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Review

REVIEW

Antibody-Drug Conjugate-Based Therapeutics: State of the Science

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Abstract

Antibody-drug conjugates (ADCs) are complex engineered therapeutics consisting of monoclonal antibodies, directed toward tumor-associated antigens, to which highly potent cytotoxic agents are attached using chemical linkers. This targeted drug delivery strategy couples the precision of the antibody targeting moiety with the cytocidal activity of the payload, which is generally too toxic on its own to be systemically administered. In this manner, ADCs confer a means to reduce off-target toxicities in patients by limiting the exposure of normal tissues to the payload, thus broadening the potential therapeutic window compared with traditional chemotherapy. The pace of ADC development is accelerating, with the number of investigational agents in human trials having more than tripled over the past 5 years, underscoring the enthusiasm for this transformative approach to cancer treatment. Here, we review the key structural elements of ADC design (antibody, linker, and payload), highlighting critical aspects and technological advances that have affected the clinical effectiveness of this class of biopharmaceuticals. The ADC field continues to evolve, including ongoing efforts aimed at improving target selection, developing payloads with varied mechanisms of action and increased potency, designing innovative bioconjugation strategies, as well as maximizing efficacy and tolerability in patients. An overview of the current clinical trial landscape is provided, with emphasis on the clinical experience of the four ADCs to have received regulatory approval to date, as well as additional promising candidates currently in late-stage clinical development in both solid tumor and hematological malignancies.

Antibody-drug conjugates (ADCs) are a therapeutic legacy of the "magic bullet" concept espoused by Paul Ehrlich more than a century ago (1), designed as a pharmaceutical answer to the oncologists' demand for weapons to efficiently target tumor cells with high precision and specificity. Although a variety of site-selective drug delivery strategies has been explored for delivering chemotherapeutics more directly to tumors (and is beyond the scope of this article), the most important translational progress has been seen in the ADC field. ADCs comprise a monoclonal antibody that recognizes tumor-associated antigens to which a potent cytotoxic agent is conjugated via chemical linkage (2). In this manner, ADCs couple the targeting and pharmacokinetic features of the antibody moiety with the cancer-killing impact of the payload. This tumor-directed delivery system is designed to reduce off-target toxicities in patients by limiting exposure of normal tissues to the active cytotoxic component (3). The development of the first generation of ADCs was hampered by a number of pharmacological and safety considerations, resulting in a decline in popularity for this clinical approach. Leveraging the lessons learned from the cumulative experience of the early successes and failures has resulted in substantial technological advancements that now affect diverse aspects of ADC design, including antibody engineering, chemical linker optimization, and conjugation strategies (4, 5). This has prompted renewed enthusiasm for ADC-based therapy as a transformative approach for cancer treatment, as evidenced by four approved ADCs available in the United States today, and more than 60 others currently in clinical trials (6,7).

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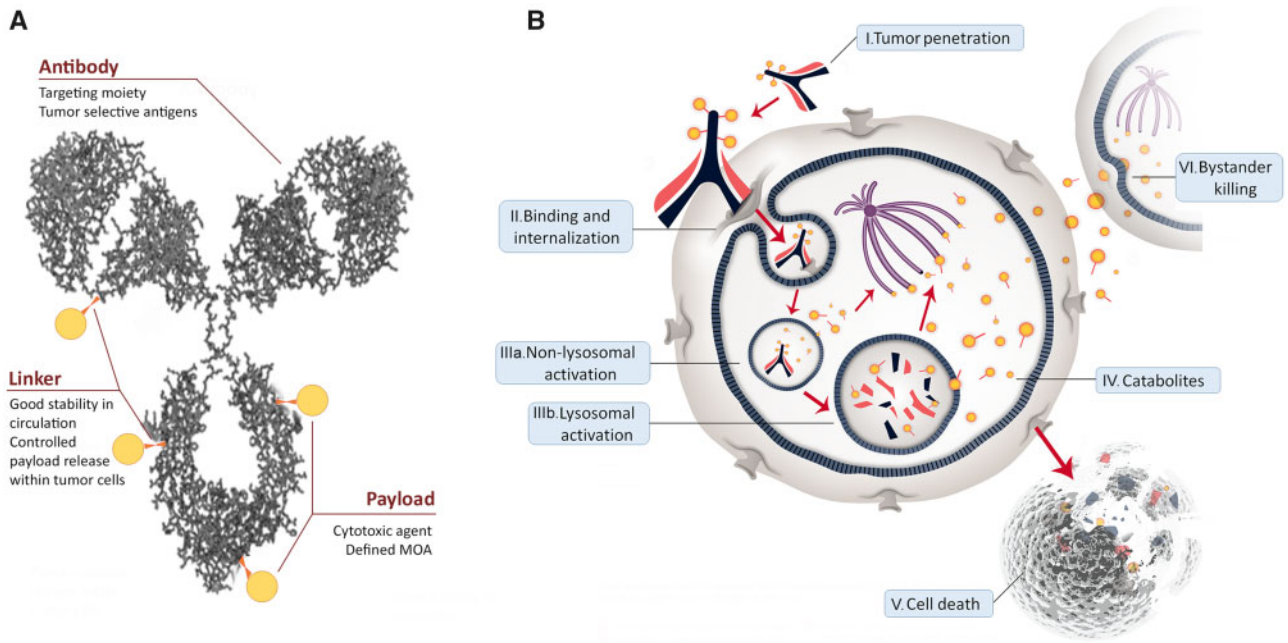

Figure 1. Antibody-drug conjugates (ADCs) structure and mechanism of action. **A)** General structure of an ADC, consisting of a humanized monoclonal antibody (**grey**), bound to a cytotoxic drug payload (**gold**) using a cleavable/noncleavable linker (**orange**). Also shown are key properties of each structural component. **B)** General ADC mechanism of action. Following distribution to tumor tissues through the vasculature (**I**), the ADC binds to its cell surface target and the ADC-receptor complex becomes internalized via antigen-mediated endocytosis (**II**). Processing of the ADC (linker cleavage and/or antibody degradation) occurs during trafficking within the endo–lysosomal pathway (**IIIa, IIIb**). This results in release of the payload in a bioactive form that is free to enter into the cytoplasm to reach its target (**IV**). The illustration depicts payloads that disrupt microtubule dynamics via binding to tubulin; DNA-targeting payloads must further diffuse from the cytoplasm into the nucleus. Intracellular accumulation of the active payload results in cell death (**V**). The cytotoxic metabolites may, if freely membrane diffusible, enter neighboring cells to effect bystander killing (**VI**). Panel image adapted from (3) .

