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Continuing Medical Education (CME) articles

Antibody drug conjugates (ADCs): an expanding rational treatment paradigm in breast cancer

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Recent advances in bioengineering and manufacturing have catapulted Antibody–drug conjugates (ADCs) to broader clinical applications. ADCs take advantage of the exquisite specificity of monoclonal antibodies (mAb) to deliver a highly potent cytotoxic agent to a specifically targeted cell expressing a selected antigen. HER2-positive breast cancer has served as a testing ground for ADC development in solid tumors that over-express HER2/neu by linking trastuzumab to a payload agent. With the current advances, ADCs leverage the selective targeting of monoclonal antibodies to deliver highly potent agents which otherwise have a narrow therapeutic index. Ado-trastuzumab emtansine (T-DM1) was the first ADC approved for patients with HER2-postive metastatic breast cancer (MBC) and fam-trastuzumab deruxtecan-nxki (T-DXd) was recently approved as well. Sacituzumab govitecan-hziy (SG) was approved in 2020 for patients with triple negative breast cancer (TNBC). Studies focusing on utilizing ADCs in earlier stages of breast cancer in the neoadjuvant or adjuvant setting, and central nervous system (CNS) disease are in progress. New ADCs and bispecific antibodies (bAbs) are also in development.

ARTICLE HIGHLIGHTS

- 2 ADCs are approved in HER2-positive breast cancer; 1 ADC approved in triple negative breast cancer
- ADCs have demonstrated activity in the neoadjuvant and adjuvant settings, with one ADC (T-DM1) currently approved as adjuvant therapy
- ADCs have demonstrated potential CNS antitumor activity
- ADCs may be active on HER2 mutation and HER2-low expression

1. INTRODUCTION

Despite innovations and improvements in the treatment for early-stage breast cancer, the disease is incurable in the metastatic setting. Antibody-drug conjugates (ADCs) are designed to precisely target specific antigens, and have become a new and advanced class of drugs used for cancer treatment. The initial approval of T-DM1 targeting human epidermal growth factor receptor 2 positive (HER2+) breast cancers produced significant clinical progress, laying a foundation and inspiring the introduction of ADCs in cancer treatment.[1]

2. ADCS

There are three components of an ADC: the monoclonal antibody (mAb), a highly potent cytotoxic agent or payload, and a linker.[2] Even in the context of low antigen expression on tumor cells, a high drug-to-antibody ratio (DAR) maximizes anti-tumoral performance, whereas a low DAR adversely affects efficacy.[3] Regarding the payload, there are only select chemotherapy agents appropriately suited as a cytotoxic agent. Two subtypes of linkers are commonly used to bind the mAb to the payload: cleavable and non-cleavable linkers. Cleavable linkers release the cytotoxic agent based on enzymatic proteolysis or pH, whereas non-cleavable linkers undergo lysosomal degradation upon endocytic internalization of the ADC-antigen complex, in order to subsequently release the payload in the cancer cell.[4] A cleavable linker increases systemic release, while a non-cleavable linker increases specificity for the target cell.[5]

Currently, there are three FDA-approved ADCs targeting breast cancer: ado-trastuzumab emtansine (T-DM1), fam-trastuzumab deruxtecan-nxki (T-DXd), and sacituzumab govitecan-hziy (SG). T-DM1 and T-DXd target the HER2 antigen. SG targets the human trophoblast cell-surface antigen 2 (Trop-2) in triple negative breast cancer (TNBC). This review dives deeper into each of the current ADCs used in breast cancer.

2.1. CURRENT APPROVED ADCS IN BREAST CANCER MANAGEMENT

2.1.1. ADCS IN METASTATIC BREAST CANCER

2.1.1.1. T-DM1

T-DM1 is an ADC that incorporates trastuzumab with the microtubule-inhibitory agent emtansine (DM1), a derivative of maytansine; the antibody and the cytotoxic agent

are conjugated by a non-cleavable linker.[6] T-DM1 allows intracellular drug delivery specifically to HER2-overexpressing cells, thereby improving the therapeutic index and minimizing exposure of normal tissue. Clinical development of unconjugated DM1 was stopped early due to unfavorable toxicity despite promising clinical activity.[7] In contrast, T-DM1 has a favorable toxicity profile and clinically meaningful antitumor activity in HER2+ breast cancer.

