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REVIEW ARTICLE

Clinical Development of New Antibody–Drug Conjugates in Breast Cancer: To Infinity and Beyond

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Abstract

Metastatic breast cancer remains an incurable disease, and new therapies are needed. One major limitation of chemotherapy is the toxicity associated with higher dose exposure. Antibody–drug conjugates (ADCs) are a complex and evolving class of agents specifically designed with the objective of delivering antineoplastic medicines in the most precise and selectively targeted way. ADCs are composed of four key components: (1) the target antigen, (2) an antibody construct, (3) a payload (most commonly a cytotoxic agent), and (4) a linker moiety that couples the payload and the antibody. In this review, we discuss the clinical development of ADCs for the treatment of breast cancer, focusing on two recently FDA-approved agents, trastuzumab deruxtecan and sacituzumab govitecan, and discuss the ongoing efforts exploring new agents. Finally, we summarize the current portfolio of clinical trials that could change the algorithm of treatment for early and advanced breast cancer.

Key Points

Antibody–drug conjugates (ADCs) are specifically designed with the objective of delivering antineoplastic agents in the most precise and selectively targeted way, increasing the antitumoral efficacy while minimizing toxicity to normal tissues.

ADCs are composed of four key components: the target antigen, an antibody construct, a payload (most commonly a cytotoxic agent), and a linker moiety that couples the payload and the antibody.

The ADCs trastuzumab deruxtecan and sacituzumab govitecan were recently granted FDA approval for the treatment of human epidermal growth factor receptor 2 (HER2)-positive and triple-negative advanced breast cancer, respectively.

Ongoing clinical trials evaluating ADCs are likely to reshape the standard of care for both early and advanced breast cancer.

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1 Introduction

Breast cancer is the most frequently diagnosed cancer and the second most common cause of cancer death in women in the USA [1]. In the metastatic setting, despite available therapies, the majority of patients will die from their disease. Thus, new treatments are needed.

Antibody–drug conjugates (ADCs) are designed to deliver antineoplastic medicines precisely and in selectively targeted ways. ADCs are composed of four key components: (1) the target antigen, (2) the antibody construct, (3) a payload (most commonly a cytotoxic agent), and (4) a linker moiety that couples the payload and the antibody [2]. In general, following the binding of the antibody to overexpressed (or specifically expressed) target tumor antigens, the ADC is then internalized and the payload released. The payload release process can be due to proteolytic degradation of the entire ADC molecule, as is the case with trastuzumab emtansine (T-DM1) or due to the cleavage of the linker because of extracellular or intracellular conditions, including low pH or proteasome-mediated degradation, as in the case of trastuzumab deruxtecan and sacituzumab govitecan (Fig. 1). Advances in the biotechnology associated with the construction of linkers and the emergence of new payloads led to the development of new ADCs. Some ADCs also have activity via bystander effects, leading to off-target cancer cell killing.

In this review, we focus on the clinical development of the recent data that led the US FDA to grant approval for trastuzumab deruxtecan and sacituzumab govitecan in

breast cancer and on the new agents in development for treating this disease (Table 1).

2 Antibody–Drug Conjugates (ADCs) Targeting Human Epidermal Growth Factor Receptor 2 (HER2)

2.1 Trastuzumab Emtansine

Trastuzumab emtansine is an ADC that comprises the humanized monoclonal antibody trastuzumab, conjugated via a non-cleavable thioether linker to DM1, a derivative of the naturally occurring maytansinoid toxin. DM1 is a highly potent cytotoxin that inhibits tubulin polymerization and causes death in proliferating cells [3]. T-DM1 has a drug-to-antibody ratio (DAR) of 3.5.

T-DM1 was the first ADC to be granted FDA approval. In 2013, based on data from the EMILIA study [4] that demonstrated improved progression-free survival (PFS) and overall survival (OS) in patients treated with T-DM1 compared with patients treated with lapatinib and capecitabine, the drug was approved as a single agent in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) who have progressed on previous therapy with trastuzumab and a taxane. More recently, the KATHERINE study [5] established T-DM1 as the standard of care in the adjuvant setting for patients with HER2-positive disease treated with neoadjuvant trastuzumab-based therapy who present with residual disease at the time of surgery. The most commonly reported T-DM1-related adverse events are thrombocytopenia and elevated levels of liver enzymes. Patients may also experience neuropathy with prolonged exposure to the drug.

To date, the development of T-DM1 as first-line treatment for HER2-positive MBC or as a neoadjuvant treatment option has not yet been successful. In the phase III MARIANNE trial, T-DM1 with or without pertuzumab showed noninferior PFS to trastuzumab plus a taxane as first-line

