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Antibody-Drug Conjugates in Oncology: Mechanisms, Clinical Progress, and Future Directions

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Abstract

Antibody-drug conjugates (ADCs) are a rapidly evolving therapeutic modality that integrates the target specificity of monoclonal antibodies with the potent cytotoxicity of small-molecule drugs, thereby redefining precision oncology. By enabling selective delivery of highly toxic payloads to malignant cells, ADCs aim to maximize antitumor efficacy while limiting systemic toxicity. This review provides a comprehensive overview of ADC development, focusing on the rational design and functional interplay of the four core components: tumor-associated antigens, antibody scaffolds, linker chemistries, and cytotoxic payloads. Key considerations in target selection, antibody isotype choice, linker stability and cleavage mechanisms, and payload potency are discussed in detail. In addition, we summarize the principal *in vivo* mechanisms underlying ADC activity, including canonical intracellular payload release, bystander killing, antibody-mediated immune effector functions, and immunogenic cell death. These mechanisms collectively contribute to therapeutic efficacy, particularly in heterogeneous and treatment-resistant tumors. The review also provides an updated overview of 19 antibody-drug conjugates that have received regulatory approval worldwide, highlighting their clinical indications, linker-payload combinations, and representative efficacy outcomes. Safety profiles and treatment-related toxicities are examined, with emphasis on class-specific adverse events and tolerability considerations observed in clinical practice. Finally, we discuss emerging strategies and unresolved challenges in ADC development, including resistance mechanisms, linker-payload optimization, novel target discovery, and integration with immunotherapy and combination regimens. By synthesizing current clinical progress with mechanistic and technological insights, this review serves

as a comprehensive reference to support future preclinical research, clinical trial design, and the rational advancement of next-generation ADC-based cancer therapies.

Keywords: antibody-drug conjugates; ADC; linker design; immunogenic cell death; ICD; tumor microenvironment; targeted therapy; translational oncology.

1. Introduction

Cancer is a major disease that threatens human health and is the second leading cause of death globally. By 2025, an estimated 2,041,910 new cancer cases will be diagnosed in the United States, and 618,120 people will die from the disease (1). Chemotherapy, historically a cornerstone of antineoplastic therapy, was the first systemic approach to cancer treatment. However, its mechanism of action, which involves non-specific targeting of both neoplastic and benign cells, inherently limits its therapeutic index and often causes toxicity, thereby raising a series of adverse effects (2). In the post-1980s era, as the molecular intricacies of cancer biology have been progressively unraveled, targeted therapeutic strategies have become a focus of translational oncology. These strategies aim to target genetic driver aberrations and dysregulated signaling pathways. A key milestone in this field was the approval of rituximab (an anti-CD20 antibody) in 1997, representing the first targeted therapy for lymphoid malignancies. While these targeted agents have demonstrated enhanced clinical efficacy and reduced toxicity relative to conventional chemotherapy, challenges remain. These primarily include the emergence of acquired drug resistance mechanisms and the intrinsic biological heterogeneity of tumors (3, 4). To overcome these obstacles, a novel therapeutic paradigm has been conceptualized that focuses on the on-target delivery of potent cytotoxic agents to neoplastic cells via carrier systems. This innovative approach has led to the development of antibody-drug conjugates (ADCs), a next-generation class of agents in personalized oncology (5). Antibody-drug conjugates are targeted therapeutic agents that couple monoclonal antibodies with highly potent cytotoxic payloads, enabling selective delivery of chemotherapy directly to tumor cells while minimizing systemic toxicity. Although ADCs show promise in cancer treatment, their development faces several challenges. For example, ADC manufacturing involves complex steps, including antibody production, small-molecule toxin synthesis, and intricate conjugation, all of which require strict quality control. Biologically, tumor cells can develop resistance by downregulating drug targets or overexpressing drug efflux pumps, which reduces the cytotoxic effect of ADCs (6). Additionally, ADC therapy often causes adverse reactions due to factors such as off-target toxicity (7).

This review covers the four main ADC components (targets, antibodies, linkers, payloads) and discusses their *in vivo* mechanisms, including the general mechanism of action, bystander effects, immunogenic cell death, and antibody-mediated immune functions. It also highlights the clinical use of currently approved ADCs (as monotherapies and in combination), safety issues, challenges, and future directions. Together, these advances position ADCs as a central platform technology in modern precision oncology, integrating targeted therapy, cytotoxic chemotherapy, and immunomodulation into a single therapeutic modality.

2. ADC design and structure components

2.1 Target Selection

Target antigens on tumor cell surfaces act as baits, allowing the antibody to bind with high specificity. This precisely guides ADCs within the tumor microenvironment (TME), promotes drug uptake through endocytosis, and facilitates the release of cytotoxic agents into lysosomes, enabling their action via

standard chemotherapy (8). Primarily, selecting the right target antigen is crucial for ADCs to achieve high specificity, usability, and internalization efficiency (9). Although ADCs target different antigens, the core principles of effective antigen selection remain consistent. The therapeutic performance of antibody-drug conjugates is determined by the coordinated interactions among four structural modules: target antigen, antibody scaffold, linker chemistry, and cytotoxic payload, which together define the conjugate's pharmacological behavior and clinical efficacy.

Four key rules apply: First, strong specificity is vital. To minimize off-target toxicity, target antigens should be highly expressed on tumor cells but absent or minimally present in normal tissues (10). This enhances tumor-specific targeting, reduces extratumoral toxicity, and improves the therapeutic index. Second, the target antigen or epitope should ideally be expressed on the cell surface or in the extracellular space, allowing circulating ADCs to recognize and bind it (11). Third, target antigens should not be secreted. Secreted antigens entering the circulation can cause ADCs to bind off-site, reducing tumor specificity and increasing side effects (12). Fourth, efficient internalization is necessary.

When ADC-antigen complexes form, rapid internalization via endocytosis ensures their entry into cancer cells. Inside, they are trafficked to lysosomes where enzymes degrade the complexes, releasing cytotoxic payloads into the cytoplasm and triggering multiple chemotherapeutic mechanisms (13).

Since the approval of first-generation ADCs in the early 21st century, research and development in this field have expanded rapidly. To date, 19 ADCs have received regulatory approval (Tables 1A and 1B), with over 100 clinical development programs ongoing (14).

Table 1A. Clinical and regulatory characteristics

ADC Name	Indication	Approved Date	Developer	Brand Name	Target
Gemtuzumab ozogamicin	AML	May 2000 (FDA)	Pfizer/Wyeth	Mylotarg	CD33
Brentuximab vedotin	ALCL, CTCL, HL, PTCL	August 2011 (FDA)	Seagen/Takeda	Adcetris	CD30
Trastuzumab emtansine	BC, HER2 ⁺ BC, Metastatic BC	August 2011 (FDA)	Genentech/Roche	Kadcyla	HER2
Inotuzumab ozogamicin	ALL	August 2017 (FDA)	Pfizer/Wyeth	Besponsa	CD22
Moxetumomab pasudotox	HCL	September 2018 (FDA) Withdrawn 2021	AstraZeneca	Lumoxiti	CD22
Polatuzumab vedotin	DLBCL	June 2019 (FDA)	Genentech/Roche	Polivy	CD79b
Enfortumab vedotin	UC	December 2019 (FDA)	Astellas/Seagen	Padcev	Nectin-4
Trastuzumab deruxtecan	GOJ, HER2 ⁺ BC, HER2 ⁺ GC, HER2 ^{low} BC, HER2 ^{mu} NSCLC	December 2019 (FDA)	Daiichi Sankyo/AstraZeneca	Enhertu	HER2
Sacituzumab govitecan	HR ⁺ /HER2 ⁻ BC, TNBC, UC	April 2020 (FDA)	Immunomedics	Trodelvy	TROP-2

Belantamab mafodotin	MM	August 2020 (FDA) withdrawn 2022	GlaxoSmithKline	Blenrep	BCMA
Cetuximab sarotalocan	HNSCC	September 2020 (PMDA)	Rakuten	Akalux	EGFR
Loncastuximab tesirine	BCL, DLBCL	April 2021 (FDA)	ADC Therapeutics SA	Zynlonta	CD19
Disitamab vedotin	HER2 ⁺ GC, HER2 ⁺ UC	June 2021 (NMPA)	RemeGen	Aidixi	HER2
Tisotumab vedotin	Cervical cancer	September 2021 (FDA)	Genmab/Seagen	Tivdak	TF
Mirvetuximab soravtansine	OC	November 2022 (FDA)	ImmunoGen/ Zhongmei Huadong	Elahere	FR α
Sacituzumab tirumotecan	TNBC, NSCLC	November 2024 (NMPA)	Kelun- Biotech/MSD	Ji Tailai	TROP-2
Datopotamab deruxtecan	HR ⁺ /HER2 ⁻ BC, NSCLC	December 2024 (PMDA)	Daiichi Sankyo/ AstraZeneca	Datroway	TROP-2
Telisotuzumab vedotin	NSCLC	May 2025 (FDA)	AbbVie	Emrelis	c-MET
SHR-A1811	NSCLC	May 2025 (NMPA)	Hengrui	Aivda	HER2

Table 1A: This table summarizes the approved indications, initial regulatory approval dates, developers, brand names, and molecular targets of ADCs authorized by major regulatory agencies, including the U.S. Food and Drug Administration (FDA), the National Medical Products Administration of China (NMPA), and the Pharmaceuticals and Medical Devices Agency of Japan (PMDA). Approval dates refer to the date of the first regulatory approval. ADCs that have been withdrawn from the market are indicated accordingly. Data are current as of September 1, 2025. Abbreviations: AML, acute myeloid leukemia; ALCL, anaplastic large-cell lymphoma; CTCL, cutaneous T-cell lymphoma; HL, Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; BC, breast cancer; ALL, acute lymphoblastic leukemia; HCL, hairy cell leukemia; DLBCL, diffuse large B-cell lymphoma; GOJ, gastro-oesophageal junction cancer; UC, urothelial carcinoma; GC, gastric cancer; NSCLC, non-small-cell lung cancer; TNBC, triple-negative breast cancer; MM, multiple myeloma; HNSCC, head and neck squamous cell carcinoma; BCL, B-cell lymphoma; OC, ovarian cancer. SHR-A1811 is a development code name; an International Nonproprietary Name has not yet been assigned.

Table 1B. Conjugation and payload characteristics of approved antibody-drug conjugates (ADCs).