Key Elements of ADC Design

The three structural components of an ADC—the antibody, linker, and payload (Figure 1A)—as well as the bioconjugation method, that is, the way the components are assembled, are each critical in the design of an effective therapeutic (3), because together they define the overall biophysical and physiological disposition properties of the ADC molecule itself.

Antibody

The primary function of the antibody moiety is to selectively target and deliver the cytotoxic drug payload directly to the site of tumors. Despite a plethora of tumor-associated antigens that have been proposed as candidates for immunotherapy-based strategies in cancer, the number of potential cellular targets suitable for ADC-directed intervention is far more restricted. Ideally, the target antigen should be abundantly expressed on the surface of cancer cells and demonstrate a differential distribution pattern relative to normal tissues to reduce off-target toxicities (8). The reality is that the antigenic targets of most ADCs currently in development are at best preferentially expressed in malignant cells, exhibit low expression on normal cells, and/or are absent in vital or regenerative tissues (9). The antibody should bind with sufficient affinity for selective accumulation and durable retention at the tumor site, although it has been suggested that very high affinity may actually serve to compromise delivery of antibodies throughout solid tumors (10,11). The vast majority of current ADCs have been designed to directly target tumor cells. However, an emerging area of interest involves ADC targeting of the tumor stromal compartment. Because the tumor-associated stroma of diverse cancer types can share common features, this approach may ultimately expand ADC therapeutic utility beyond strictly tumor-targeting strategies, which are limited to select groups of antigen-positive patients (12).

Antibody binding to its cellular ligand must result in internalization of the antibody–antigen complex to enable intracellular delivery of the payload. Thus, the endocytic properties of the target are a key determinant in the selection of an appropriate antigen (13). Unlike unconjugated antibody therapeutics, the ADC approach does not require the antibody itself to possess any functional activity (eg, antibody-dependent cellular cytotoxicity), although such features may confer additional therapeutic benefit. Indeed, depending on the desired activity profile, it may be appropriate to design an ADC with defined effector functions or ability to interact with the immune system, which may be achieved by selection of the appropriate IgG subclass or engineering of the Fc region (13).

Linker Chemistry

The engineered linker system that forms the connection between payload and antibody is an essential structural component of an ADC. The linker should be stable in the circulation to allow the cytotoxic moiety to remain attached to the antibody as it is distributed into tumor tissues, yet permit efficient release once internalization and trafficking in specific subcellular compartments has occurred (8). Linkers with limited stability are prone to nonspecific cleavage, which contributes to higher systemic levels of drug and a broader toxicity profile (14).

Linkers may be broadly classified into two groups: cleavable and noncleavable (15).

Cleavable linkers contain a site located between the payload and the point of antibody attachment, where cleavage can occur by a number of mechanisms including hydrolysis of acid-labile bonds, enzymatic cleavage of amide or ester bonds, or reductive cleavage of disulfide bonds (4). These processes may occur within the endosome and/or lysosome compartments or in the cytosol. Noncleavable linkers, often containing a thioether bond, require complete lysosomal proteolytic degradation of the antibody in order to release the final active metabolite (16). Increasingly sophisticated medicinal chemistry approaches are ongoing for improved linker technologies in the design of more effective and better tolerated ADCs (15).

Payload

The effector component of an ADC is the cytotoxic payload, which should meet several core requirements (17). First, it should have cytotoxic potency in the subnanomolar range to be effective. Indeed, final payload concentrations achievable within tumor cells are restricted by limitations on distribution into tumor tissues, number of target antigens on the cell surface, and efficiency of internalization and delivery. Second, the payload molecule should contain a functional group to allow for successful conjugation to the antibody moiety. Finally, the payload should be soluble and stable under physiological conditions. The first ADCs to be clinically evaluated employed approved anticancer drugs such as doxorubicin as a payload, but insufficient potency in human subjects contributed to their lack of clinical utility (18). The recognition that ADC technology provided an opportunity to revive highly potent compounds that were too toxic to be clinically useful on their own stimulated considerable research effort into developing suitable payloads for incorporation into ADCs. An additional consideration is that proteolytic enzymes are often overexpressed in tumor cells and/or the stromal compartment and can thus be exploited for the activation of ADCs in tumor therapy. Alterations in proteases can affect the efficiency of linker cleavage in ADCs and consequently the release of active payload into the cell (19). The majority of ADCs currently in the clinic use potent microtubule inhibitors, such as auristatins and maytansinoids, as their payload (20). There has been a recent shift towards evaluating DNA-interacting agents as ADC payloads (21, 22). However, despite clinically validated and promising ADCs that bear such compounds, there remains considerable interest in the development and application of cytotoxic agents with alternative mechanisms of action.

Tubulin Inhibitors

Auristatins are synthetic analogs of dolastatin-10, a natural product originally isolated from the sea hare *Dolabella auricularia*, which inhibits tubulin polymerization to cause cell cycle arrest and eventual death, with a potency 20–50 times greater than that of other tubulin-interacting agents, such as vinblastine (23). Monomethyl auristatin-E (MMAE) and monomethyl auristatin-F (MMAF) are peptide analogs of dolastatin-10 and are currently used in ADCs, including the approved CD30-targeting ADC brentuximab vedotin (24). The proteolytically cleavable linkers used in auristatin ADCs maintain stability in the circulation yet allow for easy payload release by the action of specific intracellular proteases such as cathepsin B (25). MMAE is membrane permeable, allowing it to diffuse from antigen-positive tumor cells into neighboring cells and kill them in an antigen-independent manner, an effect known as "bystander" killing. Because MMAF is more hydrophilic and membrane impermeable, it lacks bystander activity and MMAF ADCs are less effective in vivo than those with MMAE, although they are also comparatively less toxic (4).

Maytansinoids are another class of antimitotic tubulin inhibitors employed in ADC development. They derive from maytansine, a natural product isolated from the bark of African shrubs (26), which shares the same mechanism of action as the vinca alkaloids to destabilize microtubule assembly (27). Maytansine was one of the first compounds discovered to have picomolar half maximal inhibitory concentration (IC_{50}) values and potency up to 1000-fold more than that of tubulin inhibitors such as paclitaxel (17). Through a semi-synthesis strategy, a series of maytansine analogs (including DM1, used in the approved agent ado-trastuzumab mertansine, and DM4) suitable for covalent linkage with antibodies was developed (28).

