Chapter

Antibody Drug Conjugates

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Abstract

Antibody drug conjugates (ADCs) continue to change the treatment paradigm of breast cancer and recent regulatory approvals of next generation ADCs are shifting how breast cancer is classified and treated. ADCs combine precision targeting with traditional cytotoxic treatment allowing for the delivery of highly potent chemotherapeutic agents to malignant cells. This chapter will cover ADCs used for the treatment of breast cancer including pharmacology, novel mechanism of action, pharmacokinetic and pharmacodynamic properties, clinical outcomes and role in breast cancer therapy, key toxicities and monitoring.

Keywords: breast cancer, antibody drug conjugates, ADC, bystander effect, HER2 low, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan, sacituzumab govitecan

1. Introduction

Antibody drug conjugates (ADCs) continue to change the treatment paradigm of breast cancer and recent regulatory approvals of next generation ADCs are shifting how breast cancer is classified and treated. ADCs combine precision targeting with traditional cytotoxic treatment allowing for the delivery of highly potent chemotherapy to malignant cells. There are three U.S. Food and Drug Administration (FDA) approved ADCs in breast cancer including ado-trastuzumab emtansine (T-DM1), fam trastuzumab deruxtecan (T-Dxd), and sacituzumab govitecan (SG). The 3 approved ADCs in breast cancer are summarized in **Table 1**. T-DM1 is approved for the treatment of human epidermal growth factor receptor 2 positive (HER2+) early breast cancer (EBC) and advanced, recurrent or metastatic breast cancer (MBC). T-Dxd is approved for the treatment of HER2+ MBC and hormone receptor positive (HR+), HER2 low MBC. HER2 overexpression or HER2+ is defined as having immunohistochemistry (IHC) 3+ or IHC 2+ with positive HER2 gene amplification measured by in situ hybridization (ISH) [4]. Approximately, 15–20% of breast tumors are HER2+ [5]. HER2 low is defined as IHC 1+ or IHC 2+ and ISH negative [4]. Approximately, 50–55% of HR+, HER2 negative breast cancer is HER2-low [6]. HER2-low breast tumors do not respond to trastuzumab or T-DM1 [7, 8].

SG is approved for the treatment of metastatic triple negative breast cancer (TNBC) and HR+ MBC after progressing on prior lines of chemotherapy. Both SG and T-Dxd have a topoisomerase I inhibitor cytotoxic payload, which presents a clinical challenge in terms of how to best sequence these two agents when used for the treatment of HR+ MBC. In this chapter, we will describe ADCs pharmacology,

Drug	mAb	Linker	Target antigen	Payload	Payload mechanism of action	DAR
T-DM1	IgG1	Non-cleavable (4-MCC)	HER2	DM1	Microtubule inhibitor-inhibit tubulin polymerization	3.5
T-Dxd	IgG1	Cleavable peptide linker	HER2	Dxd	Topoisomerase 1 inhibitor	8
SG	IgG1	Cleavable hydrolysable linker	Trop-2	SN-38	Topoisomerase 1 inhibitor	7.6

Abbreviations: ADCs, antibody drug conjugates; DAR, Drug-to-antibody ratio; FDA, U.S. Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IgG, immunoglobulin G; mAb, monoclonal antibody; MMC, maleimidomethyl cyclohexane-1-carboxylate; SG, sacituzumab govitecan; T-DM1, ado-trastuzumab emtansine; T-Dxd, fam-trastuzumab deruxtecan.

Table 1.
Approved ADCs in breast cancer [1–3].

pharmacokinetic and pharmacodynamic properties, pharmacogenomic implications, clinical outcomes and place in breast cancer therapy, safety and monitoring.

2. Pharmacology

ADCs allow for a targeted delivery of cytotoxic chemotherapy agents that are too potent to be given in a similar fashion to traditional chemotherapy agents [9]. An advantage of the novel design of ADCs is the efficient delivery of highly toxic chemotherapy afforded by the high specificity of the antibody to the target antigen that is usually highly expressed on cancer cells. ADCs consist of a monoclonal antibodies (mAb) and a cytotoxic payload covalently attached to the mAb via a chemical linker [9].

Designing a successful ADC depends on various factors and properties of each individual component of the ADC [10]. In order to be safe and effective, an ADC needs to be chemically stable in circulation until it reaches the target cancer cell where it will be internalized followed by degradation of the linker or the mAb and subsequent release of the cytotoxic payload in the cell and adjacent cancer cells [10]. Each ADC component plays an important role and should be taken into consideration when designing and developing ADCs. Desired characteristics of ADCs are summarized in **Table 2**.

