Current understandings and prospects of antibody-drug conjugates (ADCs) for the treatment of breast cancer: a narrative review

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Objective: To provide a review of the advances of antibody-drug conjugates (ADCs) for the treatment of breast cancer.

Background: The recent successes and approval of ADCs for hematologic malignancies and solid malignant tumor including breast cancer have transformed cancer therapy. By May 2021, 10 different ADCs have been approved by the USA FDA, among which three ADCs have been approved in breast cancer. Remarkably, the phenomenon of numerous successes with the next-generation ADCs in breast cancer, offers the prospect of completely shifting the paradigm of breast cancer treatment. Most anticipated is that these breakthroughs would ultimately translate to the benefit of patients.

Methods: A literature search was conducted for up-to-date publications and ongoing clinical trials of ADCs and breast cancer, and then the review report was developed. In the beginning of the report, a brief introduction of ADC was given in the perspective of structure and mechanism of action. Following which, the great advances of three approved ADCs were evoked, and the important value of these clinical trials was highlighted. Meanwhile, a list of several promising ADCs targeting human epidermal growth factor receptor 2 (HER2), trophoblast cell-surface antigen 2 (TROP-2) and beyond that have been under development for breast cancer therapy were provided. Finally, it is expected that these ADCs will enlighten the future of breast cancer treatment.

Conclusions: Herein, we present a brief overview of ADCs for breast cancer, with the understanding that novel ADCs will demonstrate great clinical value over the next few years.

Keywords: Human epidermal growth factor receptor 2 (HER2); trastuzumab emtansine (T-DM1); antibody-drug conjugate (ADC); sacituzumab govitecan; trastuzumab deruxtecan

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A brief introduction of antibody-drug conjugates (ADCs): structure and mechanism of action

ADCs consist of a highly specific recombinant monoclonal antibody (mAb) that recognizes tumor-associated antigens and is covalently conjugated to a high potency cytotoxic drug via stable chemical linkage through a synthetic linker. Though targeted antibody-delivered cytotoxic payload is based on a century-old concept of “magic bullet” by German chemist Paul Ehrlich (1), with the first human trial of ADC in the 1980s (2), only until recently, advances in antibody engineering, linker optimization chemistries, and conjugation strategies (3) have improved ADC design and paved the way for transformative cancer therapy with potent and safer ADCs.

ADCs are complex biochemical platforms used in cancer treatment and exhibit unique mechanisms of action (4). After administration, ADCs may be transported in the systemic circulation as three components: naked antibody, free payload, and intact conjugate due to incomplete conjugation with different production processes and conjugation technologies. Meanwhile, ADCs may have different drug-antibody ratios (DARs). The homogeneity of ADCs is the precondition for limiting toxicity and improving the therapeutic window (5). As ADCs approach tumor site, some payload might be released prematurely into the tumor microenvironment before antibody-antigen binding, leading to some ADCs to exhibit their efficacy via slow-release chemotherapy (6,7). In addition, the antibody component of some ADCs retains its activity profile post conjugation and continue to inhibit target function, block downstream signaling and/or generate immune-related effects. For example, in preclinical studies, human epidermal growth factor receptor 2 (HER2)-targeted ADCs, trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), retain the function of trastuzumab, and thus can exhibit their potency via inhibiting HER2 signaling and mediating antibody-dependent cell-mediated cytotoxicity (ADCC) (8,9). Following antigen binding, most ADCs are internalized via endocytosis. Once inside the lysosomes or endosomes, the payloads are released from their antibody carriers by acidolysis, enzymatic hydrolysis or reduction, following which the payloads act on their target substrates, finally resulting in cell death. Membrane permeable payloads can also diffuse through cell membranes into the tumor microenvironment, thus killing neighboring cells irrespective of target antigen expression, a phenomenon known as “bystander killing effect (10)”.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/tbcr-21-30>).

