Rise of Antibody-Drug Conjugates: The Present and Future

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Overview

Antibody-drug conjugates (ADCs) embody a simple, but elegant, vision for cancer therapy—the delivery of a potent cytotoxic agent to tumor cells with minimal damage to normal cells—so-called smart chemo. Although there were significant challenges in achieving this milestone culminating in the first Food and Drug Administration approval in 2000, subsequent advancements in technology have led to rapid drug development with regulatory approvals for ADCs targeting a variety of tumor types. The most successful application for solid tumors has been in breast cancer, with ADCs becoming the standard of care across traditional human epidermal growth factor receptor 2 (HER2)+, hormone receptor+ (HR+) and triple-negative disease subtypes. Moreover, the improved features and gains in potency with the development of ADCs have expanded the treatment-eligible population to those with low/heterogeneous expression of the target antigen on the tumor with trastuzumab deruxtecan or in the case of sacituzumab govitecan, agnostic to target expression. Despite their antibody-directed homing, these novel agents come with their share of toxicities obligating appropriate patient selection and vigilant monitoring while on treatment. As more ADCs are included in the treatment armamentarium, mechanisms of resistance need to be studied and understood for optimal sequencing. Modifying the payload to use immune-stimulating agents or combination therapies with immunotherapy and other effective targeted therapies may further extend the utility of these agents in the treatment of solid tumors.

INTRODUCTION

Antibody-drug conjugates (ADCs) are a rapidly emerging class of therapeutic agents that combine the target specificity of a monoclonal antibody (mAb) with the lethality of cytotoxic cellular poison. With ongoing advancements in drug engineering and fresh biologic insight into mechanisms of drug action, the ADC field is still early in its evolution. Despite this, there are over a 100 new ADCs in clinical trials encompassing a wide variety of tumor types. This explosion of interest is, in part, due to the spectacular success in the past 5 years, particularly in some highly treatment-refractory diseases. This review will provide a brief overview on ADC design and mechanism of action, highlighting ADCs currently in use for breast and urothelial cancer (UC) where some of the most significant clinical advancements have been achieved. The toxicity profile of these agents, development of resistance, and the potential of combination therapies with ADCs will be explored.

HISTORY OF ADC DEVELOPMENT

The idea of targeted chemotherapy was conceptualized by a German scientist, Paul Ehrlich, over a century ago. His magic bullet would target a cytotoxin to intended structures in unwanted cells but spare healthy tissues.[1] The structures were later conceptualized to be cell surface antigens to attract antibodies that could grant the desired target specificity. Ehrlich also coined the term chemotherapy, where he proposed to use chemicals to kill the pathogenic cells. Early progress in the development of chemotherapy included generation of some cellular toxins that might be too potent and toxic to administer without a targeted approach. Inception of the hybridoma technology for generation of mAbs[2] helped realize Ehrlich's vision with the first ADC trials underway in the 1980s.[3-5] The first approved ADC was gemtuzumab ozogamicin[6] in 2000, where a CD33 antibody is conjugated to an antitumor antibiotic, calicheamicin.[7] Growing understanding of the ADC mechanism of action and technological breakthroughs have heralded the approvals of over a dozen ADCs, including two on the basis of trastuzumab backbone, an antibody against human epidermal growth factor receptor 2 (HER2).

ADC DESIGN

The fundamental components of an ADC are a mAb directed against a tumor-associated antigen, a cytotoxic agent called payload, and a connecting linker. Each component and their interactions play crucial roles in determining the efficacy and toxicity profiles of an ADC.

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PRACTICAL APPLICATIONS

- The fundamental components of an antibody-drug conjugate (ADC) include an antibody, a linker, and a payload, and the choice and construction determine the clinical characteristics of the ADC.
- Recent drug development has focused on altering linker chemistry and tapping into novel cytotoxic payloads to generate high-potency ADCs that have dramatically improved outcomes, especially in breast cancer.
- Some novel ADCs demonstrate clinical efficacy regardless of the level of tumor antigen expression, enabling the treatment of tumors with heterogeneous expression of the target.
- Most ADCs are associated with unique toxicities, such as pneumonitis/interstitial lung disease, and ocular or skin toxicities that warrant careful monitoring and mitigation strategies.
- The next wave of agents looking to build on the success of ADCs include immune-stimulating antibody conjugates, engineered toxin bodies, and radioligand conjugates that aim to improve therapeutic index while minimizing toxicity.

Antibody Moiety

The antibody moiety of an ADC dictates its plasma circulation duration, immunogenicity, immune functions, and target specificity. Current ADCs are predominantly based on immunoglobulin G (IgG), particularly IgG1. IgG1 offers a long serum half-life and strong Fc-mediated immune functions, including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.[8] Murine antibodies in the early ADCs have been replaced with chimeric or humanized antibodies to minimize immunogenic side effects.[9] Selection of a suitable target antigen has also proven to be instrumental in modulating the specificity and processing of an ADC. An ideal target should exclusively, or preferentially, be expressed at high levels on the surface of tumor cells and not on normal cells. HER2 and trophoblast cell surface antigen 2 (TROP2) are two such targets being used for ADC development in breast cancer (BC) because of their overexpression on tumor cell surfaces[10,11] while sparing normal tissue.