2.1 The target antigen

Binding of the antibody to the target antigen is needed to gain access into the cancer cells. This process is referred to as internalization, which occurs via endocytosis [11]. Internalization is required before releasing the cytotoxic payload. It is also desired that the target is an extracellular antigen in order to be recognized by the corresponding antibody. Additionally, the antigen should be non-secreted to prevent ADC binding outside of the tumor vicinity [12]. Secreted antigen in the bloodstream can also lead to significant increase in toxicities. Lastly, the ideal target antigen is highly expressed on cancer cells with minimal to no expression on healthy cells to reduce off-target toxicity [13]. This makes HER2 a great target antigen for T-DM1 and

Antigen selection	Antibody	Linker	Payload
High expression on tumor cells	Target specificity	Stable to avoid release of cytotoxic drug to an off-target tissue	High stability in plasma
Low to no expression on healthy cells	Target binding affinity	Maintain inactive state while being bound to antibody	Cell membrane permeable
Displayed on the surface of tumor cells (i.e., extracellular)	Good retention to payload and long half-life	Ability to unleash cytotoxic drug once internalized	Small molecular weight
Internalization properties	Low immunogenicity	Hydrophilic	High drug to antibody ratio

Table 2.
Desired characteristics of ADCs [9].

T-Dxd [9]. Trophoblast cell-surface antigen 2 (Trop2) is a transmembrane glycoprotein that is highly and differentially expressed in certain solid tumors including breast cancer making it an ideal target antigen for SG [9].

2.2 The monoclonal antibody

Ideal characteristics of mAbs used in ADCs include high affinity to the target antigen, efficient internalization upon binding to the antigen, low immunogenicity, and long plasma half-life [14]. Immunogenicity was a significant challenge associated with mouse-derived antibodies leading to serious adverse events [15]. Current technology employes humanized and fully human mAbs with reduced immunogenicity [14]. The most commonly utilized mAb is immunoglobulin G (IgG) antibody, and specifically IgG1, which exhibits long half-life and can induce antibody-dependent cell-mediated cytotoxicity, phagocytosis, and complement dependent cytotoxicity [16]. The mAb component of T-DM1, T-Dxd and SG is humanized, IgG1 mAb [1–3].

2.3 The linker

The linker is the chemical bond that connects the cytotoxic payload to the antibody of ADCs. The linker is important to maintain stability of ADCs in plasma and to control the release of payload in the desired tumor site [9]. The linker can be cleavable or non-cleavable. Cleavable linkers are designed to be sensitive to the tumor environment where they can be chemically (hydrazone and disulfide based) or enzymatically degraded (glucuronide and peptide based) to release the payload [17]. Hydrazone-based linkers are acid sensitive or pH dependent [18]. These bonds are stable in plasma but hydrolyze in the lysosome and endosome where pH < 7 [18]. SG utilizes an acid sensitive, carbonate linker that is cleavable at low pH [19]. The most commonly utilized linker is the peptide linker, which is cleaved via lysosomal proteases such as cathepsin B that are typically overexpressed in cancer cells [20, 21]. This type of bond is employed in T-Dxd [22].

Non cleavable linkers such as thioether based linkers are more stable compared to cleavable linkers leading to less off-target toxicity. These bonds are not sensitive to the enzymatic and chemical environment of the tumor [23, 24]. When non-cleavable linkers are utilized, such as in T-DM1, the release of the cytotoxic agent takes place

after catabolism of the antibody component whereas enzymatic or chemical degradation of the linker releases the payload when cleavable linkers are utilized such as in T-Dxd and SG [25].

2.4 The cytotoxic payload

The novel design of ADCs allows for use of potent cytotoxic agents with half-maximal inhibitory concentrations in nano and picomolar range [26]. High potency of the payload is required since only a small fraction of the ADC reaches the tumor site [27]. As previously mentioned, internalization of the ADC is the first step required for release of the cytotoxic payload followed by linker or mAb degradation in cleavable and non-cleavable linkers-based ADCs, respectively. Other desired characteristics of the cytotoxic payload include stability in physiological conditions, ability to chemically conjugate with the antibody and cell membrane permeability [28]. Currently, the majority of approved ADCs utilize one of three pharmacologic categories of payloads including tubulin inhibitors, DNA damaging agents, and immunomodulators [29].

Tubulin inhibitors can be classified either as tubulin polymerization promoters (e.g., auristatin derivatives monomethyl auristatin E and monomethyl auristatin F) or tubulin polymerization inhibitors (e.g., maytansinoid derivatives DM1 and DM4) [30, 31]. Tubulin inhibitors halt cell division by interfering with mitosis and are considered cell-cycle specific [30]. T-DM1 was the first FDA approved ADC with a maytansinoid derivative cytotoxic payload [1].