ADC Name	Conjugate Type	Payload	Linker	DAR
Gemtuzumab ozogamicin	Lysine	Calicheamicin	AcButDMH	2-3
Brentuximab vedotin	Cysteine	MMAE	Mc-Val-Cit-PABC	4
Trastuzumab emtansine	Lysine	DM1	SMCC	3.5
Inotuzumab ozogamicin	Lysine	Calicheamicin	AcButDMH	6
Moxetumomab pasudotox	Amide bonds	PE38	Mc-Val-Cit-PABC	NA
Polatuzumab vedotin	Cysteine	MMAE	Mc-Val-Cit-PABC	3.5

Enfortumab vedotin	Cysteine	MMAE	Mc-Val-Cit-PABC	3.8
Trastuzumab deruxtecan	Cysteine	DXd	Maleimide-GGFG peptide	7.7
Sacituzumab govitecan	Cysteine	SN38	CL2A	7.6
Belantamab mafodotin	Cysteine	MMAF	Mc-MMAF	4
Cetuximab sarotalocan	NA (photosensitizer)	IRDye700DX	Linear alkyl	1.3-3.8
Loncastuximab tesirine	Cysteine	SG3199	Mal-PEG8-Val-Ala-PABC	2.3
Disitamab vedotin	Cysteine	MMAE	Mc-Val-Cit-PABC	4
Tisotumab vedotin	Cysteine	MMAE	Mc-Val-Cit-PABC	4
Mirvetuximab soravtansine	Lysine	DM4	Sulfo-SPDB	3.4
Sacituzumab tirumotecan	Sulfonylpyrimidine	KL610023	CL2A	7.4
Datopotamab deruxtecan	Cysteine	DXd	Mc-Gly-Gly-Phe-Gly	4
Telisotuzumab vedotin	Cysteine	MMAE	Mc-Val-Cit-PABC	3.1
SHR-A1811	Cysteine	SHR9265	Mc-Gly-Gly-Phe-Gly	5.7

Table 1B: This table summarizes the conjugation chemistry, cytotoxic payloads, linker types, and drug-to-antibody ratios (DARs) of ADCs that have received regulatory approval from major agencies. Conjugation type refers to the predominant amino acid residue or chemical bond used to attach the payload. DAR values indicate reported averages or ranges. ADCs are listed with development code names. SHR-A1811 is a development code name; an International Nonproprietary Name has not yet been assigned. Data are current as of September 1, 2025. Abbreviations: DAR, drug-to-antibody ratio; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; NA: not applicable; DM1, mertansine; DM4, soravtansine; DXd, deruxtecan; SN-38, 7-ethyl-10-hydroxycamptothecin.

While most ADC-related research focuses on clinically validated targets, especially those confirmed by marketed products or other therapies, recent studies show that molecules in neovascular systems, subendothelial extracellular matrices, and tumor stroma could serve as new target antigens for ADC development (17). For instance, emerging targets like folate receptor alpha (FR α) and tissue factor (TF) are broadening traditional clinical therapeutic approaches (18, 19).

Therefore, exploring new target antigens is likely to expand ADC indications and unlock greater market potential. Notably, 18 candidate drugs, including both approved and investigational ADCs, have entered Phase III/IV clinical trials. These target antigens include CD33, CD30, CD22, CD79b, Nectin-4, HER2, and Trop-2 (13–16) (Figure 1) (Table 2).

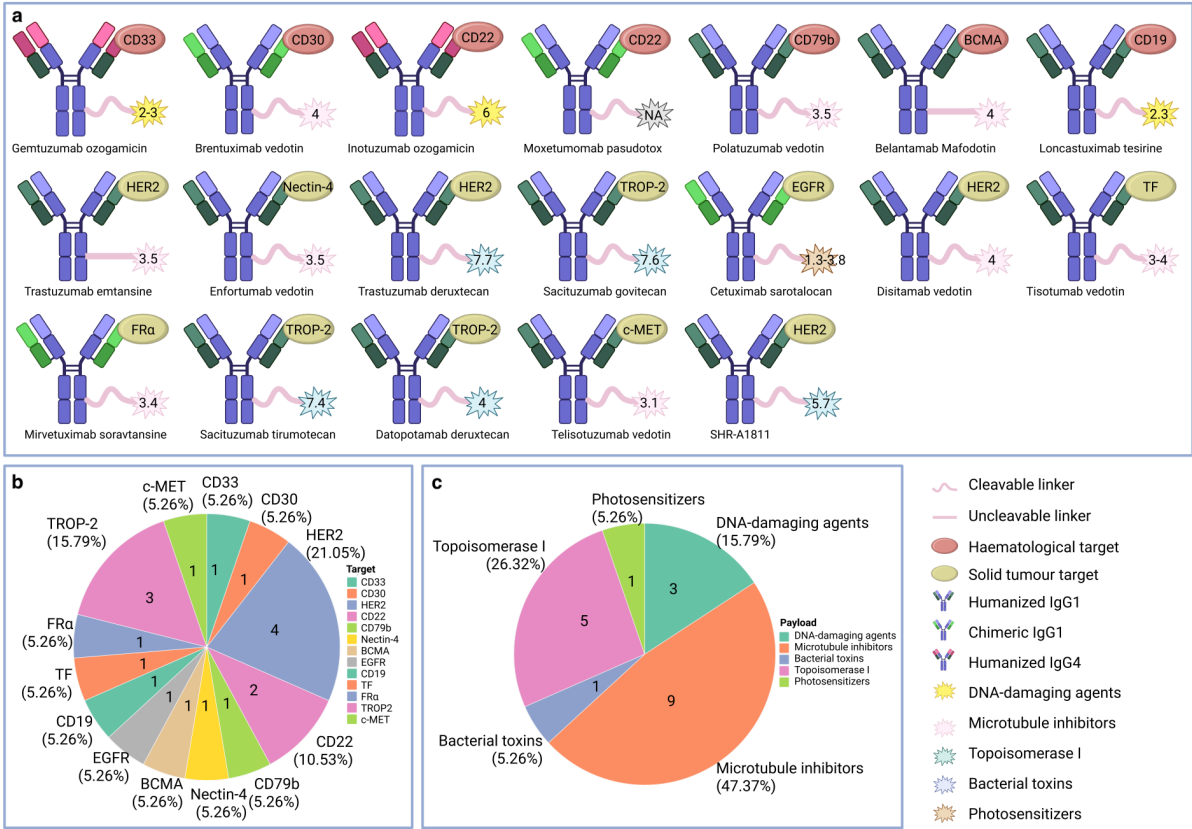


Figure 1. Main characteristics of approved antibody-drug conjugates (ADCs). (a) Structural features of currently approved ADCs. Among 19 ADCs approved to date, 7 are indicated for hematologic malignancies (including moxetumomab pasudotox, which has since been withdrawn from the market), and 12 are approved for solid tumors. Thirteen ADCs employ humanized IgG1 antibodies, four use chimeric IgG1 antibodies, and two utilize humanized IgG4 antibodies. Payload classes are indicated by distinct colors, and numerical values denote the drug-antibody ratio (DAR). Curved linker representations indicate cleavable linkers, whereas straight linker representations indicate non-cleavable linkers. (b) Distribution of target antigens among marketed ADCs. Human epidermal growth factor receptor 2 (HER2) is the most frequently targeted antigen, with four approved ADCs targeting it. (c) Distribution of payload classes among marketed ADCs. Microtubule inhibitors represent the predominant payload category, accounting for 47.37% of approved ADCs. Figure created with Biorender.

Table 2. Antibody-drug conjugates (ADCs) in phase III and phase IV clinical trials

ADC Name	Clinical Phase	NCT Number	Representative Indication	Sponsor	Outcomes
FDA018	III	NCT06519370	TNBC	FDZJ	Ongoing
Disitamab vedotin	III	NCT05302284	UC	RemeGen	Ongoing
Disitamab vedotin	III	NCT04714190	GC	RemeGen	Ongoing
Disitamab vedotin	III	NCT04400695	BC	RemeGen	Ongoing
Disitamab vedotin	III	NCT05904964	HR ⁺ /HER2 ^{Low} BC	Sun Yat-Sen Memorial Hospital	Ongoing

Disitamab vedotin	III	NCT05911295	UC	Seagen	Ongoing
TQB2102	III	NCT07008976	metastatic BC	Nanjing Shunxin	Ongoing
TQB2102	III	NCT07043725	HER2 ⁺ BC	Nanjing Shunxin	Ongoing
Enfortumab vedotin	IV	NCT06764095	BLCA	Mayo Clinic	Ongoing
GSK5764227	III	NCT07099898	SCLC	GlaxoSmithKline	Ongoing
Trastuzumab deruxtecan	III	NCT05950945	BC	Daiichi Sankyo	Ongoing
Trastuzumab deruxtecan	III	NCT03734029	HER2 ^{low} BC	Daiichi Sankyo	PFS, 8.8 vs. 4.2 months, OS, 23.4 vs. 16.8 months, ORR, 51.7% vs. 16.8%
Trastuzumab deruxtecan	III	NCT04494425	HER2 ^{low} /HR ⁺ BC	AstraZeneca	PFS, 12.8 vs. 7.0 months, OS, 28.9 vs. 27.4 months, ORR, 65.8% vs. 31.6%
Trastuzumab emtansine	III	NCT03529110	HER2 ⁺ /unresectable/ metastatic BC	Daiichi Sankyo	PFS, 25.1 vs. 7.2 months, ORR, 77.0% vs. 36.9%
MRG002	III	NCT05754853	advanced or metastatic UC	Shanghai Miracogen	Ongoing
SHR-A2102	III	NCT06738251	advanced UC	Shanghai Hengrui	Ongoing
SHR-A1811	III	NCT06123494	HER2 ⁺ advanced GC, GOJ	Jiangsu HengRui	Ongoing
Mirvetuximab soravtansine	III	NCT05445778	OC, PC, FTC	AbbVie	Ongoing
Mirvetuximab soravtansine	III	NCT02631876	OC, FTC	ImmunoGen	PFS, 4.14 vs. 4.44 months, OS, 15.57 vs. 13.93 months, ORR, 22% vs. 12%
Sacituzumab tirumotecan	III	NCT06074588	NSCLC	MSD	Ongoing
Sacituzumab tirumotecan	III	NCT06841354	TNBC	MSD	Ongoing
BNT323/DB-1303	III	NCT06340568	EC	BioNTech SE	Ongoing
Sacituzumab govitecan	III	NCT05609968	NSCLC	MSD	Ongoing
Sacituzumab govitecan	III	NCT06431633	NSCLC	Fundación GECP	Ongoing
Sacituzumab govitecan	IV	NCT04319198	metastatic solid tumors	Gilead Sciences	SAE, 66.7% vs. 100% vs. 91.7%