DNA-Damaging Agents

Two of the four currently approved ADCs (gemtuzumab ozogamicin and inotuzumab ozogamicin) carry a payload that is derivative of calicheamicin, a potent antibiotic that binds the minor groove of DNA to induce DNA double-strand cleavage (29). Calicheamicins were among the first DNA damaging agents evaluated in ADC design, but some of the resulting ADCs were originally limited by narrow therapeutic indices and serious late toxic effects (30). These limitations have now been largely overcome with improvements in ADC technologies, especially with regard to linker chemistry, and adjustment of dosing schedules in the clinic.

In an effort to broaden the effectiveness of ADCs to tumors that are insensitive to tubulin-disrupting agents, more emphasis is being placed on DNA-interacting agents as effector molecules. Duocarmycins are another class of potent antitumor antibiotics employed as payloads for ADCs that bind in the minor groove of DNA, causing alkylation and cell death (31). The most clinically advanced of the duocarmycin ADCs is [vic]-trastuzumab duocarmine (SYD985) (32), which recently entered phase III evaluation. [vic]-Trastuzumab duocarmine consists of the same HER2 antibody found in ado-trastuzumab emtansine conjugated with a cleavable linker-duocarmycin analog vc-*seco*-DUBA (33). In contrast to the maytansinoid payload found in ado-trastuzumab emtansine, the cytotoxicity of the DUBA payload is independent of the stage of the cell cycle (34).

The development of ADCs that incorporated pyrrolobenzodiazepine dimers (PBDs), sequence-selective DNA minor-groove binding agents with exceptionally potent DNA cross-linking activity (35), generated enthusiasm in the ADC field. Despite promising early clinical results, the initial conjugates SGN-CD70A and vadastuximab talirine (SGN-CD33A), have already been discontinued due to lack of efficacy and/or safety concerns. Disappointing efficacy was recently reported from the phase II TRINITY trial of rovalpituzumab tesirine, a delta-like protein 3-targeting PBD ADC being evaluated in patients with small cell lung cancer (SCLC) (36). More recently, a new chemical class of cytotoxic DNA-interacting payloads was developed, indolinobenzodiazepine pseudodimers (termed IGNs) (37), which are structurally distinct and more potent than PBDs. IGNs may be prepared in either a mono- or diimine form, which acts via DNA alkylation or DNA crosslinking, respectively. Although both forms are highly active, it was determined that ADCs with alkylating IGNs possessed a more favorable safety

profile and high therapeutic indices in preclinical models (37,38). The first two IGN-bearing ADCs, the CD33-targeting IMGN779 and CD123-targeting IMGN632 (39, 40), have now entered phase I trials.

Bioconjugation

All four Food and Drug Administration (FDA)-approved ADCs employ random conjugation of the cytotoxic drug to either lysine or cysteine residues present in the antibody backbone, resulting in a heterogeneous mixture of conjugate molecules with different drug-antibody ratios (DARs). The DAR is an important consideration in the design of ADCs, particularly for those with lower potency payloads where a higher DAR would be expected to provide greater delivery of toxin. However, higher DARs have not consistently translated into better therapeutic activity, and may also result in increased plasma clearance and off-target cytotoxicities (41). Controlled site-specific conjugation, whereby reactive chemical handles are introduced at specific positions within the antibody moiety, is now more widely employed amongst ADCs currently in development to overcome limitations from heterogeneity and to further broaden therapeutic indices in comparison with chemotherapy (42). The expectation is that site-specific conjugation would decrease off-target toxicity and improve the pharmacokinetic properties of the antibody.

Mechanism of Action

ADCs have a clearly defined mechanism of action (Figure 1B). Following intravenous administration, ADCs distribute to the sites of tumors facilitated by the long circulating half-life characteristics of the antibody moiety within the blood stream. Upon binding its cellular target, the ADC-antigen complex becomes internalized and intracellular trafficking and processing occurs along a decreasing pH gradient through the endolysosomal pathway. The actual site of processing is largely dependent on the type of linker present (43). For ADCs with non-cleavable linkers, which require complete proteolytic degradation of the ADC, efficient lysosomal trafficking is necessary. Cleavage mechanisms vary for ADCs with cleavable linkers, and may include hydrolysis of acid-labile bonds in acidic intracellular compartments, enzymatic cleavage of peptide or ester bonds by an intracellular protease or esterase, or reductive cleavage of disulfide bonds in a reducing environment within cells. Such mechanisms may additionally operate in early or late endosomes, without a strict requirement for lysosomal trafficking (3). The free payload then diffuses to the appropriate intracellular compartment to exert its specific cytocidal activity. For antimitotic agents, this involves release into the cytoplasm and subsequent microtubule binding, whereas for DNA-targeting agents, entry into the nucleus and permeation of the nucleosome. In addition, membrane permeable metabolites that are able to diffuse from antigen-positive tumor cells into neighboring cells can elicit bystander killing activity.

Optimizing ADC Therapeutics

Effective Delivery Considerations

The biodistribution properties of an ADC are also an important factor in determining therapeutic effectiveness. First-generation ADCs that used murine monoclonal antibodies caused immunogenicity in patients, a problem that now has been largely overcome with the incorporation of humanized antibodies into ADCs (44). Despite the fact that antibodies exhibit inherently long half-lives and low clearance in the circulation, theoretical calculations suggest that only around 1% of an administered ADC dose can eventually reach its intracellular target in solid tumors (44). High affinity binding and retention in the perivascular space is one mechanism proposed to limit diffusion into tumor masses (45).

An important translational consideration relates to how much ADC the cell receives. Clinical observations for a number of ADCs, such as ado-trastuzumab emtansine and mirvetuximab soravtansine in breast and ovarian cancer patients, respectively (46, 47), support the concept that the amount of ADC internalized and metabolized by the cell, with subsequent accumulation of the cytotoxic payload and activity, is directly related to target antigen density. Therefore, personalization of ADC therapy may be optimized by selecting patients whose tumors express target antigens above a threshold level necessary for antitumor activity (48). Although this parameter alone is not sufficient to predict efficacy, because other aspects of target biology (eg, payload sensitivity, antigen internalization, and processing) also play critical roles in determining the response to a given ADC, these findings underscore the importance of incorporating patient stratification, based on antigen expression status, into the design of ADC clinical trials.