Linkers

A linker's function is to ensure that the payload remains bound to the antibody during circulation but is released at the tumor site. Linkers can be cleavable or noncleavable.[8] Cleavable linkers release the payload on reduction, proteolysis, or hydrolysis because of tumor cell–associated factors (eg, proteases or pH), but noncleavable linkers require complete lysosomal degradation for the payload release. Of the three ADCs approved for BC, ado-trastuzumab emtansine (T-DM1) is the only one with a noncleavable linker,[12] which provides stability to the ADC during circulation and might contribute to a better safety profile compared with other trastuzumab-based ADCs. However, the noncleavable linker may also hinder the potential for bystander killing, wherein payload is released into the tumor microenvironment (TME) and can kill antigen-less cancer cells or even cancer-supporting cells.[13]

Cytotoxic Payloads

Payloads are the chemotherapeutic agents that exert cytotoxic effects on the tumor cells targeted by the ADCs. These are commonly microtubule binding or DNA damage (DNA cleavage or alkylation)-inducing agents. Because of advances in linker conjugation chemistry and our understanding of the ADC mechanism of action in vivo, an increasing breadth of anticancer agents are now being incorporated in newer ADC designs. Among all the newer payloads, however, the most effective have been topoisomerase I (Topo 1) inhibitors including camptothecin derivatives. Fam-trastuzumab deruxtecan (T-DXd) is an anti-HER2 ADC on the basis of an exatecan derivative,[14] and sacituzumab govitecan (SG) is an anti-TROP2 ADC that uses SN-38 (the active metabolite of irinotecan) as its payload.[15] Both ADCs have high drug to antibody ratios (DARs), which can enhance ADC efficacy in vivo given low hepatic clearance.[16] In the case of T-DXd, the membrane permeable deruxtecan is also proficient at diffusing to neighboring cells to exert a bystander effect. This characteristic is integral to the activity in HER2-low or HER2-heterogeneous tumors. Continuous progress is moving the field forward toward the development of more powerful ADCs with varied payloads[17,18] including even nonchemotherapeutic[19] payloads like immune-stimulating agents,[20] while improving the therapeutic window and decreasing systemic side effects to healthy cells.

MECHANISM OF ADC ACTION

The primary antitumor action of ADCs is via targeting of the cytotoxic payload to the tumor cells. On binding of the mAb to the target antigen, the ADC is internalized into the tumor cell. The eventual linker breakdown promotes intracellular release of the payload, where it exerts its microtubule- or DNA-damaging effects.[16] The process of antibody binding and internalization may be subject to further pharmacologic manipulation or enhancement. For instance, recent work has highlighted the potential to increase antigen availability through the use of statin[21] or increase internalization and

lysosomal sorting through the use of kinase inhibitors.[22] These and other studies highlight the multistep process to ADC-mediated killing, which may be enhanced through such drug combinations and may also prove to be relevant to drug resistance.

In addition to the canonical payload release mechanism of drug action, the antibody moiety can exert anticancer effects in a payload-independent manner. The binding of the antibody to its target antigen can disrupt the antigen's downstream function by preventing interaction with its binding partners[23] or promoting its degradation.[24] Furthermore, ADC antitumor action can also be mediated through antibody-dependent activation of immune response including ADCC,[25] such as trastuzumab. Indeed, some of these particular effects may be insufficient as a single agent but provide critical support to the chemotherapy combination akin to how trastuzumab combines with chemotherapy to realize synergistic antitumor effects.

TOXICITIES OF ADCs APPROVED FOR BC AND UC

A major goal of ADCs is to achieve high specificity and low toxicity, beyond the capability of traditional chemotherapeutic agents that lack tumor selectivity.[26] However, despite nuanced drug development strategies, important toxicities exist in clinical practice for approved ADCs. While the toxicities are often attributed to the payload, the target antibody and linker have important implications in determining the implicated organs of observed adverse reactions.[26] Key trial data for ADCs approved for BC and UC and the toxicities associated with them are discussed below. The most common treatment-related adverse events (TRAEs) with these ADCs and the clinical monitoring recommended during treatment are included in Tables 1 and 2, respectively.

T-DM1

T-DM1 is an ADC composed of the mAb trastuzumab, the cytotoxic payload maytansine (DM1), and a nonreducible thioether linker MCC (4-[*N*-maleimidomethyl] cyclohexane-1-carboxylate).[27] The use of a stable noncleavable linker maximizes the therapeutic index of DM1 by minimizing the systemic exposure to free DM1 and improving exposure to T-DM1.[28]

T-DM1 was the first ADC that was granted regulatory approval for solid tumors; it was Food and Drug Administration (FDA)–approved for the treatment of HER2-positive metastatic breast cancer (MBC) on the basis of results from the EMILIA trial.[29] It now has expanded use as an adjuvant therapy for residual disease in early-stage HER2-positive BC after neoadjuvant therapy, on the basis of KATHERINE trial data.[30]

The EMILIA trial also reported a superior toxicity profile associated with T-DM1 compared with capecitabine plus lapatinib (40.7% *v* 57% ≥grade 3 events). The rate of ≥grade 3 adverse events (AEs) was 41% in patients treated with T-DM1, the most common being thrombocytopenia (13%) and elevated serum concentrations of aspartate aminotransferase (4%) and alanine aminotransferase (3%; Table 1).[29]

TABLE 1. TRAEs of Antibody-Drug Conjugates

Drug	Antibody/Payload	Cancer Type	Most Common TRAEs	
			All Grade	TRAEs ≥ Grade 3
T-DXd (*DESTINY-Breast03*, *DESTINY-Breast04*)	Trastuzumab (anti-HER2)/deruxtecan	Breast, colorectal, gastric, non–small-cell lung cancers	Nausea (77%, 73%), vomiting (52%, 34%), alopecia (40%, 38%), anemia (37%, 33%), constipation (37%, 21%), fatigue (31%, 48%)	Neutropenia (16%, 14%), anemia (9%, 8%), platelet count decreased (8%, 5%), nausea (7%, 5%), fatigue (6%, 8%)
EV (*EV-301*)	Anti–nectin-4/MMAE	Urothelial carcinoma	Alopecia (45%), peripheral sensory neuropathy (34%), pruritus (32%), fatigue (31%), decreased appetite (31%)	Maculopapular rash (7%), fatigue (6%), decreased neutrophil count (6%)
T-DM1 (*EMILIA*, *KATHERINE*)	Trastuzumab (anti-HER2)/DM1	Breast cancer	Nausea (39%, 42%), fatigue (35%, 50%), thrombocytopenia (28%, 29%), elevated AST (22%, 28%)	Thrombocytopenia (13%, 4%), elevated AST (4%, 0.5%), ALT (3%, 0.4%)
SG (*ASCENT*, *TROPICS-02*)	Anti-TROP2/SN-38	Breast, urothelial carcinoma	Neutropenia (63%, 70%), diarrhea (59%, 57%), nausea (57%, 55%), alopecia (46%, 46%), fatigue (45%, 37%), anemia (34%, 34%)	Neutropenia (51%, 51%), diarrhea (10%, 9%), anemia (8%, 6%), febrile neutropenia (6%, 5%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transferase; EV, enfortumab vedotin; HER2, human epidermal growth factor receptor 2; MMAE, monomethyl auristatin E; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TRAEs, treatment-related adverse events; TROP2, trophoblast cell surface antigen 2.