Approved anti-HER2 ADCs and anti-trophoblast cell-surface antigen 2 (TROP-2) ADCs in breast cancer

HER2 is a receptor tyrosine-protein kinase and a member of the epidermal growth factor receptor (EGFR) family. It is overexpressed or amplified in approximately 15% to 20% of metastatic breast cancer (MBC) patients (11-13), which predicts an adverse outcome (13). Trastuzumab is a humanized mAb targeting the extracellular domain of HER2 and as the first approved anti-HER2 drug, has become the backbone of HER2 positive breast cancer management, from neoadjuvant/adjuvant in the early setting for cure to first-line treatment and beyond in the metastatic setting for rescue. Numerous other anti-HER2 drugs have since been approved, including anti-HER2 mAb such as pertuzumab and margetuximab, and small molecule tyrosine kinase inhibitors (TKIs) including lapatinib, neratinib, pyrotinib and tucatinib. T-DM1 is the first approved anti-HER2 ADC, initially as second-line treatment in HER2 positive MBC and subsequently as adjuvant treatment of HER2 positive early breast cancer (EBC) with residual invasive disease after neoadjuvant anti-HER2 regimen. T-DXd became the second approved anti-HER2 ADC in 2019 (14), with impressive data from the Phase II single arm Destiny-Breast01 trial, promising to change the landscape of breast cancer treatment. TROP-2, a transmembrane calcium signal transducer that is highly expressed in multiple tumor types, including breast cancer (>90%), is identified as an ideal antigen allowing for targeted delivery by ADCs (15). In 2020, sacituzumab govitecan (SG), the first anti-TROP-2 ADC, was approved for later line therapy in metastatic triple negative breast cancer, enlarging the population of breast cancer patients treatable with ADCs. The successful story of ADCs in breast cancer has driven rapid changes for breast cancer treatment and ignited the enthusiasm of ADC research and development. The number of novel ADCs in clinical studies has dramatically increased over the past few years.

T-DM1

T-DM1 (Kadcyla) has been one of the most successful ADCs so far. It consists of a trastuzumab mAb to which the

maytansinoid DM1, a microtubule inhibitory molecule, is conjugated via a non-cleavable thioether linker attached to random lysines with an average DAR of 3.5:1 (16). Similar to trastuzumab, T-DM1 inhibits HER2 receptor signaling, mediates ADCC and suppresses shedding of the HER2 extracellular domain in human breast cancer cells overexpressing HER2. The reported and ongoing clinical trials of T-DM1 were listed in *Table 1*.

As early as in 2012, the Phase III EMILIA (17) trial demonstrated that T-DM1 significantly prolonged progression-free survival (PFS) and overall survival (OS) than lapatinib plus capecitabine in HER2 positive advanced breast cancer patients previously treated with trastuzumab and a taxane. A subsequent phase III TH3RESA trial demonstrated that T-DM1 significantly prolonged the median PFS of progressive HER2 positive advanced breast cancer patients who had received two or more HER2-directed regimens in the advanced setting. T-DM1 has since become the standard second line treatment for HER2 positive MBC (18). A few years later, the phase III, open-label KATHERINE trial showed that T-DM1 achieved a significant higher invasive disease-free survival (iDFS) rate versus trastuzumab (19) in HER2 positive EBC patients with residual invasive disease at surgery after trastuzumab and taxane-based neoadjuvant therapy. These results, for the first time, indicated that treatment escalation in the adjuvant setting with T-DM1 could become a new standard of care for HER2 positive EBC with residual invasive disease after completion of neoadjuvant therapy.

However, the development of T-DM1 as a first-line treatment for HER2 positive MBC or as a neoadjuvant/adjuvant treatment has not been satisfactory hitherto (20-22). In several phase III trials, T-DM1-based regimens failed to show superior efficacy when compared with standard of care with trastuzumab (H) or trastuzumab + pertuzumab (H + P), among treatment naïve patients in early lines. As shown in the conclusion from the trials above, T-DM1 seems to become the “back-up” option to trastuzumab-based treatment. The heterogeneous and low DAR of T-DM1 could impact its pharmacokinetics (PK) profile and limit its therapeutic window (5,8). Though T-DM1 retains the function of trastuzumab and shows great potency in preclinical studies, the clinical recommended dose (3.6 mg/kg) is notably lower than routine trastuzumab dosage (6 mg/kg). T-DM1 is designed to be stable in systemic circulation with a stable non-cleavable linker. The intracellular active metabolite of T-DM1, smcc-DM1, is a membrane impermeable payload; thus, T-DM1 has no bystander effect, which may limit its efficacy compared with

trastuzumab plus chemotherapy (10,16).