Understanding and Managing Toxicities

A fundamental element of ADC-mediated, site-directed delivery of antineoplastic agents is to limit the potential for off-target effects. However, ADCs have been associated with unexpected dose-limiting toxicities, which are predominantly unrelated to the target antigen and driven by the payload (14). For example, ocular toxicities have been reported in more than a dozen ADCs that target a variety of cellular antigens, the majority of which have limited expression in the eye (49). These involve the ocular surface and manifest as blurred vision, corneal abnormalities, or dry eye. Most of the ADCs involved contain either MMAF or DM4 as their cytotoxic moiety, suggesting a clear association between these tubulin-inhibiting payloads and the development of ocular side effects. Similar corneal-related adverse events have been seen with unconjugated tubulin-binding drugs, such as docetaxel and paclitaxel (50–52). ADC-induced ocular toxicities are usually of mild severity, reversible, and resolve with dose discontinuations or alterations (49). It has been postulated that such effects, at least in part, arise from damage to stem cells residing in the corneal limbus that then migrate centripetally, typically leading to the development of microcystic deposits (frequently observed in patients) and blurred vision (49, 53). Sloughing of these cells during the normal regenerative cycle of the ocular epithelium would also account for reversibility of symptoms and restoration of normal vision following discontinuation of ADC exposure.

In contrast to MMAF, ocular toxicities are less frequent with MMAE-containing ADCs. Instead, most MMAE conjugates share a similar toxicity profile, characterized by neutropenia and peripheral neuropathy (54). These events likely occur in response to a number of factors including plasma instability and/or as a bystander effect resulting from the release of drug products from the catabolized ADC (24). Peripheral neuropathy is a commonly observed side effect of a variety of microtubule inhibitor drugs; however, because adult neurons do not actively divide, it

appears that neuronal cell death occurs independent of mitotic blockade. Instead, peripheral neuropathy is thought to occur due to disruption of interphase microtubule function, whereby microtubule-dependent transport within the neural body is compromised (55). Thrombocytopenia has also been reported for tubulin-acting ADCs that use noncleavable linkers (eg, ado-trastuzumab emtansine); however, it is more widespread with calicheamicin-containing ADCs (14). Decreased differentiation and enhanced destruction of megakaryocytes are thought to contribute to this hematological abnormality in patients (56, 57). Another toxicity associated with calicheamicin payloads is hepatic dysfunction, including veno-occlusive disease (VOD), a life-threatening disorder that emerged as an important clinical concern for both gemtuzumab ozogamicin and inotuzumab ozogamicin (58, 59).

With respect to toxicities associated with the newer classes of DNA-interacting compounds, such as PBDs, there is less clinical evidence to date. The two most advanced ADCs of this type, rovalpituzumab tesirine and vadastuximab talirine, each exhibited hematopoietic dose-limiting toxicities in human trials (60, 61). The development of vadastuximab talirine has been discontinued due to unfavorable safety, including a higher rate of fatal infections in patients who received the ADC compared to those in the control arm in a phase III study. Vadastuximab talirine targets CD33, and myeloablation seen with this conjugate may be an on-target effect, induced through myeloid progenitor cells (14). Currently, minimal safety information is available for IGN-containing ADCs, although no DLTs have been reported though the first nine dose escalation levels in an ongoing first-in-human study of the CD33-targeting IGN ADC IMGN779 (62).

Trials comparing ADCs with approved drug regimens are most informative on tolerability and, although many ongoing studies incorporate this design, only a handful of completed trials have been reported, including for gemtuzumab ozogamicin, ado-trastuzumab emtansine, and inotuzumab ozogamicin (see below). However, from this small group of available studies, it has emerged that ADC toxicities are more limited in contrast to broader systemic effects observed in the comparator arms (14).

FDA-Approved ADCs

To date, four ADC therapeutics have received marketing approval, and it is perhaps not surprising that three of these compounds were developed for hematologic malignancies, where the target antigens tend to be more readily accessible to circulating ADCs compared with those on solid tumors (63). Further, the antigens involved (eg, CD33, CD30, CD22) are lineage-specific cell surface molecules with highly restricted distribution patterns, allowing nonhematopoietic tissue and pluripotent stem cells to avoid targeting by the ADC to provide improved specificity and tolerability (3).

Gemtuzumab Ozogamicin (Mylotarg)

Gemtuzumab ozogamicin (Mylotarg) has the distinction of being the first ADC to be granted FDA approval, and also reapproval following withdrawal from market, for the treatment of patients with acute myeloid leukemia (AML). It comprises an anti-CD33 humanized IgG4 monoclonal antibody to which calicheamicin is conjugated via an acid-labile hydrazone linker (Figure 2A) that is cleaved within the acidic lysosomal environment to release the DNA-damaging payload (64). The initial, accelerated approval was granted in 2000 for use as monotherapy for patients with CD33-positive AML who were 60 years of age or older and not considered candidates for cytotoxic chemotherapy (65). This was based on efficacy outcomes observed in three single-arm phase II studies wherein gemtuzumab ozogamicin was administered as two 9-mg/m^2 doses given 14 days apart (66). The side effect profile was characterized by a high incidence of myelosuppression and hepatic toxicities, including an increased risk of potentially fatal VOD, particularly in hematopoietic stem cell transplant (HSCT) patients (66, 67). A confirmatory phase III trial evaluating the addition of 6 mg/m^2 gemtuzumab ozogamicin to standard induction chemotherapy (daunorubicin and cytarabrine) vs chemotherapy alone in patients with newly diagnosed AML was terminated early due to a lack of clinical benefit and higher mortality rate in the ADC-containing arm (5.5% vs 1.4%) (68). These findings prompted market withdrawal of gemtuzumab ozogamicin in 2010.

Despite this setback, meta-analyses of a number of subsequent randomly assigned phase II and III studies evaluating lower and fractionated doses of gemtuzumab ozogamicin [reviewed in (69–71)] confirmed the clinical efficacy of this ADC, including in subsets of individuals with favorable and intermediate risk cytogenetics and in patients with newly diagnosed AML (72). Moreover, administration of gemtuzumab ozogamicin at lower fractionated doses (3–6 mg/m^2) was shown to improve the tolerability profile. In light of these considerations, gemtuzumab ozogamicin gained FDA approval once again in 2017 for the treatment of adults with newly diagnosed, CD33-positive AML as well as monotherapy in CD33-positive relapsed or refractory AML patients aged 2 years or older.