The EMILIA trial showed that T-DM1 significantly prolonged progression-free survival (PFS) and overall survival (OS) with less toxicity than lapatinib plus capecitabine (XL) in patients with HER2+ metastatic breast cancer (MBC) previously treated with trastuzumab and a taxane.[8] Among 991 patients, median PFS (mPFS) was 9.6 months with T-DM1 versus 6.4 months with XL, median OS (mOS) was 30.9 months vs. 25.1 months respectively. The objective response rate (ORR) was higher with T-DM1 (43.6% vs 30.8% with XL). In addition, rates of adverse events (AEs) of grade 3 or above were higher with XL than with T-DM1 (57% vs 41%).

This trial led to the FDA approval of T-DM1 in 2013 as the very first ADC for HER2+ MBC. In addition to the EMILIA trial, the TH3RESA trial[9] validated T-DM1 as today's standard of care (SOC) for second-line treatment of HER2+ MBC.

There are two clinical trials evaluating T-DM1 in the first-line setting in HER2+ MBC. TDM4450 randomized 137 patients with treatment-naïve HER2+ MBC to T-DM1 or docetaxel plus trastuzumab.[10] While the ORR and clinical benefit rate (CBR) were similar, patients in the T-DM1 arm had a significantly improved PFS (14.2 vs 9.2 months) and experienced fewer grade 3 or greater AEs compared with the control arm (46% vs 91%). In the MARIANNE trial,[11] patients with untreated HER2+ MBC were randomized to one of three arms: T-DM1 plus placebo, T-DM1 plus pertuzumab (T-DM1/P), or trastuzumab plus a taxane. Neither experimental arm showed PFS superiority to trastuzumab plus taxane. Given the improved tolerability and noninferior PFS observed with T-DM1, it may provide an alternate first-line treatment option to trastuzumab plus taxane in HER2+ MBC. It should be noted that the NCCN panel only considers TDM-1 as an alternative first-line therapy for patients with HER2+ MBC who are unsuitable for taxane-based chemotherapy, given the MARIANNE study did not include a trastuzumab, pertuzumab and taxane arm, which has been shown to improve OS in the CLEOPATRA study compared to the taxane and trastuzumab arm.

2.1.1.2. T-DXD

Following the approval of T-DM1, the second ADC authorized by the FDA for HER2 amplified breast cancer was T-DXd. This ADC-complex (DS8201a) combines trastuzumab with a topoisomerase I inhibitor, DX-8951f (DXd), a derivative of exatecan via a cleavable tetrapeptide-based linker.[12]

T-DXd was initially approved in 2019 for HER2+ MBC patients who have progressed on two or more anti-HER2 therapies, based on the phase 1 DS8201-A-J01[13] and phase 2 DESTINY-Breast01 trials.[14] In DS8201-A-J101, 111 patients with HER2+ MBC received T-DXd. The ORR was 59.5%, and the median response duration (mDOR) was 20.7 months. In DESTINY-Breast01, 184 patients received T-DXd. ORR was 60.9%, DOR was 14.8 months, mPFS was 16.4 months. T-DXd was associated with interstitial lung disease (ILD) in 13.6% of the patients (grade 1 or 2, 10.9%; grade 3 or 4, 0.5%; and grade 5, 2.2%).

The DESTINY-Breast03 study compared the efficacies of T-DXd and T-DM1 in the second-line setting.[15] This phase III study included 524 randomized patients. The mPFS by blinded independent central review (BICR) was not reached for T-DXd compared to 6.8 months for T-DM1, mPFS by investigator was 25.1 months for T-DXd versus 7.2 months for T-DM1. The ORR was 79.1% with T-DXd versus 34.2% with T-DM1. Adjudicated drug-related ILD occurred in 10.5% of those in the T-DXd arm (9.7% being grade 1 or 2 and none being grade 4 or 5), compared to 1.9% in the T-DM1 arm. It should be noted that steroids were used aggressively in this study, which may explain why grade 4 and 5 ILD was not seen. Left-ventricular ejection decreases, all grade 1 or 2, were seen in 2.7% and 0.4%, respectively. Overall, the DESTINY-03 data demonstrated that T-DXd significantly outperformed T-DM1, suggesting the use of T-DXd as a promising new second-line therapy in HER2+ MBC. It should be noted that T-DXd is not yet approved by regulatory authorities in the second-line setting.