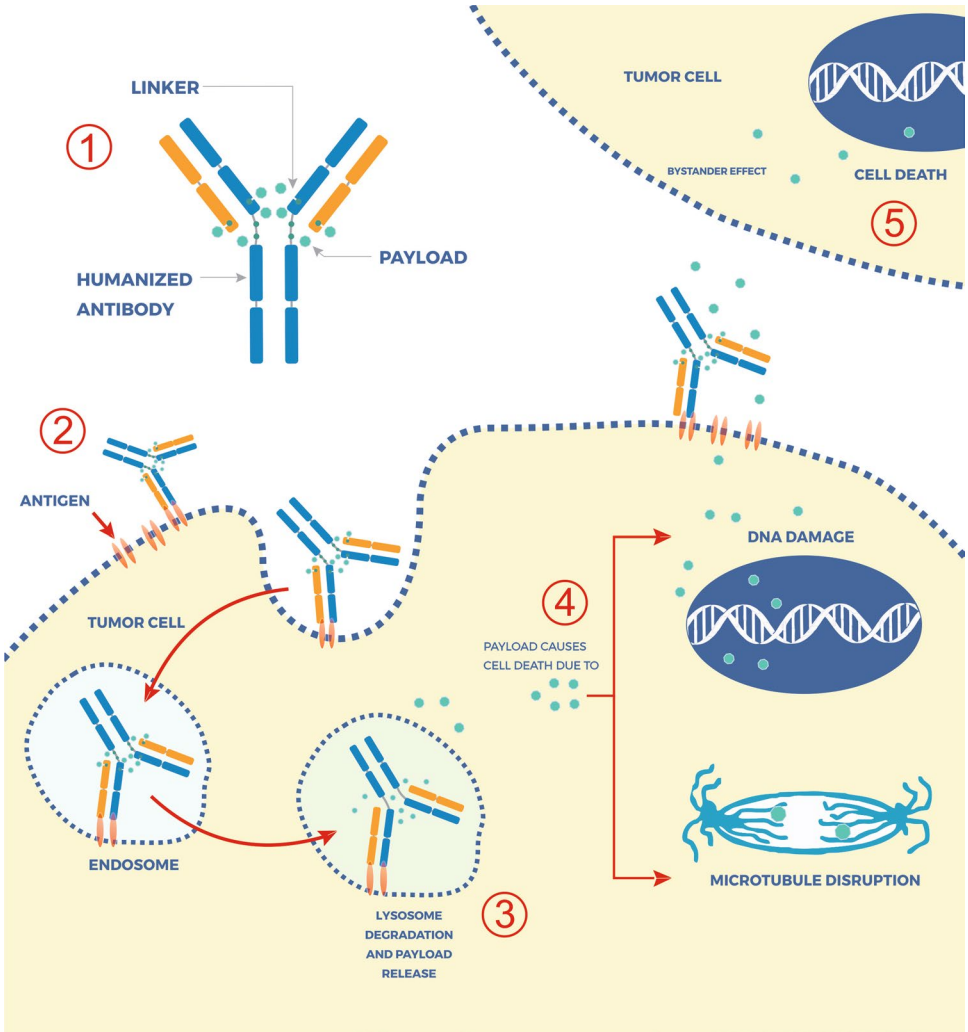

Fig. 1 Basic composition of an antibody–drug conjugate (ADC) and its mechanisms of action. (1) ADCs are composed of four key components: the target antigen, an antibody construct, a payload (most commonly a cytotoxic agent), and a linker moiety that will couple the payload and the antibody. Once the ADC is administered (2), there is the binding of the antibody to overexpressed (or specifically expressed) target tumor antigens leading to ADC internalization. Within lysosomes (3), the payload is released when the linker is cleaved by intracellular conditions, such as low pH or proteasome-mediated degradation. Depending on its mechanism of action (4), the payload will kill tumor cells through DNA damage, such as topoisomerase I inhibitors SN-38 and exatecan, or through microtubule disruption such as emtansine. Additionally, some payloads, such as SN-38 and exatecan, have a membrane-permeable nature and can cross cell membranes and exert a cytotoxic effect on bystander tumor cells (5), regardless of target antigen expression levels

Table 1 Characteristics of the antibody–drug conjugates currently approved or in late stages of development (phase III studies)

Agent	Target	Payload (mechanism of action)	DAR	Bystander effect	US FDA-approved indications	Toxicities of special interest
Ado-trastuzumab emtansine	HER2	Maytansine (antimicrotubule)	3–4	No	HER2+ MBC previously treated with trastuzumab and taxane Early-stage HER2+ BC with residual disease following neoadjuvant therapy (adjuvant)	AST/ALT elevations, thrombocytopenia, neuropathy
Trastuzumab deruxtecan	HER2	Exatecan (topoisomerase 1 inhibitor)	8	Yes	HER2-positive MBC previously treated with trastuzumab, taxane and T-DM1	ILD, neutropenia, anemia, nausea
Trastuzumab duocarmazine (SYD985)	HER2	Duocarmycin prodrug	2.8	Yes	Not approved to date	Fatigue, conjunctivitis, dry eyes
Disitamab vedotin (RC48-ADC)	HER2	Monomethyl auristatin E	4	No	Not approved to date	Neutropenia, AST/ALT elevations
Sacituzumab govitecan	TROP-2	SN-38 (topoisomerase 1 inhibitor)	7.6	Yes	Metastatic TNBC previously treated with at least two lines of CT in the metastatic setting	Neutropenia, anemia, diarrhea
Ladiratuzumab vedotin	LIV-1	Monomethyl auristatin E	4	No	Not approved to date	Neutropenia, anemia

ALT alanine transaminase, *AST* aspartate aminotransferase, *BC* breast cancer, *CT* chemotherapy, *DAR* drug-to-antibody ratio, *HER2+* HER2-positive by American Society of Clinical Oncology/College of American Pathologists guidelines, *ILD* interstitial lung disease, *MBC* metastatic breast cancer, *T-DM1* trastuzumab emtansine, *TNBC* triple-negative breast cancer

therapy for metastatic HER2-positive disease [6]. However, data from the CLEOPATRA study demonstrated that added pertuzumab to a taxane and trastuzumab improved both PFS and OS [7–9]. Therefore, T-DM1 remained a second-line standard. In the neoadjuvant KRISTINE trial, docetaxel, carboplatin, trastuzumab plus pertuzumab resulted in significantly more patients achieving a pathologic complete response than T-DM1 plus pertuzumab [10], although toxicity was substantially better in the T-DM1 + pertuzumab arm. Importantly, studies combining T-DM1 with the recently approved anti-HER2 tyrosine kinase inhibitor tucatinib are ongoing: the CompassHER2-RD trial (NCT04457596) is evaluating whether the combination of T-DM1 plus tucatinib is superior to T-DM1 alone in the adjuvant setting, and the HER2CLIMB-02 trial (NCT03975647) is evaluating whether the combination of T-DM1 plus tucatinib is superior to T-DM1 alone in patients previously treated with a trastuzumab plus taxane regimen in the metastatic setting.

2.2 Trastuzumab Deruxtecan

Trastuzumab deruxtecan (DS-8201 or T-Dxd) is an ADC composed of a humanized anti-HER2 monoclonal antibody with the same amino acid sequence as trastuzumab and a cleavable tetrapeptide-based linker coupled to a potent topoisomerase I inhibitor payload: an exatecan derivative (Table 1). Trastuzumab deruxtecan has a high DAR: eight molecules of the exatecan derivative per monoclonal antibody, which allows the delivery of high concentrations of the payload [11]. Following binding to HER2, the ADC is internalized and trafficked intracellularly to lysosomes [12]. Importantly, while stable in plasma, the linker undergoes selective cleavage by lysosomal cathepsins, which are upregulated in tumor cells [13–16]. Furthermore, given the membrane-permeable nature of the payload, it can cross cell membranes and exert its potent cytotoxic effect on bystander tumor cells regardless of HER2 expression levels [17].

In 2015, a phase I, first-in-human study accrued heavily pretreated patients with advanced HER2-positive breast, or with gastric or gastro-esophageal cancer, with the primary objective of establishing the recommended dose for study expansion and assessing the safety, tolerability, and activity of trastuzumab deruxtecan [11]. Based on preliminary antitumor activity and safety data, the doses of 5.4 and 6.4 mg/kg were selected as the recommended doses for the expansion phase of this study. In this trial, the maximum tolerated dose was not reached.

2.2.1 Use in HER2-Positive Breast Cancer

During the dose-expansion phase of the aforementioned study, the safety, tolerability, and activity of trastuzumab deruxtecan were further assessed in five patient cohorts (Table 2). The study included 115 patients (seven from

cohort 1; 100 from cohort 2a; and eight from cohort 2e) with HER2-positive breast cancer who received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion of 5.4 mg/kg ($n = 49$) or 6.4 mg/kg ($n = 66$) every 3 weeks [18]. Patients in this study had received a median of seven previous cancer therapies (range 5.0–11.0) and 70% had hormone receptor (HR)-positive tumors. At the time of data cutoff, the median duration of treatment was 8.3 months (interquartile range [IQR] 4.4–12.0), and 60 (52%) patients had discontinued therapy, most commonly due to progressive disease per RECIST 1.1 in 30 (26%) patients, clinical progression in 12 (10%), or adverse events in 13 (11%). The most common classes of treatment-emergent adverse events were gastrointestinal and hematological. Notably, there were 20 cases (17%) of interstitial lung disease (ILD), pneumonitis, or organizing pneumonia, including one grade 3 event and two treatment-related deaths due to pneumonitis. Of the 20 cases, six were observed with 5.4 mg/kg (6 [12%] of 49) and 14 with 6.4 mg/kg doses (14 [21%] of 66). No cases of decreased ejection fraction were reported. Among the 111 patients included in the efficacy analysis, 66 (59.5%) had a confirmed objective response. The median time to response was 1.6 months, and the median duration of response was 20.7 months. The median PFS was 22.1 months, and the median OS has not been reached. Post hoc analysis showed similar objective response rates (ORRs) independent of previous pertuzumab treatment (62.5%), dose group (5.4 mg/kg = 56.5%; 6.4 mg/kg = 61.5%), and HR status (HR positive = 59.5%; HR negative = 61.1%).