TABLE 2. Precautions, Baseline Investigations, and Monitoring for T-DXd, EV, and T-DM1

Drug	Precautions	Baseline Investigations	Monitoring During Treatment and Prophylactic Measures
T-DXd	Pneumonitis, ILD, history of drug-induced pneumonitis Symptomatic or history of congestive heart failure	Assessment of LVEF	Assessment of LVEF clinically as indicated, consider regular assessment throughout Regular assessment of respiratory symptoms (cough, dyspnea, fever)
EV	Hyperglycemia (increased risk in baseline hyperglycemia, BMI > 30) Pre-existing peripheral neuropathy	Assessment of glycemic control (consider HbA1C)	Glucose monitoring Consider ocular prophylaxis with artificial tears Clinical assessment of neuropathy
T-DM1	Pneumonitis, ILD, history of drug-induced pneumonitis Symptomatic or history of congestive heart failure	Assessment of LVEF	Assessment of LVEF as clinically indicated, consider regular assessment throughout Platelet count Liver enzymes Regular assessment of respiratory symptoms (cough, dyspnea, fever)

Abbreviations: EV, enfortumab vedotin; HbA1C, hemoglobin A1C; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Trastuzumab and T-DM1 bind to FcγRIIa on megakaryocyte progenitors, but only T-DM1 is associated with thrombocytopenia, indicating that this toxicity is due to DM1 or its metabolite lys-SMCC-DM1.[26] For most patients, the first occurrence of grade 3 or 4 thrombocytopenia was observed during the first two cycles of T-DM1 treatment and, with appropriate dose modifications, did not result in treatment discontinuation.[29] Interestingly, the incidence of thrombocytopenia after treatment with T-DM1 has been reported to be higher in Asians than White patients, with grade 3 events in 45% and 12%, respectively.[26] Although rare, studies have reported left ventricular dysfunction and the appearance of interstitial lung disease (ILD) associated with the use of TDM-1.[31] Careful patient monitoring is required throughout treatment in an effort to prevent more serious toxicity, and baseline assessment of left ventricular ejection fraction (LVEF) is recommended (Table 2).

T-DXd

Fam-T-DXd is a novel ADC with a humanized HER2 antibody with the same sequence as trastuzumab, covalently linked to a Topo I inhibitor (DXd). This ADC was designed with several unique features: (1) a potent payload DXd; (2) a novel linker that permits a high DAR of 8, with reduced hydrophobicity; (3) a tumor-selective cleavable linker susceptible to lysosomal proteases in the tumor; (4) short systemic half-life to avoid systemic exposure; and (5) bystander effect caused by the high membrane permeability of DXd that enables its diffusion out of tumor cells to exert its cytotoxic effects in the TME.[32]

The FDA granted accelerated approval for T-DXd in December 2019, on the basis of the efficacy in pretreated HER2-positive MBC in DESTINY-Breast01.[33] The DESTINY-Breast03 study demonstrated an unprecedented 1.5-year improvement in median progression-free survival (PFS) with T-DXd compared with T-DM1 in predominantly second-line HER2+ MBC (25.1 *v* 7.2 months; hazard ratio [HR], 0.28; $P = 7.8 \times 10^{-22}$), earning T-DXd a confirmatory FDA approval in this patient population.[34,35] Furthermore, the DESTINY-Breast04 trial in patients with pretreated HER2-low (HER2 immunohistochemistry [IHC]1+ or HER2 IHC2+/in-situ hybridization) MBC demonstrated the superiority of T-DXd over TPC with improved median progression-free survival (HR, 0.50; $P < .0001$) and overall survival (OS; HR, 0.64; $P = .0010$).[36] T-DXd received FDA approval in HER2-low MBC on August 5, 2022, expanding the pool of patients with MBC eligible for treatment with this HER2-targeted ADC.[37]

In DESTINY-Breast01, the most common of these TRAEs associated with T-DXd were decreased neutrophil count (21%), anemia (9%), nausea (8%), and fatigue (6%). Of note, 14% of patients receiving T-DXd had ILD related to the receipt of the study drug, resulting in death among 2% (four patients) of patients. Just three patients experienced decreased LVEF (1.6%), with only one patient (0.5%) experiencing grade 3 severity, suggesting that cardiac toxicity is infrequently observed with this anti-HER2 ADC.[38]

In DESTINY-Breast03, a phase III study comparing T-DXd with T-DM1 in metastatic HER2-positive BC (Table 1), AEs were similar to those in DESTINY-Breast01 and drug-related ILD or pneumonitis occurred in 15% of patients treated with T-DXd, with no grade 4 or 5 ILD/pneumonitis events. Proactive monitoring, early diagnosis, and management were thought to have contributed to the lack of grade 4 or 5 events in this large trial.[39] Nausea and fatigue were also the most common drug-related AEs reported on the DESTINY-04 trial,[36] and a two- to three-drug prophylactic antiemetic regimen (5 Hydroxytryptamine 3, steroid ± neurokinin-1) is recommended for all patients receiving T-DXd.[40]