An ongoing clinical trial is currently comparing T-DXd with or without pertuzumab to a taxane, trastuzumab and pertuzumab in HER2+ MBC in the first-line setting (DESTINY-Breast09, NCT04784715).

2.1.1.3. SG

SG is an ADC that targets the Trop-2 antigen and has the humanized anti-trophoblast antibody, hRS7 IgG1κ (RS7) linked via a cleavable CL2A linker to the payload, SN-38, which is an active metabolite of irinotecan.

The randomized phase 3 ASCENT study demonstrated that SG prolonged PFS and OS in 529 patients with and without brain metastasis (BM) compared to single agent chemotherapy.[16] mPFS was 4.8 months with SG versus 1.7 months with SOC chemotherapy; mOS was 11.8 months compared with 6.9 months, respectively. The ORR was higher at 35% compared to 5% with SOC chemotherapy. Rates of AEs of grade 3 or above were similar though no deaths were directly related to receiving SG. The ASCENT trial led to regular FDA-approval of SG in 2021 as the very first ADC recommended for metastatic TNBC.

Given Trop-2 is expressed in epithelial cancers, including HR+ MBC and metastatic urothelial carcinoma (mUC). A phase I/II basket trial also indicate encouraging activities of SG in patients with HR+/HER2 negative MBC.[17] Further evaluation in a randomized phase III trial (TROPiCS-02) is ongoing (NCT03901339).

Data from TROPHY[18] (a single-arm, multicenter trial that enrolled 112 patients with locally advanced or mUC who received prior treatment with a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor) led to accelerated approval of SG in patients with locally advanced mUC in the second-line setting.

2.2. ADCS IN EARLIER STAGES OF BREAST CANCER

2.2.1. ADJUVANT THERAPY

The KATHERINE trial compared T-DM1 with trastuzumab in the adjuvant setting. Among HER2+ early breast cancer patients who had residual invasive disease after neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab (the estimated percentage of patients who were free of invasive disease at 3 years was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group),[19] which led to the FDA approval of T-DM1 in 2019 in the adjuvant setting for patients with residual disease after neoadjuvant therapy.

For the patients who did not receive neoadjuvant therapy, the phase 3 KAITLIN trial compared adjuvant anthracycline-based chemotherapy followed by T-DM1 plus pertuzumab (AC-KP) to a taxane plus trastuzumab and pertuzumab (AC-THP). Replacing adjuvant taxane and trastuzumab with T-DM1 did not result in a significant improvement in invasive disease-free survival (IDFS) in the node-positive or intent-to-treat population.[20] The ATEMPT trial also looked into adjuvant T-DM1 compared to paclitaxel plus trastuzumab (TH) among patients with stage I Her2+ breast cancer, one year of adjuvant T-DM1 was associated with excellent 3-year DFS, but not associated with fewer clinically relevant toxicities compared to TH.[21]

T-DXd is currently being evaluated in the adjuvant setting compared to T-DM1 in the Destiny-Breast05 trial, NCT04622319.