Loncastuximab tesirine	III	NCT05991388	B-cell NHL	University of Birmingham	Ongoing
Datopotamab deruxtecan	III	NCT06103864	BC	AstraZeneca	Ongoing
Brentuximab vedotin	III	NCT05675410	HL	NCI	Ongoing
Brentuximab vedotin	III	NCT02166463	HL	NCI	EFS, 82.5% vs. 92.1%
Brentuximab vedotin	III	NCT03907488	HL	NCI	EFS, 8.4% vs. 16.8%, OS, 1.4% vs. 2.9%
Inotuzumab ozogamicin	IV	NCT03677596	ALL	Pfizer	PFS, 6.3 vs. 6.3 months, OS, 9.6 vs. 8.1 months

Table 2: This table describes Phase III and IV clinical trials evaluating antibody-drug conjugates (ADCs) across solid tumors and hematologic malignancies. The listed information includes the ADC name, clinical phase, ClinicalTrials.gov identifier (NCT number), representative indication, trial sponsor, and reported clinical outcomes, where available (<http://clinicaltrials.gov>). Efficacy endpoints include progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and event-free survival (EFS); safety outcomes include serious adverse events (SAE). In comparative trials, outcomes are reported as experimental versus control. For phase IV studies with multiple safety cohorts, serious adverse event (SAE) rates are reported separately for each cohort and do not represent head-to-head comparisons. Ongoing studies are indicated where final efficacy data have not yet been reported. Abbreviations: BLCA, bladder urothelial carcinoma; BC, breast cancer; EC, endometrial cancer; FTC, fallopian tube cancer; GC, gastric cancer; GOJ, gastro-oesophageal junction cancer; HL, Hodgkin lymphoma; HR, hormone receptor; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, peritoneal cancer; SCLC, small cell lung cancer; UC, urothelial carcinoma; ALL, acute lymphoblastic leukemia; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; EFS, event-free survival; SAE, serious adverse event; NCI, National Cancer Institute; FDZJ, Shanghai Fudan-Zhangjiang Bio-Pharmaceutical; MSD, Merck Sharp & Dohme.

2.2 Antibody Selection

Antibodies, also known as immunoglobulins (Ig), are large proteins made by plasma cells. Their primary function is to detect and neutralize foreign invaders, such as bacteria and viruses, as well as other substances called neoantigens. Structurally, antibodies usually take a “Y” shape, made of four polypeptide chains, two identical heavy chains and two identical light chains. These chains form two distinct functional regions: the Fab and Fc fragments (20). The Fab region has variable domains with different amino acid sequences that create antigen-binding sites, giving antibodies their specificity. The more conserved Fc region interacts with other parts of the immune system. In cancer treatment, therapeutic monoclonal antibodies like trastuzumab act as targeted agents. They exhibit direct cytotoxic activity against tumor cells, often by triggering apoptosis, a common mechanism used in clinical settings (21). Antibody isotypes mainly include IgG1, IgG2, IgG3, and IgG4 (22). Among them, IgG1 is the most common subclass, with a serum half-life of about 21 days. It triggers antitumor effects through Fc receptor-mediated mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) (23). Currently, most ADCs use humanized IgG1 antibodies, such as sacituzumab govitecan, whereas some earlier ADCs, such as gemtuzumab ozogamicin (GO), use a humanized IgG4 backbone (24, 25). Although some chimeric antibodies, such as brentuximab vedotin (BV), are still in use, their murine variable regions paired with human constant domains can lead to immunogenicity (26). Additionally, bispecific antibodies, which simultaneously target two distinct antigens, are a promising area of

research, offering improved tumor targeting and reduced off-target effects (27). In ADC design, four essential criteria guide antibody selection. First, reducing immunogenicity lowers the risk of anti-drug antibody (ADA) formation, thereby decreasing neutralization and clearance and enhancing safety. Second, antibodies must demonstrate strong binding avidity and high selectivity for target antigens to enable precise delivery of cytotoxic payloads. Third, effective induction of endocytosis is necessary after antigen engagement to promote cellular uptake of ADC complexes. Additionally, prolonged circulatory persistence ensures ADC stability and sufficient tumor eradication (8, 22). Standard IgG antibodies, with a molecular weight of approximately 150 kDa, have limited penetration into solid tumors due to their large size. Engineered smaller formats, including bispecific antibodies or single-chain variable fragments generated by Fc domain removal, provide improved tissue penetration and reduce adverse immune activation (8, 28).

2.3 Design of linker

The linker forms covalent bonds between monoclonal antibodies and cytotoxic payloads, enabling precise payload delivery and serving as a key part of ADC function, acting as a “biological missile” (9). To reduce off-target toxicity, the linker must be highly stable in systemic circulation, while rapid payload release upon tumor-cell internalization is crucial for maximizing cytotoxic effectiveness (29). The linker's physicochemical properties, including hydrophilicity and hydrophobicity, greatly affect the solubility, tendency to aggregate, and in vivo clearance of ADCs (30). Increased hydrophilicity can improve pharmacokinetic profiles, greatly decreasing nonspecific uptake and off-target side effects (31).

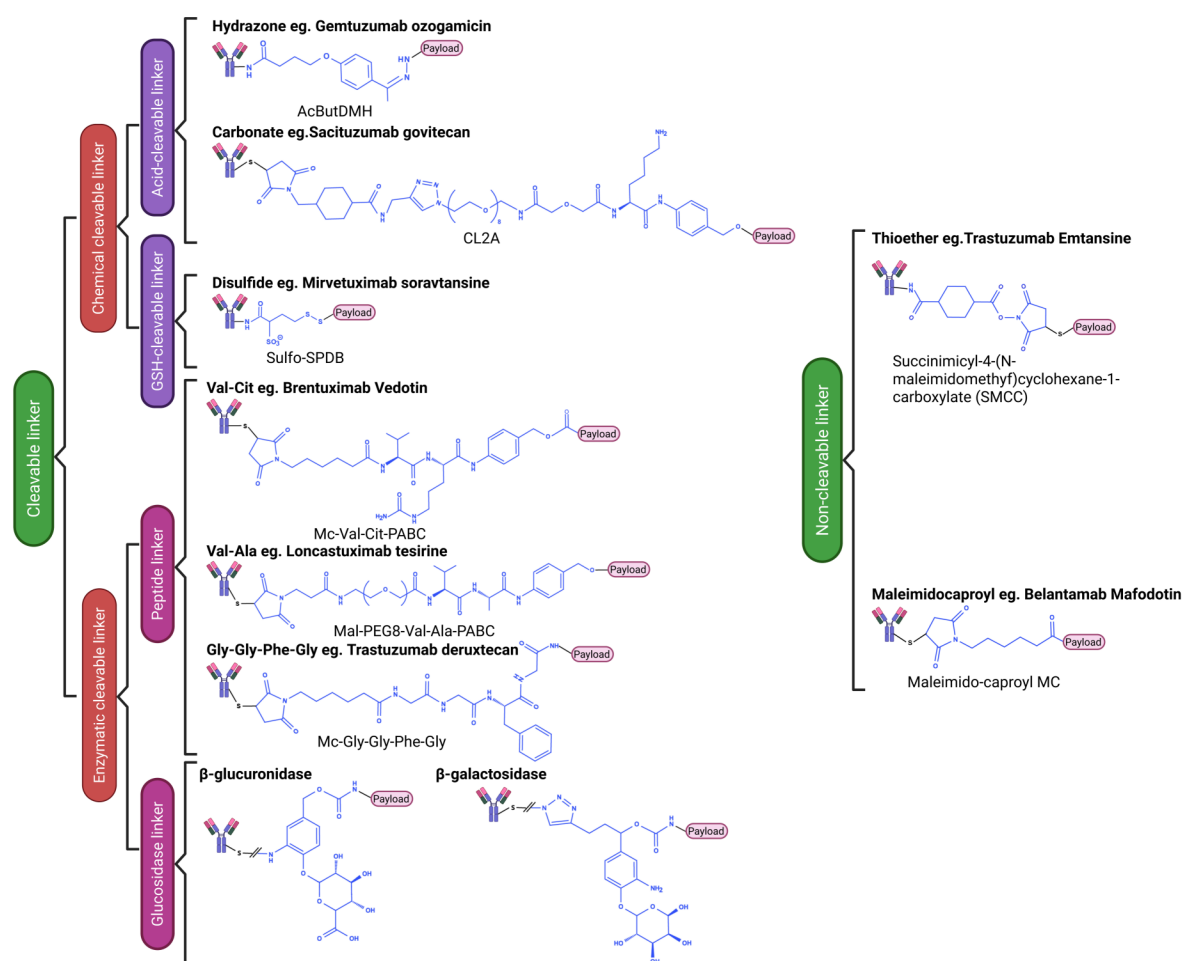


Figure 2. Classification of linkers used in antibody-drug conjugates (ADCs). *Based on their cleavage mechanisms, ADC linkers are broadly divided into cleavable and non-cleavable categories. Cleavable linkers are further subdivided into chemically cleavable and enzymatically cleavable types. Chemically cleavable linkers include acid-sensitive and reducible linkers. Acid-sensitive linkers typically form covalent bonds via hydrazone linkages, created by reactions between the ketone carbonyl groups on the linker and the acylhydrazine groups on the payload. Reducible linkers depend on thiol-disulfide exchange reactions, where free thiol groups on the antibody react with activated disulfide bonds on the linker-payload complex to form new disulfide bonds. Enzymatically cleavable linkers are often classified as dipeptide- or glycosidase-based. In dipeptide linkers, a maleimide group establishes a stable thioether bond with interchain cysteine residues of the antibody, while the opposite end uses the carboxyl group of para-aminobenzylcarbamate (PABC) to form an amide bond with the payload. Glycosidase-based linkers generally incorporate β -glucuronide or β -galactoside moieties and also use PABC as a self-immolative spacer. Non-cleavable linkers directly connect the antibody and payload through stable thioether or amide bonds. Figure created with Biorender.*

Additionally, the linker's chemical structure should be designed to avoid introducing immunogenic regions, thereby reducing the risk of immune recognition and ADA development. This approach maintains consistent pharmacokinetics and therapeutic potency while enabling safe metabolic clearance and preventing the buildup of toxic byproducts. Linkers are generally classified into two main types based on their cleavage: cleavable and non-cleavable (Figure 2). Cleavable linkers exploit microenvironmental differences between tumor cells and the systemic circulation to achieve selective payload release, facilitating the bystander effect (discussed in detail later). This feature is especially beneficial for treating tumors with diverse antigen expression. Chemically cleavable and enzymatically cleavable linkers are the two main types of cleavable linkers (32).

