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Antibody–Drug Conjugates for Cancer Treatment

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Abstract

The concept of exploiting the specific binding properties of monoclonal antibodies as a mechanism for selective delivery of cytotoxic agents to tumor cells is an attractive solution to the challenge of increasing the therapeutic index of cell-killing agents for treating cancer. All three parts of an antibody–drug conjugate (ADC)—the antibody, the cytotoxic payload, and the linker chemistry that joins them together—as well as the biologic properties of the cell-surface target antigen are important in designing an effective anticancer agent. The approval of brentuximab vedotin in 2011 for treating relapsed Hodgkin's lymphoma and systemic anaplastic large cell lymphoma, and the approval of ado-trastuzumab emtansine in 2013 for treating HER2-positive metastatic breast cancer, have sparked vigorous research in the field, with >65 ADCs currently in clinical evaluation. This review highlights the ADCs that are approved for marketing, in pivotal clinical trials, or in at least phase II clinical development for treating both hematologic malignancies and solid tumors.

INTRODUCTION

PBD: pyrrolobenzodiazepine

Ever since cancer patients first were treated with cytotoxic chemicals with the goal of eradicating tumor tissue (1), oncologists have looked for ways to increase the antitumor efficacy of cytotoxic drug therapy without substantially increasing overall toxicity to the patient. Combining different anticancer drugs with different mechanisms of action and non-overlapping toxicity profiles has improved antitumor activity (2), but systemic toxicity limits what can be achieved, and long-term remissions are rarely observed. Another approach that has been tried with the goal of increasing tumor cell kill is to use cytotoxic agents having potency in the picomolar (or lower) range, such as the tubulin-acting agents maytansine and dolastatin 10, and DNA-alkylating agents like adozelesin and pyrrolobenzodiazepine (PBD) dimers (SJG-136) (3). Unfortunately, clinical evaluation of such compounds demonstrated that they lacked a sufficient therapeutic window to be useful in cancer treatment (3–5).

The invention of monoclonal antibodies (6) offered the possibility of exploiting their specific binding properties as a mechanism for the selective delivery of cytotoxic agents to cancer cells via chemical conjugation of cytotoxic effectors to create antibody–drug conjugates (ADCs), as represented in **Figure 1*a***. This simple concept is a particularly attractive solution to the challenge of increasing the therapeutic index of a cytotoxic chemical agent (3, 7). Besides selective delivery to antigen-positive cancer cells, conjugation of the cytotoxic agent to the large, hydrophilic antibody protein is expected to restrict penetration of the cytotoxic compound across cellular membranes of antigen-negative normal cells. In addition, the small-molecular-weight cytotoxic agent acquires the *in vivo* distribution properties of an antibody, which has the potential to reduce systemic toxicity. Although this "simple concept" proved challenging to translate into clinical practice, the approvals by the US Food and Drug Administration (FDA) of two ADCs, brentuximab vedotin (BV) in 2011 (8) and ado-trastuzumab emtansine (T-DM1) in 2013 (9), spawned vigorous research in the field. More than 65 ADCs are currently under clinical evaluation (10).

CHALLENGES IN DEVELOPING EFFECTIVE ANTIBODY–DRUG CONJUGATES

The early work in the field of ADCs sought to increase the specificity of existing chemotherapeutic drugs, such as the *vinca* alkaloids (11) and doxorubicin (12). However, the results of clinical trials of these conjugates were disappointing (e.g., 13, 14), and by the early 1990s there was a greater appreciation of the challenges that the in vivo biodistribution properties of antibodies imposed on ADC design. These include the slower rate of penetration of antibodies from blood plasma into tissues relative to that of small molecules, and the limit on the amount of antibody retained in tumor tissue imposed by the number of target cell-surface antigens (15, 16). Clinical dosimetry studies with radiolabeled antibodies in patients demonstrated that only ~0.01% of the injected dose of antibody per gram of tumor tissue could be localized to a solid tumor mass 24 h after infusion (approximately the peak delivered concentration), irrespective of tumor type or antibody target (17). Thus, it was reasoned that conventional chemotherapeutic drugs were not potent enough to serve as payloads for ADCs, and this notion has guided much of the subsequent research in the field (5, 7, 10).

KEY ELEMENTS IN THE DESIGN OF AN ANTIBODY–DRUG CONJUGATE

All three parts of an ADC—the antibody, the cytotoxic payload, and the linker chemistry that joins them together—are important in designing an effective therapeutic. However, the selection of the