2.2.2. NEOADJUVANT THERAPY

The KRISTINE trial examined the combination of docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) versus T-DM1/P in the neoadjuvant setting for patients with HER2+ disease.[22] This trial showed a higher pathologic complete response (pCR) rate with neoadjuvant TCHP (55.7%) over T-DM1/P (44.4%). Importantly, additional chemotherapy was not recommended for patients with residual disease who had received neoadjuvant TCHP, but approximately 9% of the patients assigned to T-DM1/P with residual tumor > 1 cm or nodal disease (> ypN0) received anthracycline-based chemotherapy, and there were 15/223 (7%) locoregional events prior to surgery in the T-DM1/P arm versus 1/221 (<1%) in TCHP arm, suggesting the presence of a subgroup of patients with disease that was primarily refractory to HER2 ADC-based therapy alone due to the inability to internalize the antibody–toxin.[23] A three-year follow up of the KRISTINE trial suggested that compared with TCHP, T-DM1/P resulted in a higher risk of an event-free survival (EFS) event owing to locoregional progression events before surgery, a similar risk of an IDFS event, fewer grade 3 or greater AEs during neoadjuvant treatment, and more AEs leading to treatment discontinuation during adjuvant treatment.[24] In the recent published I-SPY2, pCR rates were 63%, 72% and 33% for T-DM1/P, paclitaxel, trastuzumab and pertuzumab (THP) and paclitaxel/trastuzumab (TH), respectively.[25] Three-year EFS was 88% for T-DM1/P, 92% for THP and 87% for TH. It was found that the degree of HER2 pathway signaling and phosphorylation in pretreatment biopsy specimens were associated with response to T-DM1/P. Overall, the results suggested T-DM1/P is currently not the SOC in the neoadjuvant setting; patients should be carefully selected to consider a chemotherapy–sparing neoadjuvant regimen. More biomarker studies are warranted in this setting.

T-DXd is being studied in the neoadjuvant setting (alone or followed by THP, versus standard treatment AC-THP, NCT05113251).

2.3. CENTRAL NERVOUS SYSTEM (CNS) PENETRATION OF ADCS

The development of CNS disease is associated with debilitating neurological symptoms and poor survival. The efficacy of systemic therapy may be limited by an inability to access the brain, drug efflux pumps that may exclude cytotoxic and ADCs, and acquired resistance to prior treatment regimens.[26,27] Accumulating evidence, however, suggests a potential role for ADCs in HER2+ and TNBC MBC patients with brain metastases (BM).[28]

A subgroup analysis from the phase 3 ASCENT trial[29] showed SG led to improvement in response rate and PFS compared to chemotherapy for a patient with metastatic TNBC who had stable BM (5.6 months compared to 1.7 months). The ORR was 35% with SG and 5% with physician's choice of treatment.

Exploratory analysis of KAMILLA trial in patients with HER2+ MBC and BM showed that T-DM1 is active and well-tolerated in this population.[30] In 126 patients with measurable BM, the best ORR and CBR were 21.4% and 42.9%. In the 398 patients with baseline BM, mPFS and OS were 5.5 months and 18.9 months, respectively.

However, subgroup analysis of the KATHERINE trial showed that the CNS was more often the site of first recurrence in the T-DM1 arm versus the trastuzumab arm (5.9% vs 4.3%). However, T-DM1 was not associated with a difference in overall risk of CNS recurrence.[31] More studies are clearly needed to optimize adjuvant therapy to prevent CNS recurrence.

A subgroup analysis of the DESTINY-Breast01 trial investigated T-DXd in 24 patients with HER2+ MBC with BM.[32] The ORR, mPFS, and mDOR with T-DXd were 58.3%, 18.1 months, and 16.9 months, respectively. Most recently, the phase 3 DESTINY-Breast03 trial (NCT03529110) was reported at SABCS 2021. The study compared T-DXd and T-DM1 in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane. In patients with stable brain metastases at baseline, treatment with T-DXd resulted in higher PFS compared to T-DM1 (HR 0.25; 95% confidence interval [CI] 0.13-0.45). T-DXd improved PFS to a median of 15 months versus 3 months for T-DM1.

There is currently an ongoing, open-label, multicenter study assessing the efficacy and safety of T-DXd in HER2+ MBC participants with or without BMs who have had progression of disease on trastuzumab, pertuzumab, or T-DM1 (DESTINY-B12, NCT04739761).

2.4. ADCS ON HER2 MUTATION AND HER2-LOW EXPRESSION

Studies of Her2-targeted ADCs has expanded to patients with negative HER2 expression, as well as patients with Her2 mutation and those with low expression level of HER2.