2.3.1 Chemically cleavable linkers

Chemically cleavable linkers that rely on tumor-specific chemical triggers for disruption include acid-labile and reduction-labile types (33). Acid-sensitive linkers exploit the acidic microenvironment (pH 4.5–5.0) of tumor cell endosomes and lysosomes for hydrolytic cleavage, often via hydrazone bonds. For example, GO uses a 4-(4-acetylphenoxy) butanoic acid (AcBut) linker to conjugate a calicheamicin derivative (CalichDMH) to a humanized IgG4 anti-CD33 antibody (34). Sacituzumab govitecan (SG) uses a carbonate linker, which is also acid-cleavable (31). However, their clinical use is limited by poor stability; a ketone-derived hydrazone linker showed a hydrolysis half-life of only 2 days in human and murine plasma (35). Reduction-sensitive linkers utilize the significant difference in glutathione (GSH) concentration between intracellular (1–10 mM) and extracellular (~5 μ M) environments to promote disulfide bond reduction (9,36). They remain stable in circulation but undergo reductive cleavage upon internalization into tumor cells. Mirvetuximab soravtansine (MIRV), which uses a sulfo-SPDB linker, illustrates this mechanism and received accelerated FDA approval in 2022 for the treatment of platinum-resistant ovarian cancer (37).

2.3.2 Enzymatically cleavable linkers

Enzymatically cleavable linkers in ADCs exploit hydrolases that are overexpressed in tumors for degradation and are predominantly peptide- or glycosidase-based. Peptide linkers, recognized by lysosomal proteases such as cathepsin B, include sequences like Val-Cit, Val-Ala, and Gly-Gly-Phe-Gly. These linkers are a cornerstone of ADC technology, ensuring high selectivity and stability (38,39). For example, BV, an FDA-approved ADC, combines a CD30-specific antibody, a cleavable dipeptide linker (Mc-Val-Cit-PABC), and MMAE to treat Hodgkin lymphoma and systemic anaplastic large cell lymphoma (40). Val-Ala is more hydrophilic than Val-Cit, providing clear benefits for use with lipophilic payloads like pyrrolobenzodiazepine (PBD), as seen with the approved ADC loncastuximab tesirine (Lonca) (39). The MC-GGFG tetrapeptide linker used in trastuzumab deruxtecan (T-DXd) allows proteolytic degradation in lysosomes to release the payload (41). Glycosidase linkers, cleaved

by enzymes such as β -glucuronidase or β -galactosidase, improve ADC solubility and stability, enabling higher drug-to-antibody ratios (DARs). Burke et al. showed that anti-CD30 conjugates with glucuronic acid-AE linkers demonstrated efficacy and immunospecificity (42). Kolodych et al. reported that galactosidase-based ADCs outperformed trastuzumab emtansine (T-DM1) in vitro (43).

2.3.3 Non-cleavable linkers

Non-cleavable linkers, including thioether and maleimidocaproyl variants, form strong covalent bonds between antibodies and cytotoxic payloads. These linkers preserve structural integrity during systemic circulation and within cellular compartments. Payload release occurs only after lysosomal proteolysis of the antibody into amino acids, creating “amino acid-linker-payload” conjugates. Unlike cleavable-linker ADCs, the metabolites of non-cleavable-linker ADCs have limited membrane permeability, which prevents the bystander effect—an advantage for tumors that uniformly express the antigen (44, 45). For example, T-DM1 uses the SMCC thioether linker to attach maytansinoid DM1 to trastuzumab (46), while belantamab mafodotin employs an MC linker to couple MMAF to its antibody via an amide bond (47). However, these ADCs face challenges, including suboptimal payload release and potential therapeutic limitations. Future research should focus on optimizing linkers, exploring combination immunotherapies, and developing new conjugation methods to mitigate resistance and improve efficacy.

2.4 Design of the Payload

The anti-tumor activity of ADCs mainly relies on their cytotoxic payloads, which inhibit tumor growth through various mechanisms. These include interfering with DNA replication, causing structural alterations in the genome, and preventing microtubule assembly, as previously documented (48). An ideal payload must have seven key attributes: high cytotoxic effectiveness, low immunogenicity, strong stability during manufacturing and in systemic circulation, and adjustable functional groups for conjugation (49). The current range of approved ADC payloads includes five main categories: Topoisomerase I (Topo I) inhibitors, microtubule-targeting agents, DNA-damaging compounds, photosensitizers, and bacterial toxins (Figure 3).

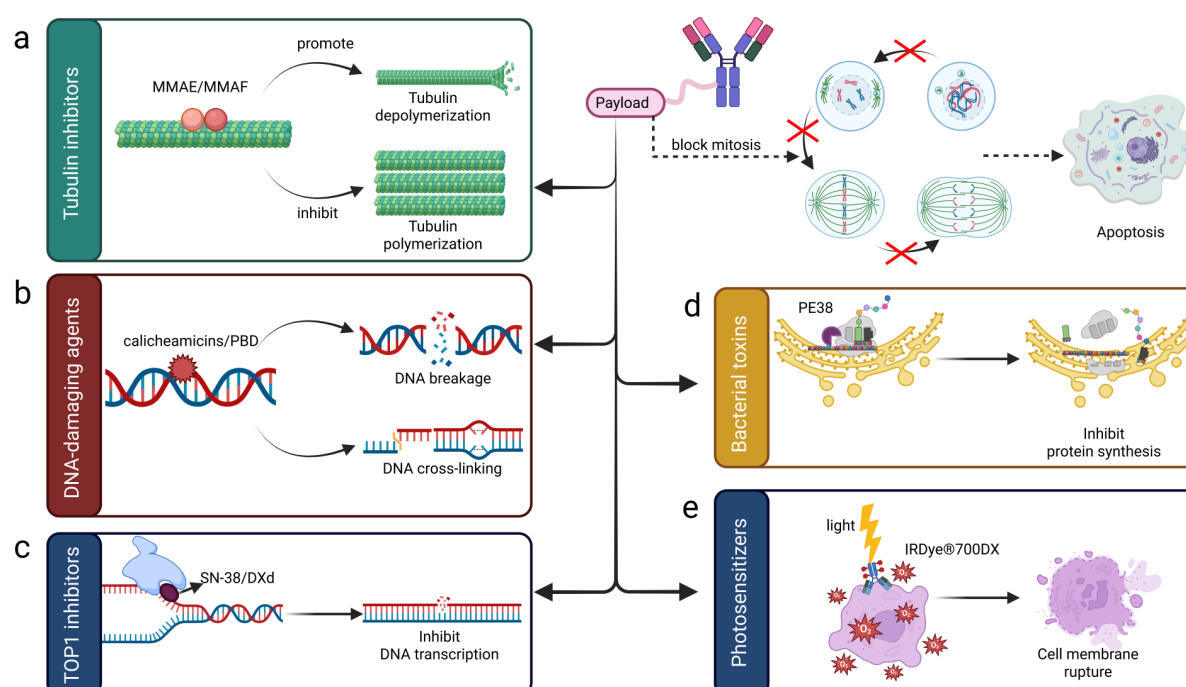


Figure 3. Classification of payloads used in antibody-drug conjugates (ADCs) and their mechanisms of action. (a) Microtubule inhibitors exert cytotoxic effects by binding to tubulin, either suppressing microtubule polymerization or inducing excessive microtubule stabilization. These disruptions impair mitotic spindle formation, arrest the cell cycle at the G2/M phase, and ultimately trigger apoptotic cell death. (b) DNA-damaging agents induce cytotoxicity by directly disrupting DNA integrity through mechanisms such as alkylation, interstrand or intrastrand cross-linking, and induction of DNA strand breaks, leading to irreparable genomic damage and cell death. (c) Topoisomerase I inhibitors act by stabilizing the topoisomerase I-DNA cleavage complex, thereby preventing DNA religation. This results in stalling of the replication fork and accumulation of DNA double-strand breaks during DNA replication. (d) Bacterial toxin-based payloads primarily induce apoptosis by inhibiting protein synthesis, leading to rapid loss of cellular viability. (e) Photosensitizers mediate cytotoxicity through photodynamic therapy (PDT). Upon activation by specific wavelengths of light, these agents generate reactive oxygen species (ROS), which induce oxidative damage and cancer cell death. Figure created with BioRender.com.

In preclinical and clinical development, new payload classes are expanding this list, introducing Topoisomerase II (Topo II) inhibitors, RNA-targeting agents, Bcl-xL antagonists, and immunomodulatory molecules (9, 52).

2.4.1 Microtubule inhibitors

Microtubule inhibitors are essential in the mechanism of ADCs. By binding to tubulin subunits, these inhibitors either block microtubule polymerization or cause significant disruption. This prevents proper cell division, leading to cell cycle arrest at the G2/M checkpoint and subsequent programmed cell death (53) (Figure 3a). Among approved ADC payloads, natural products dominate, with microtubule inhibitors comprising over half of this category. Auristatins and maytansinoids are two main subclasses. Auristatins, such as monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF), are preferred due to their high cytotoxicity, good aqueous solubility, stability under physiological conditions, and compatibility with various linker chemistries, making them popular for ADC toxin development (48). Examples of related ADCs include commercially available drugs like BV and polatuzumab vedotin (Pola), as well as Phase III candidates such as MK-2140 and ABBV-399 (25). Maytansinoids, represented by DM1 and DM4, also show excellent stability and solubility. T-DM1, approved for HER2-positive breast cancer (BC), uses DM1 with a very low IC₅₀ (10⁻¹¹–10⁻⁹ M) (54), while MIRV employs DM4 to target FR α in ovarian cancer (55).

2.4.2 DNA-damaging agents

DNA-damaging agents cause direct structural damage to DNA via alkylation, cross-linking, or the induction of double-strand breaks, thereby triggering cell death. These highly potent payloads are active against both proliferating and quiescent cells and are accompanied by a pronounced bystander effect (56). They are primarily classified into calicheamicins, PBD dimers, and duocarmycins. Calicheamicins, as enediyne antibiotics, generate sequence-specific DNA double-strand breaks, and derivatives are used in FDA-approved ADCs such as GO and inotuzumab ozogamicin (InO) (57–59). PBD dimers bind to the minor groove of DNA, forming irreversible cross-links that impede replication and transcription (Fig. 3b). Lonca, the first PBD-containing ADC, received approval in 2021 (60). Duocarmycins induce DNA alkylation via adenine adducts, as exemplified by trastuzumab duocarmazine (Phase III), which employs seco-DUBA to treat advanced HER2⁺ BC (61).