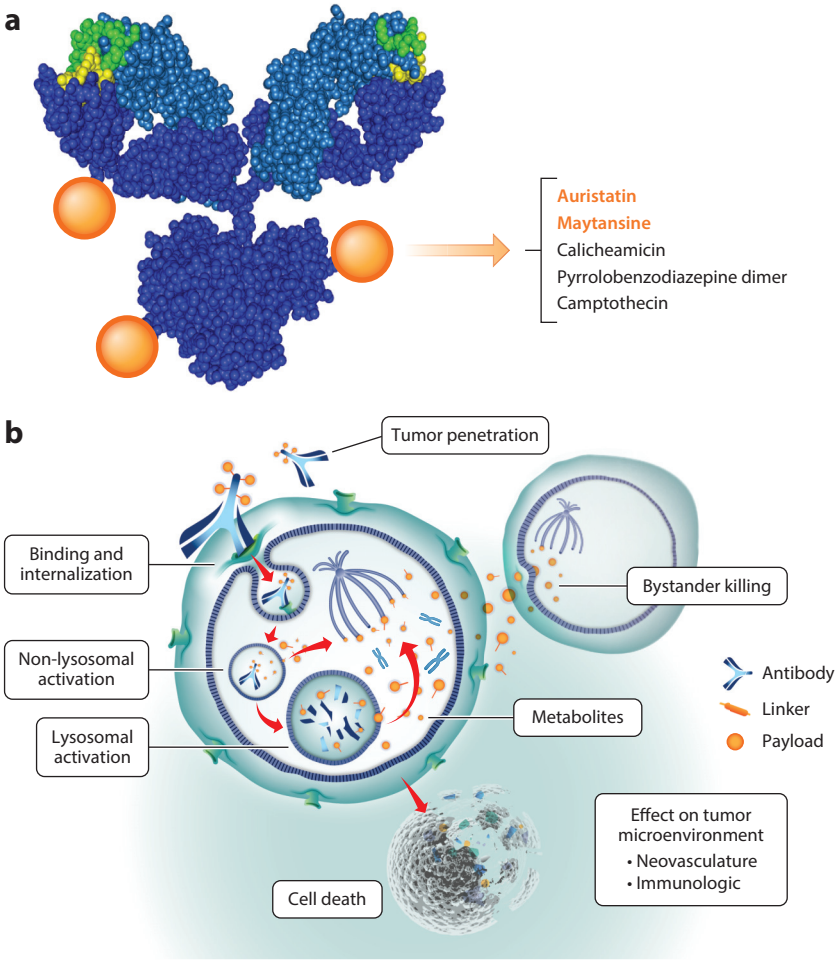

Figure 1

(*a*) Structure of an antibody–drug conjugate (ADC). A space-filling atomic model of an IgG1 molecule is shown conjugated to three cytotoxic payloads (*orange spheres*). The heavy chains and light chains are shown as dark blue and light blue spheres, respectively. The complementarity-determining regions are shown in yellow for the heavy chain and green for the light chain. The five payload classes among the 19 ADCs listed in **Tables 1** and **2** are listed in the figure. Payloads in orange font are tubulin-acting agents; those in black font disrupt DNA. (*b*) Mechanism of action of ADCs armed with payloads (auristatin, maytansine) that disrupt microtubule dynamics via binding to tubulin in the cytoplasm of a cell (28, 29, 31). The ADC must enter tumor tissue from the vasculature, bind to its cell surface target, and then be internalized via the endosome–lysosome pathway, where the linker is cleaved and/or the antibody is degraded to release the payload, which ultimately diffuses into the cytoplasm to reach its target (tubulin). Other widely used payloads, such as calicheamicin and pyrrolobenzodiazepine dimers, which target DNA, must further diffuse from the cytoplasm into the nucleus (not represented in the figure). The cytotoxic metabolites may, if freely membrane diffusible, enter neighboring cells to effect bystander killing (31, 33). Charged metabolites are generally ineffective at bystander killing (34, 35). Cytotoxic metabolites may also have effects on cells of the tumor microenvironment [e.g., immune cells (86–88)] or neovasculature (101) as a component of their antitumor activity.

target antigen to which the ADC binds is, perhaps, the most critical factor in developing an effective molecule. The number of target molecules expressed on the tumor cell surface, their differential expression on tumor versus normal cells, the rate of internalization and route of intracellular trafficking, and whether the target is amenable to selecting an antibody with intrinsic biologic activity [e.g., HER2 (18)] all influence ADC design and ADC activity (**Figure 1*b***) (5, 7, 10). Besides specificity for its target, an antibody should bind with sufficient affinity for selective accumulation and durable retention at the tumor site. Few published data address the optimal binding affinity for an ADC; most ADCs have K_D values in the range of 0.1–1.0 nM. Some studies with antibodies suggest that very high affinity may compromise delivery of antibodies throughout solid tumors, the so-called binding-site barrier (15, 19).

The payload should have cytotoxic potency in the picomolar range (3, 7, 10) so that it can kill tumor cells at the intracellular concentrations achievable following distribution of the ADC into tumor tissue. The cytotoxic compounds used in most of the >65 ADCs in current clinical development are either derivatives of dolastatin 10 (auristatins) (20) or maytansine (21), which are potent antimitotic microtubule-disrupting agents, or derivatives of one of several highly cytotoxic DNA-damaging agents: calicheamicin, which causes DNA double-strand breaks (22); duocarmycin, which alkylates DNA (23); PBD dimers, which crosslink DNA (24); and indolinobenzodiazepine pseudodimers, which alkylate DNA (25).

The third vital component of an ADC is the linker that forms the connection between payload and antibody. The linker should be sufficiently stable in circulation to take advantage of the pharmacokinetic properties of the antibody moiety (i.e., long half-life) and to allow the payload to remain attached to the antibody as it distributes into tissues, yet should allow for efficient release of an active cell-killing agent once the ADC is taken up into cancer cells (3, 7). The linkers used in early-stage ADCs had only limited stability in vivo, with rapid release of payload contributing to their poor therapeutic index and resulting in side-effect profiles little different from those of standard cytotoxic chemotherapy (10, 26). Interest in ADCs was reinvigorated upon application of new linker chemistries toward the conjugation of potent tubulin-acting agents to antibodies (3, 7, 26).