Theoretically, combining T-DM1 with other treatment could further boost its efficacy. The phase II TEAL study is conducted comparing the combination regimen of T-DM1, lapatinib, and nab-paclitaxel (KLT) with the standard treatment of trastuzumab, pertuzumab, and paclitaxel (PHT) as neoadjuvant treatment in HER2 positive EBC (23). The small size trial surprisingly showed KLT regimen had higher residual cancer burden (RCB) 0 or I than PHT (100% *vs.* 62.5%, $P=0.0035$). The combination treatment of T-DM1 with tucatinib and atezolizumab has under evaluation in several phase III trials (NCT03975647, NCT04740918, NCT04873362 and NCT04457596).

Interestingly, de-escalation ATEMPT (TBCRC-033 trial) has been carried to determine if T-DM1 could cause less toxicity than paclitaxel plus trastuzumab (TH) and yielded clinically acceptable benefit among patients with stage I HER2 positive EBC (24). However, the incidence of clinically relevant toxicities was comparable between T-DM1 and HT arm (46% *vs.* 47%, $P=0.83$), while the amenorrhea was less likely in recipients of T-DM1 than TH (25). The 3-year iDFS for T-DM1 was 97.8% (95% CI: 96.3% to 99.3%), while a descriptive analysis of TH treatment showed an iDFS rate of 93.4% (95% CI: 88.7% to 98.2%). Considering this trial included 75% hormonal receptor positive patients with low event rate, longer follow-up is needed to obtain more meaningful DFS data (24). More attractively, the ATEMPT 2.0 trial (NCT04893109) is evaluating a more optimized regimen in this setting (T-DM1 $\times 6$ cycles $\rightarrow$ trastuzumab subcutaneous $\times 11$ cycles).

Trastuzumab deruxtecan

Trastuzumab deruxtecan (26) (DS-8201a, T-DXd, Enhertu) is a next-generation ADC with a trastuzumab biosimilar conjugated to a novel topoisomerase I inhibitor, deruxtecan, via a hydrophobic, enzymatically cleavable tetrapeptide-based (GGFG) linker with a homogeneous DAR of 8 to 1 (8). In preclinical study, T-DXd was proved to retain the function of trastuzumab post conjugation. The membrane permeable payload grants tumoricidal effect against HER2 heterogeneous tumor via bystander killing effect (8). The pivotal clinical trials of T-DXd were listed in *Table 2*.

In a pivotal phase II study (DESTINY-Breast01) of HER2 positive MBC patients previously treated with T-DM1, T-DXd demonstrated durable antitumor activities with an impressive objective response rate (ORR) of 60.9% (95% CI: 53.4% to 68.0%) and a median PFS of 16.4 months (95%