Drug-related ILD is an important toxicity that must be considered in patient selection and monitoring throughout

treatment with T-DXd. Of note, there seems to be increased risk with the use of T-DXd in the management of HER2-mutated non–small-cell lung cancer, with 26% of patients experiencing drug-related ILD in DESTINY-Lung01.[41] Patients with pre-existing or suspected ILD or pneumonitis should not be offered this therapy and were excluded from DESTINY-Breast01 and subsequent clinical trials investigating T-DXd.[38,42] If ILD is suspected during treatment, consultation with a pulmonologist is recommended, along with high-resolution computed tomography, testing of pulmonary function, and monitoring of oxygen saturations[38,42] (Table 3). Systemic glucocorticoids may be indicated, and further treatment with T-DXd may be contraindicated depending on the severity of toxicity.[38,42]

ENFORTUMAB VEDOTIN

Enfortumab vedotin (EV) is an ADC with proven survival benefits in the treatment of UCs.[43] EV consists of a fully human mAb specific for nectin-4, a cell adhesion molecule, and monomethyl auristatin E (MMAE), an agent that disrupts microtubule formation.[44] EV received accelerated FDA approval in 2019 and regular approval in July 2021, after the publication of EV-301.[45] EV-301 was a global phase III trial, which showed significantly prolonged survival with EV compared with standard chemotherapy in patients with advanced urothelial carcinoma who had previously received platinum-based treatment and an immune checkpoint inhibitor (ICI; HR, 0.70; 95% CI, 0.56 to 0.89).[43]

In EV-301, TRAEs of grade 3 or higher occurred in 51% of patients who received EV, which was similar to the chemotherapy control arm. The most common of these events included maculopapular rash (7%), fatigue (6%), and decreased neutrophil count (6%).[43] Skin reactions and peripheral neuropathy were the most frequent TRAEs of special interest, occurring in 44% and 46% of patients, respectively. The majority of peripheral neuropathy events were grade 1 and 2 sensory events, but they were identified as the TRAE most commonly leading to drug interruption, withdrawal, or dose reduction. This AE appears to accumulate with time and has both motor and sensory components.[43]

Postmarketing reports of severe and fatal cutaneous adverse reactions, including Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with the use of EV.[46] Most commonly, these serious cutaneous toxicities occur during the first cycles of treatment, and therefore, careful initial monitoring with early drug interruption is recommended[47] (Table 3). In cases of severe (grade 3 or higher) dermatologic events, treatment should be withheld and referral for specialized dermatologic care should be considered. In confirmed cases of SJS or TEN, treatment with EV should be permanently discontinued. Mild skin reactions can be managed with supportive care, including topical corticosteroids and oral antihistamines, and treatment may be continued.[47] The role of oral steroids is unproven.

The precise mechanism for SJS or TEN with the use of EV remains unknown, but both the nectin-4–directed antibody and MMAE payload have been implicated. Nectin-4 is expressed in the skin, where it is involved in cell–cell adhesion[47] and may be a case where the target is not specific enough to tumor cells only. In skin biopsies of patients taken 7 days after treatment, EV has been shown to localize to healthy tissues including epidermis, epithelium, and sweat glands.[47]

In EV-301, treatment-related hyperglycemia occurred in 6% of patients, occurring more frequently in patients with hyperglycemia at baseline or with a BMI of 30 or higher,[43] and glucose monitoring is helpful. Ocular toxicities, including dry eyes, blurred vision, and keratitis, have been reported.[48] Artificial tears may be used prophylactically, treatment should be interrupted for ≥grade 3 toxicity, and consultation with ophthalmology is recommended for consideration of additional therapy, including ophthalmic topical steroids[48] (Table 3).

EV has also been investigated in a phase II study of EV plus pembrolizumab in previously untreated UC.[49] No new safety signals were reported in combination with PD-1 therapy; the toxicity profile was similar to that of EV and pembrolizumab monotherapy. However, AEs were more frequent than those with EV monotherapy. This combination is being evaluated further in a phase III study (Table 4). An ongoing clinical trial, EV-202, is investigating the efficacy of EV in the treatment of breast, lung, head and neck, and gastroesophageal cancers, all of which have been shown to express nectin-4[59] (ClinicalTrials.gov identifier: NCT04225117). Overall, EV should not be considered more toxic than chemotherapy in the treatment of UC. Rather, it has a distinct toxicity profile that requires education and awareness.

DISITAMAB VEDOTIN (RC48)

Disitamab vedotin (DV) also has MMAE as its payload but targets HER2 rather than nectin-4 (as is the case with EV).[60] It is licensed in China for advanced UC and has a single-agent response rate of over 50% in a cohort of 107 patients with HER2 positivity. ≥Grade 3 AEs occurred in 58% of patients, the most common of which were hypoesthesia (23%) and neutropenia (14%).[60] Skin toxicity appears less than that seen with EV. The differences in toxicity profile compared with EV are likely due to the distribution of the target as the payload is the same. Larger randomized trials with DV are ongoing.