Linkers fall into two general classes: those that are noncleavable during cellular processing and those that are cleavable once the ADC has reached the tumor (3, 7, 27). With noncleavable linkers, the final active metabolite released within the cell includes the payload and all elements of the linker still attached to an amino acid residue of the antibody, typically a lysine or a cysteine residue, following complete proteolytic degradation of the ADC within the lysosome (28, 29). Efficient lysosomal trafficking becomes a key selection criterion for the antibody and its target for ADCs of this design (30). Cleavable linkers are those whose structure includes a site of cleavage between the payload and the amino acid attachment site on the antibody. Cleavage mechanisms include hydrolysis of acid-labile bonds in acidic intracellular compartments, enzymatic cleavage of amide or ester bonds by an intracellular protease or esterase, and reductive cleavage of disulfide bonds by the reducing environment inside cells (3, 7, 28). These mechanisms may operate in early or late endosomes within cells, without a strict requirement for lysosomal trafficking. Varying the linker–payload chemistry to alter the release mechanisms and the chemical properties of the final active metabolite is part of the design space for developing an effective, well-tolerated ADC (3, 31, 32). For example, increasing the hydrophobicity of the cytotoxic metabolite may increase the rate of transfer across cellular membranes for more efficient exit of the released payload moiety from lysosomes and may facilitate bystander killing (**Figure 1*b***) (33). Alternatively, increasing the hydrophilic nature of the cytotoxic metabolite, for example via charged groups, may decrease the rate of transmembrane transfer, thereby increasing cellular retention while minimizing bystander effects (34, 35).

Most ADCs in current clinical development were made by conjugation to endogenous lysine or cysteine residues of the antibody, carefully controlling the average degree of modification to yield an average drug-to-antibody ratio (DAR) in the range of 3.5–4.0. This ratio was selected on the basis of (*a*) minimizing the amount of nonconjugated antibody and (*b*) avoiding species in the mixture with very high DAR, which may be problematic in manufacturing and formulation because of higher hydrophobicity and lower solubility (7, 9, 36, 37), and may result in poor pharmacokinetic properties (36, 37). Recently, a variety of genetic, chemical, and enzymatic methods have been developed for site-specific conjugation, which can enable DARs of 2 (or 4) while avoiding under- or overmodification of the antibody. This is especially useful for highly potent and/or particularly hydrophobic payloads, for which DARs >2 are undesirable (e.g., 24). Several ADCs (~10 in current clinical evaluation) incorporate these approaches (10, 38, 39).

CRi: complete response with incomplete hematologic recovery

CLINICAL DEVELOPMENT OF ANTIBODY–DRUG CONJUGATES IN HEMATOLOGIC MALIGNANCIES

The first ADC therapeutics to reach the market were developed for hematologic malignancies, where target antigens are usually well-characterized, lineage-specific cell-surface molecules that are highly restricted in their distribution. Hematologic malignancies are also thought to be more accessible to antibodies than are solid tumors (40). **Table 1** lists the ADC compounds that are approved or currently in at least phase II development for treatment of hematologic malignancies. The clinical results for the four compounds that are either approved for marketing or in phase III clinical trials are further discussed in this section.

Gemtuzumab Ozogamicin

The first ADC to receive marketing approval from the FDA was gemtuzumab ozogamicin (GO; Mylotarg®), a calicheamicin ADC that targets the myeloid antigen CD33 (41). On the basis of a single-arm phase II study, it received accelerated approval in 2000 as a single agent (dosing 9 mg/m^2 on days 1 and 15) for treating patients ≥60 years old with acute myeloid leukemia (AML) in first relapse (42). The complete response (CR) rate, including a subset of patients having incomplete platelet recovery (CRi), was 26% (41, 42). Side effects included delayed hematopoietic recovery and an increased risk of hepatic veno-occlusive disease, especially in hematopoietic stem cell transplant patients (41, 43). The ADC was withdrawn from the US and European markets (although it is still marketed in Japan) following an unsuccessful confirmatory phase III trial that compared the effect of adding a single dose of 6 mg/m^2 to standard remission induction therapy in patients <60 years old (44). However, meta-analysis of several other randomized studies, adding a single 3 mg/m^2 dose or fractionated doses (3 mg/m^2 on days 1, 4 and 7) of GO to various remission-induction regimens, has suggested improved overall survival (OS) in AML patients whose disease has favorable and intermediate cytogenetic characteristics (45). Dose fractionation appears to reduce the incidence of hepatic veno-occlusive disease. An application for marketing approval of GO was resubmitted to the FDA in early 2017 on the basis of this analysis.