Table 1 Summary of Pivotal Trials for T-DM1

Trials	Phase	Patients	Study arm	Control arm	Outcome
EMILIA (17)	III	HER2 ⁺ MBC previously treated with trastuzumab and a taxane	T-DM1	L + X	mPFS: 9.6 months (T-DM1) vs. 6.4 months (L + X), hazard ratio 0.65, P<0.001; ORR: 43.6% (T-DM1) vs. 30.8% (L + X), P<0.001; mOS: 30.9 months (T-DM1) vs. 25.1 months (L + X), hazard ratio 0.68, P<0.001
TH3RESA (18)	III	HER2 ⁺ MBC who had received two or more HER2-directed regimens	T-DM1	TPC	mOS, 22.7 months (T-DM1) vs. 15.8 months (TPC), hazard ratio 0.68, P=0.0007
KATHERINE (19)	III	HER2 ⁺ EBC with residual invasive disease	T-DM1	H	3-year iDFS: 88.3% (T-DM1) vs. 77.0% (H); hazard ratio 0.50, P<0.001
MARIANNE (20)	III	HER2 ⁺ MBC who have received no prior chemotherapy or HER2 ⁺ targeted therapy	T-DM1; T-DM1 + P	HT	mPFS: 13.7 months (H + T), 14.1 months (T-DM1), and 15.2 months (T-DM1 + P); ORR: 67.9% (H + T), 59.7% (T-DM1), and 64.2% (T-DM1+P); mOS: 50.9 months (H + T), 53.7 months (T-DM1), and 51.8 months (T-DM1 + P). T-DM1 showed noninferior, but not superior, efficacy than did HT in 1L
KRISTINE (21)	III	HER2 ⁺ EBC, stage II–III breast cancer	T-DM1 + P	DCbHP	pCR: 44.4% (T-DM1 + P) vs. 55.7% (DCbHP), P=0.016; EFS: T-DM1 + P vs. DCbHP, hazard ratio 2.61; iDFS: TDM-1 + P vs. DCbHP, hazard ratio 1.11
KAITLIN (22)	III	HER2 ⁺ EBC	AC-T-DM1 + P	AC-THP	LN+ patients 3-year iDFS: 94.1% (AC-THP) vs. 92.7% (AC-T-DM1 + P), hazard ratio 0.98, not significant; ITT population 3-year iDFS: 94.2% (AC-THP) vs. 93.1% (AC-T-DM1+P), not tested
TEAL (23)	II	HER2 ⁺ EBC	T-DM1 + L + nab-paclitaxel	PHT	RCB 0 or 1: 100% (T-DM1 + L + nab-paclitaxel) vs. 62.5% (PHT), P=0.0035
ATEMPT (24)	II	HER2 ⁺ EBC, stage I	T-DM1	HT	3-year iDFS: 97.8% (T-DM1); 3-year iDFS: 93.4% (TH, descriptive analysis); clinical relevant toxicity: 46% (T-DM1) vs. 47% (HT), P=0.83
ATEMPT2.0 (NCT04893109)	II	HER2 ⁺ EBC, stage I	T-DM1 → H-SC	H-SC + T	Ongoing
HER2CLIMB-02 (NCT03975647)	III	HER2 ⁺ MBC previously treated with trastuzumab and a taxane	T-DM1 + tucatinib	T-DM1	Ongoing
KATE3 (NCT04740918)	III	HER2 ⁺ PD-L1 ⁺ MBC previously treated with trastuzumab and a taxane	T-DM1 + atezolizumab	T-DM1	Ongoing
Astefania (NCT04873362)	III	HER2 ⁺ EBC with residual invasive disease	T-DM1 + atezolizumab	T-DM1	Ongoing
CompassHER2 RD (NCT04457596)	III	HER2 ⁺ EBC with residual invasive disease	T-DM1 + tucatinib	T-DM1	Ongoing

T-DM1, trastuzumab emtansine; MBC, metastatic breast cancer; L, lapatinib; X, capecitabine; mPFS, median progression-free survival; ORR, objective response rate; mOS, median overall survival; TPC, treatment of physician's choice; H, trastuzumab; iDFS, invasive disease-free survival; T, taxane; P, pertuzumab; D, docetaxel; Cb, carboplatin; pCR, pathological complete response; EFS, event-free survival; A, anthracycline; C, cyclophosphamide; LN+, lymph node positive; ITT, intention to treat population; RCB, residual cancer burden; H-SC, trastuzumab subcutaneous; PDL1+: programmed death ligand 1 positive; 1L, first-line treatment.

Table 2 Summary of pivotal trials for trastuzumab deruxtecan (T-DXd)

Trials	Phase	Patients	Study arm	Control arm	Outcome
DESTINY-Breast01 (27)	II	HER2 ⁺ MBC previously treated with T-DM1	T-DXd	NA	ORR 61.4%, DCR 90.8%, mPFS 19.4 months, mDOR 20.8 months, mTTR 1.6 months
DESTINY-Breast02 (NCT03523585)	III	HER2 ⁺ MBC previously treated with T-DM1	T-DXd	TPC (HX or LX)	Ongoing
DESTINY-Breast03 (NCT03529110) (28)	III	HER2 ⁺ MBC previously treated with trastuzumab and a taxane	T-DXd	T-DM1	mPFS: not reached (T-DXd) vs. 6.8 months (T-DM1), hazard ratio 0.284, $P=7.8\times10^{-22}$
DESTINY-Breast09 (NCT04784715)	III	HER2 ⁺ MBC who have received no prior chemotherapy or HER2-targeted therapy	T-DXd; T-DXd + P	HP + T	Ongoing
DESTINY-Breast05 (NCT04622319)	III	HER2 ⁺ EBC with residual invasive disease	T-DXd	T-DM1	Ongoing
DESTINY-Breast04 (NCT03734029)	III	HER2 ⁻ low expressing unresectable and/or metastatic breast cancer	T-DXd	TPC (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel)	Ongoing
DESTINY-Breast06 (NCT04494425)	III	HER2 ⁻ low, hormone receptor positive breast cancer progressing on endocrine therapy in the metastatic setting	T-DXd	TPC (capecitabine, paclitaxel, or nab-paclitaxel)	Ongoing

T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; MBC, metastatic breast cancer; ORR, objective response rate; DCR, disease control rate; mDoR, median duration of response; mTTR, median time to response; TPC, treatment of physician's choice; P, pertuzumab; H, trastuzumab; T, taxane.