2.4.3 Topo I inhibitors

Topo I inhibitors increase their affinity for the Topo I-DNA complex, thereby blocking DNA religation. This mechanism causes replication forks to stall and eventually leads to double-strand DNA breaks. SN-38 and DXd are examples of this class of inhibitors (62) (Figure 3c). Regulatory approvals for these agents began with T-DXd, followed by SG (63, 64). T-DXd features a humanized anti-HER2 IgG1 monoclonal antibody (mAb) conjugated to DXd through a cleavable mc-Gly-Gly-Phe-Gly linker,

promoting cancer cell apoptosis and bystander killing. SG, using the anti-TROP2 IgG1 mAb hRS7 and a hydrolyzable CL2A carbonate linker for SN-38 delivery, shows efficacy in metastatic triple-negative breast cancer (TNBC) and other malignancies (62).

2.4.4 Bacterial toxins

Bacterial toxins, classified as exotoxins and endotoxins, are bioactive compounds produced by bacteria that can harm human and other biological systems. Exotoxins, mainly protein-based, are actively secreted by bacteria into their surroundings, while endotoxins are essential parts of the bacterial cell wall and are usually released when bacteria break apart (65). *Pseudomonas aeruginosa* exotoxin A (PEA) is a particularly important virulence factor of *P. aeruginosa* (66). As shown by the FDA-approved moxetumomab pasudotox, which combines the anti-CD22 mAb's variable fragment (Fv) with PE38 (a truncated PEA variant), PE38 causes ADP-ribosylation of the diphthamide residue in elongation factor 2 (EF-2). This post-translational modification prevents EF-2 from functioning, thereby blocking polypeptide chain elongation, hindering protein synthesis, and ultimately causing cell death (67) (Figure 3d).

2.4.5 Photosensitizers

Photosensitizers, an important class of compounds, can absorb electromagnetic radiation within specific spectral ranges, spanning 250–420 nm (ultraviolet) or 400–800 nm (visible light). Upon absorption, they undergo electronic excitation, producing reactive intermediates such as free radicals and cations that trigger photochemical processes. In photodynamic therapy (PDT), the synergistic interaction of photosensitizers, molecular oxygen, and appropriate light wavelengths induces therapeutic photochemical reactions (68, 69) (Figure 3e). Akalux (ASP-1929), an FDA-approved photoimmunotherapy agent, demonstrates this mechanism. Consisting of cetuximab and IRDye® 700 DX, a water-soluble silicon phthalocyanine-based photosensitizer, it targets EGFR-positive tumor cells. Upon near-infrared irradiation, the photosensitizer produces singlet oxygen, leading to tumor cell death and microvascular disruption, providing a treatment option for advanced head and neck cancer (50, 70, 71).

2.4.6 New potential payload

Topo II inhibitors

Topo II, a crucial nuclear endonuclease, mediates topological transformations in double-stranded DNA by temporarily cutting and rejoining the helix. This enzyme activity is vital for resolving topological problems during key genomic processes, including DNA replication, transcription, recombination, and mitotic chromosome segregation (72). Exploiting the higher Topo II expression and activity in cancer cells compared to normal tissues, this enzyme has become a validated target for anticancer drug development. Topo II inhibitors are a class of oncolytic agents that block Topo II's catalytic activity, thereby hindering DNA replication and transcription, and producing antitumor effects (62). These chemotherapeutics targeting Topo II are mainly divided into two categories: Topo II poisons (e.g., etoposide, doxorubicin) and catalytic inhibitors (73). Analysis of patent literature from 2016 to 2025 shows significant progress in the design of Topo II inhibitors, with new chemotypes such as quinolines (WO18107112) and lapidipines (CN108947916 B) highlighting the therapeutic promise of this drug class in cancer treatment (72).

RNA inhibitors

RNA inhibitors that target RNA synthesis or function have emerged as a new class of anticancer agents. Their ability to target both actively dividing and non-cycling cancer cells provides a significant therapeutic benefit, potentially preventing tumor recurrence linked to dormant cancer cells and certain drug resistance pathways (74). Key examples of RNA inhibitors used in ADCs include RNA polymerase II inhibitors, such as amatoxins, and RNA splicing inhibitors, which interfere with gene transcription and RNA maturation, ultimately stopping protein synthesis and inducing apoptosis. An example is HDP-101, a BCMA-targeted ADC that uses an amatoxin derivative as its cytotoxic payload. This ADC is currently being studied in a Phase II clinical trial for the treatment of multiple myeloma (75).

BCL-XL inhibitors

BCL-XL, a pivotal anti-apoptotic protein, plays a central role in tumor progression, metastasis, and drug resistance. BCL-XL inhibitors, as payloads in ADCs, offer a promising strategy for inducing tumor cell apoptosis. However, a critical challenge in ADC development is mitigating platelet toxicity. Because platelet survival depends on BCL-XL expression, targeting this protein expands the therapeutic index (76). ABBV-155 (mirzotamab clezutoclax) is a significant achievement, as it is the first ADC targeting the cell-surface protein B7-H3 (CD276) with a highly selective and potent BCL-XL inhibitor as its payload. Ongoing clinical investigations are exploring its efficacy in treating glioma, advanced non-small cell lung cancer (NSCLC), and BC (62, 77).

Immune stimulant

Immune stimulant payloads, unlike cytotoxic agents, are designed to activate innate immune responses within the TME. Examples include STING activators and Toll-like receptor (TLR7/8/9) agonists. These compounds trigger signaling pathways in tumors, including the STING and TLR pathways, leading to increased production of type I interferons and other cytokines. This cytokine surge activates macrophages, dendritic cells, natural killer cells, and T lymphocytes, thereby boosting anti-tumor immune surveillance (78–80). A notable example is XMT-2056, an ADC carrying a STING agonist payload. Currently in Phase I clinical trials, this HER2-targeting ADC, which recognizes a novel epitope, shows enhanced anti-tumor effects when combined with trastuzumab or pertuzumab (81).

3. Mechanism of action of ADC in vivo

ADCs are a new class of targeted therapeutic agents that combine the specificity of monoclonal antibodies with the potent cytotoxicity of small-molecule drugs. The multifaceted mode of action of ADCs comprises three main parts: the mAb, which specifically binds to tumor-associated antigens; the linker, which securely attaches the payload to the antibody while maintaining its stability in circulation; and the cytotoxic payload, which exerts anti-tumor effects upon internalization by target cells. This modular design enables ADCs to achieve both accurate tumor targeting and strong therapeutic effects while reducing systemic toxicity compared with traditional chemotherapy. Through this modular design, ADCs bridge targeted therapy, cytotoxic chemotherapy, and tumor immunology, enabling both direct tumor cell killing and modulation of the tumor microenvironment.

3.1 The canonical model of ADC action

The therapeutic action of ADCs begins with intravenous injection, resulting in systemic circulation in three forms: intact conjugates, unbound antibodies, and free payloads. The immunoglobulin domain (e.g., IgG1) remains structurally stable in circulation while exhibiting high specificity and affinity for tumor-associated antigens. These antigens are either overexpressed or uniquely found on tumor cell

membranes or within the TME (82, 83). When the antigen is recognized, the ADC-antigen complex is internalized into the cell via endocytosis, primarily via clathrin- or caveolin-mediated pathways, forming early endosomes. These vesicles mature along the cytoskeleton, changing from early to late endosomes before reaching lysosomes (84) (Figure 4).

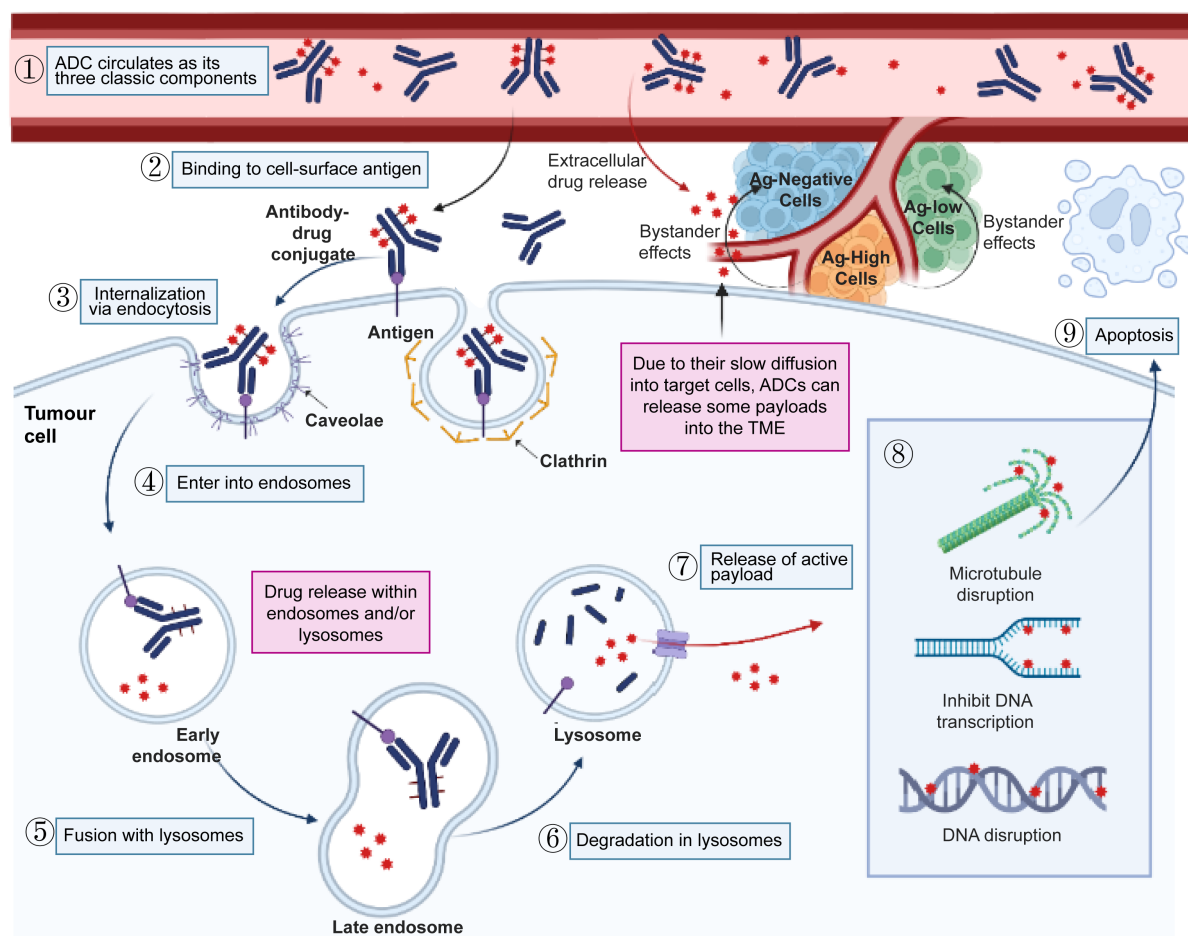


Figure 4. Core mechanism of action of antibody-drug conjugates (ADCs). After intravenous administration, ADCs circulate in the bloodstream as a mixture of intact conjugates, unconjugated (naked) antibodies, and free payload molecules. The antitumor activity of ADCs involves three main steps. (1) The monoclonal antibody (mAb) component of the ADC recognizes and binds to target antigens that are highly expressed on tumor cell surfaces. (2) Once bound to the antigen, the antibody-antigen complex undergoes receptor-mediated endocytosis, leading to internalization and formation of an endosomal vesicle. (3) The endosome then matures and fuses with lysosomes, where lysosomal processing and degradation of the ADC result in payload release. The freed cytotoxic payload then exerts its antitumor effect, ultimately causing tumor cell death. Figure created with Adobe Illustrator.