TABLE 3. Management Recommendations for Important ADC Toxicities

Toxicity (*ADC*)	Severity	Management of Toxicity
Skin reactions (*EV*)	Suspected SJS or TEN	Immediately withhold EV and refer to specialized care Permanently discontinue in confirmed cases
	Grade 2	Withhold until ≤grade 1 Consider referral to specialized care Consider dose reduction if rechallenging after grade 2 toxicity
Hyperglycemia (*EV*)	Blood glucose >13.9 mmol/L (>250 mg/dL)	Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL) Resume treatment at the same dose
Peripheral neuropathy (*EV*)	Grade 2	Withhold until ≤grade 1 For first occurrence, resume treatment at the same dose level. Consider dose reduction for rechallenge after recurrences
	Grade ≥3	Permanently discontinue
Pneumonitis (*trastuzumab deruxtecan*, *trastuzumab emtansine*)	Grade ≥2	Referral to pulmonary, CT thorax, PFT if pneumonitis/ILD suspected Permanently discontinue
Ocular toxicity (*EV*)	Grade ≥2	Consider referral to specialized care Consider topical ophthalmic corticosteroids

Abbreviations: ADC, antibody-drug conjugate; CT, computed tomography; EV, enfortumab vedotin; ILD, interstitial lung disease; PFT, phenylalanine mustard, fluorouracil, tamoxifen; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

SACITUZUMAB GOVITECAN

SG consists of a humanized mAB specific for TROP2 linked to SN-38, the active metabolite of the Topo I inhibitor irinotecan.[15] This conjugation is achieved using a hydrolyzable, proprietary linker, CL2A, which allows for delivery of SN-38 inside tumor cells expressing TROP2. CL2A linker also allows for release of SN-38 into the nearby TME, resulting in a bystander effect killing adjacent tumor cells. SG is linked with high DAR.[15] SG has FDA approval for the treatment of metastatic triple-negative breast cancer (TNBC) and metastatic UC and most recently for the treatment of hormone receptor+ (HR+)/HER2– MBC.[61-63]

ASCENT was a phase III study comparing SG with physician's choice chemotherapy in patients with TNBC who had received two or more previous systemic therapies for metastatic disease. SG was found to improve PFS (HR, 0.41; 95% CI, 0.32 to 0.52) and OS (HR, 0.48; 95% CI, 0.38 to 0.59) compared with single-agent chemotherapy.[64] In this trial, the most common TRAEs of any grade were neutropenia (63%, ≥grade 3—51%), diarrhea (59%, ≥grade 3—10%), nausea (57%), alopecia (46%), fatigue (45%), and anemia (34%, ≥grade 3—8%); see Table 1. Febrile neutropenia was also observed (≥grade 3—6%). Low frequencies of rash (9%, any grade), ocular toxicity effects (5%; all grade 1), and neuropathy (1% ≥grade 2) were reported.[64]

TROPICS-02 randomly assigned patients with HR+/HER2– MBC 1:1 to receive SG or TPC.[65] SG demonstrated statistically significant and clinically meaningful improvements in PFS (HR, 0.66; $P < .0003$) and OS (HR, 0.79; $P = .02$) over TPC.[66] The safety profile in TROPICS-02 was consistent with previous studies (Table 1).

TROPHY-U-01 was a phase II study investigating SG in the treatment of metastatic UC in patients who experienced disease progression after platinum-based chemotherapy and ICI therapy. This study reported a very similar toxicity profile to that observed in ASCENT. There was again a low rate of TRAE involving skin (6%), ocular disorders (4%), and peripheral neuropathy (4%).[67]

There has been rapid development of ADCs in the treatment of other solid tumors as well, with promising activity compared with conventional cytotoxic chemotherapy. Tisotumab vedotin (targeting human tissue factor) is already a standard treatment for advanced cervical cancer,[68] and mirvetuximab soravtansine (targeting FRα) received FDA approval recently for FRα-expressing recurrent epithelial ovarian cancer/fallopian tube cancer/primary peritoneal carcinoma,[69] expanding the treatment options for these patients.

The therapeutic success with novel ADCs in relapsed disease is prompting their evaluation in earlier lines of treatment including the curative setting (Table 4). However, with the use of potent cytotoxic agents and imperfect mechanisms of targeting tumor cells, toxicity is an important consideration while using these agents. Patient selection and careful monitoring continue to be critical components in prescribing systemic therapy, with attention to the unique toxicities associated with these novel agents.

TABLE 4. Select Ongoing Trials With ADC Combinations

ADC	ADC Target	Trial ID (name)	Phase	Combination Therapy	Patient Population	Clinical Trial Data (if applicable)
ADC + IO combinations						
T-DM1	HER2	NCT04740918 (KATE3)	III	Atezolizumab (anti–PD-L1 antibody)	HER2-positive and PD-L1+ MBC	
		NCT04873362 (ASTEFANIA)	III	Atezolizumab (anti–PD-L1 antibody)	HER2+ BC with residual disease after NAC	
		NCT02924883 (KATE2)	II	Atezolizumab (anti–PD-L1 antibody)	HER2-positive MBC	mPFS: HR, 0.082, $P = .33$,[50] atezolizumab arm: 8.2 months, placebo arm: 6.8 months Treatment-related SAEs: atezolizumab arm: 19%, placebo arm: 3%
		NCT02605915	Ib	Atezolizumab (anti–PD-L1 antibody)	HER2-positive BC	
		NCT03032107	I	Pembrolizumab (anti–PD-1 antibody)	1-2L metastatic HER2+ MBC	ORR (N = 20): 20%[51] mPFS: 9.6 months G3 AEs: 20% Pneumonitis: 20% (n = 4; G2 = 3, G3 = 1)
T-DXd	HER2	NCT04538742 (DESTINY Breast-07)	Ib/II	Durvalumab (anti–PD-1 antibody)	1L metastatic HER2+ MBC	
		NCT04556773 (DESTINY Breast-08)	Ib/II	Durvalumab (anti–PD-1 antibody) + paclitaxel	1-2L metastatic HER2-low MBC	
		NCT03742102 (BEGONIA)	Ib/II	Durvalumab (anti–PD-1 antibody)	1L HER2-low TNBC	ORR (n = 12): 66.7%[52] (regardless of PD-L1 expression) G3/4 AE (n = 21): 38.1%, pneumonitis: two cases
		NCT03523572	Ib	Nivolumab (anti–PD-1 antibody)	≥2L HER2+ MBC	ORR (n = 32): 65.6%[53] mPFS: 11.6 months, no benefit with addition of nivolumab to T-DXd, adjudicated ILD/pneumonitis[a]: 14.6%
		NCT03523572	Ib	Nivolumab (anti–PD-1 antibody)	≥2L HER2-low MBC	ORR (n = 16): 50%[53] mPFS: 7.0 months, adjudicated ILD/pneumonitis[a]: 14.6%
		NCT04042701 (KEYNOTE KN-797)	I	Pembrolizumab (anti–PD-1 antibody)	HER2+ MBC (treated with previous T-DM1) and HER2-low MBC	
SG	TROP2	NCT04468061 (Sacı-IO TNBC)	II	Pembrolizumab (anti–PD-1 antibody)	1L mTNBC, PD-L1–negative	
		NCT04448886 (Sacı-IO hormone receptor+)	II	Pembrolizumab (anti–PD-1 antibody)	1-2L hormone receptor+/HER2– MBC	
		NCT05633654 (ASCENT-05)	III	Pembrolizumab (anti–PD-1 antibody)	TNBC with residual disease after NAC	
		NCT04434040 (ASPRIA)	II	Atezolizumab (anti–PD-L1 antibody)	TNBC with residual disease after NAC	
		NCT03971409 (InCITe)	II	Avelumab (anti–PD-1 antibody)	Metastatic TNBC	
		NCT04863885	I/II	Ipilimumab (anti-CTLA4 antibody) + nivolumab (anti–PD-1 antibody)	1L cisplatin-ineligible metastatic UC	Phase I results: ORR: 66.6% (4/6 evaluable –1 CR, 3 PR)[54] DLTs: G3 skin rash (n = 2), G3 pneumonitis (n = 1) RP2D: 8 mg/kg SG IV D1, 8 q3 weeks + 3 mg/kg Ipi IV q3 weeks + 1 mg/kg nivo IV q3 weeks