In 2019, the preliminary results of the DESTINY-Breast01 study (NCT03248492) were published [19]. This two-part, open-label, single-group, multicenter, phase II study evaluated trastuzumab deruxtecan in patients with HER2-positive MBC who had previously received treatment with trastuzumab emtansine. Of note, patients with untreated or symptomatic brain metastases, a history of noninfectious ILD or pneumonitis resulting in the use of glucocorticoids, or current or suspected ILD or pneumonitis were excluded. In the first part of the study, the investigators explored three different doses of trastuzumab deruxtecan (5.4, 6.4, and 7.4 mg/kg every 3 weeks) to determine a recommended dose; in the second part, the efficacy and safety of the recommended dose was assessed. The study showed a significant relationship between drug exposure and both efficacy outcomes and key adverse events, including ILD. Thus, considering the balance of safety and efficacy, the 5.4 mg/kg dose was chosen as the recommend dose for the second part of the study. Among the 253 patients who were enrolled and received at least one dose of trastuzumab deruxtecan, 184 received the recommended dose of intravenous trastuzumab deruxtecan of 5.4 mg/kg every 3 weeks. The median number of previous lines of therapy for metastatic disease was six. After a median follow-up of 11.1 months, the ORR was 60.9% (112 of 184 patients), with a median duration of response of 14.8 months. The median PFS was 16.4 months. At the time of the data cutoff, 52.1% who had received the recommended dose had discontinued trastuzumab deruxtecan. The primary reasons for discontinuation were progressive disease according to RECIST 1.1 (28.8%) and adverse events (15.2%). During the study, the most common grade 3 or higher adverse events were neutropenia (20.7%), anemia (8.7%), and nausea (7.6%). Only three patients had a decrease in the left ventricular ejection fraction (two grade 2 and one grade 3); those events were asymptomatic, and patients recovered after drug hold. No patients permanently discontinued treatment because of a decrease in the ejection fraction. Drug-related ILD, as determined by an independent adjudication committee, occurred in 25 patients (13.6%; grade 1 or 2, 10.9%; grade 3 or 4, 0.5%; and grade 5, 2.2%).

The robust efficacy data from this single-arm phase II study led the FDA to grant accelerated approval to trastuzumab deruxtecan for patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting [20]. In an updated analysis of the DESTINY-Breast01 study, the median PFS was 19.4 months and the estimated 12- and 18-month OS rates were 85% (95% confidence interval [CI] 79–90) and 74% (95% CI 67–80), respectively. The updated toxicity data revealed a slightly higher rate of ILD of 15.2% [21].

Ongoing international randomized phase III studies aim to address whether trastuzumab deruxtecan can improve efficacy outcomes compared with other approved anti-HER2-based regimens, such as T-DM1 (NCT03523585) or lapatinib plus capecitabine (NCT03529110), in both early and advanced stages of HER2-positive breast cancer. DESTINY-Breast05 (NCT04622319) is a phase III, multicenter, randomized, open-label study that will evaluate the efficacy (as assessed by invasive disease-free survival) of trastuzumab deruxtecan versus T-DM1 in patients with high-risk HER2-positive primary breast cancer who have residual invasive disease in breast or axillary lymph nodes following neoadjuvant therapy and who meet one of the following high-risk criteria: inoperable breast cancer at presentation (prior to neoadjuvant therapy), defined as clinical stages T4, N0–3, M0 or T1–3, N2–3, M0; operable at presentation, defined as clinical stages T1–3, N0–1, M0, with axillary node-positive disease (ypN1–3) following neoadjuvant therapy (Table 2).

2.2.2 Use in HER2-Low Breast Cancers

Between 40 and 50% of patients with breast cancer have tumors with low HER2 expression (defined as immunohistochemistry [IHC] 1 + or IHC 2 + with no HER2 amplification) [22]. This mixed population, including HR-positive breast cancer and triple-negative breast cancer (TNBC), does

Table 2 Ongoing clinical trials evaluating trastuzumab deruxtecan in patients with breast cancer

Register number (target accrual, N)	Design; arms and regimen	Study population	Primary outcome	Status/results
DESTINY-Breast02 NCT03523585 *N* = 600	Phase III; open label, randomizing to one of two arms: T-Dxd vs. TPC	HER2-positive MBC; previously treated with T-DM1	PFS	Accruing
DESTINY-Breast03 NCT03529110 *N* = 500	Phase III; open label, randomizing to one of two arms: T-Dxd vs. T-DM1	HER2-positive MBC; progressed during (or <6 months after) a trastuzumab/taxane-based regimen in the adjuvant or metastatic setting	PFS	Completed accrual; results pending
NCT04539938 *N* = 70	Phase II; single arm: tucatinib plus T-Dxd	HER2-positive MBC; previously treated (two or more prior HER2-based regimens in the metastatic setting)	ORR	Accruing
DESTINY-Breast07 NCT04538742 *N* = 350	Phase I dose escalation (part1) and dose expansion (part 2). Single-arm, four cohorts (T-Dxd with one of these four regimens: durvalumab, pertuzumab, paclitaxel, pertuzumab plus paclitaxel)	HER2-positive MBC; part 1—disease progression on or after the last systemic therapy prior to starting study treatment. At least one prior treatment line in metastatic setting required. Part 2—no prior lines of therapy for advanced/MBC allowed	Occurrence of AEs and serious AEs (part 1 and 2)	Not yet recruiting
DESTINY-Breast05 NCT04622319 *N* = 1600	Phase III; open label, randomizing to one of two arms: T-Dxd vs. T-DM1	HER2-positive early-stage with residual disease following neoadjuvant chemotherapy containing trastuzumab and taxane	IDFS	Not yet recruiting
DESTINY-Breast04 NCT03734029 *N* = 540	Phase III; open label, randomizing to one of two arms: T-Dxd vs. TPC	HER2-low (IHC 1+ or 2+/FISH-negative) MBC. One to two prior CT for metastatic breast cancer	PFS	Accruing
DESTINY-Breast 06 NCT04494425 *N* = 850	Phase III; open label, randomizing to one of two arms: T-Dxd vs. TPC	HR+/HER2-low (IHC 1+ or 2+/FISH-negative) MBC. No prior CT for advanced BC or MBC	PFS	Accruing
NCT04553770 *N* = 88	Phase II, open label, randomizing to one of two arms: T-Dxd or T-Dxd plus anastrozole	Early-stage HR+/HER2-low (IHC 1+ or 2+/FISH-negative). Candidate for neoadjuvant therapy	pCR rate	Not yet recruiting
DESTINY-Breast 08 NCT04556773 *N* = 185	Phase I dose escalation (part 1) and dose expansion (part 2). Single-arm, five cohorts (T-Dxd with one of these five regimens: durvalumab plus paclitaxel, capivasertib, anastrozole, fulvestrant, capecitabine)	HER2-low BC	Occurrence of AEs (part 1) and serious AEs (part 2)	Not yet recruiting
BEGONIA NCT03742102 *N* = 57[a]	Phase Ib/II, single-arm, multicohort; arm 6-durvalumab plus T-Dxd	HER2-low BC	Incidence of AEs (part 1); ORR (part 2)	Accruing
DEBBRAH NCT04420598 *N* = 39	Phase II, single arm; T-Dxd monotherapy	HER2-positive BC or HER2-low BC with brain metastasis or leptomeningeal dissemination	Efficacy (depending on the arm PFS, ORR, OS)	Accruing
NCT03523572 *N* = 99	Phase Ib, single arm T-Dxd plus nivolumab; part 1—dose escalation; part 2—dose expansion	HER2-positive BC, HER2-low BC and urothelial carcinoma	Occurrence of DLT (part 1), ORR (part 2)	
NCT04042701 *N* = 115	Phase I dose escalation (part1) and dose expansion (part 2). Single arm with T-Dxd plus pembrolizumab	HER2-positive BC, HER2-low expressing BC, HER2-expressing NSCLC, and HER2-mutant NSCLC	Occurrence of DLTs (part 1) and ORR (part 2)	Accruing