Brentuximab Vedotin (Adcetris)

The second ADC to reach the market was brentuximab vedotin (Adcetris), a conjugate of a chimeric IgG1 monoclonal antibody that targets CD30 with the auristatin derivative MMAE coupled by a cleavable peptide linker (73) (Figure 2B). Brentuximab vedotin received accelerated approval in the United States in 2011 for the treatment of relapsed or refractory CD30-positive Hodgkin lymphoma (HL) as well as patients with systemic anaplastic large cell lymphoma (ALCL) after prior failure of at least one multiagent chemotherapy regimen (74). Approval was based on two single-arm phase II trials conducted in patients with relapsed HL (75) or systemic ALCL (76). In the pivotal HL study (n = 102 patients) evaluating brentuximab vedotin as salvage therapy, 75% of patients achieved an objective response, including 34% with complete remissions (CRs). Subsequent analyses after a 3-year follow-up period showed that the remissions were durable (median progression-free survival [PFS] of 53.3 months) (77). Of 58 patients treated in the ALCL trial, 86% achieved an objective response, including 57% with a CR. Brentuximab vedotin received additional approval in 2015 based on the results of the phase III AETHERA trial evaluating monotherapy in HL patients with high risk of residual disease following autologous HSCT (78). In this consolidation therapy setting, brentuximab vedotin treatment resulted in a statistically significantly improved median PFS compared with placebo (42.9 vs 24.1 months). In both the clinical trial and real world settings, brentuximab vedotin therapy is generally well tolerated, with the principal toxicities of interest (neutropenia and peripheral sensory neuropathy) manageable with dose reductions and/or delays (79).

In response to the impressive single agent efficacy of brentuximab vedotin and synergism demonstrated by preclinical

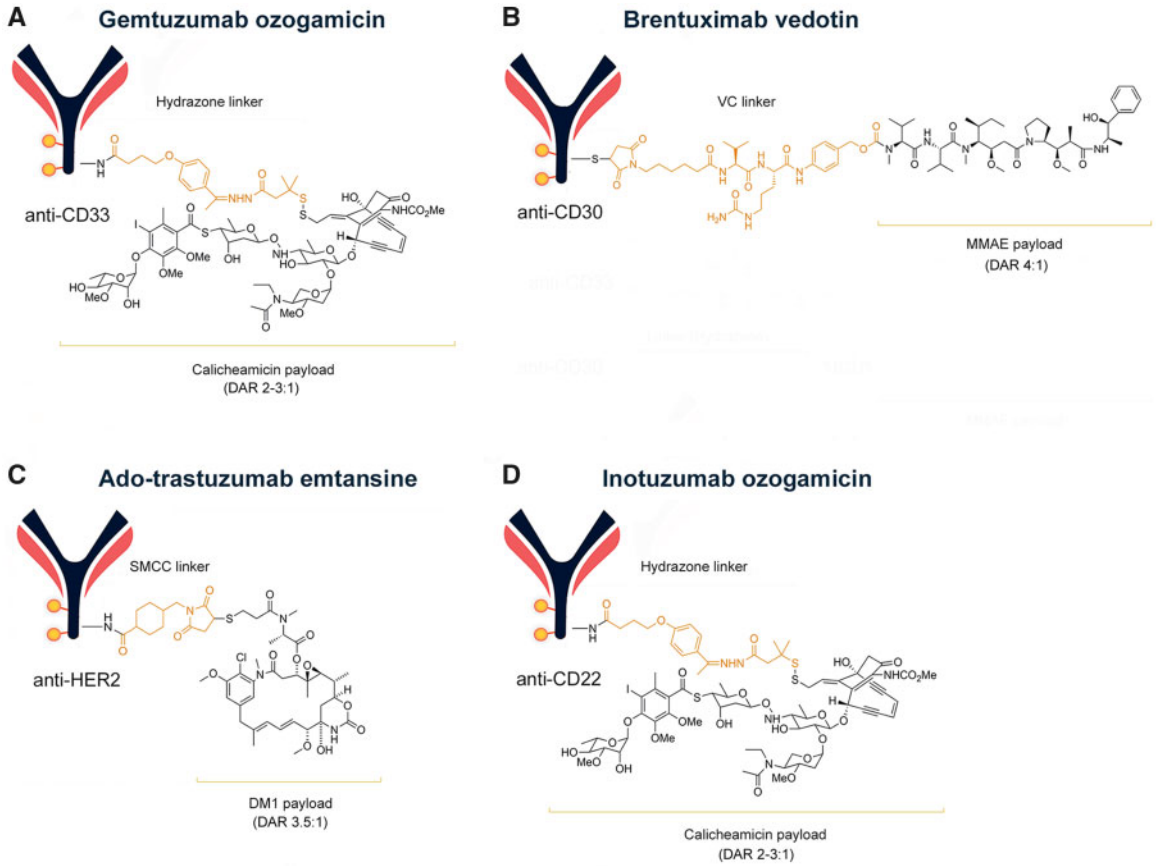

Figure 2. Structural composition of approved antibody-drug conjugates (ADCs). Linkers (**orange**) and payloads (**gold boundary**), as well as average drug-antibody ratio (DAR) values, are illustrated within the context of each ADC. Structures are shown for **A**) gemtuzumab ozogamicin; **B**) brentuximab vedotin; **C**) ado-trastuzumab emtansine; and **D**) inotuzumab ozogamicin. MMAE = monomethyl auristatin E; DM1 = maytansinoid DM1 ; SMCC = N-succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate; VC = valine-citrulline.

data (80), a number of pivotal phase II and III trials have subsequently been initiated to establish clinical benefit for brentuximab vedotin in combination with chemotherapeutic agents or therapeutic monoclonal antibodies in multiple lymphoma indications (81). Positive results were reported from one of these phase III studies, ECHELON-1, which enrolled 1334 patients with previously untreated HL (82). Brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine was associated with a 23% reduction in the risk of progression, death, or need for additional treatment compared with standard chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine). The results of this and other ongoing combinatorial studies are expected to define an expanded role for brentuximab vedotin in the treatment of classical HL and other CD30-positive hematological malignancies.