CI: 12.7 months to not reached) (27). An update result on SABCS 2020 with longer follow-up showed that the PFS and duration of response (DoR) were further extended to 19.4 and 20.8 months, respectively (29). Interestingly, T-DXd seemed to be active in patients with brain metastases, with an ORR of 58.3% and a median PFS of 18.1 months, similar to the overall population (30,31). Among the patients with information available on baseline brain metastasis diameter, the central nervous system response rate per investigators was 50% (7 of 14 patients) (30). The phase III DESTINY-Breast02 trial (NCT03523585), which is ongoing for evaluating T-DXd *vs.* standard of care after T-DM1 in HER2 positive unresectable and/or MBC with PFS as the primary endpoint, will provide confirmative results.

Moreover, in a recently reported head-to-head comparison study (DESTINY-Breast03, NCT03529110) of T-DXd *vs.* T-DM1 in patients previously treated with trastuzumab and taxane in the advanced/metastatic setting,

T-DXd demonstrated statistically significant and clinically meaningful improvement in PFS (28). The hazard ratio for PFS was 0.2840 ($P=7.8\times10^{-22}$); median PFS not reached for T-DXd *vs.* 6.8 months for T-DM1. At the time of the planned interim analysis, a strong OS benefit trend was showed. The estimated 12-month OS event rates were 94.1% (95% CI: 90.3% to 96.4%) for T-DXd and 85.9% (95% CI: 80.9% to 89.7%) for T-DM1; hazard ratio: 0.5546 (95% CI: 0.3587 to 0.8576; $P=0.007172$ did not cross pre-specified boundary for significance). It is worth noting that lung toxicity is the critical safety concern related to T-DXd. Comparing to previously reported 2.7% grade 5 treatment related interstitial lung disease (ILD) (29), there was no grade 4–5 treatment related ILD reported in DESTINY-Breast03 trial (28). It seems that higher awareness and earlier line treatment may help reduce the risk of T-DXd-related ILD. Nevertheless, lung event should be closely monitored and proactively intervened to avoid any

untoward outcome in clinical practices.

Three factors contribute to the greater efficacy of T-DXd. The conjugate carries a highly membrane permeable payload with strong bystander effect, which enhances the tumoricidal activities of T-DXd against tumor cells with no, weak or moderate HER2 expression (8,10). Furthermore, tumor-specific peptide linker and site-specific conjugation contribute to a homogeneous and high DAR, ensuring a delivery of greater payload to HER2⁺ cells, and a stable PK profile, which helps maintain synergy during long-term treatment. Finally, the function of trastuzumab is not only comprehensively retained in T-DXd at the molecular fusion level but also at the clinical dosage level (27).

There is a continued need for novel treatment for patients with HER2 positive MBC who experience disease progression after initial treatment with standard of care. The results of these trials could transform the standard of care of second-line treatment in HER2 positive MBC. Moreover, in both early and advanced setting of HER2 positive breast cancer, ongoing randomized phase III clinical trials aim at investigating the clinical benefit of T-DXd compared with other approved anti-HER2 treatments.

DESTINY-Breast09 (NCT04784715), a phase III trial, is currently evaluating the efficacy and safety of T-DXd either alone or in combination with pertuzumab *vs.* first-line standard of care (pertuzumab, trastuzumab and taxane) in patients with HER2 positive breast cancer who have received no prior chemotherapy or HER2-targeted therapy. DESTINY-Breast05 (NCT04622319), a phase III, randomized, open-label study, evaluates the iDFS of T-DXd *vs.* T-DM1 in patients with high-risk HER2 positive breast cancer with residual invasive disease in breast or axillary lymph nodes in the post-neoadjuvant setting.