AE adverse event, *BC* breast cancer, *CT* chemotherapy, *DLT* dose-limiting toxicity, *FISH* fluorescence in situ hybridization, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *IHC* immunohistochemistry, *IDFS* invasive disease-free survival, *MBC* metastatic breast cancer, *NSCLC* non-small cell lung cancer, *ORR* objective response rate, *OS* overall survival, *pCR* pathologic complete response, *PFS* progression-free survival, *T-DM1* trastuzumab emtansine, *T-Dxd* trastuzumab deruxtecan, *TPC* treatment of physician's choice

[a]Number of patients that will be included in the arm containing Trastuzumab deruxtecan

not benefit from the currently approved anti-HER2 therapies. However, in preclinical studies, trastuzumab deruxtecan demonstrated antitumor activity in a variety of tumor types, including those with low HER2 expression [16]. Such activity in HER2-low-expressing tumors may be due to the already mentioned bystander effect in conjunction with the high DAR of trastuzumab deruxtecan with the high potency of payload [16, 17, 23]. Thus, trastuzumab deruxtecan was also tested for the treatment of MBC in patients with low HER2 expression in the previously discussed phase I study (NCT03734029) [24]. During the dose-expansion part of the study, patients with HER2-low breast cancer were enrolled (Table 2). The data of 54 patients with HER2-low advanced/unresectable or MBC who received at least one dose of trastuzumab deruxtecan at the recommended dose (5.4 mg/kg [n = 21] or 6.4 mg/kg [n = 33]) were jointly reported [24]. All patients had visceral disease at baseline, and most (87.0%) had HR-positive disease. Although these patients were heavily pretreated (median 7.5 prior therapies), the confirmed ORR by independent central review was 37.0%, the median duration of response was 10.4 months, the median PFS was 11.1 months, and the median OS was 29.4 months. The antitumor activity of trastuzumab deruxtecan was similar between patients with HER2 1+ (n = 28; ORR = 35.7%) or 2+ (n = 26; ORR = 38.5%) and patients with (n = 16; ORR = 43.8%) or without (n = 38; ORR = 34.2%) prior cyclin-dependent kinase 4/6 inhibitor therapy. Objective responses were less frequent in patients with HR-negative tumors (14.4%) than in those with HR-positive tumors (40.3%). Eleven (20.4%; one with 5.4 mg/kg and ten with 6.4 mg/kg) potential ILD events were reviewed by the independent adjudication committee and eight (14.8%; all 6.4 mg/kg) were attributed to trastuzumab deruxtecan, including three (5.6%) grade 1, two (3.7%) grade 2, and three (5.6%) grade 5 events.

Data from this phase I study suggest a promising antitumor activity of trastuzumab deruxtecan, especially in HR-positive breast cancer, and justify the ongoing randomized, multicenter study phase III studies DESTINY-Breast04 (NCT03734029) and DESTINY-Breast06 (NCT04494425). The primary objective of these studies is to compare the efficacy (PFS) of trastuzumab deruxtecan at the 5.4 mg/kg dose versus chemotherapy of physician's choice in patients with HER2-low, unresectable, and/or MBC. While DESTINY-Breast 04 allows inclusion of any HER2-low breast cancer independently of HR status, DESTINY-Breast06 restricts the inclusion to only HR-positive tumors (Table 2).

2.2.3 Other Clinical Trials with Trastuzumab Deruxtecan

Data from the central nervous system (CNS) subgroup included in the DESTINY-Breast01 trial demonstrated a consistent safety and efficacy profile when compared with the overall population [25]. The confirmed ORR for the 24 patients with CNS metastases at baseline was 58.3%, including 4.2% with complete response. At median follow-up of 11.0 months, the median PFS in the CNS subgroup was 18.1 versus 16.4 months in the overall population. As per protocol, patients with untreated or progressing brain metastases were not eligible for DESTINY-Breast 01. It is unknown whether trastuzumab deruxtecan is as effective in treating or preventing brain metastasis as has been shown for non-CNS disease. To help address this, a multicohort phase II study is exploring the efficacy of trastuzumab deruxtecan for patients with both HER2-positive or HER2-low breast cancer and untreated or progressive brain metastasis (NCT04420598).

Studies are also exploring trastuzumab deruxtecan in combination with tucatinib and pertuzumab (NCT04539938) and with immune checkpoint inhibitors (NCT03742102; NCT04042701; NCT04556773; NCT04538742). A phase Ib study evaluating trastuzumab deruxtecan in combination with nivolumab that included patients with advanced/MBC (either HER2 positive or HER2 low) (NCT03523572) had 48 patients who received the recommended phase II dose (RP2D) of trastuzumab deruxtecan (5.4 mg/kg) in combination with nivolumab 360 mg every 3 weeks (HER2 positive, n = 32; HER2 low, n = 16) [26]. After a median follow-up of approximately 7 months, the confirmed ORR was 59% in the HER2-positive cohort, with a median PFS of 8.6 months. In the HER2-low cohort, the ORR was 38% and the median PFS was 6.3 months. Among these 48 patients, five (10.4%) had adjudicated drug-related ILD, including one fatal case (2.1%). With similar ORR to trastuzumab deruxtecan monotherapy, longer follow-up and additional studies will be necessary to determine whether this combination provides more clinical benefit than trastuzumab deruxtecan alone. Additionally, other clinical trials are exploring the combination of trastuzumab deruxtecan with more traditional partners, including anastrozole (NCT04553770) and conventional cytotoxic chemotherapy (NCT04556773) (Table 2).

2.2.4 Management of Trastuzumab Deruxtecan-Associated Interstitial Lung Disease

Other HER2-directed therapies, including trastuzumab, trastuzumab emtansine, and topoisomerase I inhibitors, have been associated with pulmonary toxicity; however, trastuzumab deruxtecan has higher rates, including some grade 5 events [27].