Ado-Trastuzumab Emtansine (Kadcyla)

Ado-trastuzumab emtansine (T-DM1, Kadcyla) consists of a humanized anti-HER2 monoclonal antibody (trastuzumab) backbone to which the maytansinoid DM1 is conjugated via a noncleavable linker (83) (Figure 2C). In 2013, T-DM1 gained fast-track approval by the FDA for the treatment of patients with HER2-positive metastatic breast cancer who had previously received trastuzumab and a taxane, either separately or in combination, to become the first ADC to be approved in a solid tumor indication (83). It was also the first to receive approval based on the findings of a randomly assigned trial, the phase III EMILIA study comparing T-DM1 to lapatinib plus capecitabine therapy in patients with advanced HER2-positive breast cancer who had progressed following prior trastuzumab and taxane treatment. EMILIA enrolled 991 patients, and the objective response rate (ORR; 43.6% vs 30.8%), PFS (9.6 vs 4.8 months), and overall survival (OS; 30.9 vs 25.1 months) outcomes all statistically significantly favored the T-DM1 arm over the control arm (84). Further, T-DM1 showed less toxicity than the lapatinib-capecitabine doublet, with a lower incidence of adverse events of grade 3 or worse seen with the ADC compared with those receiving standard therapy (41% vs 57%). The survival benefit was maintained through the final OS analysis, as was the safety profile, reaffirming the efficacy and tolerability of T-DM1 for patients with previously treated HER2-positive metastatic breast cancer (85).

T-DM1 was also compared to physician's choice therapy in a subsequent phase III trial (TH3RESA) conducted in heavily pretreated patients with progressive HER2-positive advanced breast cancer, who had failed two or more prior HER2-directed regimens in the advanced setting and previous taxane therapy (86). Treatment with the ADC conferred statistically significantly improved efficacy [PFS 6.2 vs 3.3 months; OS at final

analysis of 22.7 vs 15.8 months (87)] over the control arm, which was achieved along with a reduced incidence of higher-grade adverse events (86, 87). Further, potentially practice-changing results were recently reported for the KATHERINE phase III study, which enrolled 1486 patients with HER2-positive, early breast cancer who had received neoadjuvant therapy containing a taxane and trastuzumab and were found to have residual disease at the time of surgery (88). Patients were randomly assigned to receive adjuvant T-DM1 or trastuzumab, and it was found that T-DM1 reduced the risk of invasive recurrence or death by 50% compared with trastuzumab therapy. Moreover, the superiority of T-DM1 was preserved irrespective of patient characteristics (eg, menopausal or hormone receptor status), degree of residual disease, or lymph node involvement. Together, these findings have validated a role for T-DM1 in the clinical management of HER2-positive breast cancer.

Inotuzumab Ozogamicin (Besponsa)

In August 2017, inotuzumab ozogamicin (Besponsa), based on the same calicheamicin payload-linker platform present in gemtuzumab ozogamicin (Figure 2D) but coupled to a humanized anti-CD22 IgG4 monoclonal as the targeting moiety (89), became the fourth ADC to be granted FDA approval. Inotuzumab ozogamicin is indicated for use in adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia, the most common type of adult ALL. CD22 is a highly endocytic, recycling receptor (90) that is expressed on leukemic blasts in more than 90% of B-cell ALL patients, both features that contributed to its attractiveness as a target for ADC-based therapeutic intervention in this disease (91).

The approval of inotuzumab ozogamicin followed the findings of the INO-VATE ALL trial, which confirmed its superiority over standard chemotherapy (92). This phase III study recruited 326 patients with relapsed or refractory B-cell ALL who were randomly assigned 1:1 to receive inotuzumab ozogamicin or investigator's choice of one of three standard chemotherapy regimens. The most common adverse reactions occurring in both treatment groups were cytopenias, similar to what was observed in earlier phase clinical investigations (59, 93, 94). Abnormalities in liver function were more common in the inotuzumab ozogamicin group, and, as seen with gemtuzumab ozogamicin, a higher incidence of VOD was observed in the inotuzumab ozogamicin arm compared with standard chemotherapy (11% vs 1%). Most cases occurred following HSCT and two treatment-related deaths occurred due to this toxicity. Taken together, this finding suggests that the risk of VOD induced by these two ADCs is not a target-mediated effect but rather is associated with the calicheamicin payload.

With respect to efficacy, analyses were performed on the initial intent-to-treat population of 218 patients (109 patients in each arm). CR rates (including CR with incomplete platelet recovery) were statistically significantly higher in the inotuzumab ozogamicin group (80.7% vs 29.4% with standard therapy), independent of age, first remission duration, or salvage status. Further, PFS and OS were also longer with inotuzumab ozogamicin and more patients were able to proceed to post-study HSCT [reviewed in (95, 96)]. Ongoing studies are currently evaluating inotuzumab ozogamicin in combination with conventional chemotherapy in the frontline setting, thus allowing evaluation of this ADC in uncompromised patients and against disease that is more sensitive. In this regard, preliminary findings from a single arm phase II trial investigating inotuzumab ozogamicin alongside low-intensity chemotherapy in older patients (≥60 years) with newly diagnosed B-cell ALL show that the combination is well tolerated and active, with encouraging survival outcomes (97).

Current Clinical Trial Landscape

ADCs rank among the most actively pursued classes of therapeutics in oncology, with the number of agents in clinical trials having more than tripled over the past 5 years (21). Today, there are more than 60 distinct ADCs under clinical evaluation in more than 200 active or recently completed studies (Clinicaltrials.gov). Although the landscape is still dominated by ADCs with antimitotic payloads, there is a trend away from these types of conjugates to those that carry more potent cytotoxic drugs, including DNA-interacting compounds and chemotherapeutics with alternate mechanisms of action (6). Table 1 lists ADC compounds currently in at least phase II development for the treatment of both solid tumor and hematologic malignancies.

Select ADCs in Phase III Trials

Mirvetuximab Soravtansine

Mirvetuximab soravtansine (IMGN853) is an ADC consisting of a humanized anti-folate receptor alpha (FRα) monoclonal antibody coupled via a cleavable disulfide linkage to the maytansinoid DM4 (98). In contrast to a highly restricted distribution pattern in normal tissues, FRα overexpression is characteristic of a variety of epithelial tumors, including ovarian, endometrial, and non-SCLC (NSCLC) (99, 100). The dose-escalation stage of the first-in-human phase I study of mirvetuximab soravtansine enrolled 44 patients with FRα-positive solid tumors and included individuals with ovarian, endometrial, NSCLC, cervical, and renal cancers (101). Based on a collective evaluation of safety, activity, and pharmacokinetic (PK) data, dosing at 6.0 mg/kg (based on adjusted ideal body weight) once every 3 weeks was established as the recommended phase II dose. This regimen was well tolerated, with the principal treatment-related adverse effects being manageable gastrointestinal events and fatigue. Similar to what has been reported for other ADCs bearing DM4 payloads (49), reversible corneal toxicity and blurred vision have been observed with mirvetuximab soravtansine. These effects are typically low grade and are alleviated with appropriate ocular management measures.