A portion of the early endosome associates with Fc receptors and is transported back outside the cell via transcytosis, while the remainder matures into late endosomes that eventually fuse with lysosomes. Not all ADCs require internalization, but this process is necessary for those using non-cleavable linkers or membrane-impermeable payloads (25). Lysosomes contain abundant proteases (e.g., Cathepsin B), acid hydrolases, and a low-pH environment (~pH 4.5–5.0), where ADC structures break down. Cleavable linkers enable specific disassembly; for example, peptide linkers are cleaved by proteases, and hydrazone bonds hydrolyze under acidic conditions, releasing cytotoxic payloads. In contrast, ADCs with non-cleavable linkers undergo complete degradation of their antibody component into amino acids by lysosomal enzymes, thereby releasing cytotoxins attached to residual amino acid residues (29). The cytotoxic payload is released into the cytoplasm in its active form. These highly

potent toxins (e.g., MMAE, DM1, DXd, SN-38) subsequently act on their respective intracellular targets. This series of reactions finally induces apoptotic or necrotic cell death, exerting cytotoxic effects on tumor cells.

3.2 Bystander effects of ADCs

The bystander effect, characterized by the diffusion of lipophilic, membrane-permeable payloads from antigen-positive tumor cells to adjacent antigen-negative tumor cells, extends ADC payload delivery beyond strictly antigen-positive cells (85). This effect effectively overcomes resistance mechanisms related to target antigens, such as antigen heterogeneity, downregulation, or loss.

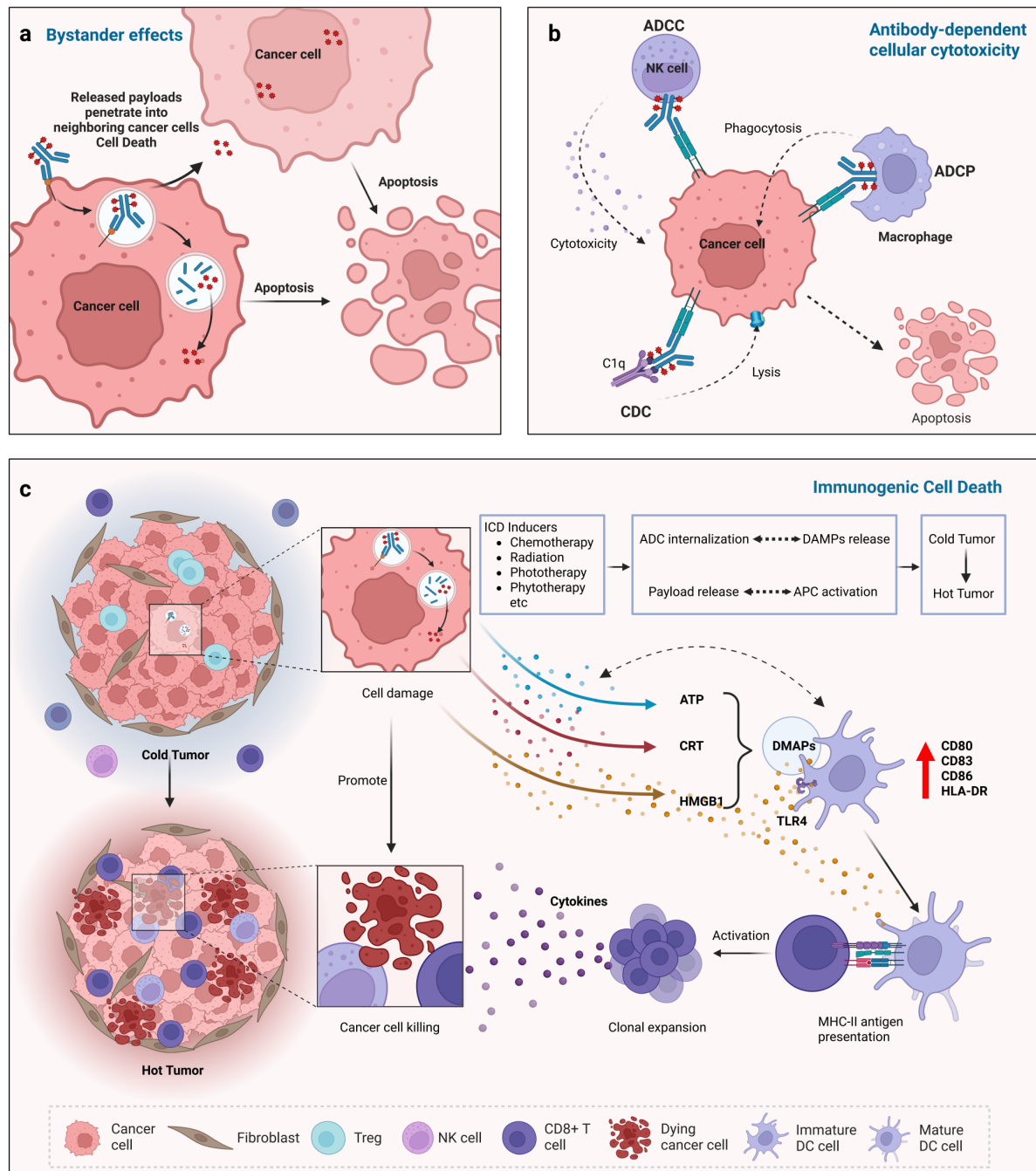


Figure 5. Additional mechanisms of action of antibody-drug conjugates (ADCs). (a) *Bystander effect.* Certain ADCs induce cytotoxicity not only in tumor cells expressing the target antigen but also in neighboring antigen-negative tumor cells

by allowing released cytotoxic payloads to diffuse within the tumor microenvironment. (b) Antibody-mediated immune effector functions. The monoclonal antibody component of ADCs can engage immune effector cells, activating antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). (c) Immunogenic cell death. ADC-induced tumor cell death can trigger the release of immunogenic danger signals, which stimulate the host's antitumor immune responses. This process promotes both direct tumor cell killing and the development of immune memory, helping to convert immunologically "cold" tumors into "hot" tumors. Figure created with BioRender.com.

Tumor cells can decrease surface antigen expression (e.g., HER2, CD33) through transcriptional repression, proteasomal degradation, or alternative splicing. Traditionally, ADCs were thought to require binding to the target antigen and internalization to release the payload (86). However, ADCs capable of the bystander effect can operate via an alternative pathway. In the TME, acidic pH, reducing agents, and proteases can induce premature linker cleavage, releasing the payload before ADC internalization (87). Lipophilic, membrane-permeable payloads like MMAE and SN-38 diffuse from targeted cells into the surrounding microenvironment, thereby killing neighboring antigen-negative tumor cells (85, 88). This process is shown in Figure 5a, illustrating how the released payload (red dots) penetrates neighboring antigen-negative cells, emphasizing the spatial advantage of the bystander effect in addressing tumor heterogeneity.

The bystander effect is strongly influenced by factors such as DAR and the TME. Clinically, higher DAR values are typically associated with greater effectiveness in heterogeneous tumors (89). Additionally, the complex TME, including factors such as pH and protease activity, regulates the efficiency of payload release and diffusion. For instance, T-DXd (DAR = 7) showed a higher objective response rate (ORR) in HER2-mutated NSCLC than ADCs with stable, non-cleavable linkers such as T-DM1 (DAR = 5) (90, 91). Cleavable linkers and permeable payloads are vital for this, whereas ADCs with non-cleavable linkers typically lack significant bystander activity because they rely on lysosomal degradation to release the payload (92). The effectiveness of ADCs largely depends on the synergy between their linkers and payloads, as the structural and functional features of these components directly influence payload delivery, release timing, and antitumor activity. Table 3 outlines the efficacy profiles of key linker/payload combinations in approved ADCs, focusing on the main clinical endpoints across major uses. Payload diffusion can also affect normal cells within the TME, increasing the risk of off-target toxicity (e.g., corneal damage or hepatocyte injury) (89). Therefore, optimizing ADC design is essential to balance effectiveness and safety.

Table 3. Comparative efficacy outcomes of representative approved antibody-drug conjugates (ADCs) stratified by linker chemistry and cytotoxic payload class.

ADC Name	Linker Type	Payload Class	Target	Indication	Efficacy Endpoints
Trastuzumab deruxtecan (T-DXd)	Cleavable (mc-Gly-Gly-Phe-Gly)	Topo I inhibitor (DXd)	HER2	HER2 ⁺ BC	PFS, median: 28.8 months (vs. 7.2 months for T-DM1), ORR: 79.7%
Sacituzumab govitecan (SG)	Cleavable (CL2A carbonate)	Topo I inhibitor (SN-38)	TROP2	TNBC	PFS, median: 5.6 months (vs. 1.7 months for chemotherapy), ORR: 31.7%
Brentuximab vedotin (BV)	Cleavable (Mc-Val-Cit-PABC)	Microtubule inhibitor (MMAE)	CD30	HL/ALCL	ORR: 86% (sALCL), DOR, median: 12.6 months
Trastuzumab emtansine (T-DM1)	Non-cleavable (SMCC)	Microtubule inhibitor (DM1)	HER2	HER2 ⁺ BC	PFS, median: 9.6 months, OS, median: 30.9 months (second-line setting)

Loncastuximab tesirine (Lonca)	Cleavable (Mal-PEG8- Val-Ala- PABC)	DNA-damaging agent (SG3199)	CD19	DLBCL	ORR: 48.3%, OS, median: 10.3 months (relapsed/refractory)
Mirvetuximab soravtansine (MIRV)	Cleavable (sulfo-SPDB)	Microtubule inhibitor (DM4)	FR α	Platinum- resistant OC	PFS, median: 5.6 months (vs. 3.9 months for chemotherapy), ORR: 32.4%

Table 3. Comparative efficacy outcomes of selected approved antibody-drug conjugates (ADCs), organized by linker chemistry and cytotoxic payload class. This table summarizes key clinical efficacy endpoints reported for FDA-approved ADCs, including median progression-free survival (PFS), objective response rate (ORR), overall survival (OS), and duration of response (DOR), as measured in pivotal phase II or phase III trials. Indications cover HER2-positive breast cancer (HER2+ BC), triple-negative breast cancer (TNBC), Hodgkin lymphoma (HL), anaplastic large-cell lymphoma (ALCL), diffuse large B-cell lymphoma (DLBCL), and platinum-resistant ovarian cancer (OC). Payload types include topoisomerase I inhibitors, microtubule inhibitors, and DNA-damaging agents. Data are sourced from original trial publications and associated ClinicalTrials.gov records. Because of variations in study design, patient populations, and prior treatments, cross-trial comparisons should be made cautiously. Abbreviations: ADC, antibody-drug conjugate; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; DOR, duration of response; HER2, human epidermal growth factor receptor 2; TROP2, trophoblast cell-surface antigen 2; FR α , folate receptor alpha; BC, breast cancer; TNBC, triple-negative breast cancer; HL, Hodgkin lymphoma; ALCL, anaplastic large-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; OC, ovarian cancer.

