

REVIEW



Exploration of the antibody–drug conjugate clinical landscape

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ABSTRACT

The antibody–drug conjugate (ADC) field has undergone a renaissance, with substantial recent developmental investment and subsequent drug approvals over the past 6 y. In November 2022, ElahereTM became the latest ADC to be approved by the US Food and Drug Administration (FDA). To date, over 260 ADCs have been tested in the clinic against various oncology indications. Here, we review the clinical landscape of ADCs that are currently FDA approved (11), agents currently in clinical trials but not yet approved (164), and candidates discontinued following clinical testing (92). These clinically tested ADCs are further analyzed by their targeting tumor antigen(s), linker, payload choices, and highest clinical stage achieved, highlighting limitations associated with the discontinued drug candidates. Lastly, we discuss biologic engineering modifications preclinically demonstrated to improve the therapeutic index that if incorporated may increase the proportion of molecules that successfully transition to regulatory approval.

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ADCs as a new class of targeted therapeutics

A new class of precision medicines, antibody–drug conjugates (ADCs), was ushered into oncology clinical practice in 2000 with the US Food and Drug Administration (FDA)'s approval of MylotargTM for the treatment of acute myeloid leukemia (AML). ADC molecules marry the precision of antibody-mediated tumor antigen targeting with potent cytotoxic agents, thereby creating a targeted delivery vehicle for malignant tumors. In this manner, ADCs provide a means to reduce off-tumor toxicities by limiting payload exposure in normal tissues. While most ADC clinical candidates utilize cytotoxic chemotherapeutic payloads, recent ADC candidates have also incorporated targeted small molecules¹ and immunomodulatory agents.² In the 23 years since MylotargTM's first registration, only 12 of 267 clinically tested ADCs have made it to regulatory approval; 10 occurring in the last 6 years [Figure 1]. Insights into biologic engineering and utilization of less potent linker-payloads (e.g., EnhertuTM) have re-energized the field and ushered a new wave of drug approvals.

Factors affecting activity of ADCs




ADCs offer several advantages over standard chemotherapies, notably: 1) precision delivery of cytotoxic payloads to cells expressing the selected target antigen, 2) enablement of more potent cytotoxic payload utilization than can be administered systemically, and 3) potential minimization of on target/off tumor toxicity. The promise of ADCs, when successfully designed, is the ability to broaden the therapeutic index over that of systemically administered chemotherapy. By directly delivering the cytotoxic payloads to the tumor tissue, the

minimum effective dose (MED) is lowered with corresponding reduction in on target/off tumor adverse events.

Effective analysis of the clinically tested ADC molecules necessitates a fundamental understanding of the factors that modulate their biological activity. The basic cellular processes underlying ADC cytotoxic payload delivery have three key parts. First, the antibody binds to the target antigen on the surface of an antigen-positive cell. Second, the antigen-ADC complex is internalized into the target cell by receptor-mediated endocytosis. Third, the antigen-ADC complex is digested by lysosomal enzymes, releasing the cytotoxic payload that triggers cell death. As illustrated in Figure 2 and discussed below, the effectiveness of these basic cellular processes underlying ADC clinical activity are further modulated by various factors, notably the target antigen, functional attributes of the created antibody, conjugation chemistries, linker attributes, and payload potency and effectiveness for a chosen tumor indication.

Target antigen

For an ADC to be effectively internalized within a given cell, a requisite target antigen density needs to exist to trigger efficient receptor-mediated endocytosis. A target antigen density of approximately 10,000 copies/cell or greater has been proposed as a minimum threshold for efficient biologic-mediated ADC internalization.³ Cells with target antigens expressed at lower molecular densities exhibit inefficient ADC internalization with a subsequent reduction in payload delivery. Inefficient ADC internalization can also result in ADC recycling outside of the cell prior to payload processing and release, further reducing the ADC's cytotoxic effect.⁴ In addition to requisite tumor antigen densities to trigger efficient

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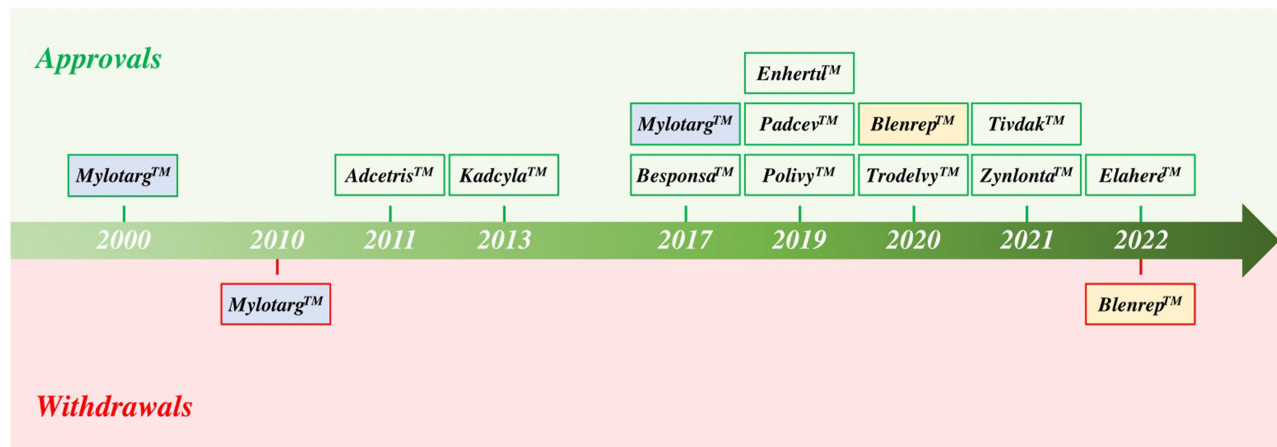


Figure 1. Timeline of FDA Approvals. To date, 12 ADCs have been granted FDA approval (green boxes). Two candidates, Mylotarg™ and Blenrep™, had their approvals withdrawn (red boxes) due to failure to meet requisite endpoints in post-approval trials. Mylotarg™ was subsequently re-approved at a lower dose in combination with chemotherapy. Eleven ADC therapeutics are currently FDA approved.

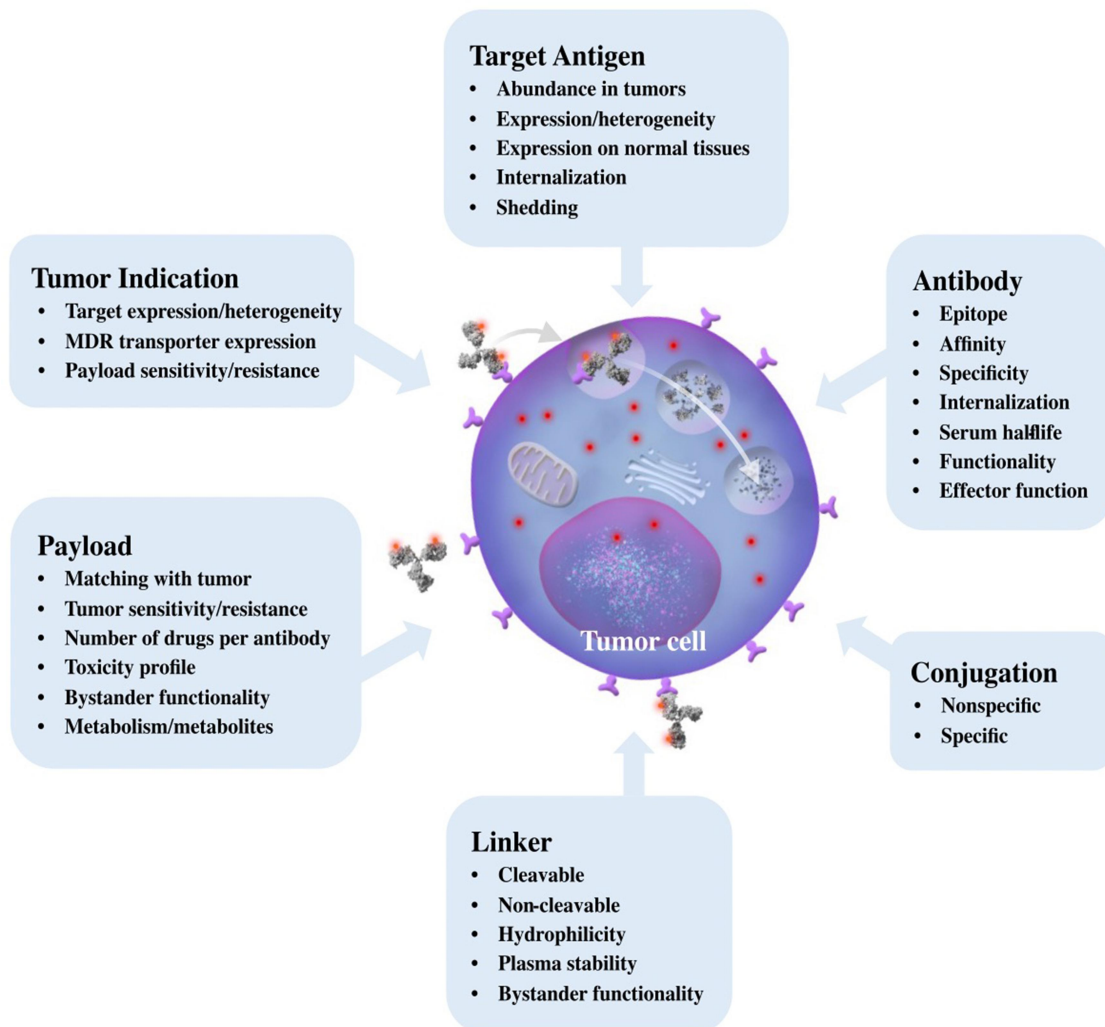


Figure 2. Factors Governing ADC Activity. Grey arrows indicate the path of an ADC into a cell. The antibody binds to the target antigen on the surface of the cell, the antigen-ADC complex is internalized by endocytosis, and the antigen-ADC complex is either recycled back to the cell surface, or transitions to the lysosomal compartment. Lysosomal processing releases the cytotoxic payload (red dots) ultimately triggering cell death. Factors governing this process include the target antigen, the antibody, the conjugation methodology to attach the payload to the biologic, the linker, the payload, and the selected tumor indication.

internalization, the ideal targets chosen for ADC drug development would demonstrate significantly elevated tumor antigen expression over that of normal tissues to minimize the

potential for on target/off tumor toxicities. A favorable example of a target that is significantly overexpressed in tumor tissues relative to normal tissues is the HER2/neu antigen

that is expressed at lower levels on a subset of normal cells, but expressed at hundreds of thousands to over a million copies on HER2+ cancer cells.⁵ Indeed, ADCs targeting the HER2 antigen have demonstrated robust internalization into HER2-targeted tumor cells with efficient payload delivery^{6,7} that has translated to clinical benefit and ultimate drug approval.^{8,9} In contrast, ADCs targeting tumor antigens with heterogeneous/low target antigen expression, such as the prolactin receptor with antigen densities of thousands to tens of thousands of molecules/cell,¹⁰ failed to demonstrate clinical responses at the biologic doses tested and were subsequently terminated from future clinical development.¹¹

Antibody

Target epitope choice of a given biologic can greatly alter the effectiveness of the created ADC. Notably, biologics targeting epitopes that promote rapid receptor-mediated internalization show greater activity than biologics targeting non-internalizing epitopes.¹² In addition to epitope choice, biologic affinity can also alter the effectiveness of ADC biologics. Indeed, biologics with lower affinities may demonstrate insufficient binding and/or internalization at lower target antigen densities¹³ and biologics with too high cellular affinities may result in reduced receptor occupancy and/or internalization.¹⁴ Biologic affinity tuning may also help mitigate on target/off tumor toxicities for antigens expressed in normal tissues of concern. Creating biologics with lower cellular affinities could help mitigate toxicity toward target positive normal cells while retaining potency against tumor cells where the given antigen is overexpressed. A preclinical example of this concept is the low affinity EGFR ADC RN765C that demonstrated robust killing of EGFR-positive cell lines/tumor models where EGFR is overexpressed with reduced toxicity against EGFR-positive normal human keratinocytes.¹³

Conjugation

Most ADCs use nonspecific lysine or cysteine residue-directed biologic conjugation. Both conjugation approaches have been found to generate heterogeneous ADC products.^{15,16} In contrast, site-specific conjugation to native or engineered amino acid residues has been shown to generate more homogenous ADC drug products with improved pharmacokinetic (PK) properties and safety profiles.^{17,18}

Linker

Linkers can be cleavable or non-cleavable. Cleavable linkers are designed to release the payload inside the targeted cell by protonolysis, thiol reduction, proteolysis, or carbohydrate hydrolysis. In addition to cytosolic payload release, cleavable linkers have also been shown to be cleaved extracellularly due to the presence of cleaving agents in the blood and/or tumor microenvironment (TME). These linkers can be associated with both increased adverse events (due to systemic payload release)¹⁹ and increased efficacy due to noted “bystander effects” (wherein released payload can diffuse across the plasma membrane of a higher tumor antigen expressing cell to adjacent tumor cells with lower antigen expression).²⁰ An ADC can also be created with a non-cleavable linker that only releases payload after proteolysis by lysosomal enzymes. These

released payload-adducts are modified such that they do not diffuse across plasma membranes, which limits both their systemic adverse effects but also mitigates the efficacy benefit to neighboring tumor cells due to diminished bystander diffusion.²¹ An excellent example of this concept is the approved clinical ADC, KadcylaTM, that employs a non-cleavable linker, limiting its systemic toxicity as well as efficacy to bystander cells expressing lower target antigen densities. EnhertuTM, in contrast, uses a cleavable linker, and demonstrates bystander killing and greater clinical activity in tumors with lower HER2 target expression.⁹ In a head-to-head clinical trial, EnhertuTM demonstrated superior clinical activity (mPFS 28.8 months, EnhertuTM versus 6.8 months, KadcylaTM) with comparable incidence of Grade 3 or higher treatment-emergent adverse events (56%, EnhertuTM versus 52%, KadcylaTM) and serious treatment-emergent adverse events (25%, EnhertuTM versus 22%, KadcylaTM).²² In addition to linker choice, choice of payload and presence of tumor drug efflux pumps could have also contributed to these clinical results. Linkers can also vary by their degree of hydrophilicity. Indeed, more hydrophilic linkers have been shown to increase the solubility and favorable PK properties of the ADCs, especially those that use more hydrophobic drug payloads.²³

Payload

The traditional chemotherapeutic ADC payloads fall into three general classes: 1) microtubule inhibitors, 2) DNA-damaging agents, and most recently 3) topoisomerase I inhibitors. The potencies of these payload classes dictate the ADC efficacy and toxicity. Early ADC candidates utilizing low potency payloads of systemically administered chemotherapies (e.g., doxorubicin, $IC_{50} \sim 10^{-7}$ M) were ultimately abandoned due to insufficient clinical activity at administered drug exposures.^{24,25} As a result, the ADC field pivoted to the use of increasingly more potent cytotoxic payloads, such as the DNA damaging agents calicheamicin ($IC_{50} \sim 10^{-10}$ M) and pyrrolobenzodiazepines (PBDs) ($IC_{50} \sim 10^{-12}$ M) and microtubule inhibitors such as monomethyl auristatin E, MMAE ($IC_{50} \sim 10^{-10}$ M) for follow-on drug development.²⁶ Utilization of very potent payloads, however, limited the biologic doses that could be administered, often resulting in suboptimal payload delivery to tumors with lower target antigen densities.^{27–31} In addition to payload choice, payload ADC effectiveness is also influenced by the 1) number of payload molecules per ADC (drug-antibody ratio, DAR), 2) presence of multi-drug resistance (MDR) efflux pumps in tumors that can expel select payloads, 3) potential bystander functionality of the payload once released, and 4) payload clearance. Bystander functionality is determined by whether the free payload, once released, can diffuse across cellular membranes to trigger a cytotoxic effect. The net charge on the released payload has been found to influence this functionality. For example, released neutral lipophilic MMAE payloads can diffuse across cell membranes to produce a bystander effect, whereas charged MMAF (monomethyl auristatin F) molecules cannot.³²

Payload hydrophobicity has been found to modulate the clearance of the payload. More hydrophobic payloads tend to exhibit more rapid clearance, altering the on-target efficacy and off-target toxicity of a given ADC.²³ *In vivo* payload

metabolism can also modulate ADC safety and efficacy. For example, the SN-38 payload becomes inactivated in the liver with the opening of the lactone ring, dampening its cytotoxic functionality.³³ Finally, clinical success of the ADC depends upon appropriate matching of the payload class to the desired indication as described below.

Indication

The clinical effectiveness of an ADC also depends on the nature of the tumor being targeted. In general, tumors with heterogeneous and/or low target antigen levels are difficult targets for ADCs. Engineering ADCs with bystander activity may in part overcome this challenge as was demonstrated with EnhertuTM's recent approval in HER2 low breast cancer.⁹ Tumors with robust expression of multidrug efflux pumps, which expel payloads from tumors, also present challenges for certain classes of ADC payloads. Indeed, ADC resistance in these high efflux tumors can be circumvented with different payload utilization.^{34,35}

In summary, matching the appropriate tumor antigen to selected ADC linker-payloads for a given cancer indication is critical for development of successful ADC therapeutics.

Analysis of oncology ADCs that have entered clinical trials

Here, we review ADCs registered for at least one human clinical trial for an oncology indication by January 1, 2023, that were included in the Beacon Targeted Therapies Clinical Trials and Pipeline Database (beacon-intelligence.com). We included ADCs that possessed the following two elements: 1) a targeting moiety comprising an antibody, antibody-fusion, or antibody fragment and 2) a payload. The utilized payload is

one from either a conventional chemotherapeutic class or a targeted small molecule and/or immune-modulator. Radioisotope ADCs were excluded from this analysis.

In the 26 years since the first ADC clinical trial in 1997, 266 additional ADCs have been tested in over 1200 clinical trials. During this period, 54 ADC programs have been formally discontinued and 38 ADCs have been removed from company pipelines. ADCs covered in this review are classified as 1) Approved (by FDA), 2) Active (not approved by FDA but currently in ≥ 1 clinical trial), and 3) Discontinued (no longer listed in the company's clinical pipeline, irrespective of an announcement of discontinuation) [Figure 3]. It should be noted that all Approved ADCs are also currently active in several clinical trials though they are not included in the 'Active' category for the purpose of this review (to eliminate double-counting). Additionally, all of the FDA Approved ADCs are approved in other countries in addition to the United States.

Summary of tumor antigens targeted by clinically tested ADCs

The tumor antigen targets and the most advanced stage of clinical testing are illustrated in Figure 4. To date, a total of 106 tumor antigens have been targeted by ADC drug candidates. The 11 approved ADCs target 10 unique cancer antigens: 5 ADCs target hematologic cancer antigens and 6 target solid tumors [Figure 5, Table 1]. Select antigens are the targets of multiple ADCs, including HER2 (41 candidates), Trop-2 (14), CLDN18.2 (11), and EGFR (11). Fewer than 2% of the clinical ADC candidates target more than 1 epitope of selected cancer antigen(s): four bispecific and one biparatopic ADCs are included in this review.