Brentuximab Vedotin

The second ADC to receive marketing approval (in 2011) was brentuximab vedotin (BV; Adcetris®), made by conjugation of mono methyl auristatin E to an anti-CD30 antibody (8, 20). Reed-Sternberg cells of Hodgkin's lymphoma (HL), as well as malignant cells of anaplastic large cell lymphoma (ALCL), express high levels of CD30 (8). BV (1.8 mg/kg once every 3 weeks) received accelerated FDA approval based on phase II trials in patients with relapsed HL (46) or

Table 1 Antibody–drug conjugates (ADCs) marketed, in pivotal clinical trials, or in phase II development for treating hematologic malignancies

ADC	Target antigen	Linker cytotoxic compound	Antibody[a]	Indication[d]	Development status[c]	References
Gemtuzumab ozogamicin	CD33	Cleavable hydrazone N-acetyl-γ calicheamicin	Engineered huIgG4	AML	FDA accelerated approval 5/2000. Withdrawn 8/2011 (marketed in Japan) Re-application under FDA review 2017	45
Brentuximab vedotin	CD30	Cleavable dipeptide (vc) MMAE (auristatin)	chIgG1	HL and systemic ALCL	FDA accelerated approval 8/2011. Full approval in 8/2015 Multiple phase I to IV trials	8
Inotuzumab ozogamicin	CD22	Cleavable hydrazone N-acetyl-γ calicheamicin	Engineered huIgG4	B-ALL, other B cell malignancies	FDA full approval 8/2017 Multiple phase I to III trials	52
Vadastuximab talirine	CD33	Cleavable dipeptide (va) PBD dimer	huIgG1 engineered for site-specific linking	AML	Phase III in combination with HMAs—trial discontinued 6/2017 (older patients, newly diagnosed)	24
Polatuzumab vedotin	CD79b	Cleavable dipeptide (vc) MMAE (auristatin)	huIgG1	DLBCL and FL	Phase II in combination with rituximab, R-ben Multiple phase I combinations	91, NCT01691898, NCT02257567, NCT02611323, NCT02729896
Denintuzumab mafodotin	CD19	Noncleavable (mc) MMAF (auristatin)	huIgG1	DLBCL and FL	Phase II in combination with R-ICE, R-CHOP, or R-CHP	75, NCT02592876, NCT02855359
Naratuximab emtansine	CD37	Noncleavable (SMCC) DM1 (maytansinoid)	huIgG1[b] (selected to induce apoptosis)	DLBCL and FL	Phase II combination with rituximab	92, NCT02564744
Coltuximab ravtansine	CD19	Cleavable disulfide (SPDB) DM4 (maytansinoid)	huIgG1[b]	DLBCL	Phase II as single agent and in combination with rituximab	74
Indatuximab ravtansine	CD138	Cleavable disulfide (SPDB) DM4 (maytansinoid)	chIgG4	Multiple myeloma	Phase II in combination with lenalidomide or pomalidomide	93, NCT01638936

[a]Antibody abbreviations: huIgG, humanized IgG; chIgG, chimeric IgG.

[b]Although these antibodies were humanized, changes in naming methodology at International Nonproprietary Names resulted in the "ximab" suffix of chimeric antibodies (100).

[c]Trials active and/or open for enrollment on or before March 31, 2017 (**http://www.clinicaltrials.gov**).

[d]Abbreviations: ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; B-ALL, B cell acute lymphoblastic leukemia; DLBCL, diffuse large cell lymphoma; FDA, United States Food and Drug Administration; FL, follicular lymphoma; HL, Hodgkin's lymphoma; HMA, hypomethylating agent; MMAE/F, mono methyl auristatin E, mono methyl auristatin F; PBD, pyrrolobenzodiazepine; R-ICE, rituximab/ifosfamide/carboplatin/etoposide; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; R-CHP, rituximab/cyclophosphamide/doxorubicin/prednisone; R-ben, rituximab/bendamustine; SMCC, succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate; SPDB, *N*-succinimidyl-4-(2-pyridyldithio)butyrate; vc, valine-citrulline; va, valine-alanine; DM1, $N^{2'}$-deacetyl-$N^{2'}$-(3-mercapto-1-oxopropyl)-maytansine; DM4, $N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine.

systemic ALCL (47), which reported overall response rates (ORRs) of 75% (34% CR) and 86% (57% CR), respectively. The principal dose-limiting toxicity (DLT) was neutropenia, and the main toxicity upon repeated administration was neuropathy (46–48). In 2015, BV received full approval from the FDA based on the results of the phase III AETHERA trial that compared giving BV once every three weeks to giving placebo plus best supportive care in HL patients with high risk of residual disease following autologous stem cell transplant (49). The median PFS was 43 months for patients who received BV versus 24 months for the comparator arm ($p = 0.001$). A recently reported randomized phase III trial (ALCANZA) provides compelling evidence in favor of BV for treating cutaneous T cell lymphoma, with progression-free survival (PFS) of 16.7 months versus 3.5 months for investigator's choice of single-agent chemotherapy ($p < 0.001$) (50). Several other phase III trials are in progress to confirm clinical benefit of BV in randomized studies in combination with approved chemotherapeutic agents (NCT01712490, NCT01777152) (8), as well as in combination with immune checkpoint inhibitors (NCT02684292, NCT03138499).

DLT: dose-limiting toxicity

Inotuzumab Ozogamicin

A second ADC using the calicheamicin payload, inotuzumab ozogamicin (InO), targets the B cell antigen CD22. InO has completed a phase III trial (INO-VATE ALL) in relapsed or refractory acute lymphoblastic leukemia (ALL) (51, 52). Treatment at 1.8 mg/m^2 total dose of ADC each cycle (0.8 mg/m^2 on day 1, and 0.5 mg/m^2 on days 8 and 15) produced a rate of CR, including CRi, of 80.7% versus 29.4% for the chemotherapy comparator arm ($p < 0.001$) (52). As with GO (gemtuzumab ozogamicin), the most concerning nonhematologic toxicities in patients treated with InO were adverse events in liver, especially veno-occlusive disease (52). This finding suggests that this risk is not target-mediated but rather is associated with the calicheamicin payload, an inference supported by pre-clinical studies (53). The results of the INO-VATE trial led to the recent marketing approval of InO by regulators in the United States and Europe.