3.3 Antibody-Mediated Immune Effector Functions

Beyond payload-induced killing, ADC-mediated anticancer activity also involves antibody-mediated immune effector functions: ADCC, ADCP, and CDC (Figure 5b). ADCC occurs when the ADC antibody's Fc region binds to Fc γ receptors on immune effector cells (e.g., NK cells), activating these cells to release cytotoxic substances (perforin, granzymes) that kill antibody-targeted tumor cells (93). It depends on the ADC antibody's integrity and Fc functionality—for example, a new fucosylated anti-BCMA IgG1 enhances ADCC by increasing Fc binding to Fc γ RIIIa (94). ADCP occurs when myeloid cells (mainly macrophages) with Fc γ receptors are activated by binding to the Fc region of the ADC antibody, leading to phagocytosis of antibody-coated tumor cells (95). Tumor-bound antibodies promote macrophage phagocytosis via Fc γ R, a key mechanism of action for many therapeutic antibodies. For example, the CD47-SIRP α interaction blocks maximum antibody-dependent phagocytosis. CD47 blockade therapy removes the inhibitory signal mediated by SIRP α , boosting macrophage activation and increasing ADCP (96). CDC occurs when ADC antibody-antigen binding changes the Fc conformation to bind complement C1q, triggering the complement cascade to form MAC, which lyses target cells through osmotic pressure (97). HexaBody-CD38 (GEN3014) is a next-generation CD38-targeting IgG1 antibody with an E430G mutation in its Fc domain that promotes hexamer formation upon cell-surface binding, greatly increasing complement-dependent cytotoxicity (CDC) (98).

3.4 Immunogenic cell death (ICD)

ADCs not only deliver cytotoxic payloads but also employ diverse strategies to modulate the immune system, thereby enhancing antitumor efficacy. Immunogenic cell death (ICD), a precisely regulated form of cell death, stimulates host adaptive immunity during the cell death process. Certain payloads, especially DNA-damaging agents, can trigger ICD in tumor cells (99). This process involves apoptotic cells releasing damage-associated molecular patterns (DAMPs), such as extracellular adenosine triphosphate (ATP), high-mobility group box 1 protein (HMGB1), and surface-exposed calreticulin (CRT) (100). These DAMPs help attract and activate antigen-presenting cells (APCs), including dendritic cells (DCs), potentially initiating a tumor-specific immune response. Combining ADCs with

immune checkpoint inhibitors (ICIs) results in synergistic therapeutic effects (100, 101). Extracellular ATP acts as a chemoattractant, guiding DCs and other APCs to tumor sites (102). Released HMGB1 binds to Toll-like receptor 4 (TLR4) on DCs, increasing the expression of major histocompatibility complex class II (MHC-II) and co-stimulatory molecules (CD80, CD83, CD86, HLA-DR), thereby boosting DC activation and maturation (103–105). CRT serves as an “eat-me” signal to enhance the phagocytosis of apoptotic cells by DCs (106). Activated DCs then present processed tumor antigens to naive CD8⁺ T cells, promoting T cell infiltration and activation, and ultimately triggering systemic antitumor immunity (107) (Figure 5c).

ICD results from cells’ inadequate adaptation to specific stressors and plays a crucial role in the development of new anticancer strategies. Current treatments like chemotherapy, radiation, and targeted oncotherapeutics mimic viral signatures to stress malignant cells, induce apoptosis, and activate tumor-specific immune responses. ICD inducers improve tumor response to immune checkpoint inhibitors (ICIs). Ongoing research explores new ICD compounds, some FDA-approved (108, 109) and others (e.g., LTX-315/VC-315) in clinical trials (110) for combined immunotherapy. The ICD pathway serves as a molecular link between the direct cytolytic activity of ADCs and systemic antitumor immune responses. It not only destroys target cells but also modulates the immunosuppressive tumor microenvironment, transforming “cold” tumors into “hot” ones. By shifting tumors from immune-excluded to immune-inflamed phenotypes, ICD facilitates effective combination therapies with ICIs. This synergistic approach offers a promising strategy to advance cancer immunotherapy. These mechanisms illustrate that ADCs operate through a multilayered therapeutic model combining targeted cytotoxicity, bystander killing, and immune activation.

4. Clinical applications of marketed ADCs

4.1 Single-Agent Clinical Application

4.1.1 ADCs in hematological malignancies

To date, seven ADCs have been approved by regulatory agencies for the treatment of hematologic malignancies. Moxetumomab pasudotox, the first FDA-approved therapy for hairy cell leukemia in over 20 years (2018) (111), was withdrawn from the U.S. market in 2023 due to toxicity, low usage, and concerns about efficacy (10). The remaining six ADCs target acute myeloid leukemia (AML), lymphoma, multiple myeloma (MM), and other malignancies. A central question in the clinical development of ADCs is how to optimize target selection, payload potency, and linker stability to maximize tumor specificity while minimizing systemic toxicity.

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin (GO), a monoclonal antibody conjugate, targets CD33 and plays a key role in AML treatment (112). Approved for newly diagnosed CD33-positive AML in adults and relapsed or refractory cases in both adults and children aged ≥ 2 years, GO's therapeutic history has been eventful. Initially, it was given as a single 9 mg/m² dose but was halted due to severe complications, especially hepatic veno-occlusive disease (VOD) (113). Later research showed that fractionated dosing (3 mg/m² on days 1, 4, and 7) maintained effectiveness while lowering peak plasma levels, reducing VOD and other serious side effects (114). This dosing approach has made GO a practical option, particularly for elderly patients and those who cannot undergo intensive chemotherapy, such as individuals over 75 years old or those aged 61-75 with a WHO performance status score > 2 who refuse aggressive treatment (115). The optimized dosing schedule was crucial to GO's subsequent regulatory reapproval.

Brentuximab vedotin

Brentuximab vedotin (BV), a CD30-targeting ADC, has transformed treatment options for many CD30-positive lymphoma subtypes, including classical Hodgkin lymphoma (cHL), anaplastic large cell lymphoma (ALCL), primary cutaneous ALCL (pcALCL), and mycosis fungoides (MF) (116, 117). In 2025, its use was expanded to include relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (118). Multiple randomized clinical trials have demonstrated BV's safety and effectiveness, with a recommended dose of 1.8 mg/kg every three weeks. For example, a key monotherapy trial involving 102 patients with relapsed or refractory Hodgkin lymphoma (HL) after autologous stem cell transplantation (auto-SCT) showed an ORR of 75% and a median response duration of 5.6 months among responders, with a good safety profile (119). Similarly, in a group of 58 patients with relapsed or refractory systemic ALCL (sALCL), single-agent BV achieved an ORR of 86% and a median response duration of 12.6 months, significantly outperforming traditional chemotherapy (120). These results highlight BV's clinical utility as a primary treatment for patients with CD30-positive lymphomas, especially those with relapsed or refractory sALCL and HL.

Inotuzumab ozogamicin

Inotuzumab ozogamicin (InO), the pioneering ADC approved for clinical use, has transformed the treatment approach for relapsed or refractory B-cell precursor acute lymphoblastic leukemia (B-ALL). This innovative therapy is approved for adult and pediatric patients aged 1 year or older and specifically targets CD22-positive B-ALL that is resistant to initial treatment regimens. For Philadelphia chromosome-positive (Ph⁺) patients, InO treatment is recommended only after failure of tyrosine kinase inhibitor therapy (121, 122). Results from a pivotal phase III randomized controlled trial (NCT01564784) involving 326 patients showed significant effectiveness of InO. With a dosing regimen of 1.8 mg/m² given in three divided intravenous infusions over a 15-day cycle, InO treatment resulted in notable improvements in complete remission (80.7% vs 29.4%) and minimal residual disease negativity (78.4% vs 28.1%) rates, as well as a median overall survival (OS) benefit (7.7 vs 6.7 months) compared to standard care (123).

Polatuzumab vedotin

Pola, the world's first ADC targeting CD79b, has demonstrated significant clinical utility. Mainly used in combination regimens, with monotherapy as an option, this agent has transformed the treatment approach for DLBCL. Clinical evidence shows that Pola-based therapy greatly increases complete remission rates and overall survival, especially in patients with relapsed or refractory DLBCL (124). These findings highlight the drug's key role in improving treatment outcomes and its significance in modern hematologic oncology practice.

Loncastuximab tesirine

Lonca, a new CD19-targeted ADC, marks a major breakthrough in the treatment of relapsed or refractory DLBCL. This innovative therapy is especially useful for patients who have tried multiple treatments without success (125). Through its unique mechanism, Lonca delivers potent cytotoxic agents directly to CD19-positive tumor cells, enhancing treatment efficacy while reducing systemic side effects. As a result, it fills a critical gap in the treatment options for this difficult patient group, providing a promising alternative when standard therapies fail.

Belantamab mafodotin

Belantamab mafodotin, an ADC targeting the B-cell maturation antigen (BCMA), has become a significant therapeutic breakthrough for patients with relapsed or refractory MM (126). Initially approved for monotherapy, the drug was later withdrawn from the market. Current clinical studies mainly assess its effectiveness when combined with other treatments. It is crucial that Belantamab mafodotin is administered strictly according to the approved indications, prescribed dosing regimens, and supporting clinical evidence to ensure its safety and efficacy profiles (127, 128).