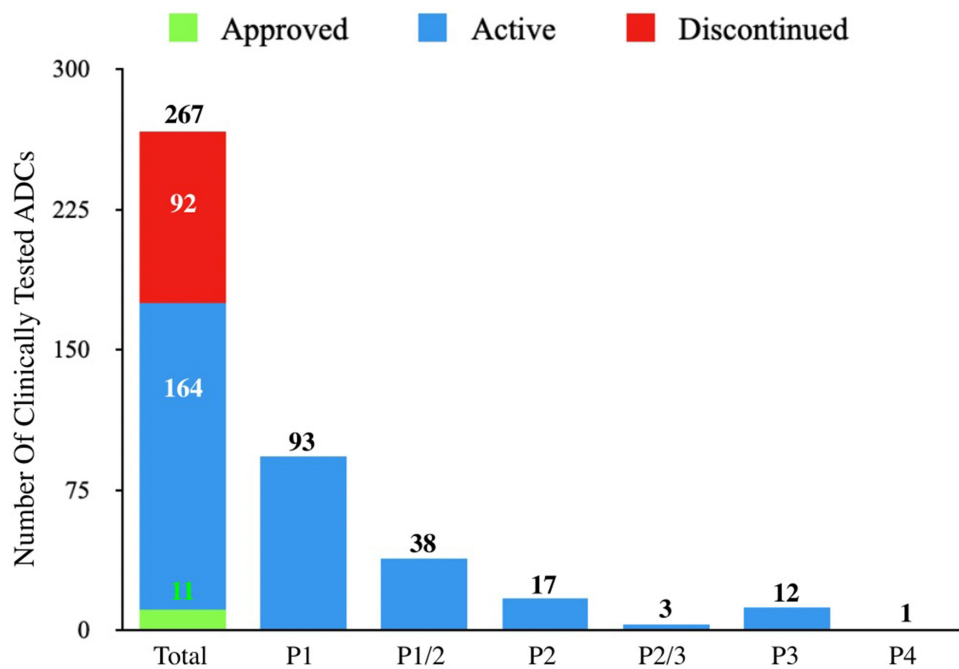


Figure 3. Clinically Tested ADCs. This bar graph captures the 267 ADC that have undergone clinical testing of which: 11 are FDA Approved (green sector), 164 are in Active clinical testing (blue sectors), and 92 have been Discontinued (red sector). Additionally, for the Active ADCs, they have been broken down to highlight their highest development stage (Phase 1-Phase 4, P1-P4). The one candidate in this class listed in Phase 4 (P4), disitamab vedotin, has been approved in China and is not yet approved by the FDA.

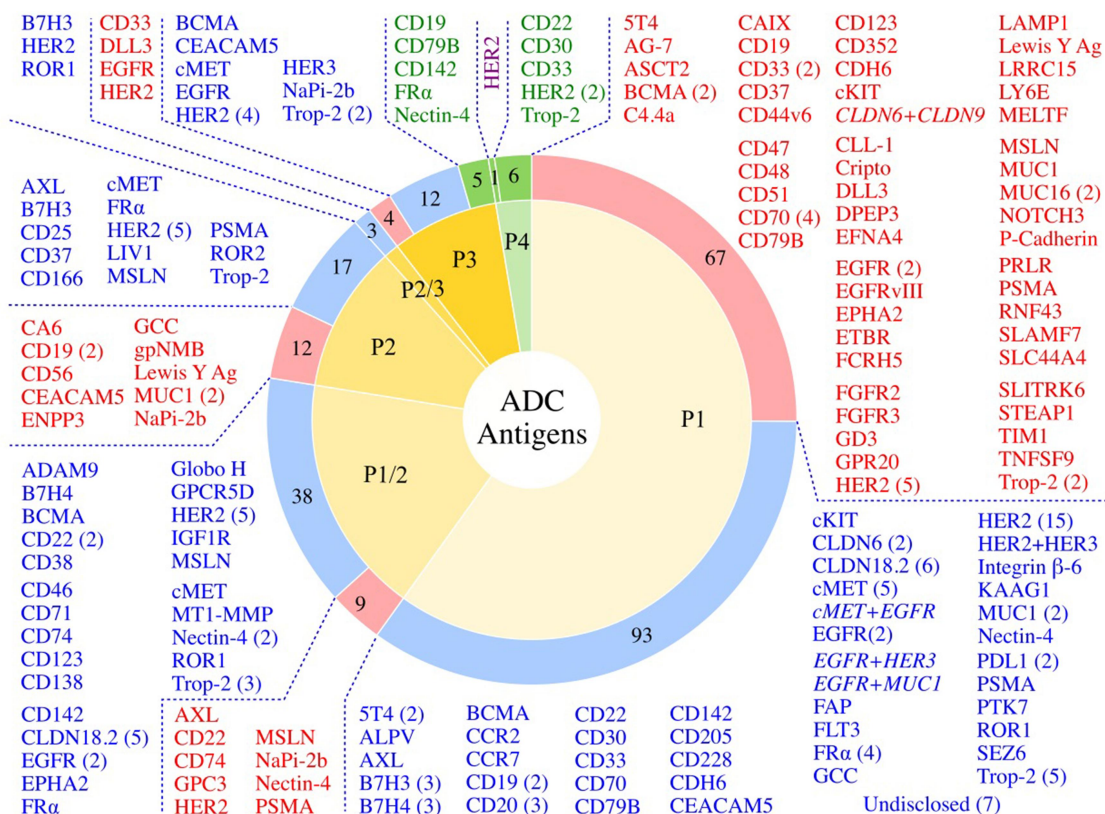


Figure 4. Antigen Targets of the Clinically Tested ADCs. Of the 267 clinically tested ADCs, 260 have known antigens (7 are undisclosed). Numbers of ADCs targeting a given tumor antigen in various stages of clinical testing (Phase 1-Phase 4, P1-P4) are shown in the categories of FDA Approved ADCs (green sectors, green text), Active ADCs (blue sectors, blue text), and Discontinued ADCs (red sectors, red text). Dual antigen targeting ADCs are shown in italics. The Phase 4 HER2 candidate shown in purple text is disitamab vedotin, that has been approved in China and is not yet approved by the FDA.

		Hematological Malignancies	Solid Tumors
Potency	DNA Damaging Agents	Zynlonta™ (PBD)	
		Mylotarg™ (Calicheamicin)	
		Besponsa™ (Calicheamicin)	
	Microtubule Inhibitors	Adcetris™ (Auristatin, MMAE)	Elahere™ (Maytansine, DM4)
		Polivy™ (Auristatin, MMAE)	Kadcyla™ (Maytansine, DM1)
			Padcev™ (Auristatin, MMAE)
			Tivdak™ (Auristatin, MMAE)
	Topoisomerase I Inhibitors		Enhertu™ (DXd)
			Trodelvy™ (SN-38)

Figure 5. Approved ADCs Classified by Payload Class and Malignancy Setting. Approved ADC drug name and payload are provided. ADCs are listed from top to bottom based upon the potency of the payload utilized with PBD payloads being the most potent and SN-38 payloads the least potent.

Summary of linkers utilized by clinically tested ADCs

Linkers fall into two major classes: cleavable and non-cleavable [Figure 6]. Of the clinical ADCs, 54% use cleavable linkers, which represent the most utilized linker class. Ten of 11 clinically approved ADCs use protease-cleavable linkers. Of the clinically tested ADCs, 16% use non-cleavable linkers, including the clinically active ADC Blenrep™. Only one

approved ADC, Kadcyla™, uses a non-cleavable linker. Linker class was not disclosed for 31% of the clinically tested ADCs.

Summary of payloads utilized by clinically tested ADCs

Payloads fall into four major classes: 1) microtubule inhibitors, 2) DNA-damaging agents, 3) topoisomerase I inhibitors, and

Table 1. Attributes of FDA Approved ADCs and Approval Indications.

Hematological Malignancies		Solid Tumors	
ADC	Indication(s)	ADC	Indication(s)
Adcetris™ brentuximab vedotin Target: CD30 Conjugation: Nonspecific cysteine Linker: Cleavable, Val-Cit Payload: MMAE DAR ~4	Hodgkin's Lymphoma after ASCT failure, > 2 L when ASCT is not an option, > 1 L sALCL (Accelerated approval based on ORR)	Kadcyla™ trastuzumab emtansine Target: HER2 Conjugation: Nonspecific lysine Linker: Non-cleavable, SMCC Payload: DM1 DAR ~3.5	HER2+ mBC after treatment with trastuzumab and a taxane, separately or together, HER2+ Early BC as adjuvant treatment in patients with residual disease after neoadjuvant taxane and trastuzumab-based treatment
Besponsa™ inotuzumab ozogamicin Target: CD22 Conjugation: Nonspecific lysine Linker: Cleavable, AcBut acyl hydrazone-disulfide Payload: Calicheamicin DAR ~2.3	r/r B cell precursor ALL	Enhertu™ trastuzumab deruxtecan Target: HER2 Conjugation: Specific cysteine Linker: Cleavable, GFG Payload: DXd DAR ~8	> 1 L u/r/m HER2+ BC, HER2-low BC, > 1 L HER2 + NSCLC, HER2+ GC/GEJC after trastuzumab-based therapy (Accelerated approval based on ORR, DOR and PFS)
Mylotarg™ gemtuzumab ozogamicin Target: CD33 Conjugation: Nonspecific lysine Linker: Cleavable, AcBut acyl hydrazone-disulfide Payload: Calicheamicin DAR ~2.3	CD33+ AML in adults, CD33 + r/r AML in patients above 2 y in age	Padcev™ enfortumab vedotin Target: Nectin-4 Conjugation: Nonspecific cysteine Linker: Cleavable, Val-Cit Payload: MMAE DAR ~4	Locally advanced or metastatic Urothelial Cancer (la/m UC) after treatment with aPD-1/PD-L1 and a platinum-containing chemotherapy (Accelerated approval based on OS, PFS, ORR)
Polyivy™ polatuzumab vedotin Target: CD79b Conjugation: Nonspecific cysteine Linker: Cleavable, Val-Cit Payload: MMAE DAR ~3.5	> 2 L for DLBCL in combination with bendamustine and a rituximab product (Accelerated approval based on CRR)	Tivdak™ tisotumab vedotin Target: Tissue Factor Conjugation: Nonspecific cysteine Linker: Cleavable, Val-Cit Payload: MMAE DAR ~4	r/m Cervical Cancer with disease progression on/after chemotherapy (Accelerated approval based on ORR and DOR)
Zynlonta™ loncastuximab tesirine Target: CD19 Conjugation: Nonspecific cysteine Linker: Cleavable, Val-Ala Payload: PBD DAR ~2.3	> 1 L r/r BCL (including DLBCL) (Accelerated approval based on ORR)	Trodelyv™ sacituzumab govitecan Target: Trop-2 Conjugation: Specific cysteine Linker: Cleavable, CLZA Payload: SN38 DAR ~7.6	> 3 L mTNBC/la/m, UC after platin-based and aPD-1/PD-L1 therapy (Accelerated approval based on ORR and DOR)
		Elahere™ mirvetuximab soravtansine Target: Folate Receptor Alpha Conjugation: Nonspecific lysine Linker: Cleavable, Sulfo-SPDB Payload: DM4 DAR ~3.4	2-4 L FRa+ platin-resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (Accelerated approval based on ORR and DOR)

Abbreviations: 1 L, first line; 2 L, second line; 3 L, third line; AcBut, 4-(4-acetylphenoxy) butanoic acid; Ala, alanine; ALL, acute lymphoblastic leukemia; ASCT, allogeneic stem cell transplant; BC, breast cancer; BCL, B cell lymphoma; Cit, citrulline; CRR, complete response rate; DAR, drug-antibody ratio; DLBCL, diffuse large B cell lymphoma; DM1, mertansine; DM4, ravtansine; DOR, duration of response; DXd, deruxtecan; FRa, folate receptor alpha; GC, gastric cancer; GEJC, gastroesophageal junction cancer; GFG, glycine-glycine-phenylalanine-glycine; la/m, locally advanced or metastatic; mBC, metastatic breast cancer; MMAE, monomethyl auristatin E; mTNBC, metastatic triple-negative breast cancer; mUC, urothelial cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PBD, pyrrolbenzodiazepine; PFS, progression free survival; r/m, relapsed/metastatic; r/r, relapsed/refractory; sALCL, systemic anaplastic large cell lymphoma; SMCC, succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate; u/r/m, unresectable/recurrent/metastatic; Val, valine.

4) targeted small molecules (SM) [Figure 7]. Microtubule disrupting agents represent the largest payload class (57%) that have undergone clinical testing. Seven of the 11 approved ADCs use microtubule inhibitor payloads. DNA damaging agents comprise the next largest payload class (17%) of ADCs. In this subgroup, 26 of 45 molecules use highly potent PBD payloads, only one of which was granted FDA approval. Two additional approved ADCs employ the DNA damaging class by utilizing the calicheamicin payload. Topoisomerase I inhibitors are included in 7% of clinically tested ADCs. Of the 11 approved ADCs, two use topoisomerase I inhibitor payloads. In addition to these traditional chemotherapeutic payload classes, roughly 5% of ADCs incorporate targeted small molecules such as Bcl-xL inhibitors, as well as immunomodulatory agents such as TLR and STING agonists. No candidate in this non-chemotherapeutic payload class has yet been granted FDA approval. Payloads for 15% of the clinically tested ADCs are not disclosed.

Summary of conjugation methods utilized by clinically tested ADCs

Of the 267 clinical ADCs, 111 candidates utilized nonspecific amino acid conjugation, 72 candidates utilized site-specific conjugation, and 84 candidates did not disclose the conjugation method for ADC creation. Of the ADC candidates that utilized site-specific ADC conjugation, 2 Approved (EnhertuTM and TrodelvyTM), 50 Active, and 26 Discontinued ADCs underwent clinical testing. With the exception of the DAR = 8 ADCs (e.g., EnhertuTM and TrodelvyTM) that utilize all natural disulfide bonds for conjugation, the remaining ADCs utilized site-specific conjugation methods that either retain the four inter-chain disulfide bonds or replace these with chemical covalent bonds (e.g., disulfide rebridging).³⁶

Approved ADCs

The FDA has approved 12 ADCs to date [Figure 1, Figure 5, Figure 8, and Table 1], 6 each for hematologic and solid tumor malignancies, respectively [Figure 5, Table 1]. Accelerated conditional approvals were granted to 9 of the 12 approved ADCs. Approvals were withdrawn for 2 (MylotargTM and BlenrepTM) of the 12 ADCs [Figure 1]. MylotargTM was withdrawn in 2010 due to safety versus clinical benefit concerns but was re-approved in 2017 at a lower dose in combination with chemotherapy.³⁷ BlenrepTM was withdrawn in 2022 when the confirmatory trial did not meet the requisite post-approval efficacy endpoints.³⁸

Of the 11 currently FDA approved ADCs, 6 utilize microtubule inhibitor payloads. Three approved ADCs use DNA damaging payloads, while 2 carry payloads that inhibit topoisomerase I [Figure 5, Figure 8]. These payloads span a range of potency from the highly potent DNA damaging agent PBD (IC₅₀ ~ pM) to the lower potency topoisomerase I inhibitor SN-38 (IC₅₀ ~ nM).³⁹ Although the sample size is small, approved ADCs used higher potency payloads when targeting hematological malignancies and lower potency payloads were used in ADCs targeting solid tumors. Higher drug exposures required for efficacy in the solid

tumor setting may limit utilization of higher potency payloads with reported increased systemic toxicity at the preferred biologic dose.

Active ADCs

Of the 164 Active ADCs, ~7% are in Phase 3 clinical testing. These active late-stage ADCs target the following tumor antigens: BCMA (belantamab mafodotin), CEACAM5 (tusamitamab ravtansine), c-Met (telisotuzumab vedotin), HER2 (trastuzumab duocarmazine and trastuzumab rezetecan), HER3 (patritumab deruxtecan), NaPi-2b (upifitamab rilsodotin), and Trop-2 (datopotamab deruxtecan and SKB264).

Microtubule inhibitor payloads are utilized by most ADCs in the active ADC group (~54%), followed by DNA damaging (10%), and topoisomerase I inhibitor (~9%) payloads. Payloads of ~22% of Active ADCs are undisclosed [Figure 9]. Among microtubule inhibitor ADCs, auristatins are most abundant, followed by maytansines. In the DNA damaging payload class, PBDs comprise ~50% of the clinically active ADCs.

Of the cancer antigens targeted by the clinically active ADCs, ~16% target hematologic tumor antigens, ~80% target solid tumor antigens, and ~4% are directed against a cancer antigen that is expressed in both hematologic and solid tumor malignancies. The most frequently targeted tumor antigens in the Active ADC category include HER2 (32 candidates), Trop-2 (11), CLDN18.2 (11), and EGFR (8).

Discontinued ADCs

Discontinuation of ADCs can be ascribed to one or more of the following three reasons: 1) insufficient therapeutic benefit due to intolerable toxicity, 2) therapeutic benefit not superior to current standard of care due to insufficient efficacy, and/or 3) business/commercial considerations. Details of all the discontinued ADCs are shown in Table 2.