Vadastuximab Talirine (SGN-CD33A)

The most recent ADC to enter into pivotal phase III development is vadastuximab talirine, also known as SGN-CD33A, an anti-CD33 antibody engineered for site-specific conjugation to a PBD dimer (~2 payloads per antibody) (24). A phase I study determined that 40 μg/kg given once every three weeks was the recommended monotherapy dose and identified a DLT of myelosuppression with delayed recovery (39). Expanded trials have shown that transplant-associated hepatic veno-occlusive disease is also a concern with this ADC (54). Patients treated at the 40 μg/kg dose ($N = 21$) in the phase I study showed encouraging antileukemic activity (33% CR including CRi). The phase I study included a cohort ($N = 53$) designed to evaluate a single low dose of SGN-CD33A (10 μg/kg every four weeks) in combination with hypomethylating agents in previously untreated AML patients who had declined intensive chemotherapy (55). Adverse events were related primarily to myelosuppression. Nonhematologic toxicities included peripheral edema (40%), an adverse event noted previously with the PBD SJG-136 (56). The rate of CR plus CRi (73%) compares favorably to historical experience with hypomethylating agents alone (17–28%), leading to the initiation of a phase III trial (55). Unfortunately, the trial (CASCADE) was recently discontinued owing to an increased rate of fatal infections in the SGN-CD33A plus hypomethylating agent arm compared with the hypomethylating agent alone arm (Seattle Genetics press release, June 19, 2017).

CLINICAL DEVELOPMENT OF ANTIBODY–DRUG CONJUGATES FOR TREATING SOLID TUMORS

RP2D: recommended phase II dose

Despite the notion that solid tumors are less amenable than "liquid" (hematologic) tumors to antibody-targeting approaches, the first ADC to receive full FDA approval in any indication based on a randomized phase III study was ado-trastuzumab emtansine (T-DM1; Kadcyla®). Its approval in 2013 was based on OS data for patients with HER2-positive metastatic breast cancer (mBC) previously treated with a taxane and trastuzumab (57). **Table 2** lists T-DM1 and the nine other ADCs that have advanced to at least phase II development in various solid tumor indications. Clinical results for T-DM1 and the three others that are in, or that have completed, a pivotal clinical trial and whose single-agent activity is comparable to that of T-DM1 [≥40% confirmed ORR (57)] are detailed below.

Ado-Trastuzumab Emtansine (T-DM1)

Ado-trastuzumab emtansine, or T-DM1, was made by conjugation of the maytansinoid DM1 to the anti-HER2 antibody trastuzumab via a noncleavable linker (9). Phase I and phase II clinical trials in heavily pretreated patients with HER2-positive mBC established a recommended phase II dose (RP2D)/schedule of 3.6 mg/kg given once every 21 days (58–60). The principal DLT was reversible thrombocytopenia, with reversible low-grade increases in hepatic transaminases also observed (58). An early signal of antitumor activity, five confirmed partial responses (PRs) from 24 enrolled patients (ORR 20.8%) in the phase I study (58), was confirmed in two phase II trials [ORRs 25.9% (59) and 34.5% (60) in 112 and 110 subjects, respectively]. Patients were enrolled in these phase II studies on the basis of having had prior treatment with trastuzumab, from which it was inferred that they were HER2-positive. The HER2 status of their disease was retrospectively reassessed by central laboratory testing on archival tumor, and most of the responders (~86%) were confirmed as HER2-positive. For example, in the study of Burris and colleagues (59), the ORR for the entire population ($N = 112$) was 25.9%, but it was 33.8% in patients confirmed as having HER2-overexpressing mBC ($N = 74$ of 95 patients with available specimens) and only 4.8% in patients ($N = 21/95$) whose disease was reassessed as HER2-normal ("negative" by the test). These observations indicate that selecting only those patients whose cancers express the target antigen above a certain threshold level necessary for antitumor activity is an important factor in the successful development of ADC therapeutics for solid tumors (61).

Approval of T-DM1 was based on a pivotal phase III trial (EMILIA) in patients with HER2-positive mBC who had progressed following treatment with a taxane plus trastuzumab and who were randomized to receive T-DM1 or the approved second-line treatment of lapatinib (a tyrosine kinase inhibitor that targets HER2) plus capecitabine (57). The ORR (43.6% versus 30.8%; $p < 0.001$), PFS (9.6 months versus 6.4 months; $p < 0.001$), and OS (30.6 months versus 25.1 months; $p < 0.001$) all significantly favored the T-DM1 arm over the comparator (57). Furthermore, the incidence of adverse events of grade ≥3 was lower in the T-DM1 arm (40.8%, with thrombocytopenia and transaminitis most common, consistent with the phase I/II experience) than in the comparator arm (57.0%, with diarrhea, hand-foot syndrome, and vomiting most common). The rate of cardiac adverse events, a concern with HER2-targeted therapy, was low (<2%) in both arms.