This higher DAR of T-DXd has been granted efficacy to deliver more payload to HER2 positive cells, especially for those with weak or moderate HER2 expression (8). Meanwhile, the bystander effect might further enhance the clinical activity even in HER2-low or HER2-heterogenous breast cancers, while ensuring a safe therapeutic index (10). In preclinical trials, T-DXd has demonstrated tumor inhibitory effects in HER2 low (IHC1⁺ or IHC2⁺/ISH⁺) or HER2 positive tumors. J101, a phase Ib study evaluating safety and efficacy of T-DXd in HER2-low expressing MBC, showed that T-DXd achieved an ORR of 37.0% (95% CI: 24.3% to 51.3%) with median DoR of 10.4 months in patients that were heavily pretreated (32). Later, HER2 low population has been explored in two phase III trials.

The DESTINY-Breast04 trial (NCT03734029) is

currently investigating T-DXd *vs.* physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel) in patients with HER2-low expressing unresectable and/or MBC. Simultaneously, the DESTINY-Breast06 (NCT04494425) trial is evaluating the efficacy of T-DXd compared with investigator's choice chemotherapy in HER2-low, hormone receptor (HR) positive breast cancer patients whose disease has progressed on endocrine therapy in the metastatic setting. The results of this study could provide evidence whether T-DXd could provide a novel targeted therapy for advanced HER2-low breast cancer that has progressed on prior lines of therapy.

Sacituzumab govitecan

Sacituzumab govitecan (SG, Trodelvy) is an anti-TROP-2 ADC. SN-38, which is the active metabolite of the camptothecin, irinotecan and a moderately toxic payload, is conjugated to humanized anti-TROP-2 mAb hRS7 IgG1k via a cleavable and moderately stable linker (6,7). The pivotal trials of SG were summarized in *Table 3*.

SG was approved for pretreated unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) based on the phase III ASCENT trial showing significantly longer PFS and OS with SG than single-agent chemotherapy among patients with mTNBC (33). In the exploratory analysis of patients with brain metastases, SG was numerically better than treatment of physician's choice (TPC) for PFS 2.8 months (95% CI: 1.5 to 3.9 months) for SG *vs.* 1.6 months (95% CI: 1.3 to 2.9 months) for TPC, but there were barely no difference in terms of ORR (SG 3% *vs.* TPC 0%) or median OS (SG 6.8 months *vs.* TPC 7.5 months) (36). SG is under further clinical investigation for patients with HER2 negative breast cancer with brain metastasis (NCT04647916).

Additional trials have been conducted to assess SG in other settings for breast cancer (NCT03901339, NCT04595565 and NCT04468061).

In a phase I/II IMMU-132-01 basket study, SG has demonstrated promising activity in heavily pretreated hormonal receptor positive and HER2 negative (HR⁺/HER2⁻) MBC (37). Phase III TROPiCS-02 study (NCT03901339) is conduct evaluating SG *vs.* TPC in HR⁺/HER2⁻ MBC. Eligible patients including HR⁺/HER2⁻ MBC have been previously treated with at least two but no more than four prior systemic chemotherapy regimens for MBC, including at least one prior taxane in any setting, at least one prior anticancer hormonal treatment and

Table 3 Summary of pivotal trials for sacituzumab govitecan (SG)

Trials	Phase	Patients	Study arm	Control arm	Outcome
ASCENT (33)	III	mTNBC, previous treated with a taxane	SG	TPC (eribulin, vinorelbine, capecitabine, or gemcitabine)	mPFS: 5.6 months (SG) vs. 1.7 months (TPC), hazard ratio 0.41, $P < 0.001$; mOS: 12.1 months (SG) vs. 6.7 months (TPC), hazard ratio 0.48, $P < 0.001$; ORR: 35% (SG) vs. 5% (TPC)
TROPiCS-02 (NCT03901339)	III	HR ⁺ HER2 ⁻ MBC who have failed at least two prior chemotherapy regimens	SG	TPC (eribulin, capecitabine, gemcitabine, or vinorelbine)	Ongoing
GBG102 SASCIA (NCT04595565) (34)	III	HER2 ⁻ EBC with residual disease after neoadjuvant chemotherapy	SG	TPC (capecitabine or platinum-based chemotherapy)	Ongoing
Saci-IO TNBC (NCT04468061) (35)	II	PD-L1 ⁻ mTNBC not prior treatment	SG + pembrolizumab	SG	Ongoing

SG, sacituzumab govitecan; mTNBC, metastatic triple negative breast cancer; TPC, treatment of physician's choice; mPFS, median progression-free survival; mOS, median overall survival; ORR, objective response rate; HR⁺, hormonal receptor positive; HER2⁻, HER2 negative; PD-L1⁻, programmed death ligand 1 negative.

at least one CDK4/6 inhibitor in any setting. Patients will be randomized 1:1 to receive SG or single-agent standard of care TPC (eribulin, capecitabine, gemcitabine or vinorelbine). Primary end points are PFS and overall response rate.