Potential factors contributing to insufficient therapeutic benefit due to intolerable toxicity include 1) on target/off tumor toxicity, 2) utilization of very high potency payloads for antigens requiring higher biologic exposures, 3) labile linkers leading to off-tumor release of payload, 4) off-target toxicity, possibly due to pinocytosis of the ADC, and 5) metabolic conversion of the payload to a more toxic metabolite. Approximately 29% of the clinically tested ADCs cited intolerable toxicity as a reason for program termination. Examples of ADCs with intolerable toxicity that could in part be due to on target/off tumor toxicity include bivatuzumab mertansine (CD44v6, expressed in skin keratinocytes) – fatal desquamation,⁷⁴ MEDI-547 (EphA2) – bleeding and coagulation adverse effects (adverse events not typically associated with the MMAE payload),⁶⁶ and PF-06664178 – rash adverse events (Trop-2, expressed on the surface of normal epithelial including skin).⁷¹ For the latter example of PF-06664178, an additional potential contributing factor to the severity of skin toxicity noted is the potent auristatin payload pairing with this Trop-2-targeting ADC. Indeed, the severity of the skin toxicity of PF-06664178 is markedly different from the approved Trop-2-targeting ADC, TrodelvyTM, which uses a lower potency topoisomerase I inhibitor payload.¹¹¹ Additionally, skin

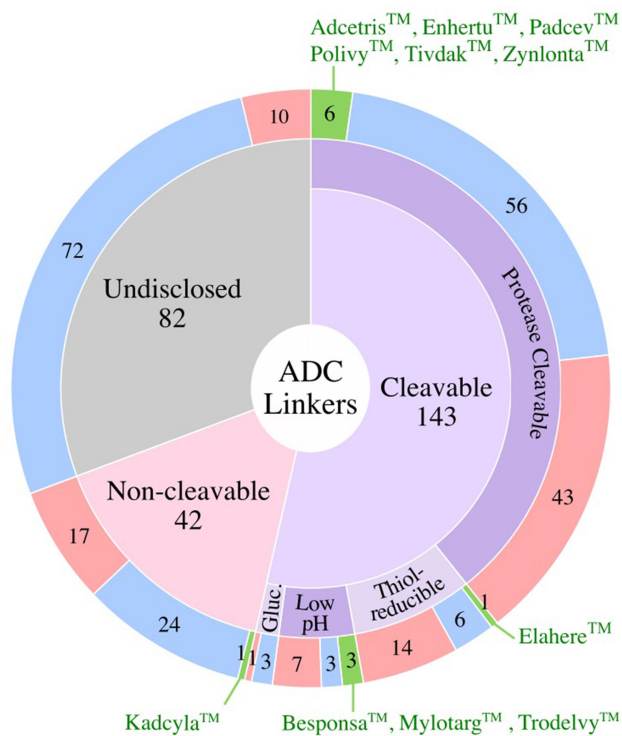


Figure 6. Linkers Used in Clinically Tested ADCs. Numbers of ADCs utilizing different linker classes are shown in the outer ring for the FDA-approved ADCs (green), active ADCs (blue), and discontinued ADCs (red). FDA approved ADCs are shown alongside their respective linkers. Gluc., α -Glucuronide.

toxicity has also been noted for another auristatin ADC, Padcev™, targeting Nectin-4 (also expressed in the skin).¹¹²

Microtubule inhibitor payload ADCs account for 63% of discontinued candidates, followed by DNA damaging (~27%) payloads. Topoisomerase I inhibitors, targeted small molecules, and undisclosed payloads combined comprise 10% of discontinued ADCs [Figure 10]. Utilization of high potency payloads for antigens requiring higher biologic exposures was a likely contributing factor to the intolerable toxicity of several discontinued ADC candidates. The payload choice of biparatopic tetravalent HER2-directed ADC MEDI4276 could have contributed to the intolerable toxicity at doses >0.3 mg/kg.⁹¹ Indeed, the chosen tubulysin analogue payload (IC₅₀ ~ low pM) is in the potency range of PBD payloads.¹¹³ None of the clinically approved ADCs for solid tumors (including 2 ADCs targeting the HER2 antigen) use payloads in this potency range – the most active of which is an ADC employing the less potent payload (Enhertu™).²² Safety was noted as the reason for termination HER2 for the PBD-conjugated ADCs ADCT-502²⁵ and DHES0815A.^{93,94}

ADCs targeting six tumor antigens of the approved ADCs (CD19, CD22, CD33, CD79b, HER2, and Trop-2) have also been discontinued, some due to intolerable toxicity. Trodelvy™, the approved Trop-2 ADC using the lower potency topoisomerase I payload SN-38 (IC₅₀ ~ nM), requires high biologic exposures to achieve the desired efficacy benefit (10 mg/kg on days 1 and 8 of a 21-day treatment cycle). Two

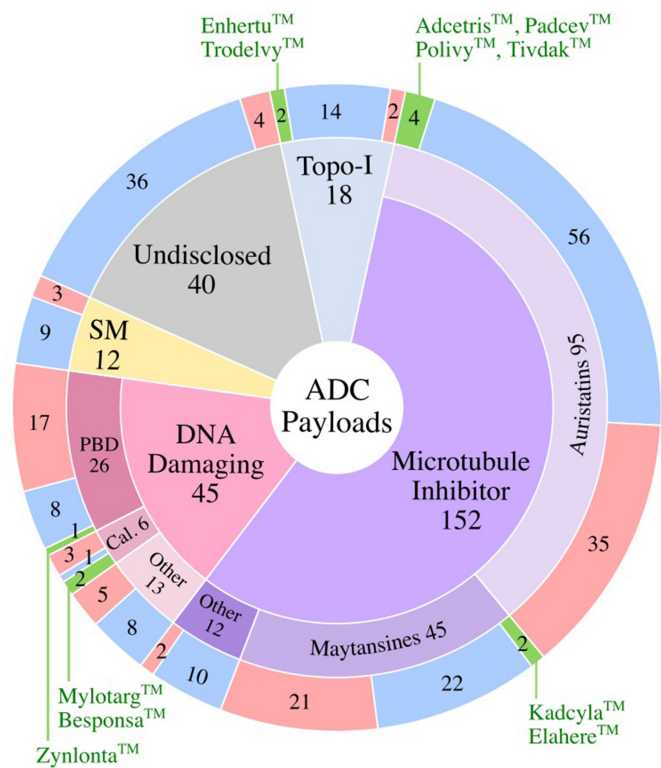


Figure 7. Payloads Used in Clinically Tested ADCs. Numbers of ADCs corresponding to the type of payload are shown in the outer ring for the FDA-approved ADCs (green), active ADCs (blue), and discontinued ADCs (red). Topo-I, Topoisomerase I Inhibitor; SM, targeted small molecules; PBD, pyrrolo-benzodiazepine; Cal., calicheamicin.

ADCs targeting Trop-2 have been discontinued, most likely due to too potent payload selection pairing with a tumor antigen target requiring higher biologic exposures. PF-06664178, which uses a highly potent auristatin analog payload (IC₅₀ ~ low pM),¹¹⁴ generated dose-limiting toxicities without any partial and/or complete responses in patients treated with doses up to 4.8 mg/kg every 3 weeks (doses ≥ 3.6 mg/kg deemed intolerable due to dose-limiting toxicities of rash, mucositis, and neutropenia).⁷¹ No clinical trial data have been published surrounding the highly potent maytansine payload ADC, BAT8003, although dose-limiting toxicities are suspected.

CD79b is targeted by the approved ADC Polivy™. A follow-on site-specific CD79b-targeting ADC, iladatuzumab vedotin, was tested in combination with rituximab. Iladatuzumab vedotin was ultimately discontinued because no improvement in the therapeutic index (vs Polivy™) was noted due to ocular toxicity at higher doses.⁶⁰

Three ADCs targeting CD33, the target of Mylotarg™, were also discontinued. AVE9633 (DM4 payload) showed no clinical activity below toxic doses;⁸⁹ IMGN779 (indolino-benzodiazepine dimer payload) where efficacy was not reported;¹⁰⁶ and vadastuximab talirine (PBD payload) that was discontinued following combination studies with hypomethylating agents citing safety concerns that included fatal infections.⁹⁷ One CD33 targeting ADC with a tubulysin payload, DXC007, is currently in Phase 1 (Registration number CTR20221074), although safety and efficacy data have yet to be released.

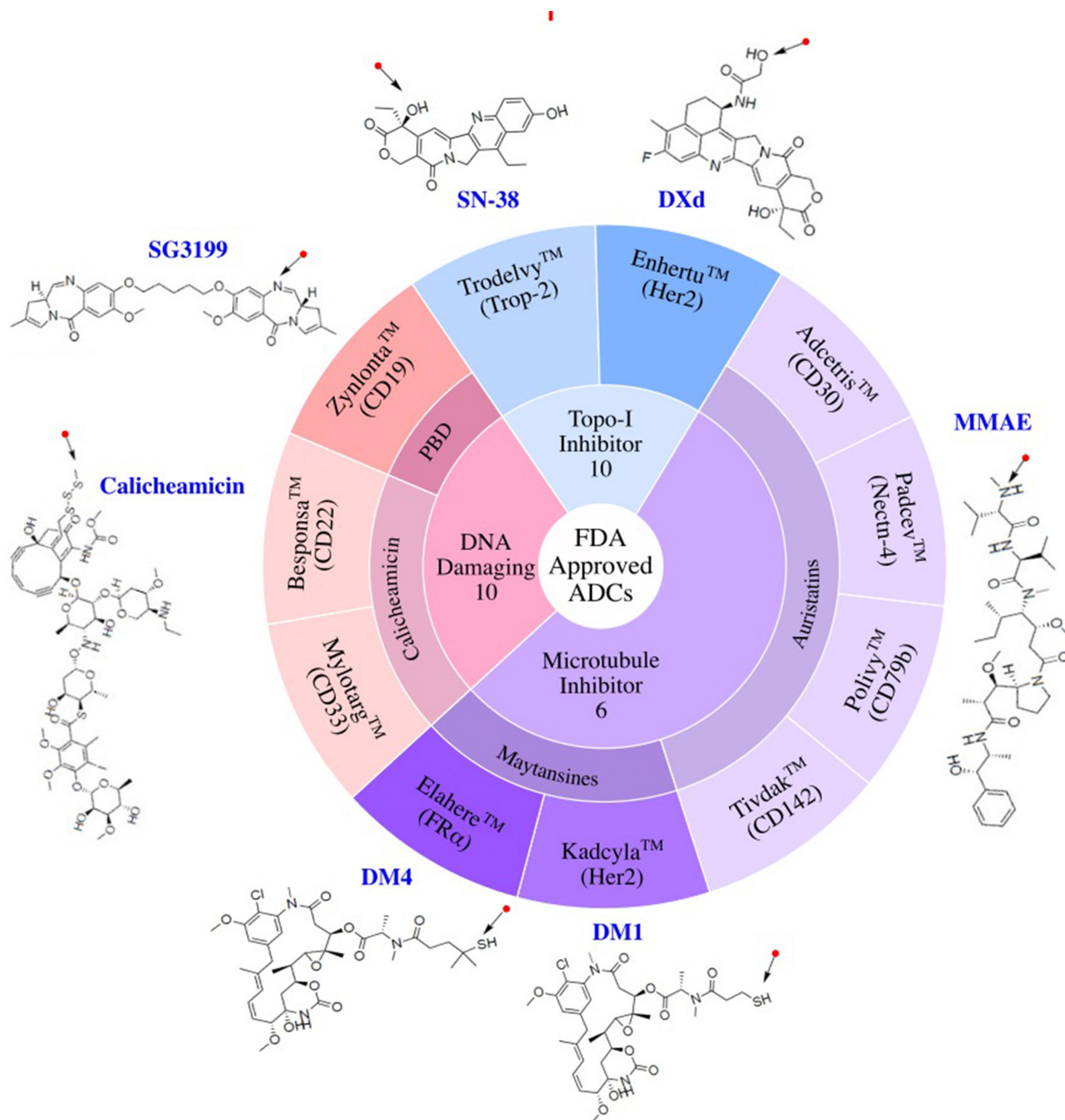


Figure 8. FDA Approved ADCs Classified by Payload Class. ADC drug name, target antigen, and names and chemical structures of payloads are shown. Arrows mark the point of attachment of payload to the antibody. Topo-I, Topoisomerase I Inhibitor; PBD, pyrrolobenzodiazepine.

Infusion-related adverse events were cited for the discontinuation of LOP628 (c-KIT)⁷⁹ and losatuzumab vedotin (EGFR).⁴⁰ Additionally, poor tolerability and lack of objective responses of DCLL9718S (CLL-1) at doses tested did not justify its further development.⁹⁹ In some discontinued ADCs, the clinical toxicity profile did not match preclinical observations, such as the CDH6 targeting ADC, HKT288, that showed neurological toxicity in patients not observed in preclinical models.⁸⁴ Similarly, aprutumab ixadotin (FGFR2) had a clinical MTD below the therapeutic threshold estimated preclinically.⁶⁸ These latter two examples highlight the need for better predictive models to guide ADC clinical development.

In addition to intolerable toxicity, insufficient efficacy is also a cause of ADC discontinuation. Factors contributing to insufficient efficacy include 1) low tumor target antigen densities and/or poor internalization properties of discontinued ADCs, 2) insufficient payload potency, 3) heterogeneous DAR ADC products resulting in sub-optimal doses of payload, 4) off-tumor payload release and/or incomplete drug release in tumors, 5) rapid clearance of ADC due to poor PK properties, 6) failure to demonstrate efficacy superiority over standard of care, and 7) multidrug resistance mediated through elevated drug efflux transporters in tumors.

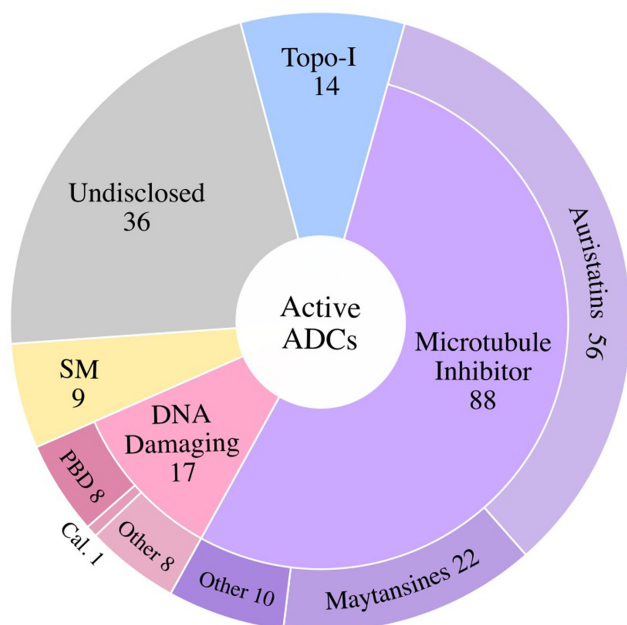


Figure 9. Active ADCs Classified by Payload Class. Of the active ADCs in clinical testing, the majority utilize microtubule inhibitor payloads, followed by DNA Damaging Agents, Topoisomerase I Inhibitors (Topo-I), and targeted small molecules (SM). ~22% of active ADCs have not disclosed the payload utilized (Undisclosed). PBD, pyrrolbenzodiazepine; Cal., calicheamicin.

Of the discontinued ADC candidates where data is available, insufficient efficacy was a likely contributing factor in ~47% of the cases. Candidates that were reported to demonstrate insufficient efficacy to warrant further clinical testing include, but are not limited to, tamrintamab pamozirine (DPEP3),²⁷ PF-06647263 (EFNA4),¹⁰⁰ and PCA062 (P-Cadherin).⁸¹ It is possible that some of these ADC targets had heterogenous tumor expression and/or insufficient tumor antigen densities to induce efficient ADC internalization.

Utilization of payloads with insufficient potency, contributing to insufficient efficacy, was a possible contributing factor leading to discontinuation of the HER2-targeting immunomodulatory ADCs NJH395 and SBT6050. No objective responses were observed in 18 patients treated with NJH395 (TLR7 agonist payload).¹⁰⁹ Likewise, only one of 14 patients achieved a partial response with SBT6050 (TLR8 agonist payload).¹¹⁰ For these TLR agonist ADCs, it is also possible that the lack of clinical activity is tied to suboptimal activation of an antitumor immune response. The clinical HER2 maytansinoid ADC BAT8001⁹⁰ was discontinued, possibly to advance a less potent topoisomerase I inhibitor payload ADC (BAT8010). This discontinuation/advancement decision is in line with the clinical experience of the two approved HER2 ADCs, KadcylaTM and EnhertuTM, where the ADC employing the lower potency payload (EnhertuTM) demonstrates greater clinical activity.¹¹⁵

ADCs with heterogenous DAR mixtures resulting in suboptimal doses of payload was the likely cause of the lower efficacy observed with the nonspecific cysteine conjugate MUC16 ADC, sofituzumab vedotin,⁵² when compared to the specific cysteine (THIOMABTM) conjugate ADC, DMUC4064A.⁵³ CMB-401 (MUC1) is an example of an ADC discontinued due to insufficient efficacy that may in

part be due to poor linker choice leading to off-tumor payload release.¹⁰² It was suggested that the failure of this calicheamicin ADC to elicit a single partial remission was due to the utilization of the labile amid linker.¹⁰² MEDI4267 is an example of an ADC discontinued due to poor PK properties (and intolerable toxicity). It was noted that this HER2-targeted tubulysin ADC, at MTD, had a very short half-life and high clearance relative to the HER2-targeted ADC, KadcylaTM, at its MTD.⁹¹

Seven ADCs were discontinued due to failure to demonstrate superiority over standard chemotherapy comparator arms: rovalpituzumab tesirine (DLL3),^{28,29} depatuxizumab mafodotin (EGFRvIII),^{64,116,117} AMG 595 (EGFRvIII),⁸⁰ AGS16F (ENPP3),⁶⁵ glembatumumab vedotin (gpNMB),⁴⁶ and lifastuzumab vedotin (NaPi-2b).⁵⁴ Supplementing standard chemotherapy with lorvotuzumab mertansine (CD56) increased incidence of adverse events without enhancing efficacy.^{76,118}

Clinical information regarding the remaining 22 of the 92 discontinued ADCs remains unpublished (AbGn-107, AGS67E, BAT8003, BIIB015, cantuzumab ravtansine, IMG388, milatuzumab doxorubicin, laprituximab emtansine, lupartumab amadotin, MEDI2228, MEDI7247, PF-06688992, SAR428926, SBT6290, SC-005, SC-006, SGN-CD19B, SGN-CD48A, SGN-CD123A, SGN-CD352A, sirtratumab vedotin, and XMT-1592). Of these 22, companies cited portfolio prioritization/strategic considerations and lack of accrual for 48% and 2% of discontinuations, respectively, but no reason for discontinuation was given for the remaining 50%.

Implications for future ADC drug design

Development of the next generation of ADCs with a potential to improve their therapeutic index can be broken down into

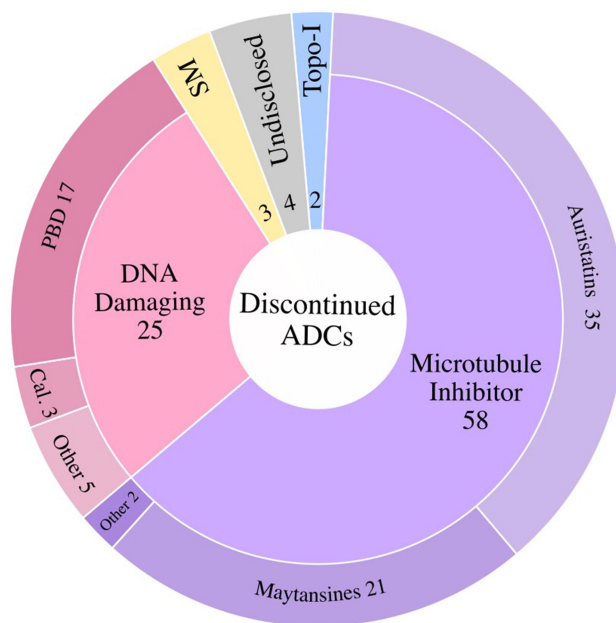


Figure 10. Discontinued ADCs Classified by Payload Class. The major payload classes utilized in the discontinued ADCs are the microtubule inhibitors and DNA Damaging Agents. Topoisomerase I Inhibitors (Topo-I), targeted small molecules (SM), and undisclosed candidates combined make up ~9% of the discontinued ADCs. PBD, pyrrolbenzodiazepine; Cal., calicheamicin.