A phase III trial (TH3RESA) in heavily pretreated patients with progressive HER2-positive mBC, who had received at least two HER2-directed regimens in the advanced setting (median of four prior regimens for advanced disease) and had received previous taxane therapy in any setting, also favored T-DM1 over the comparator arm (physician's choice) with improved PFS (6.2 months versus 3.3 months; $p < 0.001$) (62) and median OS (22.7 months versus 15.8 months

Table 2 Antibody–drug conjugates (ADCs) marketed, in pivotal clinical trials, or in phase II development for treating solid tumors

ADC	Target antigen[d]	Linker cytotoxic compound	Antibody[a]	Tumor type(s)[d]	Development status[c]	References
Ado-trastuzumab emtansine (T-DM1)	HER2 (ErbB2)	Non-cleavable (SMCC) DM1 (maytansinoid)	huIgG1 (trastuzumab)	HER2-positive mBC	FDA full approval 2/2013 Phase I to IV trials in HER2+ indications	9
Anetumab ravtansine	Mesothelin	Cleavable disulfide (SPDB) DM4 (maytansinoid)	human IgG1 (phage-derived)	Mesothelioma and other solid tumors	Pivotal phase 2 (mesothelioma); enrollment completed 02/2017; PFS endpoint not met Phase I and II monotherapy & combinations	68, NCT02610140, NCT02751918, NCT03102320
Mirvetuximab soravtansine	FOLR1 (FRα)	Cleavable disulfide (sSPDB) DM4 (maytansinoid)	huIgG1[b]	Ovarian cancer, endometrial, NSCLC	Phase III trial (FRα-positive, platinum-resistant ovarian) and phase II combinations	77, NCT02631876, NCT02606305
Rovalpituzumab tesirine (Rova-T)	DLL3	Cleavable dipeptide (va) PBD dimer	huIgG1	SCLC	Pivotal phase II, single arm (3rd or later line) Phase III trials in 1st-line and 2nd-line	82, NCT02674568, NCT03033511, NCT03061812
Sacituzumab govitecan	Trop-2	Acid-labile ester linker SN-38	huIgG1	TNBC, urothelial and other cancers	Phase III trials active Potential approval from phase I TNBC	94, NCT02574455
Glembatumumab vedotin	gpNMB	Cleavable dipeptide (vc) MMAE (auristatin)	human IgG2 (tg mouse)	mBC and melanoma	Pivotal randomized phase II (TNBC) Ongoing evaluation in combination	95, NCT01997333
Depatuxizumab mafodotin	EGFR	Non-cleavable (mc) MMAF (auristatin)	huIgG1 (ABT-806)	Glioblastoma and other EGFR+ tumors	Phase IIb/III trial in combination with temozolomide (glioblastoma) Other phase I and II trials ongoing	96, NCT02573324, NCT02343406
AGS-16C3F	ENPP3 (CD203c)	Non-cleavable (mc) MMAF (auristatin)	human IgG2 (tg mouse)	Renal cell carcinoma	Randomized phase II; single agent versus axitinib (active comparator)	97, NCT02639182
SAR566658	CA6	Cleavable disulfide (SPDB) DM4 (maytansinoid)	huIgG1[b]	TNBC and other CA6-positive tumors	Phase II trial in TNBC	98, NCT02984683
PSMA-ADC	PSMA	Cleavable dipeptide (vc) MMAE (auristatin)	human IgG1 (tg mouse)	Prostate cancer	Phase II study in castrate-resistant prostate cancer	99, NCT01695044, NCT02020135

[a] Antibody abbreviations: huIgG, humanized IgG; chIgG, chimeric IgG; tg mouse, transgenic mouse with human Ig repertoire.

[b] Although these antibodies were humanized, changes in naming methodology at International Nonproprietary Names resulted in the "ximab" suffix of chimeric antibodies (100).

[c] Trials active and/or open for enrollment on or before March 31, 2017 (**www.clinicaltrials.gov**).

[d] Abbreviations: DLL3, delta-like protein 3; EGFR, epidermal growth factor receptor; ENPP3, ectonucleotide pyrophosphatase/phosphodiesterase 3; FOLR1 or FRα, folate receptor alpha; gpNMB, glycoprotein nonmetastatic B; FL, follicular lymphoma; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer; PSMA, prostate-specific membrane antigen; MMAE/F, mono methyl auristatin E/mono methyl auristatin F; PBD, pyrrolobenzodiazepine; DM1, $N^{2'}$-deacetyl-$N^{2'}$-(3-mercapto-1-oxopropyl)-maytansine; DM4, $N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine; SMCC, succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate; SPDB, *N*-succinimidyl-4-(2-pyridyldithio)butyrate; sSPDB, *N*-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate; vc, valine-citrulline; va, valine-alanine.

for the comparator arm; p = 0.0007) (63). Again, improved efficacy was achieved along with a reduced incidence of grade ≥3 adverse events (32% for T-DM1 versus 43% for the comparator).