To evaluate potential risk factors for developing treatment-related ILD, Powell et al. [28] completed a post hoc analysis using pooled data from patients included in two open-label interventional studies with advanced solid tumors (n = 105) (NCT02564900) and breast cancer (n = 437) (NCT03248492). Patients had received at least one dose of trastuzumab deruxtecan, ranging from 1.6 to 8.0 mg/kg. Compared with the overall study population, patients in the

breast cancer population developed a higher incidence of any-grade ILD (16.8% [91/542] in the overall study population vs. 18.1% [79/437] in the breast cancer population) and developed the disease earlier (median time to onset 208 days in the overall population vs. 134 days in the breast cancer population). The study also showed that patients from Japan were more likely to develop ILD after treatment with trastuzumab deruxtecan than were those of non-Japanese ethnicity. Similarly, a pooled analysis from seven studies evaluating trastuzumab deruxtecan across multiple tumor types found a median time to onset of adjudicated drug-related ILD cases of 159 (range 46–591) days. In DESTINY-Breast01, the median time to onset of lung disease was approximately 6 months (193 days; range 42–535).

Given the limited knowledge about predictors of developing ILD, educating the medical team and patients, and closely monitoring patients for signs and symptoms of ILD (such as fever, cough, or dyspnea), are recommended for early detection. In cases where ILD is suspected, assessment with high-resolution computed tomography, consultation with a pulmonologist, pulmonary function tests, and oxygen saturation should be promptly performed. It is also important to rule out other possible etiologies, including infection, such as with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; coronavirus disease 2019 [COVID-19]).

Until more data are available, the recommendation is to hold the next trastuzumab deruxtecan dose in case of grade 1 ILD, start patients on systemic steroids (0.5–1.0 mg/kg prednisone or equivalent), and resume the drug only if this adverse event is resolved. In addition, for grade 2 or higher ILD, trastuzumab deruxtecan should be permanently discontinued and systemic steroids should be promptly started [29]. Further work is ongoing to evaluate optimal monitoring and management of ILD due to trastuzumab deruxtecan.

2.3 Trastuzumab Duocarmazine

Trastuzumab duocarmazine is an ADC composed of a humanized anti-HER2 monoclonal antibody with the same amino acid sequence as trastuzumab, covalently bound to a linker drug containing duocarmycin, with a DAR of 2.8:1. Following binding to HER2 and endocytosis, the linker is cleaved in the lysosome by proteases that release the active toxin. Duocarmycin alkylates the DNA, resulting in DNA damage in both dividing and non-dividing cells and, ultimately, cell death [30]. Given that proteases such as cathepsin B can be active extracellularly through secretion by malignant cells, there is the potential for a bystander cell-killing effect that is not HER2 mediated [31]. Lastly, trastuzumab duocarmazine showed promising preclinical antitumor activity in solid tumors with varying (low to high) HER2 expression, including breast cancer models [32].

Banerji et al. [33] reported results of a first-in-human, phase I dose-escalation and dose-expansion study (NCT02277717). Patients in this trial had locally advanced or metastatic solid tumors with variable HER2 status and were refractory to standard cancer treatment. A total of 146 patients were enrolled and treated in the dose-expansion phase at the RP2D of 1.2 mg/kg. In this phase, the most common treatment-related adverse events were fatigue (33%), conjunctivitis (31%), and dry eye (31%). Grade 3 ocular events were reported in 7% of patients. There were no treatment-related deaths. A promising ORR of 33% was reported in patients with HER2-positive breast cancer (N = 48) and, among the 47 patients with HER2-low breast cancer, the response rate was 28 and 40% for patients with HR-positive and HR-negative breast cancer, respectively.

The ongoing TULIP phase III study is investigating the efficacy (as assessed by PFS) of trastuzumab duocarmazine versus treatment of physician's choice (TPC) (containing an anti-HER2 agent) in patients with HER2-positive MBC who experienced either progression during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease or progression during or after (ado-) trastuzumab emtansine treatment (NCT03262935) (Table 3).

2.4 Disitamab Vedotin

Disitamab vedotin (RC48-ADC) is an ADC composed of a humanized monoclonal antibody targeting HER2 (disitamab) and a protease cleavable linker covalently coupled to the payload monomethyl auristatin E (MMAE), a synthetic antineoplastic agent (Table 1). Disitamab vedotin has a DAR of 4. Previous studies have shown that disitamab vedotin can kill tumor cells by targeting the HER2 protein on the surface of tumor cells as well as by releasing the payload in lysosomes following endocytosis [34].

In a phase I dose-escalation and dose-expansion study, disitamab vedotin 2.0 mg/kg every 2 weeks presented with good tolerability and promising efficacy (ORR 46.7%) in patients with HER2-positive MBC [35]. Grade 3 treatment-related adverse events occurred in four patients (13.3%), including neutropenia (10%), leukopenia (6.7%), aspartate transaminase elevation (3.3%), and alanine transaminase elevation (3.3%). No grade 4 or higher adverse events were observed. Based on these results, a randomized phase II study is evaluating the efficacy of disitamab vedotin 2.0 mg/kg administered every 2 weeks versus capecitabine in combination with lapatinib in HER2-positive MBC (NCT03500380). Furthermore, a randomized phase III study will evaluate the efficacy of this ADC versus TPC in patients with low HER2-expressing MBC who experienced progression during or after one line of therapy for MBC (NCT03262935) (Table 3).

3 ADCs Targeting Non-HER2 Proteins

3.1 Sacituzumab Govitecan

Sacituzumab govitecan is an ADC composed of the humanized anti–Trop-2 monoclonal antibody hRS7 IgG1κ and a cleavable CL2A linker coupled to the cytotoxic payload SN-38, an active metabolite of the topoisomerase I inhibitor irinotecan [36] (Table 1). Trop-2 is a calcium signal transducer overexpressed in many epithelial cancers, including breast cancer, and implicated in the promotion of cellular proliferation, survival, and invasion [37–41]. High levels of Trop-2 expression are associated with poor prognosis and worse survival in breast cancer [42, 43]. Sacituzumab govitecan has a high DAR of 7.6 molecules of SN-38 per monoclonal antibody, which allows the delivery of high concentrations of SN-38. Following binding to Trop-2, hRS7 (in free or conjugated form) is internalized and trafficked intracellularly to lysosomes [12]. SN-38 is released throughout antibody degradation followed by hydrolysis of the linker at low pH that can be found within lysosomes as well as extracellularly in the tumor microenvironment. Thus, given the fact that SN-38 is a membrane-permeable molecule, therapeutic concentration of the drug can also be reached in bystander cells to which the conjugate has not bound [44].

A total of 25 patients with different solid tumors, including four TNBC, participated in the phase I first-in-human study of sacituzumab govitecan and received the ADC at dose levels of 8–18 mg/kg [36]. The maximum tolerated dose was 12 mg/kg due to neutropenia, but the doses of 8 and 10 mg/kg were chosen for further development due to hematologic toxicities in the cycles following the dose of 12 mg/kg.