(Continued on following page)

TABLE 4. Select Ongoing Trials With ADC Combinations (Continued)

ADC	ADC Target	Trial ID (name)	Phase	Combination Therapy	Patient Population	Clinical Trial Data (if applicable)
Dato-DXd	TROP2	NCT05629585 (TROPION Breast03)	III	Durvalumab (anti–PD-1 antibody)	TNBC with residual disease after NAC	
		NCT03742102 (BEGONIA)	Ib/II	Durvalumab (anti–PD-1 antibody)	1L mTNBC	Phase I results: ORR: 74% (regardless of PD-L1 expression),[55] no DLTs Common AEs: Stomatitis, alopecia, no ILD/pneumonitis
Ladiratuzumab vedotin	LIV-1	NCT03310957 (KEYNOTE 721)	I/II	Pembrolizumab (anti–PD-1 antibody)	1L mTNBC; PD-L1 CPS <10	ORR (ITT): 35%[56] ORR (de novo): 69%
BDC-1001[a]	HER2	NCT04278144	I/II	Nivolumab (anti–PD-1 antibody)	HER2-expressing advanced solid tumors	DLTs, AEs, irAEs, MTD, ORR
EV	Nectin-4	NCT05524545 (ASPEN-07)	I	Evorpacept (CD-47 blocker)	UC after PD on previous platinum and checkpoint inhibitor	DLTs, AEs
		NCT05239624 (EV-ECLIPSE)	II	Pembrolizumab (anti–PD-1 antibody)	1L locally advanced or node-positive UC	pCR
		NCT04223856 (EV-302)	III	Pembrolizumab (anti–PD-1 antibody)	1L locally advanced/metastatic UC	PFS, OS
		NCT03924895 (EV-303)	III	Pembrolizumab (anti–PD-1 antibody) + cystectomy	Nonmetastatic muscle invasive bladder cancer eligible for radical cystectomy + pelvic LN dissection	EFS
		NCT04700124 (KEYNOTE-B15/EV-304)	III	Pembrolizumab (anti–PD-1 antibody)	Perioperative setting in muscle invasive bladder cancer	EFS
		NCT04960709 (VOLGA)	III	Durvalumab (anti–PD-1 antibody) and tremelimumab (anti-CTLA-4 antibody)	Muscle invasive bladder cancer suitable for neoadjuvant therapy	pCR, EFS
Disitamab vedotin	HER2	NCT05302284	III	Toripalimab (anti–PD-1 antibody)	HER2-expressing LA/metastatic UC	PFS, OS
ADC + anti-HER2 therapy combinations						
T-DM1	HER2	NCT03975647 (HER2CLIMB-02)	III	Tucatinib (HER2-specific TKI)	2L metastatic HER2+ MBC	
		NCT04457596 (CompassHER2 RD)	III	Tucatinib (HER2-specific TKI)	HER2+ BC with residual disease after NAC	
		NCT05372614	I/II	Neratinib (pan HER kinase inhibitor)	Solid tumors with HER2 alterations	
		NCT05388149	II	Neratinib (pan HER kinase inhibitor)	HER2+ BC receiving adjuvant T-DM1 (two to six cycles) with evidence of MRD	
T-DXd	HER2	NCT04538742 (DESTINY Breast-07)	Ib/II	Pertuzumab (anti-HER2 antibody)	1L metastatic HER2+ MBC	uORR[57] T-DXd (n = 23): 87% T-DXd + pertuzumab (n = 22): 82%
		NCT04784715 (DESTINY Breast-09)	III	Pertuzumab (anti-HER2 antibody)	1L metastatic HER2+ MBC	
		NCT04539938 (HER2CLIMB-04)	II	Tucatinib (HER2-specific TKI)	>2L HER2+ MBC	
ADC + PARP inhibitor combinations						
SG	TROP2	NCT04039230	I/II	Talazoparib (PARP inhibitor)	≥2L mTNBC	Continuous dosing (n = 7)[58]: four DLTs, ORR: 29% (2/7) Staggered dosing (n = 20): no DLTs; ORR: 45% (9/20)
Dato-DXd	TROP2	NCT04644068 (PETRA)	I/II	AZD5305 (PARP 1 inhibitor)	Advanced solid tumors including MBC	