The mechanism of action of DNA damaging agents include: DNA alkylation (e.g., duocarmycins), DNA double strand break (e.g., calicheamicins), DNA crosslink (e.g., pyrrolobenzodiazepines), and DNA intercalation (e.g., topoisomerase I inhibitors) [32]. DNA damaging agents are not cell-cycle specific and can be relatively more potent than tubulin inhibitors [32]. The payloads utilized in T-Dxd and SG are topoisomerase I inhibitors [33, 34]. The cytotoxic payload of SG is SN-38, which is the active metabolite of irinotecan. Dxd is the paylaod of T-Dxd, which is an exatecan derivative [33, 34]. It is reported that Dxd has potency that is 10-fold higher than SN-38 [8].

Drug-to-antibody ratio (DAR) is another important characteristic of ADCs that impacts efficacy and safety. DAR refers to the average number of cytotoxic molecules conjugated to the mAb [35]. Low DAR can negatively impact efficacy and high DAR can affect stability, antigen binding ability, and clearance [36]. DAR is also used to determine the therapeutic index of ADCs [35]. DAR values vary among ADCs, and low values can result in reduced potency and efficacy. Initially developed ADCs have a DAR average of 2–4 [37]. T-Dxd and SG have higher DAR values at 8:1 and 7.6:1, respectively compared to T-DM1 that has DAR of 3.5:1 [38].

2.5 The bystander effect

The bystander effect is described with certain ADCs that exhibit an antitumor activity against cancer cells located near those expressing the targeted antigen [39, 40]. In other words, the cytotoxic payload can diffuse through the target cell membrane to and kill adjacent cancer cells that are antigen negative. Properties that allow for bystander effect include having cleavable linkers and cell membrane permeable cytotoxic payload. These properties allow the payload to diffuse to neighboring cells. ADCs with bystander effect may not require high expression of the target antigen to be effective. Due to having cleavable linkers and membrane permeable payloads, both T-Dxd and SG exhibit bystander effect. Conversely, T-DM1 does not exhibit the bystander

effect. The release of payload in T-DM1 requires complete digestion of trastuzumab followed by release of the metabolite, lysine-MCC-DM1, which is charged under physiologic pH and thus is not cell membrane permeable. Therefore, T-DM1 can only exert cytotoxic effect against antigen positive cancer cells (i.e., HER2 positive cells) [9]. Unlike T-DM1, T-Dxd has demonstrated efficacy in both HER2 overexpressing cancer cells as well as cells that are HER2 low due to the bystander effect [41, 42].

3. Pharmacokinetics and pharmacodynamics

Pharmacokinetic (PK) properties of T-DM1, T-Dxd, and SG including metabolism and elimination are described in **Table 3**. The mAb component is expected to be catabolized into small peptides and amino acids via the same pathways used to degrade endogenous IgG monoclonal antibodies [1–3].

3.1 T-DM1

Based on population PK studies, covariates that can impact T-DM1 clearance include body weight, albumin, AST, and baseline trastuzumab concentrations. However, with the exception of weight, other covariates are unlikely to have meaningful impact on clearance. Exposure to T-DM1 was not shown to be affected by mild (CrCl 60–89 mL/min) or moderate (CrCl 30–59 mL/min) renal impairment. Patients with severe renal impairment (CrCl <30 mL/min) were not included in clinical trials. Therefore, no renal dose adjustment is required, but no recommendations can be made for use of T-DM1 in severe renal impairment due to lack of data in this patient population [1].

DM1 is primarily hepatically metabolized via CYP3A4 and to a lesser extent by CYP3A5. Serum concentrations of DM1 in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment were comparable to those achieved in patients with normal liver function. T-DM1 was not studied in patients with severe hepatic impairment (Child-Pugh C). Based on this, no dose adjustment is required in mild or moderate hepatic impairment and no recommendations can be made for patients with severe hepatic impairment.

Drug	Substrate of	Payload metabolism	Elimination
T-DM1	CYP3A4 (minor), P-gp	DM1 undergoes hepatic metabolism via CYP3A4/5	DM1 half-life ~4 days
T-Dxd	BCRP, CYP3A4 (minor), OATP1B1/1B3, P-pg (minor)	Dxd undergoes hepatic metabolism via CYP3A4	Dxd half-life ~5.4 to 6.1 days
SG	UGT1A1	SN-38 is metabolized via UGT1A1 to the inactive glucuronide metabolite (SN-38G)	SG half-life ~23.4 h; free SN-38 ~ 17.6 h

Abbreviations: ADCs, antibody drug conjugates; BCRP, breast cancer resistance protein; OATP, organic anion transporting polypeptides; P-gp; p-glycoprotein; SG, sacituzumab govitecan; T-DM1, ado-trastuzumab emtansine; T-Dxd; fam-trastuzumab deruxtecan; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1.