3.1.1 Triple-Negative Breast Cancer

IMMU-132-01 (NCT01631552) was a phase I/II, basket design, open-label, single-group, multicenter trial involving patients with various types of advanced solid cancers who had received at least one previous therapy for metastatic disease [45]. Patients with brain metastasis were excluded if untreated or if they needed to receive high-dose corticosteroids for at least 4 weeks before enrollment. Full data from the cohort with metastatic TNBC was reported in 2019 [46]. Overall, 108 patients received at least one single dose of intravenous sacituzumab govitecan 10 mg/kg on days 1 and 8 of 21-day cycles until disease progression or unacceptable adverse events. The ORR was 33.3% according to local assessment (34.3% according to blinded independent review), including three patients with complete responses (2.8%). The median time to response was 2.0 months, and the median duration of response was 7.7 months. The median PFS was 5.5 months, and the median OS was 13.0 months. The most common adverse events were nausea, diarrhea, fatigue, neutropenia, and anemia. Adverse events leading to interruption of treatment occurred in 44% of patients, and the most common reason was neutropenia. Based on this pivotal study, the FDA granted accelerated approval to sacituzumab govitecan-hziy for the treatment of adult patients with metastatic TNBC who received at least two prior therapies for metastatic disease [47].

The ASCENT study [48] was an international, open-label, randomized phase III trial that evaluated the efficacy of intravenous sacituzumab govitecan (10 mg/kg on days 1 and 8 of a 21-day cycle) versus single-agent TPC (capecitabine, eribulin, vinorelbine, or gemcitabine) in 468 patients with metastatic TNBC who progressed on two or more prior chemotherapies (including a taxane) in the metastatic setting. Of note, patients who progressed within 12 months from the end of (neo)adjuvant therapy were considered as having had a prior line of therapy. The primary endpoint, PFS by central review, was significantly better with sacituzumab govitecan than with TPC (5.6 and 1.7 months, respectively; hazard ratio 0.41; $p < 0.0001$). Secondary efficacy endpoints were also significantly improved with sacituzumab govitecan: median OS was 12.1 months with sacituzumab govitecan versus 6.7 months with TPC (hazard ratio 0.48; $p < 0.0001$), and ORRs were 35 and 5%, respectively ($p < 0.0001$). Safety data were in concordance with prior studies, and the most common grade 3 or higher adverse events with sacituzumab govitecan were neutropenia (51%), diarrhea (10%), leukopenia (10%), and febrile neutropenia (6%). No deaths were related to sacituzumab govitecan. More recently, an exploratory biomarker analysis evaluated the efficacy of sacituzumab govitecan according to Trop-2 expression or germline *BRCA1/2* mutation status and showed that the clinical benefit with sacituzumab govitecan versus TPC in the ASCENT study is irrespective of the level of Trop-2 expression or of germline *BRCA1/2* mutational status. Notably, better efficacy outcomes (ORR, PFS, and OS) were among sacituzumab govitecan-treated patients with Trop-2 high and Trop-2 median expression subgroups compared with TPC [49]. Furthermore, an exploratory analysis from the ASCENT study specifically in the population with stable brain metastases showed a trend in PFS favoring sacituzumab over TPC (2.8 vs. 1.6 months) [50]. The SWOG S2007 (NCT04647916) phase II study will prospectively evaluate the efficacy of sacituzumab govitecan, as assessed by intracranial ORR, in patients with HER2-negative breast cancer and brain metastases.

In addition, Brenner et al. [51] explored the pharmacokinetic profiles of sacituzumab in patients with breast cancer brain metastases or primary brain tumors who would undergo brain surgery. Before undergoing craniotomy or biopsy, sacituzumab was administered 16 h preoperatively,

Table 3 Ongoing clinical trials evaluating ladiratuzumab vedotin, trastuzumab duocarmazine, and disitamab vedotin

Register number (target accrual, N)	Design; arms and regimen	Study population	Primary outcome	Status
SGN-LIV1A				
NCT03310957 *N* = 122	Phase I/II, single arm; SGN-LIV1A plus pembrolizumab	Metastatic TNBC	ORR, incidence of AEs and DLT	Accruing
NCT01969643 *N* = 418	Phase I dose escalation and dose expansion; different cohorts will receive SGN-LIV1A monotherapy or in combination with trastuzumab	Metastatic TNBC and HER2-positive	Incidence of AEs	Accruing
Morpheus-TNBC NCT03424005 *N* = 280	Phase Ib/II, open label, randomizing to several cohorts, including one of atezolizumab plus sacituzumab govitecan	Metastatic TNBC	ORR, frequency of AEs	Accruing
Trastuzumab duocarmazine				
TULIP NCT03262935 *N* = 436	Phase III; open label, randomizing to one of two arms: trastuzumab duocarmazine vs. TPC	HER2-positive, refractory to at least two lines of CT for MBC	PFS	Completed; results pending
NCT04235101 *N* = 436	Phase I, single arm; trastuzumab duocarmazine plus niraparib	HER2-positive or HER2-low tumors for which no standard therapy exists	Frequency of AEs	Accruing
NCT04602117 *N* = 27	Phase I, single arm; trastuzumab duocarmazine plus paclitaxel	HER2-positive or HER2-low tumors for which no standard therapy exists	Frequency of AEs	Not recruiting yet
Disitamab vedotin (RC48-ADC)				
NCT04400695 *N* = 366	Phase III; open label, randomizing to one of two arms: trastuzumab duocarmazine vs. TPC	HER2-low breast cancer; one to two prior lines of treatment in the advanced setting. Prior treatment with anthracyclines	To assess efficacy (PFS) of ADC vs. control arm	Not recruiting yet
NCT03500380 *N* = 228	Randomized phase II (vs. lapatinib plus capecitabine)	HER2-positive breast cancer; prior treatment with trastuzumab; one to two prior lines of treatment in the advanced setting	To assess efficacy (PFS) of ADC vs. control arm	Accruing; no results to date

ADC antibody–drug conjugate, *AE* adverse events, *CT* chemotherapy, *DLT* dose-limiting toxicity, *HER2* human epidermal growth factor receptor 2,, *MBC* metastatic breast cancer, *ORR* objective response rate, *PFS* progression-free survival, *SGN-LIV1A* ladiratuzumab vedotin, *TNBC* triple-negative breast cancer, *TPC* treatment of physician's choice

and the pharmacokinetic profile of SN-38 and its derivatives in intracranial tumor tissue, cerebrospinal fluid, and serum were determined. For patients with breast cancer brain metastases, the use of preoperative sacituzumab resulted in therapeutically relevant concentrations of SN-38 at 150-fold mean half maximal inhibitory concentration (IC50) at 18 h post treatment.

3.1.2 Use in Hormone Receptor-Positive Breast Cancer

As part of the previously discussed IMMU-132-01 phase I/II basket study (NCT01631552), a cohort of 54 patients with HR-positive/HER2-negative MBC were treated with intravenous sacituzumab govitecan 10 mg/kg on days 1 and 8 every 21-day cycle. These patients had received a median of three prior lines of endocrine therapies and two (range 0–9) prior lines of chemotherapy for MBC. The most common grade 3/4 adverse events were neutropenia (50%), anemia (11%), and diarrhea (7.4%). After a median follow-up of 11.5 months, sacituzumab govitecan demonstrated a confirmed ORR of 31% (all partial responses). Responses were durable, with an estimated median duration of response of 7.4 months, PFS of 6.8 months, and OS of 12 months.