Early HER2 negative patients with residual disease after neoadjuvant chemotherapy (NACT) are presentative population with resistance to initial treatment and at high risk of recurrence. SG may have potential possibility to improve the prognosis of these patients. SASCIA (NCT04595565) is an ongoing phase III study (34), recruiting patients who have residual disease post taxane-based NACT and are at high risk of recurrence, defined as HER2 negative breast cancer, either hormonal receptor negative with any residual invasive disease > ypT1mi after NACT or hormonal receptor positive with a CPS (clinical and post treatment pathological stage) + EG (estrogen receptor status and grade) score ≥ 3 or CPS + EG score 2 and ypN+. Patients are randomized 1:1 to receive either SG for eight cycles or TPC (capecitabine or platinum-based chemotherapy or observation). The primary endpoint is iDFS.

In preclinical exploration, SG has shown to have synergic effect with PD-1/PD-L1 antibody (35). Saci-IO TNBC (NCT04468061) is a multi-center 1:1 randomized phase II trial to investigate whether the addition of pembrolizumab to SG improves PFS compared to SG alone in PD-L1 negative

mTNBC with no prior treatment in metastatic setting.

Other promising ADCs under clinical development in breast cancer

Besides the approved anti-HER2 and anti-TROP-2 ADCs discussed above, several novel ADCs under exploration in breast cancer were listed in *Table 4*.

For HER2-targeting ADCs, the data from clinical trials is telling different stories. BAT8001 (38) is an ADC targeting HER2 positive cells composed of a trastuzumab biosimilar linked to the drug-linker Batansine, which has a structure somewhat similar to T-DM1. However, its phase III study failed to meet the superior primary endpoint of PFS when comparing BAT8001 *vs.* lapatinib plus capecitabine in HER2 positive MBC progressing on trastuzumab and taxane regimen (39). Once again, it showed the limitation of last generation ADCs. Disitamab vedotin (RC48) is an ADC composed of an anti-HER2 humanized mAb (disitamab) coupled to average four molecules (DAR, 4:1) of monomethyl auristatin E warhead via a protease cleavable linker (40). RC48 has been approved for HER2 positive gastric cancer patients who have been treated with previous two lines of chemotherapy (49). Recently, a pooled analysis of two phase I trials (NCT02881138 and NCT03052634) showed promising activities of RC48-ADC in HER2 positive and HER2-low breast cancer (40). Several phase II/III trials