Table 3.
ADCs pharmacokinetic properties [1–3].

In a population-based PK study, age and race had no clinically meaningful impact on T-DM1 exposure. While there are no safety studies of T-DM1 in pregnant women, cases of oligohydramnios presenting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death are reported with use of trastuzumab [1]. Given the mechanism of action of DM1 and sensitivity of rapidly dividing cells to its cytotoxic antimicrotubular effect, animal studies suggest that T-DM1 has the potential to cause embryotoxicity and teratogenicity [1]. Women of childbearing age should be tested for pregnancy prior to initiating treatment. Women of childbearing age and men with female partners of reproductive potential should use effective contraception during treatment and for 7 months and 4 months after the last dose of T-DM1, respectively. Women should also be advised to avoid breastfeeding during treatment and for 7 months after the last dose of T-DM1 [1].

3.2 T-Dxd

Based on population PK studies, there was no difference observed in exposure to Dxd in patients with mild (CrCl 60–89 mL/min) or moderate (CrCl 30–59 mL/min) renal impairment. Patients with severe renal impairment (CrCl <30 mL/min) were not included in clinical trials. Patients with moderate renal impairment should be monitored for interstitial lung disease more frequently. No recommendations can be made for use of T-Dxd in patients with severe renal impairment due to lack of data in this patient population [2].

T-Dxd is primarily hepatically metabolized via CYP3A4. There was no difference in exposure to T-Dxd in patients with mild hepatic impairment (total bilirubin ≤ ULN and any AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST) compared to patients with normal hepatic function. PK of T-Dxd in patients with moderate to severe hepatic impairment is not known. T-Dxd dose adjustment is not required in patients with mild to moderate hepatic impairment, but these patients need to be monitored more closely for adverse events related to Dxd. No significant difference in exposure to Dxd was observed for age or race [2].

Given the known risk of the trastuzumab component of T-DXd to the fetus as described above and Dxd cytotoxic effect on actively diving cells, T-Dxd is considered genotoxic. Women of childbearing age should be tested for pregnancy prior to initiating treatment. Women of childbearing age and men with female partners of reproductive potential should use effective contraception during treatment and for 7 months and 4 months after the last dose of T-Dxd, respectively. Women should also avoid breastfeeding during treatment and for 7 months after the last dose of T-Dxd [2].

3.3 SG

SN-38 is metabolized via uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) to the inactive glucuronide metabolite, SN-38G, which is then eliminated by biliary excretion [43]. Based on population PK studies, there was no difference observed in exposure to SN-38 in patients with mild or moderate renal impairment, and renal elimination of SN-38 is found to be minimal [3]. Therefore, no renal dose adjustment is required for SG for mild or moderate renal function impairment. No recommendations can be made for use of SG in severe renal impairment due to lack of data in this patient population [3]. There is no difference in exposure to SG between patients with mild hepatic impairment compared to patients with no hepatic impairment. SG PK is not known for patients with severe hepatic impairment [3].

Drug	Indications	Dose and administration
T-DM1	Early, HER2+ breast cancer*adjuvant for residual disease Metastatic, recurrent HER2+ breast cancer	3.6 mg/kg IV every 3 weeks for 14 cycles (adjuvant) or until disease progression (metastatic)
T-Dxd	Metastatic, recurrent HER2+ breast cancer Metastatic, recurrent HER2 low breast cancer	5.4 mg/kg IV every 3 weeks until disease progression
SG	Metastatic, recurrent TNBC after ≥2 chemotherapy Metastatic, recurrent HR+, HER2 negative or low after progression on endocrine therapy and chemotherapy	10 mg/kg on days 1 and 8 of a 21-day cycle until disease progression

Abbreviations: HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; IV, intravenous; SG, sacituzumab govitecan; T-DM1, ado-trastuzumab emtansine; T-Dxd; fam-trastuzumab deruxtecan; TNBC, triple negative breast cancer.

Table 4.
Dose and administration [1–3].

There was no significant impact of age or race on PK properties of SG and exposure to SN-38 [3]. Given the mechanism of action of SN-38 and its effect on rapidly dividing cells, SG is considered teratogenic and genotoxic [3]. Women of childbearing age should be tested for pregnancy prior to initiating treatment. Women of childbearing age and men with female partners of reproductive potential should use effective contraception during treatment and for 6 months and 3 months after the last dose of SG, respectively. Women should also avoid breastfeeding during treatment and for 1 months after the last dose of SG (**Table 4**) [3].