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation Linker	Amino Acid Linker	Phase Regimen	Trial Identifier	DAR	Company	Years in Pipeline	Indication(s)	Trial Design Results	Ref
1	Microtubule Inhibitors – Auristatins – MMAE: Solid Tumors (16)	Tyrosine-protein kinase receptor UFO (AXL)	enaptotamab vedotin; AXL-107-MMAE; HuMax-AXL-ADC		Phase 1/2 Monotherapy NCT02988817					OC, Cervical Cancer, NSCLC, Thyroid Cancer, Melanoma, Sarcoma	n = 306, dose escal. 1Q3W (0.3–2.4 mg/kg) and 3Q4W (0.6–1.2 mg/kg); dose exp. at 2.2 mg/kg 1Q3W and 1.0 mg/kg 3Q4W. Safety: Dose escal. DLTs noted in 13.3% pts. Dose exp., 49% pts. had TSEAs; 90% pts. had treatment emergent infusion AEs. 61% pts. had Gr ≥3 TRAEs. Efficacy: Dose exp., 8% ORR. Minimal efficacy at tolerated doses.	25
2	Carbonic anhydrase 9 (CA9)	BAY79-4620	Nonspecific Cys conj.	Cleavable, Val-Cit linker	Phase 1 Monotherapy NCT01028755	Completed				Solid Tumors	n = 12, no published results	25
3	Epidermal growth factor receptor (EGFR)	losatuzumab vedotin; ABBV-221	Nonspecific Cys conj.	Cleavable, Val-Cit linker	Phase 1 Monotherapy NCT02365662	Terminated, safety		Bayer; MorphoSys	2009–2011	Solid Tumors	n = 2, no published results	25
4	Endothelin receptor type B (EDNRB)	DEDN6526A; RG7636	Nonspecific Cys conj.	Cleavable, Val-Cit linker	Phase 1 Monotherapy NCT01522664	Completed, minimal clinical efficacy at tolerated doses		Roche-Genentech; Seagen	2012–2014	Melanoma	n = 53, dose escal. 0.3–2.8 mg/kg Q3W, RP2D 2.4 mg/kg Q3W. Safety: DLTs included infusion-related reactions, increased ALT/AST, and liver injury. At RP2D, Gr 3+ AEs observed in 38% pts. including neutropenia (25%), ALT increase (7%), infusion reactions and PN (3% each). Efficacy, RP2D: 12.5% PR. Minimal clinical efficacy at tolerated doses.	41
5	Guanylyl cyclase C (GUCY2C)	indusatumab vedotin; 5F9-vcMMAE; MLN0264; TAK-264	Nonspecific Cys conj.	Cleavable, Val-Cit linker	Phase 2 Monotherapy NCT02202785	Terminated, minimal activity at tolerated doses				PC	n = 43, 1.8 mg/kg Q3W. Safety: 35% pts. experienced ≥3 Gr AEs; 12% had SAEs. Nausea (33%), fatigue (28%), and neutropenia (23%) noted. Efficacy: 3% ORR, 1 PR. Minimal clinical activity noted at tolerated doses.	42
					Phase 2 Monotherapy NCT02202759	Terminated, minimal efficacy at tolerated doses				Stomach Cancers, GEJC	n = 38, 1.8 mg/kg Q3W. Safety: 37% pts. experienced ≥3 Gr AEs that included anemia, diarrhea, and neutropenia. Efficacy: 6% ORR. Limited efficacy at tolerated doses.	43

Descriptions of Ph. 1 trials (NCT02391038, NCT01577558) are not included.

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

Target		Phase		Indication(s)		Trial Design Results		Ref	
No.	Molecule Conjugation Amino Acid Linker Payload DAR Company Years in Pipeline	Regimen Trial Identifier Status	Phase 2 Monotherapy NCT02487979	OS	OS	n = 22, Q3W, dose not specified. Safety: SAEs in 36.4% pts. including rash (13%), anemia (9%), hypokalemia (9%), and febrile neutropenia (4.5%). Efficacy: 4.5% ORR.	25		
6.	Glycoprotein NMB (GPNMB) glenatatumumab vedotin; CDX-011; CR011vcMMAE Nonspecific Cys conj. Cleavable, Val-Cit linker MMAE payload DAR~2.7 Celldex Therapeutics; Seagen Inc. 2008–2018	Phase 2 Monotherapy NCT02363283	Uveal Melanoma	Uveal Melanoma	n = 35; 1.9 mg/kg Q3W. Safety: The most common Gr 3/4 AE was neutropenia (48%), others occurring in 3–6% of pts. included elevated ALT/AST and leukopenia. One Gr 5 encephalopathy was noted. Efficacy: 6% PR, mDOR 8.6 months, mPFS 3.1 months, mOS 11.9 months. Minimal efficacy noted at doses administered.	44			
	<i>Descriptions of the six Ph2 trials are presented. Descriptions of Ph.1/2 (NCT03326258, NCT02713828, NCT00704158, NCT00412828), Ph. 1 (NCT03473691, ACTRN12617001621303), and Expanded Access (NCT03067935) trials are not included.</i>	Phase 2 Combination with varlilumab, nivolumab, pembrolizumab, or CDX-301 (Fit3L) NCT02302339	Melanoma	Melanoma	n = 132; of these 62 pts. given 1.9 mg/kg (reduced to 1.3/1.0 mg/kg in case of DLT). Safety: Gr ≥3 occurred in 37% pts., the most common of these were neutropenia (19%), rash (8%), and neuropathy (7%). A fatal pneumonia was deemed possibly drug related. Efficacy: 11% ORR, mDOR 6.0 months, mPFS 4.4 months, mOS 9.0 months.	45			
	Completed, minimal efficacy noted at doses administered	Phase 2 (METRIC) Combination with capecitabine NCT01997333	gpNMB+ TNBC	gpNMB+ TNBC	n = 327; pivotal trial, randomly assigned to 2 arms: ADC (n = 218) vs capecitabine (n = 109). Safety: Gr ≥3 AEs for ADC included neutropenia (28%), rash (12%), leukopenia (9%), SAEs included septic shock that resulted in death (3 pts.). Efficacy: ADC vs capecitabine-mPFS 2.9 vs 2.8 months (HR 1.13), mOS 8.9 vs 8.7 months (HR 1.06), ORR 16% vs 15%. Study did not meet primary endpoint of improved PFS.	46			
	Terminated, minimal efficacy at doses tested	Phase 2 (EMERGE) Monotherapy vs investigator's choice (IC) chemotherapy NCT01156753	BC	BC	n = 124; selected for gpNMB+ in ≥ 5% of epithelial/stromal cells by IHC; randomly assigned 2:1 to ADC (n = 83, 1.9 mg/kg Q3W) or investigator's choice (IC, n = 41). Safety: ADC vs IC: DLTs 8% vs 5%; 40% of ADC pts. had Gr 3/4 AEs including neutropenia (22%), fatigue (7%), PN (3%). Efficacy: ADC vs IC: ORR 12% vs 12%, PR 6% vs 7%, mOS 7.5 vs 7.4 months. ADC arm did not provide improved efficacy over comparator.	47			
	Completed, ADC arm did not provide improved efficacy over IC comparator arm	Phase 2 Monotherapy, biomarker analysis NCT02487979	OS	OS	n = 22 adolescents/YAs, 1.9 mg/kg, Q3W. Safety: DLTs in 6 pts. Gr ≥3 AEs included rash (9.8%) and hypokalemia (6.6%), one possible fatal TRAE, end organ failure. Efficacy: 4.5% PR. Limited efficacy with DLTs noted in 6/22 pts. with one possible fatal TRAE.	48			

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Phase	Regimen	Trial Identifier	Indication(s)	Trial Design Results	Ref
7.	Leucine-rich repeat- containing protein 15 (LRRC15)	Conjugation Amino Acid Linker Payload DAR Company	Phase 1 Monotherapy	ABBV-085	NCT02565758	Solid Tumors	n = 85, 0.3–6.0 mg/kg Q2W, dose exp. (n = 45) at 3.6 mg/kg Q2W. Safety. 3.6 mg/kg: Gr ≥3 AEs occurred in 31% of pts, including fatigue (7%), anemia (4%), and neuropathy (4%). Efficacy. 3.6 mg/kg: 20% ORR for osteosarcoma and undifferentiated pleomorphic sarcoma. Tolerable safety with evidence of anti-tumor activity.	49
8.	Lymphocyte antigen 6E (LY6E)	DMUC4064A; D-4064a; RG7882 Specific Cys (THIOMAB™) conj. Cleavable Val-Cit linker MMAE payload DAR~2 Abbvie; Seagen Inc. 2015–2019	Phase 1 Monotherapy	ABBV-085	NCT02092792	Solid Tumors including BC and NSCLC	n = 68, 0.2–2.4 mg/kg Q3W; no DLTs, MTD not reached. RP2D 2.4 mg/kg Q3W. Safety. RP2D: Gr ≥3 AEs occurred in 25% of pts., including neutropenia (10%) and hypertension (5%). Efficacy. RP2D: 11.5% PR in BC, 22% PR in NSCLC. Preliminary efficacy noted at doses tested.	50
9.	Mesothelin (MSLN)	DMOT4039A; oMSLN-MMAE; RG7600 Nonspecific Cys conj. Cleavable Val-Cit linker MMAE payload DAR~3.5 Roche-Genentech; Seagen Inc. 2011–2014	Phase 1 Monotherapy	Seagen-001	NCT01469793	OC, PC	n = 71 (40 PC, 31 OC), Q3W (n = 54) 0.2–2.8 mg/kg or QW (n = 17) 0.8–1.2 mg/kg. Q3W-MTD and RP2D = 2.4 mg/kg. QW-MTD 1.2 mg/kg and RP2D = 1 mg/kg. Safety. RP2D: Gr ≥3 AEs occurred in 38% of pts., including pyrexia, gastroparesis, hypotension, sinus tachycardia, and infection. Efficacy. RP2D: PC 8% PR, mPFS 1.7 months; OC 30% PR, mPFS 4.9 months. Tolerated but with limited efficacy at MTD.	51
10.	Mucin-16 (MUC16)	softizuzumab vedotin; DMUC5754A; RG7458 Nonspecific Cys conj. Cleavable Val-Cit linker MMAE payload DAR~3.5 Roche-Genentech; Seagen Inc. 2011–2016	Phase 1 Monotherapy	Seagen-001	NCT01335958	OC, PC	n = 77 (66 PSOC, 11 PC), two dosing regimens: Q3W (n = 54) 0.3–3.2 mg/kg and Q1W (n = 23) 0.8–1.6 mg/kg. RP2D of 2.4 mg/kg Q3W or 1.4 mg/kg QW. Safety. RP2D Q3W: Gr ≥3 AEs included neutropenia (10%), fatigue (10%), and peripheral neuropathy (15%). SAEs included small intestine obstruction, hypocalcemia, and neutropenia. 4 patient deaths were due to AEs: respiratory failure (2), sepsis (1), and acute renal failure (1). Efficacy. RP2D: ~17% ORR Limited efficacy noted at doses tested.	52
11.	Mucin-16 (MUC16)	DMUC4064A; D-4064a; RG7882 Specific Cys (THIOMAB™) conj. Cleavable Val-Cit linker MMAE payload DAR~2.0 Roche-Genentech; Seagen Inc. 2014–2018	Phase 1 Monotherapy	Seagen-001	NCT02146313	OC, PC	n = 65, 1.0–5.6 mg/kg. MTD not reached. RP2D of 5.2 mg/kg. Q3W. Safety. RP2D Q3W: Gr ≥3 AEs in 62% pts, including fatigue (15%), keratitis (12%), and blurred vision (4%). Efficacy. RP2D: ~42% ORR, mPFS 5.3 months. Evidence of antitumor efficacy at tolerated doses.	53

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid	Linker	Payload	DAR	Company	Years in Pipeline	Phase	Regimen	Trial Identifier	Status	Indication(s)	Trial Design Results	Ref
12.	Sodium-dependent phosphate transport protein 2B, NaPi-2b (SLC34A2)	lifastuzumab vedotin; DNIB0600A; NaPi2b ADC; RG7599	Nonspecific Cys conj.	Cleavable Val-Cit linker	MMAE payload	DAR~3.5	Roche-Genentech; Seagen Inc.	2011–2016	Phase 2	Monotherapy vs PLD (PEGylated liposomal doxorubicin)	NCT01991210	OC	Terminated, primary efficacy PFS endpoint not met	n = 95, randomized 1:1 to ADC (n = 47) vs PLD (n = 48). Safety: ADC Gr ≥3 AEs occurred in 46% pts, including 30% SAEs. Additional AEs included abdominal pain (46%), constipation (24%), diarrhea (35%), neutropenia (28%), and stomatitis (7%). Efficacy: ADC vs PLD – mPFS 5.3 vs 3.1 months, mDOR 5.5 vs 3.9 months. 34% ORR (2% CR, 32% PR) vs 15% ORR (2.1% CR and 12.5% PR). Tolerated with objective responses but primary efficacy PFS endpoint not met.	54	
13.	Choline transporter-like protein 4 (SLC44A4)	ASG-5ME; AGS-5; AGS-5ME	Nonspecific Cys conj.	Cleavable Val-Cit linker	MMAE payload	DAR~ Undisclosed	Agensys, Inc.; Astellas Pharma Inc.; Seagen Inc.	2010–2013	Phase 1	Monotherapy	NCT01228760	PC, GC, CRPC	Completed, minimal efficacy at MTD	n = 35; PC, n = 20, 0.3–1.5 mg/kg, 3XQW-one week off cycle. MTD 1.2 mg/kg; GC, n = 15, dose exp. at MTD. Safety: Gr ≥3 AEs in 68.6% PC pts, included neutropenia (20%), anemia (8.6%), and pleural effusion (5.7%). Gr ≥3 AEs in 87.6% GC pts, included keratitis (20%), dyspnea and ascites (13% each) and sepsis (6.7%). 1 probable drug-related death, sepsis, in GC patient. Efficacy: 1 PR for PC; 1 PR for GC; DCR of 33% for PC and 47% for GC. n = 46 CRPC, dose esc. (n = 26) 0.3–3.0 mg/kg Q3W, dose exp. (n = 20) at 2.4/2.7 mg/kg Q3W, MTD 2.7 mg/kg Q3W. Safety: Gr ≥3 AEs in 55% dose exp. pts, including 2 deaths attributable to drug (1 multiorgan failure, 1 sepsis). Efficacy: 2 PR. Limited efficacy at MTD.	55, 56	
14.	SLIT and NTRK-like protein 6 (SLITRK6)	sirratumab vedotin; ASG-15ME; AGS-15E	Nonspecific Cys conj.	Cleavable Val-Cit linker	MMAE payload	DAR~4	Seagen Inc.; Astellas Pharma Inc.	2013–2018	Phase 1	Monotherapy	NCT01963052	Urothelial Cancer	Completed	n = 93, no published results	25	
15.	Metalloenducase STEAP-1 (STEAP1)	vandortuzumab vedotin; DSTP3086S; RG7450	Nonspecific Cys conj.	Cleavable Val-Cit linker	MMAE payload	DAR~2.0	Roche-Genentech; Seagen Inc.	2011–2016	Phase 1	Monotherapy	NCT01283373	Prostate Cancer	Completed, minimal efficacy at doses tested	n = 84 (Q3W, n = 77; QW n = 7), 0.3–2.8 mg/kg Q3W, RP2D 2.4 mg/kg Q3W. Safety: Gr ≥3 AEs occurred in 24% of pts., the most common of which were peripheral neuropathy (5%) and ALT increase (5%). Efficacy: >50% PSA reduction in 14% pts.; 4% PR. Minimal efficacy at doses tested.	57	

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid	Linker	Phase Regimen	Trial Identifier	Status	Indication(s)	Trial Design Results	Ref
16.	Hepatitis A virus cellular receptor 1, TIM-1 (HAVCR1)	CDX-014	Nonspecific Cys conj.	Cleavable Val-Cit linker	MMAE payload	DAR~4.5	Cellidex Therapeutics	2016–2018	RCC, Kidney Cancers, OC	n = 16, 0.15 – 2.0 mg/kg Q3W or 1.2 mg/kg Q2W; RP2D 1.8 mg/kg Q3W. Safety: 1 patient death due to multiorgan failure at 2 mg/kg. Other Gr ≥3 included hyperglycemia (19%) and Gr 4 urosepsis in 1 patient. Efficacy: 6% PR, mPFS 2.7 months, OS 12.6 months. Limited efficacy at tolerated doses.	58
Microtubule Inhibitors – Auristatins – MMAE: Hematological Malignancies (6)											
17.	B-cell receptor CD22 (CD22)	pinatuzumab vedotin; DCDT2980; RG7593	Nonspecific Cys conj.	Cleavable Val-Cit linker	MMAE payload	DAR~3.5	Roche-Genentech	2010–2015	DLBCL, FL	n = 231; comparison of rituximab + pinatuzumab vedotin (R-Pina) vs rituximab + polatuzumab vedotin (R-Pola); Arms DLBCL (n = 81; 42 given R-Pina, 39 given R-Pola) and FL (n = 41; 21 given R-Pina, 20 given R-Pola). Safety: R-Pina vs R-Pola: Gr ≥3 AEs in DLBCL 79% vs 77%; in FL 62% vs 50%. Efficacy: R-Pina vs R-Pola: DLBCL -ORR 60% vs 54%; CR 26% vs 21%. FL -ORR 62% vs 70%; CR 5% vs 45%. Pola was selected for advancement based on superior clinical activity.	59
18.	Leukocyte antigen CD37 (CD37)	AGS67E	Nonspecific Cys conj.	Cleavable Val-Cit linker	MMAE payload	DAR~2.3	Astellas Pharma Inc.; Seagen Inc.	2014–2018	Lymphoid Malignancy	n = 71, no published results.	25
<i>Description of Ph. 1 trial (combination with rituximab; NCT01209130) is not included.</i>											
19.	CD48 antigen (CD48)	SGN-CD48A	Specific Cys conj.	Cleavable β-glucuronidase (BG) linker	MMAE payload	DAR~8	Seagen Inc.	2018–2019	AML	n = 23; no published results.	25
Terminated, business decision											
19.	CD48 antigen (CD48)	SGN-CD48A	Specific Cys conj.	Cleavable β-glucuronidase (BG) linker	MMAE payload	DAR~8	Seagen Inc.	2018–2019	MM	n = 14, no published results.	25
Terminated, overall benefit/risk profile											

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation Amino Acid Linker	Payload	DAR	Company	Years in Pipeline	Phase Regimen Trial Identifier Status	Indication(s)	Trial Design Results	Ref
20.	B-cell antigen receptor complex-associated protein beta chain (CD79B)	iladotuzumab vedotin; DCDS0780A; RG7986	Specific engineered Cys (THIOMAB™) conj.	Cleavable Val-Cit linker	MMAE payload	DAR~2	Roche-Genentech; Seagen Inc. 2015–2018	Phase 1 Monotherapy and Combination with rituximab or obinutuzumab NCT02453087	NHL	n = 60, Monotherapy dose esc. (n = 51) 0.3–4.8 mg/kg Q3W; Combination (n = 9) 3.6 or 4.8 mg/kg with rituximab, 375 mg/m ² . Safety: Gr ≥3 AEs in (5%) pts. included neutropenia (23%), hypercalcemia (5%), thrombocytopenia (5%), and decreased white blood cell count (5%). 53% of monotherapy and 55% of combination group had ocular toxicity. Efficacy: ADC monotherapy~47% ORR, 18% PR, 28% CR; ADC + rituximab~59% ORR, mPFS for all pts. 4.4 months, DLBCL mPFS 3.9 months. Did not demonstrate superior efficacy vs Polivy™ + rituximab with enhanced ocular toxicity.	60
21.	Fc receptor-like protein 5 (FCRL5)	DFRE4539A; RG7598	Nonspecific Cys conj.	Cleavable Val-Cit linker	MMAE payload	DAR~ Undisclosed	Roche-Genentech; Seagen Inc. 2011–2014	Phase 1 Monotherapy NCT01432353	MM	n = 39, 0.3–2.4 mg/kg Q3W or 0.8–1.1 mg/kg QW; RP2D 2.4 mg/kg Q3W. Safety: at RP2D: Gr ≥ 3 AEs in 47% pts. including neutropenia (17.6%), thrombocytopenia, acute renal failure, hyponatremia, and nervous system disorders (11.8% each). SAEs in 21% pts. PN in 21% pts. Efficacy: at RP2D: 5% PR, 3% MR. Completed, minimal efficacy noted at doses tested.	61
22.	SLAM family member 7 (SLAMF7)	azintuzumab vedotin; ABBV-838	Nonspecific Cys conj.	Cleavable Val-Cit linker	MMAE payload	DAR~ Undisclosed	AbbVie 2015–2017	Phase 1 Combination with pomalidomide, dexamethasone NCT02462525	MM	n = 75, dose escal. (n = 32) 0.6–6.0 mg/kg Q3W or (n = 8) 1.5 mg/kg Q1W or (n = 6) 3.0 mg/kg Q2W. Dose exp. (n = 29) at 5.0 mg/kg Q3W. Safety: 73.3% Gr >3 AEs including neutropenia (20.0%), anemia (18.7%), and leukopenia (13.3%). SAEs in 36.0% pts. PN in 18.7% of pts. Efficacy: 10.7% ORR (2.7% VGPR, 8.0% PR), mDOR 4 months. Limited efficacy at tolerated doses.	62
23.	Microtubule Inhibitors – Auristatins – MMAF: Solid Tumors (5)	Trophoblast glycoprotein, 5T4 (TPBG)	PF-06263507	Nonspecific Cys conj.	Non-cleavable mC linker	MMAE payload	DAR~ 4	Phase 1 Monotherapy NCT01891669	Neoplasms, NSCLC, BC, OC	n = 26, 0.5–6.5 mg/kg Q3W, MTD and RP2D 4.34 mg/kg Q3W. Safety: At the RP2D, 16.7% of the pts. had treatment related Gr 3/4 events including ocular toxicity, infection, hypophosphatemia, and embolism. 38.5% of pts. experienced Gr 1/2 ocular toxicity. Efficacy: No ORR. No ORR with severe ocular toxicity.	63

Description of withdrawn Ph.1 trial (NCT02951117) is not included.