The efficacy results of a phase III trial of T-DM1 (with and without pertuzumab) versus trastuzumab plus taxane in the first-line treatment of HER2-positive mBC (MARIANNE) (64) were disappointing in view of the initial promise of T-DM1 in early phase I and phase II trials (65, 66). All three arms had a similar ORR (60–70%), and neither experimental arm showed superior PFS to the trastuzumab plus taxane arm (~14 months) (64). Addition of pertuzumab to T-DM1 did not improve PFS despite preclinical data that showed synergistic activity for this combination (67). The duration of response was longer with T-DM1 (~21 months) than with trastuzumab plus taxane (12.5 months), and T-DM1 was better tolerated, with patients having improved (prolonged) health-related quality of life (64).

Anetumab Ravtansine

Anetumab ravtansine (BAY 94-9343) consists of a fully human anti-mesothelin antibody conjugated to the maytansinoid DM4 via a cleavable disulfide linker (68). Mesothelin is highly expressed in certain tumors, including 100% of cases of mesothelioma, and the majority of ovarian and pancreatic adenocarcinomas (68). Normal tissue expression is limited to cells lining the pleura, pericardium, and peritoneum.

A phase I study in patients with ovarian cancer or with mesothelioma established 6.5 mg/kg given intravenously once every three weeks as the RP2D. A total of 45 patients were treated during dose escalation (0.15 mg/kg to 7.5 mg/kg), and 32 patients were treated in an expansion cohort at 6.5 mg/kg (69). The DLTs at 7.5 mg/kg were peripheral neuropathy and reversible corneal toxicity (keratitis, blurred vision). At the 6.5 mg/kg dose (N = 38 subjects), peripheral sensory neuropathy (37%) and reversible corneal epitheliopathy (50%) were mostly grade 1 or 2, with only a low incidence of these toxicities at grades ≥3 (3% and 8%, respectively).

At the 6.5 mg/kg dose, there were two PRs in ovarian cancer patients (N = 21) and, notably, five PRs in patients (N = 16) with mesothelioma. All of these responses occurred in patients (N = 10) for whom anetumab ravtansine was the second-line treatment (ORR 50%) (70). The responses in mesothelioma were remarkably durable, with 4 of 5 responses continuing for >500 days (69, 70). Based on these results, a randomized phase II pivotal trial was initiated in December 2015, comparing anetumab ravtansine (6.5 mg/kg every three weeks) to vinorelbine (2:1 randomization), as second-line therapy for treating mesothelin-positive (as assessed by immunohistochemistry) metastatic pleural mesothelioma (71). The study (NCT02610140) completed its planned enrollment of at least 210 patients in January 2017. However, the sponsor (Bayer) announced recently that the phase II trial did not meet its primary endpoint of PFS in this difficult-to-treat disease (Bayer press release, July 21, 2017). Evaluation of the ADC continues, as monotherapy as well as in combination, in additional studies across multiple mesothelin-positive tumor types (NCT03102320, NCT02751918).

Mirvetuximab Soravtansine

Mirvetuximab soravtansine (IMGN853) is a folate receptor alpha (FRα)-targeting ADC that utilizes a charged, cleavable disulfide linker for conjugating DM4 to the antibody (72). FRα is expressed at high levels in the majority of cases of epithelial ovarian cancer as well as in many cases of endometrial cancer and lung adenocarcinoma (72). Most normal tissues do not express FRα (transport of nutrient folate into cells is thought to be mediated by other folate-binding proteins such as reduced folate carrier), making it a promising target for an ADC approach (72).

In a phase I study, 30 patients were treated at doses from 0.15 mg/kg to 7.0 mg/kg every three weeks (73). Further patients (seven at each dose) were given either 5.0 mg/kg or 6.0 mg/kg on the basis of adjusted ideal body weight (AIBW), which decreased the interpatient variability in drug exposure. This procedure established 6.0 mg/kg AIBW given every three weeks as the RP2D (73). As noted for anetumab ravtansine, reversible corneal toxicity was a common adverse event, with a DLT in one patient treated at 7.0 mg/kg. Reversible corneal toxicities are a common finding for ADCs having a disulfide-linked DM4 (maytansinoid) or a noncleavable linker-MMAF (mono methyl auristatin F) as the linker-payload moiety (69, 73–75). Such corneal effects are also noted as a DLT for another protein-bound microtubule-disrupting agent, nanoparticle albumin–bound paclitaxel (Abraxane®) (76).

Observations of antitumor activity during dose escalation led to investigation of mirvetuximab soravtansine (6.0 mg/kg AIBW every three weeks) in a cohort of patients (N = 46) with platinum-resistant epithelial ovarian cancer that were FRα-positive (inclusion threshold ≥2+ intensity (scale 0–3+) on ≥25% of tumor cells by immunohistochemistry) (77). There were no grade ≥3 ocular toxicities noted, and the incidence and severity of reversible grade 1 and 2 ocular events decreased with improved management including the use of preservative-free lubricating eye drops (77). The confirmed ORR was 26% (1 CR and 11 PRs) in this heavily pretreated patient population (up to five prior systemic regimens). Notably, in a pooled analysis of this expansion cohort with two other expansion cohorts of the phase I study (N = 113 patients for analysis), the confirmed ORR was 47% in the patients (N = 36) with platinum-resistant disease who had ≤3 prior lines of therapy and whose FRα expression levels were ≥2+ on ≥50% of tumor cells (78). These data have defined these subjects as the patient population for a pivotal phase III study, FORWARD I (NCT02631876), which enrolled the first patient in January 2017 (79, 80). Approximately 60% of epithelial ovarian cancer patients meet these FRα inclusion criteria (77–80).