4. Drug-drug interactions

4.1 T-DM1

There are no formal drug interaction studies with DM1. DM1 is extensively metabolized by CYP3A4, and it is anticipated that strong CYP3A4 inhibitors can increase DM1 concentrations and toxicity. Therefore, it is recommended that concomitant use of strong CYP3A4 inhibitors with T-MD1 is avoided. If concomitant use cannot be avoided, closely monitor for T-DM1 toxicities [1]. However, a phase I study evaluated the safety and efficacy of T-DM1 in combination with tucatinib, which is a strong CYP3A4 inhibitor revealed that DM1 concentration was similar to those reported in studies of T-DM1 monotherapy suggesting lack of clinically meaningful interactions [44]. The impact of strong CYP3A4 on T-DM1 has not been evaluated to date. DM1 does not inhibit or induce major CYP450 enzymes [1].

4.2 T-DXd

Dxd is a substrate of OATP1B1/3, MATE2-K, P-gp, MRP1, and BCRP. Coadministration of strong CYP3A4 inhibitors increased Dxd area under the curve (AUC) by 18%, and that was not considered clinically meaningful [2]. Coadministration of ritonavir, dual inhibitor of CYP3A4 and OATP1B increased Dxd AUC by 22%. The impact was not clinically significant. According to in vitro studies, DXd does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and

CYP3A nor induce CYP1A2, CYP2B6, or CYP3A [2]. Dxd has low potential to inhibit OAT1/3, OCT1/2, OATP1B1/3, MATE1/2-K, P-gp, BCRP, and BSEP transporters [2].

4.3 SG

No formal drug interaction studies were conducted with SG or SN-38 [3]. Given metabolism and clearance mechanism of SN-38 via UGT1A1, UGT1A1 inhibitors may increase the concentration and toxicity of SN-38 and thus coadministration should be avoided. Additionally, UGT1A1 inducers may decrease exposure to SN-38 and its efficacy [3].

There are challenges with drug interaction assessment with ADCs. There is no specific guidance from regulatory bodies on how to formally evaluate drug interactions with cytotoxic payloads. There is an unmet need for understanding how cytotoxic payloads will be affected by oxidative enzymes and drug transporters. It is speculated that given the low systemic exposure, cytotoxic payload molecules are unlikely to cause clinically meaningful interactions but can be significantly affected by enzymes and transporters. Unique considerations may be needed when designing PK studies to evaluate interactions with cytotoxic payloads [45].

5. Pharmacogenomics

The cytotoxic payload, SN-38 in SG is metabolized via UGT1A1 to an inactive metabolite. The genetic variant UGT1A1*28 has reduced enzyme activity. Patients who are homozygous (UGT1A1*28/*28; diminished enzyme activity) and heterozygous (UGT1A1*28/*1; reduced enzyme activity) are at increased risk for neutropenia, febrile neutropenia, anemia, and other toxicities due to increased exposure to SN-38 compared to wild type (UGT1A1*1/*1; normal enzyme activity) [3, 46]. There are no known pharmacogenomics implications for T-DM1 and T-Dxd [1, 2].

The frequency of having homozygous UGT1A1*28 allele varies with about 20% of the Black population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele [47]. Approximately, 40% of Black, 50% of White, and 25% of East Asian population are heterozygous for the UGT1A1*28 allele [47].

Patients presenting with acute-onset, severe neutropenia and anemia may indicate reduced UGT1A1 enzyme activity. The median time to neutropenia and febrile neutropenia was 9 days in patients who are homozygous for UGT1A1*28 allele, 15 days in patients who are heterozygous for the allele, and 20 days who are wild type for UGT1A1* [3]. The median time to anemia in patients homozygous for UGT1A1*28, heterozygous for UGT1A1*28, and homozygous for wild type UGT1A1* was 21 days, 25 days, and 28 days, respectively [3].

In a safety analysis from phase III, randomized clinical trial of SG in metastatic TNBC, the impact of UGT1A1 polymorphism was evaluated. In patients treated with SG, UGT1A1 genotype was known for 250 patients. Of 250 patients, 113 (44%), 96 (37%), and 34 (13%) were homozygous for the wild type UGT1A1 (*1/*1), heterozygous (*1/*28), and homozygous (*28/*28) [48]. Patients with homozygous *28 genotype had comparable grade 3/4 neutropenia (59%) to those with heterozygous *28 (47%) or wild type (53%), but the rate of febrile neutropenia was higher (18% vs. 5% and 3%, respectively). Grades 3/4 anemia (15% vs. 6% and 4%, respectively) and diarrhea (15% vs. 9% and 10%, respectively) occurred more frequently in patients with homozygous

UGT1A1*28 genotype compared to those with heterozygous and wild type genotypes. Treatment discontinuation due to adverse events was also more common in patients with homozygous UGT1A1*28 genotype compared to heterozygous *28 and wild type genotypes (6%, 1%, and 2%, respectively). Other adverse events including nausea, vomiting, fatigue and alopecia were not impacted by UGT1A1 genotype [48].