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target Molecule Conjugation Amino Acid Linker Payload DAR Company Years in Pipeline	Phase Regimen Trial Identifier Status	Indication(s)	Trial Design Results	Ref
24.	Epidermal growth factor receptor variant III (EGFRvIII) depatuxizumab mafodotin, ABT-414; Depatux-M Nonspecific Cys conj. Non-cleavable mc linker MMAF payload DAR~ 4 AbbVie; Seagen Inc. 2013–2018 <i>Results of Ph. 2 trials (NCT02343406, NCT02590263), Ph. 1/2 trial (NCT02590263), Ph. 1 trials (NCT01800695, NCT01741727), and one Expanded Access trial (NCT03123952) are not included.</i>	Phase 3b (UNITE) Combination with temozolomide (TMZ) + radiation (RT) vs TMZ + RT assessing differing prophylactic ophthalmologic treatments NCT03419403 Terminated, ADC was discontinued due to lack of survival benefit	GBM	n = 40 Independent Data Monitoring Committee responsible for interim analysis review recommended study termination due to lack of survival benefit.	25
25.	Ectonucleotide pyrophosphatase/phosphodiesterase family member 3 (ENPP3) AGS16F; AGS-16C3F; AGS-16M8F Nonspecific Cys conj. Non-cleavable mc linker MMAF payload DAR~ 4 Astellas Pharma Inc.; Seagen Inc. 2010–2019 <i>Descriptions of Ph. 1 trials (NCT01114230, NCT01672775) are not included.</i>	Phase 2 Monotherapy vs axitinib NCT0263912 Completed, did not meet primary PFS efficacy endpoint	RC	n = 639; double blind randomization 1:1 into 2 Arms, ADC (n = 323; 1.25 mg/kg Q2W) + TMZ + RT vs placebo (n = 316) TMZ + RT; trial amended to Ph. 3 with OS as primary endpoint based on early results of Ph. 2 INTELLANCE-2 trial. Safety: Gr >3 AEs in 80% of ADC group vs 58% placebo. Ocular AEs- 94% vs 36%; thrombocytopenia- 61% vs 36%; gamma-glutamyltransferase increase-10.8% vs 1%. Efficacy: OS 18.9 vs 18.7 months (HR 1.02); mPFS EGFRvIII group 8.3 vs 5.9 months; mPFS for pts. without EGFRvIII 6.9 vs 7.9 months. ADC provided no OS benefit over placebo arm.	64
25.	Ectonucleotide pyrophosphatase/phosphodiesterase family member 3 (ENPP3) AGS16F; AGS-16C3F; AGS-16M8F Nonspecific Cys conj. Non-cleavable mc linker MMAF payload DAR~ 4 Astellas Pharma Inc.; Seagen Inc. 2010–2019 <i>Descriptions of Ph. 1 trials (NCT01114230, NCT01672775) are not included.</i>	Phase 2 Monotherapy vs axitinib NCT0263912 Completed, did not meet primary PFS efficacy endpoint	RC	n = 133; randomized 1:1 ADC at 1.8 mg/kg Q3W vs axitinib. Safety: ADC common AEs included fatigue (53%), nausea (47%), and ocular (44%). ADC Gr >3 AEs included fatigue, dry eye, and thrombocytopenia (3–5%). Efficacy: ADC vs. axitinib – mPFS 2.9 vs. 5.7 months (p = .015), mOS 13.1 vs. 15.4 months (p = .747). Did not meet primary efficacy endpoint of improved PFS.	65
26.	Ephrin type-A receptor 2 (EPHA2) MEDI-547; MC-CP177 Nonspecific Cys conj. Non-cleavable mc linker MMAF payload DAR~ 4 AstraZeneca; Seagen Inc. 2012–2019	Phase 1 Monotherapy NCT00796055 Terminated, intolerable toxicity with no clinical responses	Solid Tumors	n = 6, 0.08 mg/kg Q3W. Safety: 4/6 (66.7%) pts. experienced SAEs including conjunctival hemorrhage, liver disorder, and hemorrhage deemed to be treatment related. Efficacy: All pts. discontinued treatment due to progressive disease (n = 4) or plan to pursue alternative treatment (n = 2). No clinical responses were observed. Study terminated due to intolerable toxicity with no efficacy benefit.	66

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid Linker	Payload	DAR	Company	Years in Pipeline	Phase Regimen	Trial Identifier	Status	Indication(s)	Trial Design Results	Ref
27.	CD70 antigen (CD70)	vorssetuzumab mafodotin; SGN-75	Non-specific Cys conj.	Non-cleavable mc linker	MMAF payload	DAR~ 4	Seagen Inc.	2009–2013	Phase 1 Monotherapy	NCT01015911	Completed, minimal efficacy at tolerated doses	RCC, NHL	n = 58 (39 RCC, 19 NHL), 0.3–4.5 mg/kg Q3W or 0.3/0.6 mg/kg Q1W. RCC: MITD 3 mg/kg Q3W NHL: dose esc. terminated due to thrombocytopenic purpura in 2 pts. Safety: Q3W AEs included dry eye (32%), nausea (30%), ocular AEs (57%), and thrombocytopenia (26%). The most common Gr ≥3 AE was thrombocytopenia (19%). Efficacy: Q3W; 1 CR (NHL, MCL), 2 PR (RCC). Minimal activity at tolerated doses.	67
	<i>Description of Ph. 1 trial (NCT01677390) is not included.</i>													
Microtubule Inhibitors – Auristatins – MMAF: Hematological Malignancies (1)														
28.	B-lymphocyte antigen CD19 (CD19)	denintuzumab mafodotin; SGN-CD19A	Non-specific Cys conj.	Non-cleavable mc linker	MMAF payload	DAR~ Undisclosed	Seagen Inc.	2012–2019	Phase 2 Combination with rituximab (R) cyclophosphamide (C), doxorubicin (H), vincristine (O), prednisone (P)	NCT02855359	Terminated, portfolio prioritization	DLBCL, FL, Transformed Lymphoma	n = 24; ADC (3 mg/kg Q6W) + RCHP, n = 11 and ADC (3 mg/kg Q6W) + RCHOP, n = 13. Safety: ADC + RCHP-100% pts. Gr >3 TEAE, 45.5% pts. with SAEs, AE with outcome of death-18.25%; ADC + RCHOP-92.3% pts. TEAE, 23.1% pts. SAEs, AE with outcome of death-7.7%. Efficacy: Efficacy outcomes of mPFS, OS, and ORR not assessed due to lack of study progression to these endpoints.	25
	<i>Descriptions of Ph. 1 trials (NCT01786135, NCT01786096) are not included; neither has published results.</i>													
Microtubule Inhibitors – Other Auristatins: Solid Tumors (7)														
29.	Tumor antigen AG-7	AbGn-107; Ab1-18H1	Non-specific Cys conj.	Cleavable Val-Cit linker	MMAF payload	DAR~ 2.5	AltruBio Inc.	2017–2021	Phase 1 Monotherapy	NCT02908451	Terminated due to COVID	GC, CRC, PC, Biliary Cancer	n = 39, no published results.	25
Urokinase plasminogen activator surface receptor, C4.4a (PLAUR)														
30.	Urokinase plasminogen activator surface receptor, C4.4a (PLAUR)	lupartumab amadotin; BAY1129980	Non-specific Cys conj.	Non-cleavable mc-hydrazide linker	Auristatin W analog payload	DAR~ 4	Bayer; Seagen Inc.	2014–2019	Phase 1 Monotherapy	NCT02134197	Terminated, reason not disclosed	Neoplasms	n = 69, no published results.	25

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid	Linker	Phase Regimen	Trial Identifier	Status	Indication(s)	Trial Design Results	Ref
31.	Fibroblast growth factor receptor 2 (FGFR2)	aprutumab	ixadotin; BAY1187982		Nonspecific Lys conj. Non-cleavable Caproyl linker	Phase 1 Monotherapy	NCT02368951	Terminated, intolerable toxicity with no clinical responses	FGFR2+ Solid Tumors	n = 20; 0.1–1.3 mg/kg Q3W, MTD 0.2 mg/kg Q3W. Safety: Gr ≥3 TEAEs included anemia, aspartate aminotransferase increase, proteinuria, and thrombocytopenia. Efficacy: No clinical responses were observed. Poorly tolerated with MTD reached below the therapeutic threshold estimated for efficacy.	68
32.	Receptor tyrosine-protein kinase erbB-2, HER2 (ERBB2)	XMT-1522; TAK-522			Nonspecific Cys conj. Cleavable Fleximer Polymer linker	Phase 1 Monotherapy	NCT02952729	Completed, minimal clinical activity at the doses tested	HER2+ BC, GC, NSCLC	n = 120 (estimated), prelim results with 19 pts., dose escal. 2.0–21.3 mg/m ² , no DLTs or SAEs, MTD and RP2D not reached. Safety: TRAEs included elevated liver enzymes, fatigue, nausea, and vomiting (Gr 1 or 2). Efficacy: At doses of 16 and 21.3 mg/m ² (6 pts.), 1 PR was observed. Tolerable safety profile but minimal clinical activity at doses tested.	69
33.	Sodium-dependent phosphate transport protein 2B, NaPi-2b (SLC34A2)	XMT-1592			Specific conj. (amino acid not disclosed) Cleavable undisclosed linker	Phase 1/2 Monotherapy	NCT04396340	Active, not recruiting	OC, NSCLC	n = 120, no published results	25
34.	Neurogenic locus notch homolog protein 3 (NOTCH3)	PF-06650808			Nonspecific Cys conj. Cleavable Val-Cit linker	Phase 1 Monotherapy	NCT02129205	Terminated, portfolio prioritization	Solid Tumors including BC	n = 40, 0.2–6.4 mg/kg Q3W, MTD 2.4 mg/kg Q3W. Safety: At MTD, 27.3% pts. had DLTs including Gr 3 rash, diarrhea, and thromboembolic event. 54.5% Gr 3 TRAEs included neutropenia, lymphopenia, and AST increase. Efficacy: At MTD, 14.3% pts. had objective responses. Minimal efficacy noted at MTD.	25, 70
35.	Tumor-associated calcium signal transducer 2, Trop-2 (TACD2)	PF-06664178; RN927C			Specific Glu conj. Cleavable Val-Cit linker	Phase 1 Monotherapy	NCT02122146	Terminated, unacceptable toxicity	Solid Tumors	n = 31, 0.15–4.8 mg/kg Q3W. Safety: ≥1 DLTs in 22.5% pts. at doses >3.6 mg/kg. Significant DLTs in skin and mucosa in the dose ranges tested. Gr 3/4 TRAEs noted in 45.5% pts. The most common Gr 4 TRAE was neutropenia and most common Gr 3 TRAE was rash. Efficacy: 0% ORR. Program discontinued due to unacceptable toxicity.	71

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target Molecule Conjugation Amino Acid Linker Payload DAR Company Years in Pipeline	Phase Regimen Trial Identifier Status	Indication(s)	Trial Design Results	Ref
Microtubule Inhibitors – Maytansine DM1: Solid Tumors (9)					
36.	Mucin-1, sialylated carbohydrate tumor antigen CA242 of Mucin-1 (MUC1) cantuzumab mertansine; huC242-DM1; SB-408075 Nonspecific Lys conj. Cleavable SPP linker DM1 payload DAR~ 3.5 GlaxoSmithKline; ImmunoGen, Inc. 1999–2014	Phase 1 Monotherapy HWID128999 Completed, tolerated with minimal activity at doses tested	CA242+ Solid Tumors	n = 37, 22–295 mg/m ² Q3W, recommended dose 235 mg/m ² Q3W. Safety: Reversible elevations of hepatic transaminases were the principal adverse events. Nausea, vomiting, and diarrhea were common but rarely severe at elevated doses. Efficacy: 2 minor regressions noted. Tolerated but with little clinical activity.	72
	<i>Description of Ph. 1 trial (HWID128964) is not included.</i>	Phase 1 Monotherapy HWID128907 Completed, no objective responses noted up to and including MTD	CA242+ Solid Tumors	n = 39, 40–138 mg/m ² Q1W, MTD: 115 mg/m ² . Safety: Gr ≥3 AEs at MTD included elevated lipase and alkaline phosphatase (4.3% each). Efficacy: No objective clinical responses (PR or CR) were noted. No objective responses noted up to and including MTD.	73
37.	CD44 antigen, variant 6 (CD44v6) bivatuzumab mertansine; B1W1-1 Nonspecific Lys conj. Cleavable SPP linker DM1 payload DAR~ Undisclosed Boehringer Ingelheim; ImmunoGen, Inc. 2002–2005	Phase 1 Monotherapy NCT02254044 Terminated, intolerable, dose limiting skin toxicity	HNSCC	n = 7, dose esc. 20–140 mg/m ² Q1W. Safety: Principal AEs- rashes, blisters, desquamation. 3 pts. developed desquamation 5–6 d after 1 st or 2 nd dose; one pt. (140 mg/m ²) died of toxic epidermal necrolysis. Efficacy: No objective clinical responses were observed at the doses tested. Program halted due to severe skin toxicity.	74, 75
38.	Neural cell adhesion molecule 1, CD56 (NCAM1) lonvotuzumab mertansine; BB-10901; huN901-DM1; IMGN901 Nonspecific Lys conj. Cleavable SPP linker DM1 payload DAR~ 3.5 ImmunoGen, Inc. 2002–2017	Phase 2 Combination with carboplatin and etoposide (CE) vs CE NCT01237678 Terminated, intolerable toxicity without efficacy benefit	SCLC	n = 91, ADC arm, n = 44, 90 mg/m ² , D1/D8 of 21-d cycle + CE vs CE, n = 47. Safety: ADC arm-88% of pts. experienced Gr ≥4 TRAEs including anemia (19%), peripheral sensory neuropathy (18%), neutropenia (17%), and thrombocytopenia (11%). TRAEs resulting in death occurred in 25% of pts. due to lethal infections. Efficacy: ADC arm vs CE-mPFS 6.2 vs 6.7 months (HR = 0.93); mOS estimates 10.1 vs 11 months. Intolerable toxicity without efficacy benefit.	76, 77
	<i>Descriptions of Ph. 1 trials (NCT02254031, NCT02254018, NCT02254005) are not included.</i>	<i>Descriptions of Ph. 2 trial (NCT02420873), Ph. 1/2 trials (NCT01237678, NCT00065429), and Ph. 1 trials (NCT00991562, NCT00346385, NCT00346255) are not included.</i>			

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

Target	Molecule	Conjugation	Amino Acid	Linker	Payload	DAR	Company	Years in Pipeline	Phase	Regimen	Trial Identifier	Indication(s)	Trial Design Results	Ref
39.	CD70 antigen (CD70)	AMG 172	Nonspecific Lys conj.	Non-cleavable MCC linker	DM1 payload	DAR~ Undisclosed	Angen; ImmunoGen, Inc.	2012–2016	Phase 1	Monotherapy		RCC	n = 172; dose esc. 0.15–2.4 mg/kg BW, MTD 1.6 mg/kg. Safety: TRAEs included thrombocytopenia (59%), anemia (32.4%), hypophosphatemia (29.7%), and AST increase (27%). Drug related DLTs included thrombocytopenia and hepatocellular injury.	78
									Completed, poor tolerability with limited clinical activity		At 1.6 mg/kg dose, 3/10 pts. had DLTs: Gr 3 liver injury, in 2 pts., Gr 3/4 thrombocytopenia in 2 pts., Gr 3 AST elevations in 2 pts. Efficacy: 5.4% PR. Poor tolerability with limited clinical activity.			
40.	Mast/stem cell growth factor receptor Kit, c-Kit (KIT)	LOP628	Nonspecific Lys conj.	Non-cleavable SMCC linker	DM1 payload	DAR~ Undisclosed	ImmunoGen, Inc.; Novartis Pharmaceuticals	2014–2016	Phase 1	Monotherapy	NCT02221505	c-KIT+ Solid Tumors	n = 3 GISTs; 0.3 mg/kg (without premedication) 1 patient and 0.15 mg/kg (with premedication) 2 pts. Safety: Hypersensitivity reactions (HSR) noted in all pts. within minutes of infusion of 1 st , 2 nd , or 3 rd dose; pts. were rescued with appropriate treatment; pre-medication controlled HSR, but reactions recurred in subsequent doses and ceased when dosing was discontinued. High serum tryptase noted in all pts. Study was terminated for safety.	79
									Terminated, intolerable toxicity					
41.	Epidermal growth factor receptor (EGFR)	laprituximab emtansine; IMG289; J2898A	Nonspecific Lys conj.	Non-cleavable SMCC linker	DM1 payload	DAR~ Undisclosed	ImmunoGen, Inc.	2013–2015	Phase 1	Monotherapy	NCT01963715	EGFR+ Solid Tumors	n = 20, no results published	25
									Terminated, reason not disclosed					
42.	Epidermal growth factor receptor variant III (EGFRvIII)	AMG 595	Nonspecific Lys conj.	Non-cleavable SMCC linker	DM1 payload	DAR~ 3.5	Amgen; ImmunoGen, Inc.	2012–2016	Phase 1	Monotherapy	NCT01475006	GBM, AA	n = 32 GBM, 0.5–3.0 mg/kg Q3W, MTD 2.0 mg/kg. Safety: DLT, Gr 4 thrombocytopenia in 31.25% pts., Gr ≥3 TRAEs noted in 53% pts. including thrombocytopenia (44%) and neutropenia, ALT/AST increase, and purpura (3% each). Efficacy: 6% PR. Minimal clinical activity at MTD.	80
									Completed, poor tolerability and minimal clinical activity at MTD					
43.	Cadherin-3, P-Cadherin (CDH3)	PCA062	Nonspecific Lys conj.	Non-cleavable SMCC linker	DM1 payload	DAR~ 3.8	ImmunoGen, Inc.; Novartis Pharmaceuticals	2015–2022	Phase 1	Monotherapy	NCT02375958	TNBC, HNC, Esophageal Cancer	n = 47; 0.4–5.0 mg/kg Q2W, MTD 3.6 mg/kg. Safety: Frequent AEs included elevated AST, anemia, pyrexia, and thrombocytopenia (34% each). 66.0% pts. had SAEs with 55.3% Gr≥3. The most frequently occurring SAE was pyrexia (6.4%), 17% of pts. observed at least one DLT event including thrombocytopenia, AST increase, and anemia. Efficacy: 1 PR (2%). Insufficient efficacy noted at MTD.	81
									Completed, poor tolerability with minimal clinical activity					