Encouraging signals of clinical activity to emerge from the phase I experience, particularly in patients with platinum-resistant epithelial ovarian cancer (EOC) (102), identified the dose, schedule, and target population for a randomly assigned phase III study (FORWARD I). Robust support for the enrollment strategy was provided by a retrospective pooled analysis of patients across the phase I trial, which showed a confirmed ORR of 47% and median PFS of 6.7 months in a subset of patients (n = 36) who met the FORWARD I eligibility criteria (103), efficacy measures that compare favorably to the less than 20% response rates and 3- to 4-month PFS values seen with standard therapy in platinum-resistant EOC (104). FORWARD I completed enrollment in April 2018 and is comparing mirvetuximab soravtansine monotherapy to investigator's choice chemotherapy (pegylated liposomal doxorubicin, paclitaxel, or topotecan) in women with advanced, platinum-resistant EOC (105). Based on the progress of the study, mirvetuximab soravtansine was granted Fast Track designation by the FDA and top line results are expected in the first half of 2019. In addition, this ADC is

Table 1. ADCs currently under phase II or III evaluation (active trials, ClinicalTrials.gov)*

ADC	Target	Payload	Indication(s)	Sponsor
Phase III				
Depatuxizumab mafodotin (ABT-414)	EGFR	MMAF	Glioblastoma	AbbVie
Enfortumab vedotin (ASG-22CE)	Nectin-4	MMAE	Urothelial cancer	Astellas Pharma Global Development, Inc.
Mirvetuximab soravtansine (IMGN853)	Folate receptor alpha	DM4	Ovarian cancer Fallopian tube cancer Primary peritoneal cancer	ImmunoGen, Inc.
Polatuzumab vedotin	CD79b	MMAE	Diffuse large B-cell lymphoma	Hoffman-La Roche
Rovalpituzumab tesirine (Rova-T)	Delta-like protein 3	PBD	Small cell lung cancer	AbbVie
Sacituzumab govitecan (IMMU-132)	TROP-2 receptor	SN-38	Triple negative breast cancer	Immunomedics, Inc.
Trastuzumab deruxtecan (DS-8201a)	HER2	DXd	Metastatic breast cancer	Daiichi Sankyo, Inc.
[vic]-trastuzumab duocarmazine (SYD985)	HER2	DUBA	Metastatic breast cancer	Synthon Biopharmaceuticals BV
Phase II				
AGS-16C3F	ENPP3	MMAF	Renal cell carcinoma	Astellas Pharma Global Development, Inc.
Anetumab ravtansine	Mesothelin	DM4	Ovarian cancer Pancreatic cancer Non-small cell lung cancer	National Cancer Institute
BMS-986148	Mesothelin	Not disclosed	Mesothelioma Non-small cell lung cancer Ovarian cancer Pancreatic cancer Gastric cancer	Bristol-Myers Squibb
Brentuximab vedotin (ADCETRIS)	CD30	MMAE	Anaplastic large cell lymphoma Hodgkin lymphoma Non-Hodgkin lymphoma T cell lymphoma	Seattle Genetics
Depatuxizumab mafodotin (ABT-414)	EGFR	MMAF	Pediatric high grade gliomas	AbbVie
Enfortumab vedotin (ASG-22CE)	Nectin-4	MMAE	Urothelial bladder cancer	Astellas Pharma Global Development, Inc.
GSK2857916	B cell maturation antigen	MMAF	Multiple myeloma	GlaxoSmithKline
Lorvotuzumab mertansine (IMGN901)	CD56	DM1	Pediatric sarcomas	Children's Oncology Group
Naratuximab emtansine (Debio 1562)	CD37	DM1	Non-Hodgkin lymphoma	Debiopharm International SA
Rovalpituzumab tesirine (Rova-T)	Delta-like protein 3	PBD	Small cell lung cancer	Stemcentrx
SAR566658	CA6	DM4	Triple negative breast cancer	Sanofi
Telisotuzumab vedotin (ABBV-399)	c-MET	MMAE	Squamous cell lung carcinoma	Southwest Oncology Group
Trastuzumab deruxtecan (DS-8201a)	HER2	DXd	Breast cancer Colorectal cancer Gastric & GE junction cancer Non-small cell lung cancer	Daiichi Sankyo, Inc.
Trastuzumab emtansine (Kadcyla)	HER2	DM1	Metastatic colorectal cancer	Fondazione del Piemonte per l'Oncologia

*ADC = antibody-drug conjugate; PBD = pyrrolobenzodiazepine dimer; GPNMB = glycoprotein non-metastatic gene B; MMAE = monomethyl auristatin E; MMAF = monomethyl auristatin F; EGFR = epidermal growth factor receptor; TROP-2 = trophoblast antigen 2; HER2 = human epidermal growth factor receptor 2; ENPP3 = ectonucleotide phosphodiesterases-pyrophosphatase 3; CA6 = CA6 glycotope on mucin 1; c-MET = tyrosine-protein kinase Met; MMAE = monomethyl auristatin E; MMAF = monomethyl auristatin F; DM1 = maytansinoid DM1 ; DM4 = maytansinoid DM4; PBD = pyrrolobenzodiazepine dimer; DUBA = duocarmycin hydroxybenzamide azaindole; Dxd = deruxtecan

also being evaluated as part of combination-based therapeutic approaches in an ongoing phase Ib trial (FORWARD II). Although early, the maturing clinical data suggest that combinations of mirvetuximab soravtansine with carboplatin, bevacizumab, or pembrolizumab each represent well-tolerated and active regimens in patients with advanced EOC (106–108).

Sacituzumab Govitecan

Another promising ADC candidate is sacituzumab govitecan (IMMU-132), made from a humanized anti-Trop-2 monoclonal antibody conjugated with the active metabolite of the topoisomerase I inhibitor irinotecan, SN-38 (109). In contrast to most ADCs that use ultratoxic drugs as payloads and stable linkers, sacituzumab govitecan utilizes a less toxic drug with a moderately stable carbonate bond between SN-38 and the linker (110). As a result, sacituzumab govitecan requires a higher DAR (approximately 8:1) than that typically seen with other ADCs to provide maximal activity (111). Originally described as a cell surface marker on trophoblast cells almost four decades ago (112), TROP-2 was subsequently shown to be expressed in a variety of human tumors, where overexpression has been linked to oncogenesis (113).