Increased risk for severe adverse reactions including neutropenia and febrile neutropenia with irinotecan in patients with reduced UGT1A1 activity is attributed to its active metabolite, SN-38, which is the cytotoxic payload of SG [49, 50]. While the FDA recommends reducing the starting dose of irinotecan in patients with colorectal cancer and known UGT1A1*28/*28 status [50], there are currently no guidelines for SG dosing recommendations for patients who have known UGT1A1*28/*28 genotype. The FDA only recommends SG dose modification or discontinuation based on tolerance [3].

6. Clinical outcomes of ADC in breast cancer treatment

6.1 T-DM1

T-DM1 was evaluated in the phase III, randomized clinical trial EMILIA, which enrolled 991 patients with metastatic, HER2+ breast cancer with disease progression after first line trastuzumab plus taxane based chemotherapy for metastatic disease or with disease recurrence during or within six months of completing adjuvant therapy [51]. Patients were randomized 1:1 to T-DM1 or lapatinib and capecitabine. The co-primary endpoints were progression free survival (PFS) and overall survival (OS). Most patients (88%) received prior chemotherapy for metastatic disease with a median of 3 prior lines of treatment. PFS was significantly improved with median PFS of 9.6 months in the T-DM1 arm versus 6.4 months in the control arm [hazard ratio (HR), 0.65; 95% CI, 0.55–0.77; $p < 0.0001$]. Overall survival was also significantly improved with median OS of 30.9 months in the T-DM1 arm vs. 25.1 months in the control arm (HR, 0.68; 95% CI, 0.55–0.85; P, 0.0006). Based on the results of this study, T-DM1 was FDA approved for the treatment of HER2+ metastatic breast cancer after progression on first line therapy, and T-DM1 became the standard second line treatment in this patient population until recent findings from DESTINY-Breast03 that demonstrated superiority of T-Dxd over T-DM1 as second line treatment for metastatic, HER2+ breast cancer [41].

Adjuvant T-DM1 for early stage, HER2+ breast cancer and residual disease post taxane and trastuzumab based neoadjuvant chemotherapy was evaluated in the KATHERINE trial, a randomized, phase III study [52]. The study enrolled 1486 patients who were randomized 1:1 to adjuvant T-DM1 or trastuzumab for 14 cycles. The primary outcome was invasive disease free survival (IDFS), which was defined as the time from randomization to first local or regional breast cancer recurrence, distant recurrence, or death from any cause. Key secondary outcomes were PFS and OS. Most patients (77%) received anthracycline based neoadjuvant chemotherapy, and 20% of patients received additional anti-HER2 therapy, 94% of which was pertuzumab. At a median follow up of 40 months, IDFS was significantly improved with T-DM1 versus adjuvant trastuzumab (HR, 0.50; 95% CI, 0.39–0.64; $P < 0.001$). The 3-year IDFS rate was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. The results of this study led to the FDA approval of T-DM1 as an adjuvant therapy for patients with early stage, HER2+ breast cancer with residual disease after neoadjuvant chemotherapy and surgery and has established adjuvant T-DM1 as a standard therapy in this patient population [5].

6.2 T-Dxd

T-Dxd was first FDA approved based on results from the single arm, multicenter, phase II DESTINY-Breast 01 trial that enrolled patients with HER2+ metastatic breast cancer who progressed on prior chemotherapy including T-DM1 [53]. The median number of prior lines of treatment was 6 (range, 2–27). T-Dxd was associated with an objective response rate of 60.9% (95% CI, 53.4–68.0) in a heavily pre-treated population. The benefit of T-Dxd for the treatment of HER2+ metastatic breast cancer after progression on T-DM1 was confirmed in the phase III, randomized clinical trial, DESTINY-Breast02 that demonstrated significant improvement in PFS and OS when compared to chemotherapy [54].

The clinical trial that changed practice when choosing a second line treatment for patients with HER2+, metastatic breast cancer whose disease progressed after first line anti-HER2 therapy plus taxane chemotherapy was the DESTINY-Breast03 trial, which was a randomized, phase III study that compared T-Dxd to T-DM1 in the second line setting [41, 55]. A total of 524 patients were randomized in 1:1 to T-Dxd or T-DM1. The primary endpoint of PFS was significantly improved with median PFS of 28.8 months with T-Dxd vs. 6.8 months with T-DM1 (HR, 0.33; $P < 0.000001$). Overall survival was significantly improved with T-Dxd with the median not reached in either treatment arm although the risk of death was reduced by 36% with T-Dxd (HR, 0.64; P, 0.0037) demonstrating superiority of T-Dxd and establishing its role as a preferred second line treatment in this patient population [5].