Recent genome sequencing projects revealed that HER2 mutations also exist in breast cancer.[33] There is recent case report of a patient with de novo MBC who harbored both HER2 amplification and the L755S mutation; the lesion responded to T-DM1 and after progression on T-DM1 to T-DXd after initially exhibiting clinical resistance to trastuzumab- and lapatinib-based therapies.[34] A recent study using isogenic cell lines stably expressing wild-type or mutant (S310F and L755S) HER2 demonstrated that HER2 mutations enhance the internalization of T-DM1.[35] There are also promising findings in patients with HER2-mutated lung cancer, showed that HER2 ubiquitination and internalization, rather than overexpression, are key mechanisms promoting endocytosis and efficacy of both T-DM1 and T-DXd. They also found that T-DXd was active in T-DM1 resistant tumors.[36] These findings support the hypothesis that HER2 mutations do not compromise the activity of HER2-directed ADCs such as T-DM1 and T-DXd.

Recent studies suggest antitumor activity by T-DXd even in HER2-low expressing tumors, possibly due to its cleavable linker allowing the payload to promote a bystander killing effect.[37] In an open-label, phase Ib clinical trial, 54 heavily pretreated patients with HER2–low MBC were treated with T-DXd at two dose levels. ORR was 37%, mDOR was 10.4 months. Notably, three patients in the cohort receiving the higher dose died of effects deemed to be due to study treatment, two of pneumonitis and one of ILD. Due to the greater potential for AEs with the higher dose, the lower dose was (5.4 mg/kg) recommended for further study.[12]

A phase 3, randomized study of T-DXd versus investigator's choice chemotherapy in HER2-Low, hormone receptor (HR) positive MBC is currently recruiting (DESTINY-Breast06, NCT04494425).

2.5. COMBINATION OF ADCS WITH OTHER THERAPIES

Patients with HER2+ MBC are often treated with a multitude of therapies, additional strategies to improve responses to anti-HER2 therapies are needed. There have been studies combining T-DM1 with capecitabine and with paclitaxel but these regimens proved quite toxic without improvement of clinical outcomes.[38,39]

2.5.1. COMBINATION OF T-DM1 AND TUCATINIB

There is evidence that dual targeting of HER2, either through the combination of 2 different HER2-targeted antibodies or through an antibody-based therapy and a tyrosine kinase inhibitor (TKI), can lead to further improvements in efficacy.[40]

A recent phase 1b study investigated the maximum tolerated dosage (MTD) of tucatinib combined with T-DM1. The ORR was 48%; mPFS was 8.2 months. The results compare favorably with those of retrospective trials suggesting a mPFS of 6 months with T-DM1 in a similar population.[41]

HER2CLIMB-02 is a randomized, double-blind, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with T-DM1 in those patients who have had prior treatment with a taxane and trastuzumab (NCT03975647).

The phase 3 CompassHER2 RD trial compares T-DM1 and tucatinib with T-DM1 alone in preventing relapses in people with high risk HER2+ breast cancer in the adjuvant setting (NCT04457596).

T-DXd is also being studied in combination with tucatinib (Her2Climb04, NCT 04539938).

2.5.2. COMBINATION OF T-DM1 AND CDK4/6 INHIBITORS

Combinations involving targets downstream of the HER2 pathway, particularly cyclin D and cyclin-dependent kinases (CDK) 4/6, could potentially enhance therapeutic efficacy in HER2+ MBC. While CDK 4/6 inhibitors have been FDA approved for the treatment of HR+ MBC, the activity has been attributed in part to the proven pathogenesis of these tumors in promoting cyclin D1 expression and CDK 4/6 activity. This activity also occurs downstream of HER2, thus making it an appealing partner with anti-HER2 therapy.[42]

A phase 1b study combined ribociclib and T-DM1 in patients with HER2+ MBC previously treated with trastuzumab and a taxane.[43] Based on the pharmacokinetic analysis, AEs, and dose reductions, 400 mg was determined to be the recommended phase II dose (RP2D) for ribociclib given with T-DM1.

There is also a multi-center, randomized, phase 2 study of T-DM1 with palbociclib in HER2+ MBC (NCT03530696).