(Continued on following page)

TABLE 4. Select Ongoing Trials With ADC Combinations (Continued)

ADC	ADC Target	Trial ID (name)	Phase	Combination Therapy	Patient Population	Clinical Trial Data (if applicable)
ADC + other targeted therapy combinations						
T-DXd	HER2	NCT04556773 (DESTINY Breast-08)	Ib/II	Capivasertib (AKT inhibitor)	1-2L metastatic HER2-low MBC	
				Anastrozole (NSAI)	1-2L metastatic HER2-low MBC	
				Fulvestrant (SERD)	1-2L metastatic HER2-low MBC	
		NCT04553770 (TALENT)	II	Anastrozole (NSAI)	Hormone receptor+/HER2-low (neoadjuvant setting)	
		NCT04704661 (DASH)	I	AZD6738 (ATR inhibitor)	Advanced solid tumors with HER2 expression	
SG	TROP2	NCT05143229 (ASSET)	I	Alpelisib (a specific PI3K inhibitor)	≥2L HER2– MBC	
		NCT05006794	I	GS9716 (Mcl-1 antagonist)	Advanced solid tumors including TNBC	
Patritumab deruxtecan	HER3	NCT05569811 (VALENTINE)	II	Endocrine therapy	High-risk hormone receptor+/HER2– BC neoadjuvant	
EV	Nectin 4	NCT04963153	I	Erdafitinib (FGFR inhibitor)	Metastatic UC with FGFR2/3 genetic alterations	

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; ATR, ataxia telangiectasia and Rad3-related; BC, breast cancer; CPS, combined positive score; CR, complete response; CTLA4, cytotoxic T-lymphocyte-associated protein 4; Dato-DX, datopotamab deruxtecan; DLT, dose-limiting toxicity; EFS, event-free survival; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; G, grade; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ILD, interstitial lung disease; irAE, immune-related adverse events; ISAC, immune-stimulating antibody conjugate; ITT, intent-to-treat; LA, locally advanced; LN, lymph node; MBC, metastatic breast cancer; Mcl-1, myeloid leukemia cell differentiation protein -1; mPFS, median progression-free survival; MRD, minimal residual disease; MTD, maximum tolerated dose; mTNBC, metastatic triple negative breast cancer; NAC, neoadjuvant chemotherapy; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PARP, poly ADP-ribose polymerase; pCR, pathologic complete response; PD, progressive disease; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PR, partial response; RP2D, recommended phase 2 dose; SAE, serious adverse event; SERD, selective estrogen receptor degrader; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; TLR, toll-like receptors; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2; UC, urothelial cancer; uORR, unconfirmed overall response rate.
[a]ISAC consisting of an anti-HER2 monoclonal antibody conjugated to a TLR 7/8 dual agonist.

RESISTANCE TO ADC THERAPY

The advent of ADCs for the treatment of metastatic cancers over the past decade has significantly improved outcomes across different solid tumors. Nevertheless, patients on these therapies eventually experience disease progression, likely because of resistance. As ADCs are a relatively new class of drugs in oncology, the mechanisms of resistance are not fully elucidated.

Resistance may be related to the components of ADCs including altered target cell surface expression or gene mutation, upregulation of drug efflux transporters to offset payload toxicity, changes in trafficking of the ADC and internalization rates, or simple payload resistance. Some of these are discussed below with the relevant preclinical and clinical findings.

Target Modulation

Target downregulation is a common resistance mechanism; for example, HER2 downregulation is well known to lead to T-DM1 resistance in HER2+ disease.[70,71] In a neoadjuvant trial of T-DM1 + pertuzumab in HER2+ BC, there was a significant association between HER2 heterogeneity (defined as HER2 positivity by FISH in 5%-50% of tumor cells or an area of tumor that tested HER2-negative in multiple core biopsies) and lack of pCR after dual HER2-targeted therapy; none of the patients with HER2 heterogeneity achieved a pCR, in contrast to a 55% pCR rate in patients without HER2 heterogeneous tumors.[72] On the other hand, T-DXd, a next-generation ADC, has significant activity in tumors classified as HER2-low, likely because of a prominent bystander activity. However, data from DAISY revealed that a high percentage of HER2 IHC 0 tumor cells and their spatial distribution relative to HER2+ cells negatively affected response to T-DXd.[73]

Although SG outperformed chemotherapy in low–TROP2 expression settings, patients with low expression had reduced response rates (22%) versus those with medium/high expression in tumors (39%-44%).[74] A three-case autopsy series from patients treated with SG also demonstrated that there was no TROP2 expression detected (mRNA and protein) in one patient who experienced rapid progression, suggesting primary resistance.[75]

Lack of access to the target antigen can also promote resistance to ADCs. The presence of the HER3 ligand neuregulin that promotes HER2-HER3 dimerization diminished

the efficacy of T-DM1 in vitro, and combining T-DM1 with pertuzumab alleviated this inhibitory effect.[76]

Drug Efflux Transporters and Defects in Internalization and Trafficking

Upregulation of genes encoding multidrug resistance proteins (MDR) that promote DM1 efflux have been reported in-T-DM1–resistant cell lines.[77,78] Inhibiting the activity of multidrug resistance–associated protein 1 (MRP1), MRP2 and MDR1 reversed the resistance to T-DM1.

T-DM1 is dependent on lysosomal trafficking for intracellular release of the cytotoxic payload. In T-DM1–resistant gastric cancer cells, trastuzumab-ADCs were internalized into caveolin-coated vesicles/endosomes instead of colocalizing to lysosomes.[79] This cell line was also cross-resistant to an auristatin-based ADC with a noncleavable maleimide linker because of its inability to degrade the antibody in the endosomes and enable payload release. This resistance could be overcome by replacing the linker with protease cleavable linker. Thus, the modular nature of the ADCs can be exploited to generate new ADCs by swapping individual components with different functional properties to bypass resistance.