These promising data support the ongoing TROPICS-02 trial (NCT03901339), an open-label, randomized, multicenter, global, phase III study that will assess the efficacy of sacituzumab govitecan versus TPC (vinorelbine, capecitabine, eribulin, or gemcitabine) in patients with HR-positive/HER2-negative MBC, after disease progression on at least two but no more than four prior lines of chemotherapy in the metastatic setting [52]. The primary endpoints for this trial are PFS and ORR according to RECIST 1.1. Key secondary endpoints include OS, clinical benefit rate, and quality of life (Table 4).

3.1.3 Other Clinical Trials with Sacituzumab Govitecan

In the early-stage setting of TNBC, a single-arm phase II study is evaluating the efficacy (assessed by the pathologic complete response rate) of this ADC as monotherapy in the neoadjuvant setting (NCT04230109) and a randomized phase III study evaluating the efficacy of adjuvant sacituzumab govitecan versus TPC for residual disease following neoadjuvant therapy. Additionally, there is great interest in the safety, tolerability, and activity of this agent in combination with other therapies in the metastatic setting for HER2-negative breast cancer, including immune checkpoint inhibitors (NCT04448886; NCT04468061; NCT03424005) and poly (ADP-ribose) polymerase (PARP) inhibitors in breast cancer (NCT04039230; NCT03992131) (Table 4).

3.2 Ladiratuzumab Vedotin

Ladiratuzumab vedotin (SGN-LIV1A) is an ADC composed of a humanized antibody targeting LIV-1, a proteolytically cleavable linker conjugated with the potent microtubule-disrupting agent (MMAE (Table 1). LIV-1 is a multispan transmembrane protein with putative zinc transporter and metalloproteinase activity frequently expressed in breast cancer (both estrogen receptor-positive breast cancer and TNBC), prostate cancer, and melanoma. Preclinical data demonstrate that SGN-LIV1A binds specifically to the extracellular domain of LIV-1, internalizes after antigen binding, and traffics to the lysosome where the payload is released by proteolysis, and causes disruption of microtubulin and induces apoptosis [53].

3.2.1 Use in Triple-Negative Breast Cancer

An ongoing phase I study has been evaluating the safety, tolerability, pharmacokinetics, and antitumor activity of SGN-LIV1A (ladiratuzumab vedotin) in patients with LIV-1-positive MBC (NCT01969643) [54]. At completion of the dose-escalation stage in patients with HR-positive/HER2-negative and TNBC, there were dose-limiting toxicities in 19 evaluable patients; the maximum tolerated dose was 2.8 mg/kg. Expansion cohorts were then opened to further evaluate the safety and antitumor activity of monotherapy in TNBC at 2.0 and 2.5 mg/kg dosing every 3 weeks. Among the 44 patients with TNBC in the combined dose-escalation and expansion cohorts, the ORR was 32% and the median PFS was 11.3 weeks. In the entire cohort, the most common grade 3 and 4 adverse events were neutropenia (25%) and anemia (15%). Enrollment is ongoing in the triple-negative monotherapy expansion cohort.

The use of SGN-LIV1A as part of the neoadjuvant treatment of patients with early-stage breast cancer was tested as part of the I-SPY 2 trial (NCT0102379). The ADC was given at 2.5 mg/kg every 3 weeks for four cycles, followed by doxorubicin/cyclophosphamide (AC) every 2–3 weeks for four cycles. The study did not show superiority of the arm with SGN-LIV1A over the control with regards to estimated pathologic complete response [55]. Additionally, the combination of SGN-LIV1A and immune checkpoint inhibitors has been investigated and two studies are ongoing: one combining the ADC with pembrolizumab (NCT03310957) and another with atezolizumab (NCT03424005) (Table 3). Preliminary data from a phase Ib/II study evaluating the safety, tolerability, activity and RP2D of ladiratuzumab vedotin and pembrolizumab in first-line patients with metastatic TNBC (mTNBC) (NCT03310957) evaluated 51 patients, including 44 patients who received SGN-LIV1A at the RP2D of 2.5 mg/kg [56]. The most common grade 3 or higher adverse events were neutropenia, diarrhea, fatigue, hypokalemia, and

Table 4 Ongoing clinical trials evaluating sacituzumab govitecan in patients with breast cancer

Register number (target accrual, *N*)	Design, arms and regimen	Study population	Primary outcome	Status/results
NCT04039230 *N* = 65	Phase I/II, single arm; sacituzumab govitecan plus talazoparib	Metastatic TNBC	DLT	Accruing
SASCIA NCT04595565 *N* = 1200	Phase III; open label, randomizing to one of two arms: sacituzumab govitecan vs. TPC	Early-stage TNBC with residual disease following neoadjuvant CT	IDFS	Not yet recruiting
Saci-IO TNBC NCT04468061 *N* = 110	Phase II, open label; randomizing to one of two arms: sacituzumab govitecan vs. sacituzumab govitecan plus pembrolizumab	Metastatic TNBC. PD-L1 negative (SP142 assay). Treatment naïve in the metastatic setting	PFS	Accruing
Saci-IO HR+ NCT04448886 *N* = 110	Phase II, open label; randomizing to one of two arms: sacituzumab govitecan vs. sacituzumab govitecan plus pembrolizumab	HR-positive/HER2-negative MBC. PD-L1 positive (CPS ≥10 assessed by 22C3 assay). Progression on or within 12 months of adjuvant ET or have progressed on at least one of ET for metastatic disease	PFS	Accruing
NeoSTAR NCT04230109 *N* = 50	Phase II; open label, single arm; sacituzumab govitecan monotherapy	Early-stage TNBC, candidate for neoadjuvant therapy	pCR	Accruing
NCT04454437 *N* = 80	Phase IIb, single arm; sacituzumab govitecan monotherapy	Metastatic TNBC refractory to at least two lines of CT for MBC	ORR	Not yet recruiting
TROPICS-02 NCT03901339 *N* = 400	Phase III, open label; randomizing to one of two arms: sacituzumab govitecan vs. TPC	HR-positive/HER2-negative refractory to at least two lines of CT for MBC	PFS	Accruing
Morpheus-TNBC NCT03424005 *N* = 280	Phase Ib/II, open label; randomizing to several cohorts, including one of atezolizumab plus sacituzumab govitecan	Metastatic TNBC	ORR Frequency of AEs	Accruing
SEASTAR NCT03992131 *N* = 329	Phase Ib/II, open label; with different cohorts including one of sacituzumab govitecan plus rucaparib	Metastatic TNBC	Occurrence of AEs, DLT and ORR (phase II)	Accruing

AE adverse events, *CPS* combined positive score, *CT* chemotherapy, *DLT* dose-limiting toxicity, *ET* endocrine therapy, *HR* hormone receptor, *IDFS* invasive disease-free survival, *MBC* metastatic breast cancer, *ORR* objective response rate, *pCR* pathologic complete response, *PFS* progression-free survival, *TNBC* triple-negative breast cancer, *TPC* treatment of physician's choice

Table 5 New antibody–drug conjugates in clinical development for treating patients with breast cancer