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target Molecule Conjugation Amino Acid Linker Payload DAR Company Years in Pipeline	Phase Regimen Trial Identifier Status	Indication(s)	Trial Design Results	Ref
44.	Prostate-specific membrane antigen, PSMA (FOLH1) MLN2704 Nonspecific Lys conj. Cleavable SPP linker DM1 payload DAR~ 3–4 Millennium Pharmaceuticals, Inc. 2002–2006	Phase 1/2 Monotherapy NCT00070837 Completed, dose-limiting neurotoxicity with an absence of objective tumor responses	Prostate Cancer	n = 62, various dose esc. Cohorts: 60–165 mg/m ² Q1W (n = 12), 120–330 mg/m ² Q2W (n = 15), 330/426 mg/m ² Q3W (n = 18), 330 mg/m ² , DID15Q6W (n = 17). Safety: PN (71%) – 10% of which were Gr 3/4; nausea (61%), fatigue (60%). Efficacy: Only 8% of pts. experienced ≥ 50% decline in PSA. No objective tumor responses were noted. Neurotoxicity was dose-limiting with no objective tumor responses, attributable in part to labile linker.	82
<i>Description of one Ph.1 trial (NCT00052000) is not included here.</i>					
Microtubule Inhibitors – Maytansines – DM1: Hematological Malignancies (1)					
45.	Tumor necrosis factor receptor superfamily member 17, BCMA (TNFRSF17) AMG 224 Nonspecific Lys conj. Non-cleavable MCC linker DM1 payload DAR~ Undisclosed Amgen 2015–2019	Phase 1 Monotherapy NCT02561962 Completed, evidence of antitumor activity noted at MTD	MM	n = 40; dose escal. 30–250 mg Q3W; n = 29; dose exp. 3 mg/kg Q3W with 2 cohorts: A (prior exposure to anti-CD38 Ab) and B (no prior exposure to anti-CD38 Ab). MTD 190 mg Q3W. Safety: Dose exp., Gr ≥ 3 TEAEs were thrombocytopenia (55%), neutropenia (27%), and anemia (18%). Treatment-emergent ocular AEs (all Gr 1 or 2) occurred in 36% pts. Drug-related SAEs occurred in 36% pts. Efficacy: 23% ORR (5% sCRs, 5% VG PRs, 13% PRs, mDOR 14.7 months). Evidence of antitumor activity noted at MTD.	83
Microtubule Inhibitors – Maytansines – DM4: Solid Tumors (7)					
46.	Mucin-1 associated sialoglycoprotein CA6 (MUC1) SAR56658; ACT14884 Nonspecific Lys conj. Cleavable SPBD linker DM4 payload DAR~ Undisclosed ImmunoGen, Inc.; Sanofi 2010–2018	Phase 2 Monotherapy NCT02984683 Terminated, limited clinical benefit with higher-than-expected rate of ophthalmological toxicity	TNBC	n = 23; 90 mg/m ² (n = 11) and 120 mg/m ² (n = 12) dosed on day 1 and 8 of a 21-d cycle. Safety: 100% of subjects experienced TRAEs; 90 mg/m ² - 9.1% of pts. experienced SAE, 27.3% had TEAEs leading to discontinuation; 120 mg/m ² -50% experienced SAE; 25% had TEAEs leading to discontinuation. Corneal toxicities were noted in 3/11 (90 mg/m ²) and 5/12 (120 mg/m ²) pts. Efficacy: 0% ORR. Limited clinical benefit with higher-than-expected incidence of ophthalmological toxicity.	25
<i>Description of Ph.1 trial (NCT01156870) is not included.</i>					

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target Molecule Conjugation Amino Acid Linker Payload DAR Company Years in Pipeline	Phase Regimen Trial Identifier Status	Indication(s)	Trial Design Results	Ref
47.	Mucin-1 associated sialoglycotopoe CA242 (MUC1) cantuzumab ravtransine; IMG242; HuC242-DM4 Nonspecific Lys conj. Cleavable SPBD linker DM4 payload DAR~ Undisclosed ImmunoGen, Inc. 2005–2009	Phase 2 Monotherapy NCT00620607 Withdrawn, lack of accrual	Stomach Neoplasms, GC, GEJ	n = 0, study not conducted.	25
<i>Description of Ph.1 trial (NCT00352131) is not included.</i>					
48.	Integrin alpha-V, CD51 (ITGAV) IMGN388 Nonspecific Lys conj. Cleavable SPBD linker DM4 payload DAR~ Undisclosed ImmunoGen, Inc. 2008–2011	Phase 1 Monotherapy NCT00721669 Completed	Solid Tumors	n = 60, no published results.	25
49.	Cadherin-6 (CDH6) HKT288; CDH6-ADC Nonspecific Lys conj. Cleavable Sulfo-SPBD linker DM4 payload DAR~ Undisclosed Novartis Pharmaceuticals 2016–2018	Phase 1 Monotherapy NCT02947152 Terminated, unanticipated neurotoxicity with unknown mechanism	RCC, EOC	n = 9 (5 RCC, 4 EOC), starting dose 0.3 mg/kg Q3W. Safety: Common AEs included pyrexia (44.4%), constipation (44.4%), fatigue and vomiting (both 33.3%); Gr 2 neurological AEs in 3 pts. (30%). Unanticipated neurotoxicity with unknown mechanism. Efficacy: No objectives responses observed in doses tested. Limited clinical benefit with unanticipated neurotoxicity with unknown mechanism.	84
50.	Teratocarcinoma-derived growth factor 1, Cripto (TDGF1) BIB015 Nonspecific Lys conj. Cleavable SPBD linker DM4 payload DAR~ Undisclosed Biogen Idec; ImmunoGen, Inc. 2008–2011	Phase 1 Monotherapy NCT00674947 Completed	Solid Tumors	n = 55, no published results.	25
51.	Fibroblast growth factor receptor 3 (FGFR3) LY3076226 Nonspecific Lys conj. Cleavable Sulfo-SPBD linker DM4 payload DAR~ Undisclosed Eli Lilly and Company; ImmunoGen, Inc. 2015–2019	Phase 1 Monotherapy NCT02529553 Completed, 0% ORR	Solid Tumors	n = 25; dose escal. n = 22, 0.2–5.0 mg/kg Q3W; dose exp. n = 3, 5.0 mg/kg Q3W. Safety: Most TEAEs were Gr 1/2 and included PN (16%), thrombocytopenia (16%), and diarrhea (32%). Gr 3 AEs in 8% pts. included Gr 3 pulmonary embolism (4%) and Gr 3 thrombocytopenia. Efficacy: 0% ORR. Acceptable safety with no reported clinical activity.	85

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid	Linker	Phase	Regimen	DAR	Company	Years in Pipeline	Indication(s)	Trial Design	Results	Ref
52.	Lysosome-associate membrane glycoprotein 1 (LAMP-1)	SAR428926	Nonspecific Lys conj.	Cleavable SPBD linker	DM4 payload	DAR~ Undisclosed	ImmunoGen, Inc.; Sanofi	2015–2018			Solid Tumors	n = 34, no published results.	25	
53.	Microtubule Inhibitors – Maytansines – DM4; Hematological Malignancies (2)													
	B-lymphocyte antigen CD19 (CD19)	coltuximab ravtansine; SAR3419	Nonspecific Lys conj.	Cleavable SPBD linker	DM4 payload	DAR~ 3.5	ImmunoGen, Inc.	2007–2018			DLBCL	n = 61, 55 mg/m ² 4xQ1W/4xQ2W; 20 pts. eliminated from efficacy analysis (some misclassified). Safety: Gr ≥3 AEs in 38% pts. including hepatotoxicity (3%) and abdominal pain. Ocular AEs observed in 25% of pts. Efficacy: 43.9% ORR, 14.6% CR, mDOR 4.7 months, mPFS 4.4 months, OS 9.2 months.	86	
	B-lymphocyte antigen CD19 (CD19)	coltuximab ravtansine; SAR3419	Nonspecific Lys conj.	Cleavable SPBD linker	DM4 payload	DAR~ 3.5	ImmunoGen, Inc.	2007–2018			DLBCL	n = 52, 55 mg/m ² + rituximab 4xQ1W/8xQ2W, dose reduced to 40 mg/m ² (in case of Gr ≥3 AE). Safety: Gr ≥3 TEAEs in 52% of pts., mostly hematologic AEs including lymphopenia, neutropenia, thrombocytopenia, and anemia. 2 SAEs noted: Gr 1 sinus tachycardia and Gr 4 bronchospasm. Efficacy: 31.1% ORR, 8.9% CR, 22.2% PR, mDOR 8.6 months, mPFS 3.9 months, mOS 9.0 months. In sufficient efficacy: primary objective of ORR, ≥40%, was not met.	87	
	<i>Descriptions of Ph.1 trials (NCT00796731, NCT00549185) are not included.</i>													
											ALL	n = 36, dose esc. (n = 19) 55–90 mg/m ² ; dose exp. (n = 17) at 70 mg/m ² . Safety: Gr ≥3 TEAEs in 44% of pts. (55 mg/m ²), 63% (70 mg/m ²), and 88% of pts. (90 mg/m ²) on study. SAEs were reported in 22%, 74%, and 88% of pts. – correlating with dose group. The most common SAEs were bacteremia, pneumonia, and febrile neutropenia. Efficacy (dose exp.): 25.47% ORR (1 CR, 2 CRi, 1 PR), mDOR 1.94 months. Tolerated with low clinical responses vs competitors.	88	
54.	Myeloid cell surface antigen CD33 (CD33)	AVE9633; IMGN-633	Nonspecific Lys conj.	Cleavable SPBD linker	DM4 payload	DAR~ 3.5	ImmunoGen, Inc.; Sanofi	2007–2009			AML	n = 54, 3 dosing regimens: Q3W, D1D8 or D1D4D7 of 28-d cycle, MTD 150 mg/m ² for D1D4D7 and 130 mg/m ² for D1D8 group. Safety: Main toxicity was allergic reaction during infusion. DL1s of keratitis, liver toxicity for D1D4D7 group. 15% of D1D8 pts. had Gr 3/4 AEs including bronchospasm, keratitis, and liver toxicity. 20% of D1D4D7 pts. had Gr 3/4 events including bronchospasm, erythema, and liver toxicity. Reduction in CD33- blasts noted in D1D8 group. Efficacy: D1D8 – 10% ORR (5% CRi, 5%PR) and D1D4D7 – 0% ORR. Minimal clinical activity at MTD.	89	

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid	Linker	Payload	Company	Years in Pipeline	Phase Regimen	Trial Identifier	Status	Indication(s)	Trial Design Results	Ref
55.	Microtubule Inhibitors – Other Maytansines: Solid Tumors (2)	Receptor tyrosine-protein kinase erbb-2, HER2 (ERBB2)	Phase 3	Monotherapy vs lapatinib + capecitabine	NCT04185649	Unknown, last update 12/4/2019	HER2+ BC	Expected/estimated n = 410, results not published.	25					
		BAT8001	Phase 1	Monotherapy	NCT04182911	Active, not recruiting	HER2+ BC or GC	n = 29, 1.2–6.0 mg/kg Q3W; MTD 3.6 mg/kg. Safety: DLTs of Gr 4 thrombocytopenia and Gr 3 transaminase elevation noted. Gr ≥3 occurred in 48.3% pts., including thrombocytopenia (41.4%), increased AST (13.8%), increased γ-glutamyl transferase (6.9%), and increased alanine aminotransferase (6.9%) of pts. Efficacy: 41.4% ORR, mPFS 4.3 months. Tolerated with evidence of antitumor efficacy.	90					
56.	Tumor-associated calcium signal transducer 2, Trop-2 (TACD2)	BAT8003	Phase 1	Monotherapy	NCT03884517	Unknown status; last update March 21, 2019	Solid Tumors	Expected/estimated n = 50, no published results.	25					
57.	Other Microtubule Inhibitor: Solid Tumors (2)	Glypican-3 (GPC3)	Phase 1/2	Combination with nivolumab (Ph. 2)	NCT02828124	Terminated; portfolio prioritization	HCC	n = 25, Combination dose escal. 3–36 mg (n = 10) with nivolumab (Nivo). Safety: Nivo combo dose escal.: 40% pts. had SAEs. Efficacy: Nivo combo dose escal.: 0% pts. had objective responses. 0% objective responses noted at doses tested.	25					
		BMS-986183	Phase 1	Monotherapy	NCT02576548	Completed, limited efficacy at MTD	HER2+ BC, GC, Stomach Cancers	n = 47, 0.05–0.9 mg/kg Q3W; MTD 0.75 mg/kg Q3W, t½ 0.5–2 d. Safety: Gr ≥3 TRAE occurred in 36.2% pts. The most common Gr ≥3 TRAE included increased AST (21.3%), increased ALT (14.9%), and increased blood bilirubin (6.4%). 10% of pts. had TRAE leading to discontinuation. At the MTD (0.75 mg/kg), MEDI4276 had poor tolerability, as evidenced by the fact that 75.0% of pts. experienced ≥1 serious and/or Gr ≥3 event. Efficacy: BC- 9.4% ORR, 3% CR, 6% PR, mPFS 1.3–15.4 months, mOS 19.1 months. GC -no ORR, mPFS 1.8 months. Limited efficacy at MTD.	91					
58.	Receptor tyrosine-protein kinase erbb-2, HER2 (ERBB2)	MEDI4276	Phase 1	Monotherapy	NCT02576548	Completed, limited efficacy at MTD	HER2+ BC, GC, Stomach Cancers	n = 47, 0.05–0.9 mg/kg Q3W; MTD 0.75 mg/kg Q3W, t½ 0.5–2 d. Safety: Gr ≥3 TRAE occurred in 36.2% pts. The most common Gr ≥3 TRAE included increased AST (21.3%), increased ALT (14.9%), and increased blood bilirubin (6.4%). 10% of pts. had TRAE leading to discontinuation. At the MTD (0.75 mg/kg), MEDI4276 had poor tolerability, as evidenced by the fact that 75.0% of pts. experienced ≥1 serious and/or Gr ≥3 event. Efficacy: BC- 9.4% ORR, 3% CR, 6% PR, mPFS 1.3–15.4 months, mOS 19.1 months. GC -no ORR, mPFS 1.8 months. Limited efficacy at MTD.	91					

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target Molecule Conjugation Amino Acid Linker Payload DAR Company Years in Pipeline	Phase Regimen Trial Identifier Status	Indication(s)	Trial Design Results	Ref
DNA Damaging – PBDs: Solid Tumors (11)					
59.	Claudin-6 (CLDN6), Claudin-9 (CLDN9) SC-004 Specific Engineered Cys conj. Cleavable Val-Cit linker PBD Dimer (SG1882) payload DAR~ 2 AbbVie; Stemcentrx 2017–2020	Phase 1/1b Monotherapy or Combination with ABBV-181 (qPD1) NCT03138408 Terminated, low tolerability with limited clinical activity	Epithelial Ovarian Cancer, Endometrial Cancer	n = 24 (11 OC, 13 EC), 0.005–0.3 mg/kg Q3W, MTD 0.2 mg/kg Q3W. Safety: Gr ≥3 TRAEs in 33% pts. including pericardial effusion, pleural effusion, renal failure, and respiratory failure (8% each). Efficacy: 5% PR. Low tolerability with limited clinical activity.	30
60.	Delta-like protein 3 (DLL3) rovalpituzumab tesirine; Rova-T; SC16LD6.5 Nonspecific Cys conj. Cleavable Val-Ala linker PBD Dimer (SG1882) payload DAR~ 2 AbbVie; Stemcentrx; Spirogen 2013–2019 <i>Descriptions of Ph.3 (NCT03334487, study withdrawn), Ph. 2 (NCT03543358, NCT02674568), Ph. 1/2 (NCT03026166, NCT02709889), Ph. 1 (NCT01901653, NCT03086239, NCT03000257, NCT02874664, NCT02819999), and one Expanded Access trial (NCT03503890) are not included here.</i>	Phase 3 (TAHOE) Monotherapy vs topotecan NCT03061812 Completed, Rova-T failed to demonstrate clinical benefit vs topotecan	SCLC	n = 444 (600 were needed for sufficient power), antigen-high (by IHC), ADC dosed at 2 × 0.3 mg/kg Q6W. Safety: ADC vs topotecan-Gr ≥3 AEs in 64% pts. ADC arm vs 88% pts.in Topotecan arm. Serious TRAEs in ADC arm (56%) included malignant neoplasm progression (10%), pneumonia (7%), pleural effusion (6%), and dyspnea (6%). Efficacy: ADC vs topotecan-ORR 15% vs 21%, mDOR 3.5 vs 4.9 months, mOS 6.3 vs 8.6 months (HR 1.46). ADC failed to demonstrate improved clinical benefit vs topotecan.	29
61.	Delta-like protein 3 (DLL3) SC-002 Specific Engineered Cys conj. Cleavable Val-Ala linker PBD Dimer (SG1882) payload DAR~ 2 AbbVie; Stemcentrx 2016–2019	Phase 3 (MERU) Monotherapy vs placebo maintenance after 1 L platin-based therapy NCT03033511 Terminated, recommendation of IDMC (toxicity)	SCLC	n = 748; 372 in ADC arm and 376 in placebo arm: ADC dosed at 0.3 mg/kg Q6W, omitting every 3 rd cycle. Safety: Gr ≥3 TEAEs in 59% pts. in ADC arm vs 30% pts. in placebo arm. The most common Gr ≥3 TEAE in ADC arm was thrombocytopenia (9%). TRAEs lead to death in 10% of ADC and placebo arms. ADC discontinuation due to TRAEs in 20% of pts. Efficacy: ADC vs placebo- mOS 8.5 vs 9.8 months; HR = 1.07 favoring placebo arm. ADC showed lack of survival benefit (did not meet primary endpoint).	28
61.	Delta-like protein 3 (DLL3) SC-002 Specific Engineered Cys conj. Cleavable Val-Ala linker PBD Dimer (SG1882) payload DAR~ 2 AbbVie; Stemcentrx 2016–2019	Phase 1 Monotherapy NCT02500914 Terminated, systemic toxicity with insufficient efficacy	SCLC	n = 35; 0.025–0.4 mg/kg Q3W, MTD 0.4 mg/kg Q9W Safety: 66% of pts. experienced ≥ 1 SAE and in at least 37% of the pts. these were considered drug related including one case of lethal pneumonia. Efficacy: 14% PR. Systemic toxicity was postulated to limit the efficacy as was seen with Rova-T.	92