Table 4 Selective ongoing trials for novel ADCs in breast cancer

Trials	Phase	Patients	Study arm	Control arm	Outcome
Trials of anti-HER2 ADCs					
BAT-8001-001-CR (NCT04189211) (38)	I	HER2 ⁺ MBC	BAT8001	–	ORR: 41.4%, 95% CI: 23.5% to 61.1%; DCR: 82.8%, 95% CI: 64.2% to 94.2%
BAT-8001-002-CR (NCT04185649) (39)	III	HER2 ⁺ MBC with previous progression on H	BAT8001	L + X	Reported as failed
C001 CANCER (NCT02881138); C003 CANCER (NCT03052634) (40)	I-IB	HER2 ⁺ and HER2 low MBC	RC48	NA	HER2-positive subgroup 2.0 mg/kg q2w (RD for phase III), ORR 42.9% (9/21), mPFS 5.7 months; HER2-low subgroup, ORR 39.6% (19/48); mPFS 5.7 months
RC48-C006 (NCT03500380)	II/III	HER2 ⁺ MBC with or without liver metastases and progression on H and taxane	RC48	L + X	Ongoing
RC48-C012 (NCT04400695)	III	HER2-low MBC with 1–2L previous chemotherapy	RC48	Physician's choice	Ongoing
SYD985.001 (NCT02277717) (41)	I	HER2 ⁺ MBC with previous progression on SOC	SYD985	NA	HER2-positive group, ORR 33% (16/48), mPFS 9.4 months; HER2-low/HR-positive disease, ORR 27% (8/30), mPFS 4.1 months; HER2-low/TNBC, ORR 40% (6/15), mPFS 4.4 months
TULIP (NCT03262935) (42)	III	HER2 ⁺ MBC ≥2L	SYD985	Physician's choice	mPFS: 7.0 months (SYD985) vs. 4.9 months (Physician's choice), hazard ratio 0.64, P=0.002
CTR20171162 (43)	I	HER2 ⁺ MBC	ARX788	NA	HER2-positive MBC 1.5 mg/kg Q3W cohort, ORR 68.4% (13/19), mPFS not reached
ZMC-ARX788-211 (CTR20200713) (44)	II/III	HER2 ⁺ MBC ≥1L	ARX788	L + X	Ongoing
KL166-I-01-CTP (CTR20181301) (45)	I	HER2 ⁺ locally advanced or metastatic solid tumors	A166	NA	ORR: 59.1% (13/22) 4.8 mg/kg cohort; 71.4% (10/14) 6.0 mg/kg cohort
KL166-II-02 (CTR20212088)	II	HER2 ⁺ MBC ≥2L	A166	NA	Ongoing, A166 with 4.8 mg/kg q3w
Trials of ADCs with other targeting					
TROPION-PanTumor01 (NCT03401385) (46)	I	mTNBC with previous progression on SOC	Dato-DXd	NA	mTNBC cohort: ORR 43% (9/21), DCR 95% (20/21)
U31402-A-J101 (NCT02980341) (47)	I/II	HER3-expressing mTNBC	HER3-DXd	NA	HER3-expressing MBC, ORR 33% (7/21), DCR 95% (20/21)
SGNLVA-002 (NCT03310957) (48)	IB/II	mTNBC without previous treatment	Ladiratumumab vedotin (SGN-LIV1A)	NA	ORR 54% (14/26)

MBC, metastatic breast cancer; ORR, objective response rate; CI, confidence interval; DCR, disease control rate; L, lapatinib; X, capecitabine; H, trastuzumab; RC48, disitamab vedotin; RD, recommended dose; mPFS, median progression-free survival; SYD985, trastuzumab duocarmazine; mTNBC, metastatic triple negative breast cancer; Dato-DXd, datopotamab deruxtecan or DS-1062; SOC, standard of care; HER3-DXd, patritumab deruxtecan or U3-1402; NA, not available; 1L, first-line treatment; 2L, second-line treatment.

are currently ongoing to explore the efficacy and safety of RC48-ADC in advanced breast cancer (NCT03500380; NCT04400695). The preliminary outcomes for other ADCs have also reported recently (41-45).

Datopotamab deruxtecan (Dato-DXd, DS-1062) is an ADC comprising a humanized anti-TROP-2 IgG1 mAb conjugated to a potent topoisomerase I inhibitor payload (DXd) via a stable tetrapeptide-based cleavable linker (46). Preliminary results from the mTNBC cohort in TROPION-PanTumor01 study showed that Dato-DXd had highly encouraging antitumor activity, ORR of 43% and DCR of 95%, and a manageable safety profile in pts with refractory mTNBC.

There are several promising ADCs targeting different antigens are also under exploring in breast cancer (47,48).

Future prospects

The success of these novel ADCs has transformed breast cancer treatment. T-DM1 has shown its value in breast cancer treatment, either as palliative therapy in metastatic or escalation therapy for cure in adjuvant setting. The unprecedented efficacy of T-DXd has been promptly translated to clinical usage and the drug conjugate is being explored in earlier setting (first-line treatment and neoadjuvant/adjuvant treatment) and challenges the position of pertuzumab and trastuzumab regimen. Meanwhile, the promising efficacy of T-DXd in HER2 low breast cancer may be proved in confirmative trials and set a new age for treatment of HER2 low breast cancer. Numerous novel ADCs have been under development targeting TROP-2 and other antigens in breast cancer and show promising efficacy in clinical trials. We are embracing a new era of ADCs in breast cancer treatment, which will provide more treatment opportunities and be translated to clinical benefits for breast cancer patients.

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Footnote

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