2.6. ADVERSE EVENTS OF SPECIAL INTEREST WITH ADCS

2.6.1. THROMBOCYTOPENIA

The most frequently occurring all-grade AEs in patients receiving T-DM1 include fatigue (46%), nausea (43%), thrombocytopenia (32%), headache (29%), and constipation (26%).[44,45] Thrombocytopenia is a common AE in patients receiving T-DM1. In EMILIA trial, grade 3-4 thrombocytopenia incidence was 12%. Almost all patients receiving T-DM1 experience a transient decline of platelet count, nadir at day 8, with subsequent recovery at day 15.[46] Experimental studies evaluating the mechanism of thrombocytopenia suggested an uptake of T-DM1 by megakaryocytes through a non-target-mediated mechanism (e.g. pinocytosis), whereas the intracellular generation of the active catabolite results in the disruption of microtubules and inhibition of pro-platelet production.[47,48]

Grade 3-4 thrombocytopenia typically occurs during the first 2 treatment cycles. Most patients are able to continue T-DM1 with dose modification or treatment delays. Guidelines suggest treatment interruption in case of grade 3 thrombocytopenia until the platelet count recovers to grade $\leqslant$ 1. In the case of a grade 4 thrombocytopenia, T-DM1 treatment should be re-initiated at a lower dose level after recovery.

2.6.2. *INTERSTITIAL LUNG DISEASE (ILD)*

Drug-induced ILD has been reported among patients with HER2+ MBC receiving anti-HER2 therapies, including trastuzumab, lapatinib, T-DM1, T-DXd, and trastuzumab duocarmazine. A recent review[49] selected 18 articles and assessed 9,886 patients who received trastuzumab, lapatinib, T-DM1, or T-DXd. The overall incidence of all-grade ILD was 2.4%, with 66.7% occurring as grade 1–2 events, 0.5% grade 3–4, and 0.2% grade 5. The studies indicated that ILD events were managed via dose interruption, dose reduction, or treatment discontinuation.

T-DXd is of special interest given the phase 1 study[13] reported ILD incidence of 17.4% (20 patients) of 115 patients. The phase 2 study[14] assessed 184 patients, 25 patients (13.6%) had a treatment-related ILD event, most of which were grade 1–2 (n=20, 10.9%). In a phase 2 clinical trial of T-DXd, Modi et al.[12] recommend T-DXd dose interruption and possible systemic steroids for grade 1 events, and permanent T-DXd discontinuation with prompt initiation of systemic steroids for grade 2, 3, or 4 events; hospitalization is required for grade 3 or 4 events.

ILD remains an important identified risk with T-DXd. A recent analysis[50] used data from 245 patients with HER2+ MBC treated with T-DXd monotherapy at 5.4 mg/kg every 3 weeks from August 2015 to June 2020; of these 61 patients participated in two phase I studies (NCT02564900, NCT03383692) and 184 patients were in the phase II DESTINY-Breast01 study (NCT03248492). During treatment, 38 (15.5%) patients experienced an ILD event that was adjudicated as drug related. Of patients with ILD, most (79%) experienced Grade 1 or 2 events. Thirty patients (12.2%) were Grade 1 or 2 events. Grade 3 and Grade 4 ILD events were reported in one (0.4%) patient each. Six (2.4%) patients died due to a Grade 5 ILD event. Most of the ILD events occurred within the first 12 months of treatment. The median time to first ILD event was 5.6 (range, 1.1 to 20.8) months, with 97% of patients experiencing the first onset of ILD prior to 12 months.

The incidence of ILD seems to be lower when T-DXd is used in the second-line setting in DESTINY-Breast03.[15] As mentioned, 524 patients with unresectable or metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane were randomly assigned 1:1 to receive T-DXd or T-DM1. Adjudicated drug-related ILD or pneumonitis was reported in 27 patients (10.5%) treated with T-DXd and five patients (1.9%) treated with T-DM1 overall, with no Grade 4 or 5 events. The data suggested that patients who were heavily pre-treated might be at higher risk to develop grade 4 or 5 ILD while receiving T-DXd.

2.6.3. *NEUTROPENIA*

Neutropenia is one of the most common treatment-related adverse events. In the ASCENT trial, 63% of patients receiving SG had any grade of neutropenia, 51% with grade 3 or higher neutropenia. The incidence of grade 3 and 4 febrile neutropenia was 5% and 1%, respectively, with SG. Neutropenia was managed with dose reduction, dose delay, or both and with growth-factor support after day 1 of cycle 1. Concomitant growth-factor support was given to 49% of the patients treated with SG.