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid	Linker	Payload	Company	Years in Pipeline	Phase	Regimen	Trial Identifier	Status	Indication(s)	Trial Design Results	Ref
62.	Dipeptidase 3 (DPEP3)	tamintamab	pamozirine; SC-003	Specific Engineered Cys conj.	Cleavable Val-Ala linker	PBD Dimer (SG1882) payload	AbbVie; Stemcentrx	2015–2018	Phase 1a/b	Combination with ABBV-181 (qPD1)	NCT02539719	Terminated, lack of requisite safety and efficacy	OC	n = 74 (n = 29 for dose esc; n = 45 dose exp.; n = 3 ABBV-181 combination), MTD 0.3 mg/kg Q3W. Safety: At MTD, 66% of pts. experienced ≥ 1 SAE; 7% experienced Gr 4/5 AEs. 1 death due to kidney injury was deemed treatment related. Common TRAEs included pleural effusion (35%) and peripheral edema (34%). Efficacy: 4% ORR, responses were not durable. Lack of requisite safety and efficacy.	27
63.	Receptor tyrosine-protein kinase erbB-2, HER2 (ERBB2)	ADCT-502	Specific Engineered Cys conj.	Cleavable Val-Ala linker	PBD Dimer (SG1882) payload	DAR~ 1.7	ADC Therapeutics S.A.	2017–2018	Phase 1	Monotherapy	NCT03125200	Terminated, safety	HER2+ BC, NSCLC, GEC, Bladder Cancer	n = 21, 0.030–0.240 mg/kg Q3W; MTD 0.240 mg/kg. Safety: At doses ≥0.060 mg/kg, 33% pts. had SAEs; 7% experienced Gr 4/5 events. At doses ≥0.060 mg/kg, 36.8% pts. had treatment emergent SAE including small intestinal obstruction (14%) and peripheral edema, sepsis, pneumonia, pleural effusion (4.8% each). Efficacy: 4.8% PR. Lack of requisite safety and efficacy.	25
64.	Receptor tyrosine-protein kinase erbB-2, HER2 (ERBB2)	DHES0815A; RG6148	Specific Engineered Cys (THIOMAB™) conj.	Cleavable disulfide linker	PBD-MA payload	DAR~ 2	Roche-Genentech	2018–2019	Phase 1	Monotherapy	NCT03451162	Completed, insufficient efficacy at tolerated doses	BC	n = 14, dose escal. 0.6–6.0 mg/kg Q3W. Safety: 29% pts. discontinued treatment due to AEs. Skin events were reported in 50% of pts. (all doses) and related included pruritus (36%), rash (36%), and skin hyperpigmentation (21%). Ocular toxicities were reported in 57% of pts. with 3 pts. having Gr 3 ocular events. Lung toxicities were reported in 36% of pts., including pneumonitis (14%). Due to these AEs, ADC dose was decreased to 2.4 mg/kg Q3W for all enrolled pts. and accrual was stopped. Efficacy: 7% CR. Insufficient efficacy at tolerated doses.	93, 94
65.	Melanotransferrin (MELTF)	SC-005	Undisclosed conj. method	Undisclosed linker	PBD payload	DAR~ Undisclosed	AbbVie; Stemcentrx	2018–2019	Phase 1	Monotherapy	NCT03316794	Terminated, sponsor strategic alignment	BC	n = 2, no published results. Insufficient efficacy at tolerated doses.	25

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target Molecule	Conjugation Linker	Phase Regimen	Company	Years in Pipeline	Indication(s)	Trial Design Results	Ref
66.	Prolactin receptor (PRLR) rolinsatamab talirine; ABBV-176 Specific Engineered Cys conj. Cleavable Val-Ala linker PBD Dimer (SFD-1882) payload DAR~ 2 AbbVie; Seagen Inc. 2017–2019	Conjugation Amino Acid Linker Payload DAR	Phase 1 Monotherapy NCT03145909 Terminated, safety			PRLR+ Solid Tumors	n = 19, 0.0027–0.10935 mg/kg Q3W. Safety: Possible cumulative toxicity in the form of effusion and edema. DLTs of thrombocytopenia, neutropenia, and pancytopenia were noted. Effusions and edema were common, and timing of onset suggested possible cumulative ABBV-176 toxicity. Efficacy: No ORR. Significant toxicity with absence of objective tumor responses.	11
67.	Prostate-specific membrane antigen, PSMA (FOLH1) ADCT-401; MED13726 Specific Engineered Cys conj. Cleavable Val-Ala linker PBD Dimer (SFD-1882) payload DAR~ 1.8 ADC Therapeutics S.A.; AstraZeneca 2017–2019		Phase 1 Monotherapy NCT02991911 Completed, lack of clinical benefit at tolerated doses			mCRPC	n = 33; 0.015–0.3 mg/kg Q3W, MTD not identified; max. administered dose 0.3 mg/kg. Safety: TRAEs in ~91% pts., primarily skin toxicities and effusions. Gr ≥3 TRAEs in ~46% pts.; 33.3% pts. discontinued due to TRAEs. Gr 3/4 TRAEs included increased gamma-glutamyltransferase (21.2%), thrombocytopenia, capillary leak syndrome (each 9.1%), and increased ALT (6%). Efficacy: 0% ORR, 3% uPR, mPFS 3.6 months, mOS 8.9 months. Lack of efficacy benefit at tolerated doses.	31
68.	E3 ubiquitin-protein ligase (RNF43) SC-006 Specific Engineered Cys conj. Cleavable Val-Ala linker PBD (SC-DR003) payload DAR~ 2 Stemcentrx; AbbVie 2017–2019		Phase 1 Combination with ABBV-181 (gPD1) NCT03035279 Terminated, strategic considerations			CRC	n = 29, no results published.	25
69.	Tumor necrosis factor ligand superfamily member 9 (TNFSF9) SC-007 Undisclosed conj. method Undisclosed linker PBD payload DAR~ Undisclosed AbbVie; Stemcentrx 2017–2018		Phase 1 Monotherapy NCT03253185 Terminated, benefit/risk imbalance			CRC, GC	n = 7, no results published.	25, 95
70.	DNA Damaging – PBDs: Hematological Malignancies and Solid Tumors (1) CD70 antigen (CD70) SGN-CD70A Specific Engineered Cys conj. Cleavable Val-Ala linker PBD Dimer (SGD-1882) payload DAR~ 2 Seagen Inc. 2014–2016		Phase 1 Monotherapy NCT02216890 Completed, drug-related thrombocytopenia severity and prevalence cited as reasons for program discontinuation			RCC, MCL, DLBCL, FL	n = 20 NHL; 0.008–0.20 mg/kg Q3W amended to Q6W due to thrombocytopenia, MTD 0.030 mg/kg Q6W. Safety: TEAEs ≥ Gr 3 occurred in 90% pts., including thrombocytopenia (65%), anemia (50%), and fatigue (50%). 55% of pts. experienced drug related SAEs. Efficacy: 20% ORR, 5% CR, 15% PR. Poorly tolerated with insufficient efficacy.	67, 96

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid	Linker	Phase	Regimen	Trial Identifier	Status	Indication(s)	Trial Design Results	Ref
DNA Damaging – PBDs: Hematological Malignancies (7)												
71.	B-lymphocyte antigen CD19 (CD19)	SGN-CD19B	Specific Engineered Cys conj.	Cleavable Val-Cit linker	PBD Dimer (SG1882) payload	DAR~ 2	Seagen Inc.	2015–2018	Phase 1 Monotherapy NCT02702141 Terminated, reason not disclosed	NHL, DLBCL, FL	n = 44, no published results.	25
72.	Neutral amino acid transporter B(0), ASCT2 (SLC1A5)	MEDI7247	Specific Engineered Cys conj.	Cleavable Val-Ala linker	PBD payload	DAR~ 2	AstraZeneca	2017–2020	Phase 1 Monotherapy NCT03106428 Completed	AML, MM, DLBCL	n = 67, no published results.	25
73.	Tumor necrosis factor receptor superfamily member 17, BCMA (TNFRSF17)	MEDI2228	Specific Engineered Cys conj.	Cleavable Val-Ala linker	PBD Dimer (SG3199) payload	DAR~ 2	AstraZeneca	2018–2021	Phase 1 Monotherapy NCT03489525 Completed	MM	n = 107, no published results.	25
74.	Myeloid cell surface antigen CD33 (CD33)	vadastuximab talirine; SGN-CD33A	Specific Engineered Cys conj.	Cleavable Val-Ala linker	PBD Dimer (SGD-1882) payload	DAR~ 1.9	Seagen Inc.	2013–2018	Phase 3 Combination with azacitidine or decitabine vs placebo NCT02785900 Terminated, safety; higher rates of deaths, including fatal infections	AML	n = 240; Trial was halted following a review of unblinded data and consultation with the Independent Data Monitoring Committee. Pts. assigned to the vadastuximab talirine arm had higher rates of death than those in the control arm, including fatal infections.	25
								Ph. 1/2 (NCT02706899, NCT02614560) and Ph. 1 trial (NCT02326584) are not included; neither had published results.	Phase 1 Combination with HMA (hypomethylating agents) azacitidine (AZA) or decitabine (DEC) NCT01902329 Completed, combination with HMA had evidence of antitumor activity at tolerated doses	AML, APML	n = 195, Monotherapy dose escal. (n = 131) 0.005–0.06 mg/kg; expansion dose 0.04 mg/kg selected. Combination (n = 53) AZA for 7 d, n = 23 or DEC for 5 d, n = 27 with ADC dosed (0.01 mg/kg) on last day of AZA/DEC treatment; 28 d treatment cycle. Safety-Monotherapy: Most TEAEs consistent with myelosuppression. 100% of 0.04 mg/kg pts. experienced Gr ≥3 TEAEs that included febrile neutropenia (72%), anemia (42%), and thrombocytopenia (25%). Efficacy-Monotherapy: 0.04 mg/kg monotherapy. CR (composite remission rate) 28%. Safety-Combination: Gr ≥3 TEAEs reported in 98% of pts. Gr ≥3 TEAEs that included thrombocytopenia (57%), febrile neutropenia (49%), and anemia (45%). Efficacy-Combination: 70% CR, mOS 11.3 months. Combination with HMA had evidence of antitumor activity at tolerated doses.	97, 98

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation Amino Acid	Linker	Payload	Company	Years in Pipeline	Indication(s)	Trial Design Results	Ref
75.	Interleukin-3 receptor subunit alpha, CD123 (IL3RA)	SGN-CD123A	Specific Engineered Cys conj. Cleavable Val-Ala linker	PBD Dimer (SGD-1882) payload	Seagen Inc. 2016–2018	Phase 1 Monotherapy NCT02848248	AML	n = 17, no published results.	25	
										Terminated, reason not disclosed
76.	SLAM family member 6, CD352 (SLAMF6)	SGN-CD352A	Specific Engineered Cys conj. Cleavable Val-Ala linker	PBD Dimer (SGD-1882) payload	Seagen Inc. 2016–2018	Phase 1 Monotherapy NCT02954796	MM	n = 27, no published results.	25	
										Terminated, sponsor portfolio prioritization
77.	C-type lectin domain family 12 member A, CLL-1 (CLEC12A)	DCLL97185; RG6109	Specific Engineered Cys (THIOMAB™) conj. Undisclosed cleavable linker	PBD payload	Roche-Genentech 2017–2019	Phase 1 Combination with azacitidine NCT03298516	AML	n = 18, dose esc. 0.01–0.16 mg/kg Q3W, MTD not identified. Safety: AEs of Gr ≥3 in 67% pts., including febrile neutropenia (33%) and pneumonia (28%). Efficacy: 0% ORR (CR/PR). Limited tolerability and lack of clinical activity.	99	
										Completed, limited tolerability and lack of clinical activity
78.	Ephrin-A4 (EFNA4)	PF-06647263	Nonspecific Lys conj. Cleavable AcBut acyl hydrazone-disulfide linker	Calicheamicin payload	Pfizer 2014–2019	Phase 1 Monotherapy NCT02078752	TNBC, Solid Tumors	n = 60 (48 in dose esc., 12 in dose exp.); dose esc. 0.015–0.134 mg/kg Q3W or 0.01–0.02 mg/kg QW; dose exp. at RP2D of 0.015 mg/kg QW. Safety: TRAEs in >82% pts., AEs of Gr 3/4 in 53.3% including thrombocytopenia (20%). Notable TRAEs are mucosal inflammation (28%), stomatitis (28%), and rash (24%). Efficacy: 10.4% ORR in dose esc; in dose exp. group, 8.3% ORR; no CR. Limited anti-tumor activity at tolerated doses.	100	
										Terminated, limited efficacy response at tolerated doses

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid Linker	Phase Regimen	Company	Years in Pipeline	Indication(s)	Trial Design Results	Ref
79.	Lewis Y antigen CMD-193 Nonspecific Lys conj. Cleavable AcBut acyl hydrazone-disulfide linker Calicheamicin payload DAR~ Undisclosed Wyeth; Pfizer 2004–2014	Lewis Y antigen CMD-193 Nonspecific Lys conj. Cleavable AcBut acyl hydrazone-disulfide linker Calicheamicin payload DAR~ Undisclosed Wyeth; Pfizer 2004–2014			Phase 1 Monotherapy (radiolabeled) NCT00293215 Terminated, abnormal distribution with rapid hepatic uptake and low tumor uptake with rapid clearance from blood		Solid Tumors	n = 9, objective was to determine the biodistribution and PK of ⁴⁸ In-CMD-193; CMD-193 demonstrated rapid blood clearance and increased hepatic uptake compared with prior studies of the parental antibody hu3S193. Safety: Myelosuppression and prolonged liver uptake which affected liver function were the most significant adverse events. Gr ≥3 AEs included thrombocytopenia (20%) and abnormal liver function (20%). Efficacy: No objective responses were observed. Abnormal drug distribution and low tumor uptake with lack of objective responses.	101	
80.	Mucin-1 (MUC-1) CMB-401; hCTMO1-calicheamicin Nonspecific Lys conj. Cleavable AcBut acyl hydrazone-disulfide linker DAR~ 2–3 Pfizer, Celltech Therapeutics 1997–2016 <i>Description of Ph. 1 trial (PMID 10942064) is not included.</i>	Mucin-1 (MUC-1) CMB-401; hCTMO1-calicheamicin Nonspecific Lys conj. Cleavable AcBut acyl hydrazone-disulfide linker DAR~ 2–3 Pfizer, Celltech Therapeutics 1997–2016 <i>Description of Ph. 1 trial (PMID 10942064) is not included.</i>			Phase 1 Monotherapy NCT00257881 Terminated, reason not disclosed Phase 2 Monotherapy Registry Trial Identifier PMID 12669249 Completed, lack of efficacy noted at tolerated doses		Solid Tumors	n = 46 (Japan), no published results. n = 21, pre-dosed with Ab hCTMO1, ADC given at 16 mg/m ² Q4W. Safety: 66% of pts. experienced at least 1 Gr ≥3 AE. TRAEs included epistaxis, anemia, AST elevation, and thrombocytopenia. Gr 4 anemia and peritonitis occurred in 1 pt. each. Efficacy: 0% ORR. No anti-tumor activity at tolerated doses. Hypothesized that amide linker may have contributed to the failure to induce PR.	102, 103	
81.	Other DNA Damaging: Solid Tumors (2) Lewis Y antigen SGN-15; BMS-182248; br96-doxPh Nonspecific Cys conj. Cleavable hydrazone linker Doxorubicin payload DAR~ Undisclosed Seagen Inc. 2000–2005 <i>Descriptions of Ph. 2 trials (NCT00031187, NCT00028483, NCT00051584, NCT00086333) are not included; none have published results.</i>	Other DNA Damaging: Solid Tumors (2) Lewis Y antigen SGN-15; BMS-182248; br96-doxPh Nonspecific Cys conj. Cleavable hydrazone linker Doxorubicin payload DAR~ Undisclosed Seagen Inc. 2000–2005 <i>Descriptions of Ph. 2 trials (NCT00031187, NCT00028483, NCT00051584, NCT00086333) are not included; none have published results.</i>			Phase 2 Combination with docetaxel vs docetaxel NCT00051571 Completed, insufficient activity benefit vs comparator arm		NSCLC	n = 62, randomized 2:1 into Arm A (ADC 200 mg/m ² Q1W + docetaxel, n = 40) and Arm B (docetaxel alone, n = 19); intrapatient dose escal. up to 350 mg/m ² Q1W. Safety: Gr ≥3 AEs in Arm A: increased lipase (25%), nausea/vomiting (18%), asthenia/fatigue (13%); Arm B: respiratory distress (16%), pneumonia (11%), asthenia/fatigue (11%). Efficacy: Arm A vs Arm B, OR 46% vs 37%, mPFS 31.4 vs 25.3 weeks, 1-y survival 29% vs 24%. Insufficient efficacy benefit versus comparator arm.	24	

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation	Amino Acid	Linker	Phase Regimen	Trial Identifier	Status	Indication(s)	Trial Design Results	Ref
82.	Mesothelin (MSLN) BMS-986148; MDX-1204 Nonspecific Lys conj. Cleavable Val-Cit linker Duocarmycin payload DAR~ 1.4 Bristol-Myers Squibb; Medarex 2009–2018 <i>Description of Ph. 1 trial (NCT02884726) is not included here.</i>					Phase 1/2 Monotherapy and Combination with nivolumab (Nivo) NCT02341625 Terminated, limited clinical activity		MESO, NSCLC, OC, PC, GC	n = 126, Arm A: ADC alone (n = 96; dose esc. 0.1–1.6 mg/kg Q3W/Q1W) and Arm B: ADC (n = 30, 0.4/0.6/1.2 mg/kg Q3W) + Nivo. Safety: Arm A: 50% pts. treated at 1.6 mg/kg had DLTs, 40% transaminase elevations, 10% Gr 3 pleuritic pain. Combination Arm B: 33% Gr 3/4 AE of ALT/AST increase and pleuritic pain. Efficacy: 2% ORR for ADC monotherapy; 6% ORR in combination group. Limited clinical activity observed alone or in combination with Nivo.	104	
83.	CD70 antigen (CD70) MDX-1203; BMS936561; aCD70_MED-A Nonspecific Lys conj. Cleavable Val-Cit linker MED-A/DNAM1GBA toxin (Duocarmycin) payload DAR~ 1.25 Bristol-Myers Squibb; Medarex 2009–2018					Phase 1 Monotherapy NCT00944905 Completed, DLTs of Gr 3 hypersensitivity (13%); no efficacy observed at doses tested		RCC, NHL	n = 26, 0.5 – 15 mg/kg Q3W; MTD not defined, RP2D of 8 mg/kg Q3W. Safety: Gr 3 hypersensitivity DLTs (13%) at highest dose; delayed toxicities of facial edema and pleural/pericardial effusion occurred in 38% of pts. at highest dose. Efficacy: 0% OR (PR/CR). No efficacy at doses tested.	105	
84.	Myeloid cell surface antigen CD33 (CD33) IMGN779 Nonspecific Lys conj. Cleavable Sulfo-SPDB linker DGN462 (DNA alkylator) payload DAR~ 3 ImmunoGen, Inc.; Jazz Pharmaceuticals 2016–2019					Phase 1 Monotherapy NCT02674763 Completed		AML	n = 62; initial results from 17 pts., dose escal. from 0.02–0.26 mg/kg on days 1 and 15 of a 28-d cycle. Safety: SAEs included Gr 3 febrile neutropenia (29%) and pneumonia (24%). Rash, respiratory failure, and constipation were reported in ≥ 24% of pts. No correlation of frequency and severity of AEs to dose was observed. Efficacy was not reported.	106	
85.	HLA class II histocompatibility antigen gamma chain (CD74) milatuzumab doxorubicin; CD74-DOX; hLL1-DOX; IMMU-110 Specific Cys conj. Cleavable Hydrzone linker Doxorubicin payload DAR~ 8 ImmunoGen, Inc. 2010–2019					Phase 1/2 Monotherapy NCT01101594 Terminated, lack of efficacy		MM	n = 17, no published results.	25	
						Phase 1/2 Monotherapy NCT01585688 Terminated, lack of efficacy		NHL, CLL	n = 13, no published results.	25	