Rovalpituzumab Tesirine (Rova-T)

The newest ADC that has transitioned into a pivotal clinical study for a solid tumor indication is rovalpituzumab tesirine or Rova-T, an ADC comprising a humanized anti-DLL3 (delta-like protein 3) antibody conjugated to a PBD dimer (81). DLL3 is expressed on the surface of certain tumor cells, including small cell lung cancer (SCLC) and large cell neuroendocrine cancer, but it is absent from normal adult tissue. It is thought to be expressed also on tumor progenitor cells and cancer stem cells (81).

Rova-T was evaluated in a phase I trial, where a total of 74 SCLC patients received doses ranging from 0.05 to 0.8 mg/kg once every three or six weeks (82). The most common grade ≥3 toxicities were thrombocytopenia (12%), serosal effusions with a median onset of 74 days (11%), and skin reactions (8%). The RP2D was 0.3 mg/kg given twice with a six-week interval between doses. At active doses (≥0.2 mg/kg) of Rova-T, the confirmed ORR was 18% (11 of 60 evaluable patients). Biopsies from 39 cases were evaluated for DLL3 expression by immunohistochemistry. Ten of the responders were among the 29 patients who showed positive staining on at least 50% of the tumor cells (35% ORR). The median duration of response was 5.6 months. The median OS in the DLL3-high subset (N = 29) was 5.8 months with 36% of patients alive at one year, an encouraging finding in third-line SCLC, where published experience suggests one-year survival of only 12% with conventional therapeutic options (82, 83). There were no responders in the 10 cases with DLL3 expression below this threshold (82). These trends are consistent with the hypothesis that DLL3 expression levels on tumor cells correlate with the degree of antitumor activity for the ADC (82) and suggest a patient-selection strategy based on DLL3 assessment. A single-arm pivotal phase II clinical study (TRINITY) evaluating Rova-T in DLL3-expressing SCLC patients after at least two prior lines of systemic treatment was opened in 2016 (NCT02674568), and phase III

trials evaluating Rova-T versus topotecan as second-line treatment (NCT03061812), or exploring its use as maintenance treatment following first-line platinum-based therapy (NCT03033511), became active in 2017.

THE ROLE OF ANTIBODY–DRUG CONJUGATES IN THE TREATMENT OF CANCER

The successful approvals of brentuximab vedotin (BV), ado-trastuzumab emtansine (T-DM1), and inotuzumab ozogamicin (InO) after decades of disappointment in developing immunoconjugates as therapeutic agents have sparked a flurry of research and development. More than 80 ADCs have entered clinical evaluation over the last 15 years (10). With one more ADC for hematologic malignancies currently under FDA review (**Table 1**), and four ADCs in pivotal clinical development for treating solid tumors (**Table 2**), several more ADCs are likely to be approved for treating cancer patients in the next five years.

The development strategies for seven of the eight ADCs reviewed in some detail above seek to generate evidence to support their initial approval as single agents (excepting SGN-CD33A, which was being developed in combination with hypomethylating agents). However, the relatively benign side-effect profiles for many ADCs (relative to cytotoxic chemotherapy) suggest that they may be well suited to combine with other agents with the goal of further improvement in treatment outcomes for cancer patients. For example, mirvetuximab soravtansine is being evaluated in combination with carboplatin, pegylated liposomal doxorubicin, bevacizumab, or pembrolizumab, in a multi-arm trial called FORWARD II (NCT02606305) (84). The latter combination arm was initiated following the excitement generated by the recent research of Zippelius and colleagues (85–88) suggesting that ADCs, including those made with potent microtubule-disrupting agents, such as T-DM1, as the payload (88), may be combined with immune checkpoint inhibitors such as the anti-PD1 antibodies (pembrolizumab, nivolumab) for enhanced and sustained antitumor effect. These findings have stimulated much interest in this approach with several ADCs besides mirvetuximab soravtansine, including BV (brentuximab vedotin) and T-DM1, in clinical trials in combination with immune checkpoint inhibitors. Other ADC-payload classes, including PBDs, may also synergize with immune-oncology drugs (89), and a trial combining Rova-T and nivolumab opened in 2017 (NCT03026166).

What are the challenges for the ADC field in the future? The large variety of ADC technologies developed over the past decade has created a large repertoire of possibilities for designing an ADC specific to a given target (10). There are new-generation linker chemistries that result in improved antitumor activity and a wider therapeutic window in preclinical studies when compared with the approved ADCs (10, 26, 33, 35, 90). However, identifying targets amenable to the successful development of active ADCs utilizing the design "toolbox" is still challenging. Also, a patient-selection strategy linked to target expression on the tumor can make the difference between success and disappointment in clinical development of ADCs (59, 61, 77, 79). There is clearly much yet to learn about the optimal application of ADCs in the treatment of different cancers, especially in establishing the best combination partners and in determining the role of ADCs in complementing immune-oncology therapies. Nevertheless, the opportunity to improve treatment outcomes for cancer patients by incorporating ADCs into cancer therapy offers exciting possibilities for the future.

DISCLOSURE STATEMENT

The authors are employees of ImmunoGen, Inc., and receive salary- and equity-based remuneration. ImmunoGen is the developer of the maytansinoid technology utilized in T-DM1, anetumab ravtansine, and mirvetuximab soravtansine, ADCs described herein.

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