Table 2. Recently discontinued late-stage ADCs*

ADC	Target/payload	Indication	Reason for discontinuation	Phase	Year
Vadastuximab talirine (SGN-CD33A)	CD33/PBD	AML	Safety: higher rates of deaths, infections	III	2017
Glembatumumab vedotin (CDX-011)	GPNMB/MMAE	TNBC	Lack of efficacy	II	2018
Denintuzumab mafodotin (SGN-CD19A)	CD19/MMAF	DLBCL	Not disclosed	II	2018

*ADC = antibody-drug conjugate; AML = acute myelogenous leukemia; DLBCL = diffuse large B-cell lymphoma; TNBC = triple negative breast cancer.

Sacituzumab govitecan has been evaluated in a series of phase II clinical trials in multiple solid tumor types including triple-negative breast cancer (TNBC), NSCLC, SCLC, and urothelial cancer (114). Promising signals of antitumor activity were seen in patients with TNBC. In a phase II study that enrolled 69 heavily pretreated women with metastatic TNBC (median of five prior therapies), 21 patients (30%) achieved a confirmed objective response, with a median duration of 8.9 months, and an acceptable safety profile with nausea, neutropenia, and diarrhea being the most frequently observed adverse events (115). Sacituzumab govitecan was awarded Breakthrough Therapy designation by the FDA for metastatic TNBC in early 2016. Accordingly, enrollment is ongoing into the phase III ASCENT trial, comparing sacituzumab govitecan to physician choice of one of four single-agent chemotherapy regimens (capecitabine, eribulin, vinorelbine, or gemcitabine), with planned recruitment of 328 patients with metastatic TNBC that is either refractory or relapsing after at least two prior chemotherapies (including a taxane) (116).

Trastuzumab Deruxtecan

Trastuzumab deruxtecan (DS-8201a) is a novel ADC compound that also employs the anti-HER2 antibody trastuzumab, connected via an enzyme-cleavable linker to deruxtecan, a cytotoxic payload composed of a camptothecin analogue that inhibits topoisomerase I (117). Of note, deruxtecan has been shown to be comparatively more potent than SN-38 in mechanistic studies (118). In addition to an alternate payload mechanism of action, trastuzumab deruxtecan may be further differentiated from ado-trastuzumab emtansine by having a higher DAR (8:1 vs 3.5:1) as well as bystander killing activity potential (119). In preclinical models, trastuzumab deruxtecan demonstrated robust antitumor activity in patient-derived breast tumor xenografts with both high and low HER2 expression, including those that were insensitive to ado-trastuzumab emtansine (117).

Trastuzumab deruxtecan is being investigated as part of an ongoing, two-part phase I trial; the dose-escalation stage reported that the ADC had an acceptable safety profile and showed activity in patients with low HER2-expressing tumors (120). Updated results from the expansion phase of this study were presented at the ASCO Annual Meeting in 2018 (121). Patients on study had high ORRs, including rates of 54.5% and 50% seen in 111 patients with HER2-positive breast cancer and 34 HER2-low breast cancer patients, respectively. In addition, the median PFS was not reached in the HER2-positive group and was 12.9 months in the HER2-low group. Most treatment-related adverse events were gastrointestinal or hematologic in nature, although it should be noted that 10 patients (4%) died during the study, including two with interstitial lung disease. Trastuzumab deruxtecan has been granted both Breakthrough Therapy and Fast Track designation by the FDA, and two large-scale phase III studies evaluating trastuzumab deruxtecan as an option for salvage-line treatment of patients with HER2-positive, metastatic breast cancer were initiated in the second half of 2018. The first is comparing trastuzumab deruxtecan to investigator's choice standard of care (trastuzumab plus capecitabine or lapatinib plus capecitabine) in subjects previously treated with HER2 therapy. The second study is a head-to-head comparison of the safety and efficacy of trastuzumab deruxtecan with ado-trastuzumab emtansine in patients previously treated with trastuzumab and a taxane.

Recently Discontinued Late-Stage ADCs

The growing number of ADC candidates is a consequence of robust improvements in the design and application of this therapeutic class; however, not all have successfully transitioned from late-stage studies to approval as new treatments (Table 2). One example is glembatumumab vedotin (CDX-011), an MMAE-bearing ADC that targets glycoprotein non-metastatic gene B (122), a transmembrane glycoprotein overexpressed in a variety of cancers (123). In the EMERGE phase II trial comparing CDX-011 to investigators choice chemotherapy in heavily pretreated TNBC patients, favorable tolerability and an OS benefit in the subgroup of individuals whose tumors overexpressed glycoprotein non-metastatic gene B was reported (124). However, a pivotal randomly assigned phase II study (METRIC) in patients with metastatic TNBC who received either CDX-011 or capecitabine failed to meet its primary endpoint (median PFS: 2.9 vs 2.8 months for CDX-011 and capecitabine, respectively), and no statistically significant advantages were seen in key secondary endpoints, including ORR, duration of response, or OS (125). The clinical development of CDX-011 across all indications was halted in response to these results during 2018.

Another example is provided by denintuzumab mafodotin (SGN-CD19A), a CD19-targeting ADC with a MMAF payload developed for use in B-cell non-HL (126). Preliminary findings reported from the first-in-human study in relapsed/refractory non-HL patients revealed encouraging signals of clinical activity as well as a manageable safety profile (127). Two separate phase II combination trials of denintuzumab mafodotin with alternate standard chemotherapy regimens were subsequently initiated in patients with B-cell lymphoma; however, both studies were terminated by the sponsor in 2018 and it remains unclear if the reasons were related to futility or safety concerns.

Conclusion

The ADC field is undergoing a period of transition, with older approaches to conjugate design giving way to newer strategies for improving therapeutic windows and clinical outcomes. A better understanding of all aspects of ADC composition and lessons learned from two decades of clinical experience are now routinely applied in ADC development, including the incorporation of fully humanized monoclonal antibodies to overcome

immunogenicity, utilization of potently toxic payloads with diverse mechanisms of action, and optimization of linker and conjugation methods to increase plasma stability and maximize drug delivery directly to tumors. Biologists, chemists, and engineers continue to investigate novel targets and innovative technological advancements to more broadly apply the platform, as well as assess strategies for further optimization of these high-precision therapeutics. In parallel, clinical scientists and oncologists are evaluating rationally designed combinations of ADCs alongside chemotherapeutics, small molecule inhibitors, and immunotherapy as other potential avenues of therapeutic intervention across a broad range of tumor types. Recent clinical developments in this field offer exciting possibilities for the future use of this class of agents as targeted therapy for patients with a variety of solid tumor and hematological malignancies.

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