T-DXd had lower incidence of neutropenia compared to SG. In the DESTINY-Breast01 trial, incidence of grade 3 or higher neutropenia was 20.7%. Incidence of grade 3 or higher neutropenia from T-DXd was 19.1% in the second-line setting in DESTINY-Breast03.

2.6.4. *CARDIOVASCULAR TOXICITIES*

Cardiotoxicity was an unusual finding among patients treated with T-DM1 after anthracycline-based chemotherapy.[43,44] Verma et al.[8] reported that 97% of patients receiving T-DM1 maintained an LVEF of ⩾ 45%. This is consistent with the results of other landmark studies reporting that very few patients discontinue treatment due to cardiotoxicity. The current recommendation includes cardiac function evaluation prior to the therapy initiation and at regular intervals throughout treatment.

2.6.5. *ALOPECIA*

Interestingly the incidence of alopecia can be different depending on the ADCs but most commonly grade 1 or grade 2. Alopecia is common in patients receiving SG (46% of any grade alopecia in ASCENT trial, no grade 3 or grade 4 alopecia) or T-DXd (48.4% of any grade alopecia in DESTINY-Breast01 and 0.5% grade 3, no grade 4 alopecia). Given the incidence, patients should be informed of the incidence and severity of alopecia.

2.7. ADCS IN LOW RESOURCE COUNTRIES AND COST-EFFECTIVENESS

Unfortunately, T-DM1, T-DXd, or SG are not available in every country. Earlier studies suggested that T-DM1 is not cost-effective when compared to the lapatinib plus capecitabine combination therapy.[51–53] However, by combining the cost of drugs with OS, T-DM1 is cost-effective for the treatment of pretreated HER2+ MBC.[54] A recent analysis[55,56] showed that compared to trastuzumab, T-DM1 in the adjuvant setting yielded lower lifetime costs (–$40,271), and higher life-years (2.980) and quality-adjusted life-years (2.336). The patent expiration date for T-DM1 in Europe was June 2020. The patent is set to expire in September 2026 in the US. We are anticipating biosimilar products will be more widely available in the next few years.

3. FUTURE DIRECTIONS

There is ongoing research to develop second-generation ADCs (Table 1), by identifying new targets and modifying the linker and/or payload. Currently, (Vic-)Trastuzumab Duocarmazine (SYD985) is being investigated in the phase 3 TULIP trial. It was reported at ESMO 2021 that treatment with SYD985 significantly improved PFS in comparison with standard physician's choice chemotherapy and may provide a new treatment option for patients with pre-treated locally advanced or metastatic HER2+ MBC (PFS of 7.0 months vs 4.9 months). ARX788 (Her2 antibody-MMAF) and Zilovertamab Vedotin (UC961-MMAE, MK-2140, VLS-101) are be-

ing investigated in phase 2 studies. There are multiple other ADCs in phase 1 studies.

Bispecific mAbs currently under development for the treatment of breast cancer target two different epitopes on HER2, HER3, B7H4, and/or an epitope on T cells. ZW25, Zenocutuzumab, PRS-343 and PF-07260437 are currently undergoing clinical trials.

4. CONCLUSION

ADCs are a revolutionary and unique approach where mABs and chemotherapy agents are linked to deliver payloads to targeted cancer cells to improve treatment specificity and reduce systemic toxicity. Clinical trials and research are exploring the possibilities of engineering newer ADCs to bind to additional targets and deliver more effective payloads. In general, this new realm of ADCs showcases encouraging treatment options for breast cancer.

FUTURE DIRECTIONS

Future attention must be paid to ADC resistance mechanisms to engineer new ADCs to bypass/overcome resistance pathways; clinical use of ADCs in combination with other treatment modalities and integration with immune-acting agents.

The general theorem of ADC action is that these drugs remain chemotherapeutics at their core. The development of "chemo-free" bispecific antibodies seems to be the future direction of personalized treatment of breast cancer.