DESINY-Breast 04 (DB-04), a phase III randomized clinical trial, has transformed the way breast cancer is categorized and treated [42]. Through demonstrating superior efficacy of T-Dxd in breast cancer cells that has reduced HER2 expression (previously categorized as HER2 negative), DB-04 provided clinical evidence that the bystander effect is an important characteristic of ADCs. Up to 60% of HER2 negative breast cancer cells express low levels of HER2, and more than 50% of HR+ breast cancer is HER2 low making the findings from DB-04 clinically relevant [56, 57]. In DB-04, patients with metastatic, recurrent HER2-low breast cancer defined as IHC 1+ or IHC 2+/ISH- were randomized 2:1 to T-Dxd or chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). More than 70% of patients with HR+ disease received prior CDK4/6 inhibitors and more than 99% of patients progressed on 1 line of prior chemotherapy. T-Dxd was associated with significant improvement in PFS and OS in the HR+ cohort and all patients. The median PFS in the HR+ cohort was 10.1 vs. 5.4 months (HR, 0.51; 95% CI, 0.40–0.64 $P < 0.001$) and in HR-negative was 8.5 vs. 2.9 months (HR, 0.46; 95% CI, 0.24–0.89). Median OS in the HR+ cohort was 23.9 vs. 17.5 months (HR, 0.64; P, 0.003) and in HR-negative was 18.2 vs. 8.3 months (HR, 0.48; 95% CI, 0.24–0.95). Benefit was observed across all subgroups including HER2 IHC 1+ and IHC 2+/ISH negative [42]. For patients with HR+ metastatic breast cancer and visceral crisis or with endocrine resistant disease, the National Comprehensive Cancer Network (NCCN) guidelines list T-Dxd as a preferred, category 1 treatment in the second line setting [5]. The NCCN guidelines list SG as a preferred, category 1 option in the second line setting for this patient population if not candidate for T-Dxd. For TNBC with HER2-low, T-Dxd is listed as preferred, category 1 treatment option in the second line setting [5].

6.3 SG

SG is the first approved ADC targeting Trop-2 [58]. SG was evaluated in the ASCENT, a phase III, randomized clinical trial in patients with metastatic TNBC who

progressed after at least two lines of chemotherapy, one of which had to be for metastatic disease [59]. Patients (N = 529) were randomized 1:1 to SG or chemotherapy (eribulin, capecitabine, gemcitabine, or vinorelbine). The primary efficacy outcome was PFS in patients without brain metastases. Key secondary outcomes were PFS in all patients and OS. SG was associated with significant improvement in PFS and OS. In patients without brain metastases, median PFS in SG was 5.6 months vs. 1.7 months with chemotherapy (HR, 0.41; 95% CI, 0.32–0.52; P < 0.001). The median OS was 12.1 with SG vs. 6.7 months with chemotherapy (HR, 0.48; 95% CI, 0.38–0.59; P < 0.001). A total of 61 patients had stable, treated brain metastases at baseline, 32 of which were treated with SG. In a subgroup analysis, patients with stable baseline brain metastases treated with SG had median PFS of 2.8 months compared to1.6 months in patients treated with chemotherapy (HR, 0.65; 95% CI, 0.35–1.22). This analysis is exploratory and limited by small sample size [60]. The NCCN lists SG as a preferred, category 1 treatment option in the second line setting for patients with metastatic TNBC who progressed on at least 2 prior chemotherapy lines, at least one of which for metastatic disease [5].

SG was also evaluated in the TROPiCS-02, a phase III, randomized clinical trial evaluating SG in 543 patients with HR+, HER2 negative or low who have progressed on the following: a CDK 4/6 inhibitor, endocrine therapy, and a taxane and at least two prior chemotherapies in the metastatic setting [61]. The primary outcome of PFS was statistically significant with median PFS of 5.5 in the SG arm vs. 4 months in the chemotherapy arm (HR, 0.661; 95% CI, 0.529–0.826; P, 0.0003). The median OS was also significantly improved in these heavily pretreated patients with endocrine resistant disease with median OS of 14.4 in the SG arm vs. 11.2 months in the chemotherapy arm (HR, 0.789; 95% CI, 0.646–0.964; P, 0.020) [62].

7. Adverse events and monitoring

7.1 T-DM1

The most common adverse events associated with T-DM1 were musculoskeletal pain (37.9%), nausea (40.6%), thrombocytopenia (45.7%), constipation (26.9%), fatigue (38.8%), and transaminitis (36.8%). T-DM1 has a low emetic risk [5]. T-DM1 is not associated with alopecia. Due to hepatotoxicity, it is recommended to monitor bilirubin and transaminases before each dose of T-DM1.