Mutations That Affect Payload Sensitivity or Antigen Binding

Whole-exome sequencing of tumor tissue from pre-SG treatment and postprogression autopsy tumor lesions identified mutually exclusive somatic mutations in *TOP1* (gene encoding topoisomerase I) and *TACSTD2* (gene encoding TROP2) in distinct lesions from the same patient.[75] TOP1 is a target of the SN-38 payload, and the $TOP1^{E418K}$ mutation prevents binding of the payload to TOP1, leading to resistance. The $TACSTD2^{T256R}$ encodes a protein that alters TROP2 binding to the antibody in SG, leading to resistance to SG. Furthermore, the mutant protein is mislocalized from the plasma membrane to the cytosol. Whether these mutations will be a frequent source of resistance to SG in the clinic remains to be seen.

Thus, diverse and numerous mechanisms likely account for the observed resistance to current ADCs in clinical use. The sequential use of ADCs with distinct mechanisms of action may offer a solution to overcoming resistance, but strong clinical trial translational work will be required to guide optimal sequencing. In addition, combinations of ADCs with other anticancer therapies can also potentially evade resistance or even overcome resistance.

COMBINATIONS WITH ADCs

Anti-HER2 Therapies

Combination of anti-HER2 ADCs and other HER2 agents that target a different epitope or function of HER2 to further improve outcomes has been explored. Although preclinical data showed synergistic activity for the T-DM1 + pertuzumab combination,[76] this was not seen in the MARIANNE trial where the addition of pertuzumab to T-DM1 did not improve PFS (stratified HR, 0.91; 97.5% CI, 0.73 to 1.13).[80] In DESTINY Breast-07, T-DXd is being combined with pertuzumab, immunotherapy, endocrine therapy, and other targeted agents. Other ADCs currently under evaluation with HER2-targeting agents are listed in Table 4.

Immunotherapy Agents

The multifaceted mechanism of action of ADCs also includes the engagement of immune effector cells with the goal of eliciting antitumor immunity.[16] This may manifest itself as the ADCC effects of the tumor-specific antibody in the ADC and direct interaction of the ADC with immune cells to modify their function.[81] In a mouse model, T-DXd + anti–PD-1 antibody was more active than T-DXd alone, potentially because of increased T-cell activity and upregulated PD-L1 expression induced by T-DXd.[82] These data formed the basis for the randomized trial of T-DM1/placebo + atezolizumab in HER2+ MBC (KATE-2) and the phase 1 trial of T-DXd with nivolumab. Disappointingly, neither trial showed significant improvement in efficacy with the combination over HER2-ADC alone.[50,53] Results from trials with ICI in TNBC suggest that setting and the line of therapy are important in BC, and there are ongoing trials in earlier lines of therapy (Table 4). On the other hand, preliminary results from T-DXd + nivolumab in HER2-expressing advanced UC reported an ORR of 37% and a medium duration of response of 13.1 months.[83]

The cytotoxic activity of Topo I inhibitors like SN-38 (payload in SG) results in the release of tumor-associated antigens into the circulation, which may upregulate PD-L1 expression on tumors and further prime the antitumor immune response. Topo I inhibitors can also alter tumor immune landscape by reducing Tregs and augmenting MHC class I–mediated tumor antigen presentation.[84] Hence, the TROP2 ADCs are under clinical investigation in combination with ICIs in TNBC (Table 4).

A phase 1 trial of SG with EV is ongoing in advanced/metastatic UC that has progressed on previous ICI therapy (ClinicalTrials.gov identifier: NCT04724018).

PARP Inhibitors

ADCs with Topo I inhibitors may be synergistic with poly ADP-ribose polymerase (PARP) inhibitors since the latter block resolution of TOP1 cleavage complexes induced by Topo I inhibitors, thus exposing the inability of remaining pathways to repair DNA damage. Unfortunately, early clinical trials exploring combinations with standard Topo I inhibitors, such as irinotecan and topotecan, were hampered by dose-limiting myelosuppression.[85,86] Preclinical models that used a temporal separation of SG and PARPi treatment demonstrated

the synergy of the combination.[58] Subsequently, a phase 1b study in TNBC revealed that staggered dosing of SG with talazoparib was well tolerated without DLTs and resulted in preliminary clinical activity.[58] Translational studies in pre- and on-treatment biopsies confirmed target inhibition. Thus, utilization of alternate dosing schedules may permit the use of promising ADC drug combinations to enhance efficacy/overcome resistance while minimizing toxicities.

CONCLUSION

It is not an understatement that the use of ADCs is revolutionizing the treatment of solid tumors, especially HER2+ BC, delaying progression and prolonging survival in one of the most aggressive subtypes of the disease. These successes have encouraged the evaluation of ADCs across a spectrum of cancers expressing a variety of tumor antigens. Advances in linker chemistry, antibody technology, and the use of potent drugs have enabled targeting of tumors regardless of the level of antigen expression, thus extending the benefit of these agents to a broader pool of patients. However, the use of these novel ADCs is associated with unique toxicities and mandates vigilance and careful monitoring of patients and continuous education on mitigation strategies. A vital practical consideration is the appropriate sequencing of these different ADCs during the course of a patient's treatment, and there are a handful of ongoing trials addressing this issue.

Understanding the mechanisms of resistance to ADC therapy and overcoming them using combination strategies or new agents are imperative. Harnessing the power of the immune system to ADC development and generating molecules that target immune cells and other components of the TME are already underway. Probody drug conjugates, immune-stimulating antibody conjugates, engineered toxin bodies, radioligand conjugates, and so on comprise the new wave of molecules in clinical development, seeking to improve efficacy and circumvent the drawbacks with existing ADCs while maintaining an acceptable safety profile.

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