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Table 1. Ongoing clinical trials on ADCs

Clinical Trial	Number	Phase	Clinical Indication	Drug	Other Names	Antigen Target	Linker	Payload
SYD985 vs. Physician's Choice in Participants With HER2-positive Locally Advanced or Metastatic Breast Cancer (TULIP)	NCT03262935	III	Metastatic Breast Cancer; solid tumors (HER2-expressing breast cancers)	(vic-)trastuzumab duocarmazine	SYD985, Trastuzumab vc-seco-DUBA	ERBB2	Cleavable linker N-[2-(2 maleimidoethoxy)ethoxycarbonyl]-L-valyl-L-citrullinyl-p-aminobenzyl oxycarbonyl-N-[2-(2-hydroxyethoxy)ethyl]- N-[2-(methylamino)ethyl]carbamoyl	Duocarmycin/Seco-DUBA
The Efficacy and Safety of BAT8001 Injection for the Treatment of HER2-positive Advanced Breast Cancer	NCT04185649	III	HER2-positive locally advanced or metastatic breast cancer with prior trastuzumab treatment	trastuzumab biosimilar	N/A	HER2	Uncleavable Batansine linker	maytansine derivative
ARX788 in HER2-positive, Metastatic Breast Cancer Subjects (ACE-Breast-03) (ACE-Breast03)	NCT04829604	II	T-DM1-resistant and HER2-low breast cancers	ARX788	ARX788	HER2	Non-cleavable Amberstatin (AS269)	Monomethyl Auristatin F (MMAF)
A Study of Zilovertamab Vedotin (MK-2140) (VLS-101) in Participants With Solid Tumors (MK-2140-002)	NCT04504916	II	HER2-negative TNBC	Zilovertamab vedotin	MK-2140, VLS-101	Receptor tyrosine kinase-like orphan receptor 1 (ROR1)	Cleavable maleimidocaproyl-valine-citrulline-para-aminobenzoate	Monomethyl auristatin E (MMAE)
RC48 for Neoadjuvant Chemotherapy of HER2 Positive Breast Cancer	NCT05134519	II	HER2-Positive Breast Cancer	Disitamab vedotin	N/A	HER2	Cleavable protease linker	Monomethyl auristatin E (MMAE)
Study of A166 in Patients With Relapsed/ Refractory Cancers Expressing HER2 Antigen or Having Amplified HER2 Gene	NCT03602079	I	Amplified HER2 Gene Locally Advanced or Metastatic Breast Cancer	A166	N/A	HER2	Cleavable valine citrulline (Val-Cit) linker	Duostatin-5 (an MMAF derivative)
Study of Antibody Drug Conjugate in Patients With Advanced Breast Cancer Expressing HER2	NCT02952729	I	HER2 Positive Advanced Breast Cancer	XMT-1522	TAK-522	HER2	drug polymer cleavable linker	Auristatin F-hydroxypropylamide (AF-HPA)
Safety, Tolerability, and Pharmacokinetic (PK) Study of DHES0815A in Participants With Human Epidermal Growth Factor Receptor (HER)2-Positive Breast Cancer	NCT03451162	I	HER2-Positive Breast Cancer	DHES0815A	RG6148	HER2	Disulfide linker	DNA minor groove crosslinking agent pyrrolo[2,1-c][1,4]benzodiazepine monoamide (PBD-MA)
Clinical Study of ALT-P7 to Determine Safety, Tolerability and Pharmacokinetics in Breast Cancer Patients	NCT03281824	I	HER2-Positive Breast Cancer	ALT-P7	N/A	HER2	Cleavable valine citrulline (Val-Cit) linker	Monomethyl auristatin E (MMAE)
B003 in Patients With HER2-positive Recurrent or Metastatic Breast Cancer (B003-101)	NCT03953833	I	HER2-Positive Recurrent or Metastatic Breast Cancer	B003	N/A	ErbB2	Thioether linker	N/A
N/A	N/A	I	Breast Cancer	LCB14-0110	Trastuzumab-	HER2	Proprietary beta-glucuronide linker	MMAF

					LC-LBG-MMAF, Herceptin-LC-LBG-MMAF			
N/A	N/A	I	HER2-Positive Recurrent or Advanced/Metastatic Breast Cancer	SHR-A1201	N/A	HER2	N/A	N/A
Study of DP303c Administered Intravenously to Subjects With HER2-Positive in Advanced Solid Tumors	NCT04146610	I	HER2-Positive Breast Cancer	DP303c	N/A	HER2	N/A	N/A

*N/A (undisclosed)

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