ADC	Construct	Study design (reference)	Study population	Objectives	Results
U3-1402	Target: HER3 Antibody: Patritumab Linker: Tetrapeptide based Payload: exatecan derivative DAR: 8	Phase I/II, single arm (NCT02980341)	HER3-positive MBC	Determine safety/tolerability, MTD, and RDE. Determine safety and efficacy	Ongoing. MTD was not reached. Most common grade 3/4 AEs: liver enzymes increase and thrombocytopenia [59]. ORR: 30 and 13%, respectively, for patients with HER3-high HR+/HER2− treated with 6.4 and 4.8 mg/kg of ADC; 33% for patients with HER3-low HR+/HER2− treated with 6.4 mg/kg; 16% for patients with mTNBC treated with 6.4 mg/kg
		Phase II window of opportunity, neoadjuvant study (NCT04610528)	Early-stage HR+/HER2-negative breast cancer	Evaluate mean change in CelTIL score per central assessment in paired samples	Pending
BA3021 (CAB-ROR2-ADC)	Target: Ror2 Antibody: CAB Linker: Undisclosed Payload: Undisclosed DAR: Undisclosed	Phase I/II, single arm	Basket (TNBC, NSCLC, and soft tissue sarcoma), NCT03504488	Assess safety and efficacy of ADC	Accruing; no results to date
Anti-CA6-DM4 immunoconjugate (SAR566658)	Target: CA6 Antibody: DS6 Linker: SPDB Payload: DM4 DAR: 1	Phase I dose escalation, single arm	Multiple advanced solid tumors (including TNBC)	Evaluate safety and MTD	RP2D: 90 mg/m^2 days 1 and 8 q3w [62]. At RP2D, tumor regression observed in about 60%. Most frequent AEs: reversible keratopathy, fatigue, peripheral neuropathy, gastrointestinal disorders
AVID100	Target: EGFR Antibody: MAB100 Linker: cleavable Payload: DM1 DAR: Undisclosed	Phase I dose escalation, single arm (NCT03094169)	Multiple advanced solid tumors (including TNBC)	Assess safety, tolerability; identify R2PD	RP2D: 200 mg/m^2 q3w [63]
		Multicenter, dose-expansion, phase IIa study (NCT03094169)	EGFR-overexpressing TNBC	Evaluate efficacy, safety, tolerability of ADC	Accruing; no results to date
DS-1062	Target: Trop-2 Antibody: humanized mAb Linker: tetrapeptide based Payload: exatecan derivative DAR: Undisclosed	Phase I dose escalation (NCT03401385)	NSCLC, TNBC	Evaluate efficacy, safety, tolerability of ADC	Accruing; no results to date in TNBC

Table 5 (continued)

ADC	Construct	Study design (reference)	Study population	Objectives	Results
XMT-1522	Target: HER2 Antibody: HT19 Linker: polymer Payload: dolaflexin (auristatin analog) DAR: 12	Phase I dose escalation (NCT02952729)	Advanced HER2-expressing (IHC ≥1+) BC, gastric cancer, NSCLC	Assess safety, tolerability; identify RP2D	RP2D not yet identified. Toxicities: transaminitis, fatigue, nausea, vomiting, headache [64]
PF-06804103	Target: HER2 Antibody: humanized mAb with same sequencing as trastuzumab Linker: protease cleavable linker Payload: Auristatin-0101 DAR: 4	Phase I dose escalation and dose expansion (NCT03284723). PF-06804103 as monotherapy or in combination with letrozole and palbociclib	HER2-positive solid tumors	Assess safety, tolerability, DLT	Preliminary ORR in patients receiving ≥3 mg/kg = 52.4% (11/21) [65]

ADC antibody–drug conjugate, *AE* adverse event, *BC* breast cancer, *CelTIL* tumor cellularity and tumor-infiltrating lymphocytes, *DAR* drug-to-antibody ratio, *DLT* dose-limiting toxicity, *EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor, *HR* hormone receptor, *IDFS* invasive disease-free survival, *IHC* immunohistochemistry, *mAb* monoclonal antibody, *MBC* metastatic breast cancer, *MTD* maximum tolerated dose, *mTNBC* metastatic triple negative breast cancer, *NSCLC* non-small cell lung cancer, *ORR* objective response rate, *q3w* every 3 weeks, *RDE* recommended dose for expansion, *RP2D* recommended phase II dose, *TNBC* triple-negative breast cancer

maculo-papular rash (8% each). The ORR was 54% among 26 patients who were assessed for efficacy. Overall, the study showed that the combination has a tolerable toxicity profile and promising efficacy in mTNBC (Table 3).

3.3 U3-1402 and Other ADCs

HER3 is overexpressed in MBC and other tumor types, and overexpression has been associated with poor outcomes [57, 58]. Patritumab deruxtecan (HER3-DXd; U3-1402) is composed of a fully human anti-HER3 IgG1 monoclonal antibody covalently linked to a topoisomerase I inhibitor payload, an exatecan derivative, via a tetrapeptide-based cleavable linker.

Results from the dose-escalation and dose-finding parts of the NCT02980341/JapicCTI-163401 study demonstrated promising antitumor activity in heavily pretreated patients with HER3-expressing MBC (Table 5) [59, 60]. Recently, data on safety and efficacy for the four separate prespecified dose-expansion cohorts in patients with advanced HR-positive/HER2-negative or mTNBC were presented [61]. Patients with HER3-high/HR-positive/HER2-negative tumors were included in two cohorts to receive HER3-DXd 4.8 or 6.4 mg/kg, whereas patients with HER3-low received 6.4 mg/kg every 3 weeks. At data cutoff, 85 patients in the HR-positive/HER2-negative cohorts and 31 in the TNBC cohort in the expansion part were evaluable for efficacy. Among 64 patients with HR-positive/HER2-negative HER3-high MBC, the ORR was 30 and 13% for patients treated with 6.4 and 4.8 mg/kg of ADC, respectively. Additionally, the ORR was 33 and 16% among 31 patients with HER3-low HR-positive/HER2-negative MBC and 31 patients with mTNBC treated with 6.4 mg/kg, respectively. The safety profile of HER3-DXd was manageable, and treatment-related adverse events were primarily gastrointestinal or hematologic, and the majority were grade 1 or 2. The rate of drug-related ILD was 5.2% (one grade 5).

Several new constructs are currently in the early stages of clinical development, using either HER2 protein as a target or other proteins with potential for treating any subtype of breast cancer. Table 5 summarizes the ADC molecule and clinical data [59, 62–65].

4 Conclusions

The emergence of new ADCs with robust efficacy data represents an important therapeutic advance in breast oncology. The advances in the linker-related biochemistry and membrane-permeable nature of both trastuzumab deruxtecan and sacituzumab govitecan certainly helps to explain the success of these agents. Notably, caution is needed to move

these drugs to the early-stage setting given the potential risk of serious adverse events, including ILD for trastuzumab deruxtecan, and neutropenia and diarrhea for sacituzumab govitecan. Additionally, three other ADCs (ladiratuzumab vedotin, trastuzumab duocarmazine, and disitamab vedotin) are in the final stage of clinical development, and ongoing phase III clinical trials will establish their efficacy versus standard of care. Thus, in the next few years, we might witness a switch from the standard treatment of cytotoxic chemotherapy to anticancer treatment based on ADCs, given either as monotherapy or in combination with other agents.

Declarations

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