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target Molecule Conjugation Amino Acid Linker Payload DAR Company Years in Pipeline	Phase Regimen Trial Identifier Status	Indication(s)	Trial Design Results	Ref
Topoisomerase Inhibitors: Solid Tumors (2)					
86.	Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) labetuzumab govitecan; hMINT4-SN38; IMMU-130 Specific Cys conj. Cleavable CL2A linker SN-38 payload DAR~ 7.6 Immunomedics, Inc. 2011–2021	Phase 2 Monotherapy NCT01915472 Withdrawn; no participants enrolled Phase 1/2 Monotherapy NCT01270698 Completed, minimal efficacy noted at doses tested	CRC CRC	n = 0, no participants enrolled. n = 86 pts, dose exp. 4–10 mg/kg QW or BIW on weeks 1 and 2 of 3-week cycle. Safety: Gr ≥ 3 AEs included neutropenia (16%), leukopenia (11%), and anemia (9%). Toxicity was similar among the 4 cohorts although Gr ≥ 3 AEs were more frequent in the 10 mg/kg QW group (36%). Efficacy: 1 PR (1.16%) from 6 mg/kg BIW treatment group. Minimal efficacy noted at doses tested.	25 107
87.	G-protein coupled receptor 20 (GPR20) DS-6157; DS-6157a; GPR20 ADC Specific Cys conj. Cleavable GGFG linker DXd/DX8951 payload DAR~ 8 Daiichi Sankyo, Inc.; Sarah Cannon Research Institute 2020–2021	Phase 1 Monotherapy NCT04276415 Completed, insufficient efficacy noted at tolerated doses	GIST	n = 34, dose esc 1.6–6.4 mg/kg QW3; MTD was 6.4 mg/kg QW3. Safety: Gr ≥ 3 TRAEs occurred in 41% of pts, including decreased platelets (21%) and anemia (18%). Serious TEAEs (SAEs) occurred in 27% of pts. Related Gr 4 SAEs in 2 pts, included abnormal hepatic function, neutropenia, thrombocytopenia, and leukopenia. There was 1 treatment related death (hepatic failure). Efficacy: One patient had a confirmed PR (~3%), mPFS across all dose levels was 3.6 months. Insufficient efficacy noted at tolerated doses.	108
Immunomodulatory Payloads: Solid Tumors (3)					
88.	Receptor tyrosine-protein kinase erbb-2, HER2 (ERBB2) NJH395 Specific Cys conj. Noncleavable linker Undisclosed TLR7 agonist payload DAR~ 4 Novartis 2018–2020	Phase 1 Monotherapy NCT03696771 Completed, insufficient efficacy noted at tolerated doses	Non-breast HER2+ Malignancies	n = 18, dose esc 0.1–1.6 mg/kg. Safety: The most common AE was cytokine release syndrome (53.6% Gr ≥ 2), pyrexia (44.4%), and AST (33.3%) and ALT (27.8%) increase. The most common Gr ≥ 3 AEs included lymphopenia (27.8%) and AST increase (11.1%). Five Gr 3 DLTs were reported, 2 AST increase, 1 ALT increase, 1 aseptic meningitis, and 1 meningism. Efficacy: 0% ORR. Insufficient efficacy noted at tolerated doses.	109
89.	Receptor tyrosine-protein kinase erbb-2, HER2 (ERBB2) SPT6050 Undisclosed Cys conj. method Undisclosed cleavable linker Undisclosed TLR8 agonist payload DAR~ 4 Silverback Therapeutics 2020–2022	Phase 1/2 NCT05091528 Terminated, sponsor portfolio prioritization Phase 1/1b Monotherapy and Combination with pembrolizumab/ cemiplimab NCT04460456 Active, not recruiting	HER2+ BC, GC, CRC, NSCLC HER2+ Solid Tumors	n = 2, study not conducted. n = 58 Interim analysis on first 18 pts.; dose escal. 0.15–1.2 mg/kg Q2W. Safety: The most frequent TRAEs (25%) were chills, diarrhea, fatigue, hypotension, injection site reaction, nausea, pyrexia, and vomiting. Gr 3 DLTs were observed at 1.2 mg/kg Q2W. Was concluded that a dose of 0.6 mg/kg Q2W had a tolerable safety profile with evidence of target saturation. Efficacy: 7% PR. Insufficient efficacy noted at tolerated doses.	25 110

(Continued)

Table 2. Discontinued ADCs by Payload Class and Malignancy Setting.

No.	Target	Molecule	Conjugation Amino Acid Linker	Phase Regimen	Trial Identifier	Indication(s)	Trial Design Results	Ref
90.	Nectin-4 (NECTIN4)	SBT6290	Undisclosed Cys conj. method	Phase 1/2 Monotherapy and Combination with pembrolizumab	NCT05234606	UC, TNBC, NSCLC, HNSCC, HR+ HER2- BC	n = 0, study not conducted.	25
		Undisclosed linker	Undisclosed linker					
		DAR~ Undisclosed	Undisclosed TLR8 agonist payload					
		ARS Pharmaceuticals; Silverback Therapeutics						
		2022–2022						
Undisclosed Payloads: Solid Tumors (2)								
91.	Leukocyte surface antigen CD47 (CD47)	SGN-CD47M	Undisclosed conj. method	Phase 1 Monotherapy	NCT03957096	STS, CRC, HNSCC, NSCLC, BC, OC, Exocrine PC, GC, Melanoma	n = 16, no published results.	25
		Undisclosed linker	Undisclosed linker					
		DAR~ Undisclosed	Undisclosed payload					
		Seagen Inc.						
		2019–2021						
92.	Alpha-N-acetylneuraminide alpha-2,8-sialtransferase, GD3 (ST6SIA1)	PF-06688992; GD3-ADC	Undisclosed conj. method	Phase 1 Monotherapy	NCT03159117	Melanoma	n = 7, no published results.	25
		Undisclosed linker	Undisclosed linker					
		DAR~ Undisclosed	Undisclosed payload					
		Pfizer						
		2017–2019						

Abbreviations: Ab, antibody; ADC, antibody–drug conjugate; AE, adverse event; Ala, alanine; ALT, alanine transaminase; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; AST, aspartate transferase; AZA, azacytidine; BLW, twice weekly; Cit, citrulline; CLL, chronic lymphocytic leukemia; conj., conjugation; CRPC, castrate resistant prostate cancer; CR, complete response; CRC, colorectal cancer; CRI, complete remission with incomplete blood count recovery; Cys, cysteine; D1D15, day 1 and day 15; DAR, drug–antibody ratio; DCR, disease control rate; DLBCL, diffuse large B cell lymphoma; DLT, dose-limiting toxicity; DM1, mertansine; DM4, ravtansine; EOC, epithelial ovarian cancer; escal., escalation; exp., expansion; FL, follicular lymphoma; Gr, grade; GBM, glioblastoma multiforme; GC, gastric cancer; GEJC, gastroesophageal junction cancer; GIST, gastrointestinal stromal tumors; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; HR+, hormone receptor positive; HSR, hypersensitivity reactions; Lys, lysine; mc, maleimidocaproyl; MCL, mantle cell lymphoma; mDOR, medium duration of response; mg/m², milligrams per meter squared; mg/kg, milligrams per kilogram; MM, multiple myeloma; MMAE, monomethyl auristatin E; MR, mixed response; mOS, medium overall survival; mPFS, medium progression free survival; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; Nivo, nivolumab; NSCLC, non-small cell lung cancer; OC, ovarian cancer; ORR, overall response rate; PBD, pyrrolbenzodiazepine; PC, prostate cancer; PK, pharmacokinetic; PLD, pegylated liposomal doxorubicin; PN, peripheral neuropathy; PR, partial response; PSA, prostate-specific antigen; PSOC, platin-sensitive ovarian cancer; pts., patients; QW, weekly; Q2W, every two weeks; Q3W, every three weeks; Q4W, every four weeks; Q9W, every nine weeks; RCC, renal cell carcinoma; RP2D, recommended phase 2 dose; RT, radiation; SAE, serious adverse event; sCR, stringent complete response; SMCC, Succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate; SPP, N-succinimidyl 4-(2-pyridylidithio) pentanoate; SPBD, N-succinimidyl 4-(2-pyridylidithio) butanoate; TEAE, treatment emergent adverse event; TESAE, young adult; TMZ, temozolomide; TNBC, triple negative breast cancer; TRAE, treatment related adverse event; uPR, unconfirmed partial response; Val, valine; VGPR, very good partial response; YA, young adults.

the three main components of the ADC (antibody, linker, payload) and the conjugation technology used to link the antibody to the payload. Also, consideration of the need to match the appropriate payload to a given tumor indication is required, while being mindful of the cancer antigen densities of the tumor targeting biologic.

Improvements to the biologic

Improvements in antibody design include binder selection and engineering to 1) select epitope(s)/affinities that promote maximal internalization, 2) optimize/lower affinity of binders for targets with higher expression on normal tissues of concern, and 3) fine tune the net charge of the ADC to mitigate target-independent toxicity.

Biologics targeting epitopes that promote rapid receptor-mediated internalization show greater activity than biologics targeting non-internalization antigen epitopes.¹² Additionally, biparatopic and bispecific ADC biologics have been reported to improve ADC internalization, increasing the ADC effectiveness in tumors with lower target antigen densities.^{119,120} Biparatopic and bispecific ADCs currently in testing include REGN5093-M114 (c-MET, c-MET), zanidatamab zovodotin (HER2, HER2), IMGN151 (FR α FR α), BL-B01D1 (EGFR, HER3), M1231 (EGFR, MUC1), and ORM-5029 (HER2, HER3).

In addition to selecting internalizing epitopes and/or biparatope/bispecific antigen targeting, biologic affinity optimization of ADC biologics would need to be tailored for the antigen (s) of choice. Indeed, biologics with lower affinities may demonstrate insufficient binding and/or internalization at lower target antigen densities¹³ and biologics with too high cellular affinities may result in reduced receptor occupancy and/or internalization.¹⁴ Biologic affinity tuning may also help mitigate on target/off-tumor toxicities for antigens expressed in normal tissues of concern. Affinity de-tuning has been shown to lower target-dependent toxicity in normal tissues while maintaining activity on tumor cells with higher target antigen expression.^{13,121}

Finally, optimizing the net charge of an ADC has been demonstrated to mitigate target-independent toxicity. An example of this is the reduction in ocular toxicity via introduction of a single Lys to Asp mutation into the biologic of the ADC, AGS-16C3F.¹²² These results suggest that creating a net negative surface charge on the ADC could dampen target-independent toxicity.

Improvements to the linker

Linkers are not mere inert bridges between an antibody and a payload; they influence the stability and PK of a given ADC. Poor performance of some early ADCs, like CMB-401, has been attributed to labile linkers.¹⁰² Improvements in ADC linkers have been shown to decrease systemic payload release and improve PK properties. Along these lines, improvements in linker development could include 1) payload masking linkers, 2) hydrophilic linkers, 3) branched linkers to increase the

drug load, 4) tandem cleavage linkers, and 5) dual cleavage-specific linkers.

Modifying the linker to mask the hydrophobic payload can increase the therapeutic index.¹²³ In general, reducing hydrophobicity of an ADC improves PK and therapeutic activity,²³ at least in part due to reduced micropinocytosis-induced off-target toxicity.¹²⁴ Indeed, incorporating hydrophilic macrocycles in the ADC to mask the hydrophobic payloads improved the *in vivo* activity of AdcetrisTM-like ADCs.¹²⁵

Modifying the linker to increase drug load is another strategy to increase the effectiveness of ADCs that incorporate low potency payloads. One challenge in creating traditional cytotoxic ADCs with higher DAR loads is the increased hydrophobicity of the ADC molecule due to increased numbers of hydrophobic payloads that both increase the probability of aggregation¹²⁶ and hasten clearance of the ADC from the organism.^{16,23} Creating polymer linkers, such as FleximerTM linkers¹²⁷ or PEG chain additions, either between the antibody and the linker or branching from a location within a traditional linker,²³ can increase the drug load on the ADC molecule without the associated liabilities of biologic degradation and/or clearance. Using such methods, the DAR can be increased without increasing the overall ADC hydrophobicity. Additionally, polypeptides composed of a pseudo-repeating pattern of hydrophilic neutral or negatively charged amino acids (Ala, Gly, Pro, Ser, Thr, Glu; XTENTM-peptide based platform) can yield ADCs with DARs as high as 18 without compromising PK.¹²⁸ Increasing linker hydrophilicity can alter the toxicity profile of the ADC by modulating the bystander effect through reduced expulsion of the payload metabolites by the MDR1 pump.¹²⁹ However, this approach may not work for all ADCs.¹³⁰

Lastly, modifying cleavable linkers to minimize systemic release while still maintaining tumor bystander effect could improve the therapeutic index of follow-on ADC molecules. Engineering linkers requiring successive cleavage by enzymes only found inside lysosomes could achieve this property. Such an example was described for a glucuronidase-cleavable linker that when cleaved uncovered a cathepsin cleavage site that enabled payload release – ensuring that both cleavage steps only occurred inside of lysosomes.¹³¹ Such tandem cleavage linkers were found to improve both the stability as well as tolerability of an ADC in a rat toxicity model.¹³¹

Improvements to the payload

Modifications to the payloads that could improve the therapeutic benefit of follow-on ADCs include the creation of 1) prodrug-based payloads to mitigate off-tumor toxicity, 2) creation of hydrophilic cytotoxic payloads, and 3) the creation of bifunctional payloads to increase tumor efficacy. Prodrug payloads exploit the acidic, hypoxic, hyper-sialylated, and protease-rich TME to trigger active payload release in tumors.¹³² Prodrugs can involve masking toxic, hydrophobic payloads such as PBDs by “capping”. The prodrug cap is designed to be cleaved by the TME enzymes, such as beta-glucuronidases, to minimize off-tumor payload release.¹³³ The identification of additional endosomal trafficking modulators and lysosomal

pathway regulators for payload release could aid in design of the next generation of prodrug payloads.¹³⁴

The creation of hydrophilic cytotoxic payloads is another potential advancement to develop ADCs with elevated DARs that retain biologic integrity with good PK attributes. An example of this is the hydrophilic payload auristatin β -D-glucuronide MMAU.¹³⁵ This glycoside-payload had the added benefit of being relatively inert in its unconjugated, free form. Lysosomal enzymatic processing to a deglycosylated state activates the payload's cytotoxic and bystander activity.

The potency of an ADC can also be enhanced with the creation of dual payloads to increase tumor efficacy. Conjugation to two or more different payloads to a given biologic has been shown to have greater antitumor activity over that of a mixture of ADCs carrying the individual payloads. Preclinical studies exploring dual payload ADCs include the two different microtubule inhibitor payloads, MMAE and MMAF,¹³⁶ as well as a microtubule inhibitor payload coupled with a DNA damaging agent such as MMAE and PBD,¹³⁷ or MMAF and PNU-159682.¹³⁸ All of these dual payload ADCs have been shown to increase the antitumor activity over that of a mixture of mono payload ADCs. Additionally, tolerability of these dual payload ADCs in healthy mice was found to be similar to the mono payload ADCs as measured by body weight loss and liver clinical chemistries.¹³⁹

Improvements in payload conjugation

Site-specific attachment of payload yields ADC preparations with controlled and defined DAR. The first method to produce such ADCs via cysteine amino acid engineering gave homogeneous preparations demonstrating superior preclinical PK properties and safety profiles compared to randomly conjugated ADCs.¹⁸ These findings triggered enthusiasm in the field and led to the development of additional methods for site-specific conjugation. To date, site-selective conjugation methods fall into eight categories: cysteine engineering, non-natural amino acid engineering, conjugation to native cysteines, peptide tags, glycan modification, enzymatic modification, disulfide rebridging, and conjugation to native lysines.¹⁴⁰ No method used to date for site-specific conjugation has been shown to have a direct effect on FcRn recycling that can alter ADC PK, efficacy, and safety.

Linker-payload conjugation via non-natural amino acid methods is currently being explored. However, it has been noted that the position of non-natural amino acid conjugation for linker-payload attachment caused a marked effect on tumor killing, although the stability and PK were equivalent.¹⁴¹

Examples of site-specific conjugation using peptide tag technology are the SMARTagTM and Glutamine Tag. SMARTagTM achieves site-specific conjugation with the use of an aldehyde tag attaching the linker-payload to formylglycine.¹⁴² Glutamine Tag technology utilizes transglutaminase to attach the linker-payload.¹⁴³ Both technologies were shown to improve PK and efficacy.^{142,143}

GlycoConnectTM is an example of a site-specific glycan modification conjugation method. Here, site-specific conjugation is achieved with attachment of the linker-payload following glycan remodeling of the antibody at the Asparagine-297

site.¹⁴⁴ However, since Asparagine-297 glycans are important for antibody Fc γ -receptor effector functions, this method needs to be balanced against the loss of Fc effector function that could otherwise provide an efficacy benefit to the developed ADC.¹⁴⁵

A notable advance in site-specific technology is the AJICAPTM method that utilizes native lysines for site-specific linker-payload attachment. This method does not require antibody engineering or enzymatic reactions. ADCs so produced were shown to have an improved therapeutic index in preclinical models.¹⁷

Clinically, the site-specific ADC DMUC4064A (MUC16) could be administered at higher biologic doses with higher overall response rates⁵³ than the nonspecific, cysteine-conjugated counterpart sofituzumab vedotin (MUC16).⁵² While promising, site-specific payload conjugation has not always resulted in therapeutic improvement. For example, the site-specific conjugated ADCs iladatumumab vedotin (CD79b) and SC-002 (DLL3) did not demonstrate an improvement in clinical responses/therapeutic index over that of the nonspecific cysteine-conjugated ADCs Polivy^{TM60} and rovalpituzumab tesirine.^{29,92}

Concluding remarks

Of the 267 ADCs tested for oncology indications, 11 have gained FDA approval; 92 have been discontinued. Analyses of the limitations associated with the discontinued drug candidates can help inform the design and selection of the next series of molecules. Importantly, new biologic engineering modifications have been shown preclinically to improve the therapeutic index. Taking an integrated, multifactorial approach of careful target selection with simultaneous optimization of the antibody, linker, and payload – matched to the indications of interest – will hopefully usher in the next wave of new ADC approvals.

Abbreviations

ADC	Antibody-Drug Conjugate
ALA	Alanine
AML	Acute Myeloid Leukemia
Asp	Aspartic acid
DAR	Drug-to-Antibody Ratio
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
Glu	Glutamic acid
Gly	Glycine
IC ₅₀	half-maximal inhibitory concentration
Lys	lysine
M	Molar
MDR	Multi-Drug Resistance
MED	minimum effective dose
mg/kg	milligrams per kilogram
MMAE	Monomethyl auristatin E
MMAF	Monomethyl auristatin F
mPFS	Medium Progression Free Survival
MTD	Maximum Tolerated Dose
nM	Nanomolar
PBD	Pyrrrolbenzodiazepine
PK	Pharmacokinetic

pM	Picomolar
Pro	Proline
Ser	Serine
SM	Targeted Small Molecules
STING	Stimulator of Interferon Genes
Thr	Threonine
TLR	Toll-Like Receptor
TME	Tumor Microenvironment
US	United States

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