

Authorship Contributions

Concept: M.N.B., B.D., Design: M.N.B., Analysis or Interpretation: M.N.B., B.D., Literature Search: M.N.B., Writing: M.N.B., B.D.

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