Decreased left ventricular ejection fraction (LVEF) has been observed with anti-HER2 therapies including T-DM1 (2–3%). Patients with history of significant cardiac disease and those with baseline LVEF <50% were excluded from clinical trials. It is recommended to monitor left ventricular ejection fraction (LVEF) before initiating T-DM1 and throughout treatment [1]. In clinical practice, LVEF is typically monitored prior to initiating treatment with T-DM1 and every 3 months thereafter.

7.2 T-Dxd

The most common hematologic adverse events associated with T-Dxd were decrease in hemoglobin (66%), white blood cells (71%), neutrophil (65%), platelets (47%), and lymphocyte (55%). The most common non-hematologic adverse events were fatigue, increase in aminotransferases, constipation, vomiting, decreased appetite, musculoskeletal pain, diarrhea, and hypokalemia [2]. T-Dxd is considered highly emetogenic [5]. T-Dxd is associated with alopecia (21 to 46%). An increased incidence

of interstitial lung disease (ILD)/pneumonitis including fatal events were observed in clinical trials (all grade, 15.4%; grades 1/2,11.9%; grades 3/4,1.3%; grade 5 or death, 2.2%). Median time to onset is approximately 5.4 months (range, <0.1–46.8 mo). Risk factors include moderate to severe kidney impairment, having pulmonary comorbidities at baseline (i.e., asthma, prior ILD, radiation pneumonitis), time since initial cancer diagnosis >4 years, age <65 years, baseline oxygen saturation < 95%, and T-Dxd dose >6.4 mg/kg. No consensus guidelines exist on type and frequency of monitoring besides symptoms assessment. High resolution chest computed tomography (CT) was obtained every 6 weeks in clinical trials investigating T-Dxd. Frequent imaging mimicking clinical trials may not be feasible in clinical practice for reasons such as cost and insurance coverage. As a result, frequent monitoring for ILD symptoms in patients receiving T-Dxd is imperative. Similarly to T-DM1, LVEF reduction was reported with T-Dxd (3–8%; mostly asymptomatic) it is recommended to monitor LVEF before starting and periodically thereafter [2]. In clinical practice, LVEF is typically monitored prior to initiating treatment with T-Dxd and every 3 months thereafter.

7.3 SG

The most common adverse events associated with SG were febrile neutropenia (6%), vomiting (5%), diarrhea (4%), dyspnea (3%), nausea (3%), and anemia (2%). It is recommended to monitor patients for severe neutropenia with known reduced activity of UGT1A1 (see pharmacogenomics for details) [3].

8. ADCs in development

Datopotamab deruxtecan (DS-1062) or Dato-Dxd is a Trop2 ADC with a topoisomerase I inhibitor payload (Dxd). Dato-Dxd is comprised of a humanized IgG1 mAb conjugated to the cytotoxic payload via a cleavable, tetrapeptide based linker, and it has an average of 4 DAR with demonstrated bystander effect [63]. Dato-Dxd is being investigated in ongoing clinical trials in solid tumors including breast cancer [64].

Dato-Dxd is being investigated in heavily pretreated patients with metastatic TNBC in the TROPIONPanTumor01 trial (NCT03401385) and has demonstrated encouraging results with an objective response rate of 34% in all patients and 52% in patients who are treatment-naïve to topoisomerase I inhibitor-based therapies [64]. Most common adverse events reported with Dato-Dxd were stomatitis (all grade, 73%; grade 3, 11%), nausea (all grade, 66%; grade 3, 2%), and vomiting (all grade, 39%; grade 3, 5%). The incidence of alopecia was 36% (grade 2, 14%) [64].

Dato-Dxd is also being investigated in the TROPION-Breast01 (NCT05104866), an ongoing randomized, phase III trial that enrolled 700 patients with metastatic, HR+ HER2 negative breast cancer. Patients are randomized 1:1 to Dato-Dxd or chemotherapy (eribulin, capecitabine, vinorelbine, or gemcitabine). Included patients had to have progressed on endocrine therapy and 1–2 prior lines of chemotherapy [65]. Results are not yet reported.

9. Conclusion

ADCs combine precision targeting with traditional cytotoxic treatment allowing for the delivery of highly potent chemotherapeutic agents to malignant cells. Recent

regulatory approvals of next generation ADCs have changed how breast cancer is classified and treated. There are three approved ADCs for the treatment of breast cancer to this dare, and more ADCs are currently in development.

Conflict of interest

The authors declare no conflict of interest.

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