4.1.2 ADCs in solid tumors

As of the latest data, 12 ADCs have been approved for the treatment of solid tumors. Clinical evidence shows that HER2-positive cancers, including breast cancer and other solid tumor types, make up a significant portion of patients who benefit from ADC therapies.

Trastuzumab emtansine

Trastuzumab emtansine (T-DM1), the first HER2-targeted ADC to achieve commercial success, has proven clinical utility in early breast cancer (EBC) and metastatic breast cancer (MBC) (129). In EBC, it is given to HER2-positive patients with residual invasive disease after neoadjuvant treatment (e.g., trastuzumab plus a taxane). Data from Trial NCT01772472 showed that T-DM1 increased 3-year invasive disease-free survival from 77.0% to 88.3% compared to trastuzumab, reducing the risk of recurrence or death by 50% (130). For MBC, a key Phase III trial (NCT00829166) found that, in HER2-positive advanced breast cancer patients previously treated with trastuzumab/taxane, T-DM1 achieved a median PFS of 9.6 months (versus 6.4 months) and a median OS of 30.9 months (versus 25.1 months), making it the standard second-line therapy (15).

Trastuzumab deruxtecan

Trastuzumab deruxtecan (T-DXd), a second-generation HER2-targeted ADC, provides distinct advantages. With a high DAR (DAR = 7.7) and strong bystander effects from its cytotoxic payload, it effectively tackles treatment challenges in HER2-positive and HER2-low-expressing cancers, showing efficacy across breast, gastric, and lung cancers. A key, open-label, randomized Phase III trial (NCT03529110) demonstrated that T-DXd significantly extended progression-free survival (PFS) compared to T-DM1 in HER2-positive recurrent/metastatic breast cancer (BC) (131). In HER2-low unresectable or metastatic BC, it outperformed physician-selected chemotherapy (NCT03734029) (132). Furthermore, it has shown activity in heavily pretreated HER2-low gastric or gastroesophageal junction adenocarcinoma (133). The randomized, double-blind Phase II DESTINY-Lung02 trial (NCT04644237) involving 152 platinum-pretreated HER2-mutated metastatic non-small cell lung cancer (mNSCLC) patients reported an ORR of 49.0%, a median PFS of 9.9 months, and a median OS of 19.5 months with T-DXd at 5.4 mg/kg (134), establishing T-DXd as the first targeted ADC for this mNSCLC subtype.

Disitamab vedotin

Disitamab vedotin (DV), the first domestically developed anti-HER2 antibody-drug conjugate (ADC) in China, provides a notable advantage. It shows strong targeted cell-killing effects against tumors with low-to-moderate HER2 levels while maintaining an acceptable safety profile. Currently, its main clinical use is in HER2-positive gastric cancer (GC), with ongoing trials investigating its potential in breast cancer (BC), urothelial carcinoma (UC), and other cancers. In a Phase II study (RC48-C008) (135), DV achieved an ORR of 24.8%, a median PFS of 4.1 months, and a median OS of 7.9 months in HER2-overexpressing GC patients who had at least two prior chemotherapy treatments. Mild-to-moderate side effects, such as leukopenia, alopecia, and neutropenia, were well managed. Two

additional Phase II trials (RC48-C005, NCT03507166; RC48-C009, NCT03809013) (136) confirmed its effectiveness and safety in platinum-pretreated, HER2-overexpressing (IHC 2⁺/3⁺) UC, leading to its approval for this use in China in December 2021.

Enfortumab vedotin

Enfortumab vedotin (EV) marks a significant breakthrough in targeted cancer therapy as the first ADC designed to directly target nectin-4, a transmembrane cell adhesion molecule that is overexpressed in various solid tumors, including UC and BC (137). This innovative treatment provides a precise mechanism of action that selectively destroys nectin-4-positive cancer cells and shows considerable efficacy even in patients with chemotherapy-resistant disease. Its main clinical use is the treatment of locally advanced or metastatic UC. The U.S. FDA granted accelerated approval in December 2019 based on the promising results of the Phase II EV-201 trial (NCT03219333). Later, in April 2022, the European Union approved EV for patients with locally advanced or metastatic UC who experienced disease progression after platinum-based chemotherapy and PD-1/PD-L1 inhibitor therapy (138).

Sacituzumab Govitecan

Sacituzumab govitecan (SG), a Trop-2-directed ADC, consists of a humanized anti-TROP2 monoclonal antibody linked to SN-38, an active Topo I inhibitor and irinotecan metabolite, via a cleavable CL2A linker with a DAR of 7.6. This design allows targeted delivery of SN-38 to cancer cells. In a pivotal global, open-label, randomized Phase III trial (NCT02574455), 468 patients with unresectable locally advanced or metastatic TNBC who had received at least two prior systemic treatments were enrolled. The study showed that SG significantly prolonged PFS compared with chemotherapy, with median PFS of 5.6 and 1.7 months, respectively (139). As a result, the U.S. FDA approved SG for patients with metastatic or advanced TNBC who had prior treatment failure in April 2020 (140). Emerging evidence also indicates its potential in UC (141), HR⁺/HER2⁻ BC (142), and recurrent or metastatic cervical cancer (143).

Cetuximab Saratolacan

Cetuximab saratolacan (RM-1929; Akalux) is a targeted photoimmunotherapy agent directed against EGFR-positive tumors. It consists of cetuximab, an anti-EGFR monoclonal antibody, conjugated to a light-activatable photoabsorber. Following binding to tumor cells, exposure to near-infrared light induces rapid, localized damage to the cell membrane and tumor cell death. Regulatory approval in Japan for unresectable locally advanced or recurrent head and neck cancer was supported by an international Phase I/II study and a Japanese Phase I trial (144). In the international Phase IIa trial (NCT02422979), RM-1929 achieved an ORR of 43.3% and median OS of 9.3 months in heavily pretreated patients. The Japanese Phase I study reported an ORR of 66.7% in a smaller cohort (145).

Tisotumab vedotin

Tisotumab vedotin (TV), the pioneering ADC targeting TF, consists of a humanized anti-TF mAb covalently linked to the microtubule-disrupting agent MMAE via a cleavable valine-citrulline (Val-Cit) linker, with a DAR of 4. Approved for adult patients with recurrent or metastatic cervical cancer progressing after prior chemotherapy, TV represents a significant advance in targeted cancer therapy. In the Phase II InnovaTV 204 trial (NCT03438396), TV demonstrated efficacy in patients with recurrent or metastatic cervical cancer who had received prior treatment, achieving an ORR of 24% (7% complete response), a median duration of response (DOR) of 8.3 months, and a median OS of 12.1 months (19). These findings supported the FDA's accelerated approval, which was later confirmed by

a Phase III trial (NCT04697628) (146). Preclinical studies have shown TF overexpression across multiple solid tumor types, including ovarian cancer (147), lung cancer, pancreatic cancer, colorectal cancer, and head and neck cancers (148). Based on these findings, clinical trials of TV for these cancers have been initiated.

Mirvetuximab soravtansine

MIRV, a groundbreaking ADC, marks a major step forward in targeted cancer treatment. Designed to target FR α , MIRV is made of a humanized anti-FR α mAb linked to DM4, a powerful microtubule inhibitor, through a cleavable disulfide linker with a DAR of about 3.4. MIRV is approved for treating adult patients with FR α -positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1 to 3 previous systemic therapies. The multicenter, open-label, randomized MIRASOL trial (NCT04209855) enrolled 453 patients and showed that MIRV monotherapy significantly outperformed investigator-selected chemotherapy (paclitaxel, pegylated liposomal doxorubicin, topotecan) in PFS, OS, and ORR, thereby slowing disease progression, extending survival, and improving tumor reduction (37). Additionally, the SORAYA trial (NCT04296890) confirmed its effectiveness in patients with high FR α expression, reporting an ORR of 32.4% and a median DOR of 6.9 months, supporting MIRV's regulatory approval (149).

Sacituzumab tirumotecan

Sacituzumab tirumotecan (sac-TMT) is an ADC targeting TROP2. It consists of a humanized anti-TROP2 monoclonal antibody conjugated via a cleavable CL2A linker to tirumotecan, a Topo I inhibitor and derivative of SN-38 (the active metabolite of irinotecan), with a DAR of 7.4. In clinical trials, sac-TMT has been extensively studied, primarily in TNBC and NSCLC, and has shown significant therapeutic potential across multiple solid tumor types. The pivotal Phase III OptiTROP-Breast01 trial provided strong evidence of its superiority in prolonging survival compared with conventional chemotherapy. In China, sac-TMT is approved for adult patients with unresectable, locally advanced, or metastatic TNBC who have received at least two prior systemic therapies, including one for advanced or metastatic disease (150). A clinical study led by Fang and Zhang from Sun Yat-sen University demonstrated that sac-TMT monotherapy showed promising antitumor activity with acceptable safety in previously treated patients with advanced NSCLC, regardless of EGFR mutation status (151). Regulatory approval for EGFR-mutated NSCLC was sought in China in October 2024 (152). The U.S. FDA designated sac-TMT as a Breakthrough Therapy for pre-treated EGFR-mutated non-squamous NSCLC (153).

Datopotamab deruxtecan

Datopotamab deruxtecan (Dato-DXd), a TROP2-targeting ADC, has shown significant clinical usefulness. Its indications include unresectable or metastatic HR⁺/HER2⁻ breast cancer patients who have been pretreated with endocrine therapy and at least one line of chemotherapy, as well as locally advanced or metastatic NSCLC patients with previous systemic treatment. Clinical data have demonstrated the effectiveness of datopotamab deruxtecan (Dato-DXd) as a monotherapy in breast cancer and NSCLC. In HR⁺/HER2⁻ advanced breast cancer, Dato-DXd significantly lowered the hazard ratio for progression or death compared to investigator-selected chemotherapy (154). In NSCLC, Dato-DXd reduced the rate of $\geq$ Grade 3 treatment-emergent adverse events by 16.5% compared with docetaxel (155).

Telisotuzumab vedotin

Telisotuzumab vedotin (Teliso-V) is the world's first ADC targeting c-MET (mesenchymal-epithelial transition factor), which is often overexpressed or amplified in solid tumors like NSCLC and GC. Teliso-V is composed of a humanized anti-c-MET mAb linked to MMAE via a cleavable Val-Cit linker, with a DAR of 3.1. Data from an open-label, single-arm trial (NCT03539536) show that in 84 c-MET-high patients, Teliso-V achieved a 35% ORR, including 100% partial responses, with a median DOR of 7.2 months (156). In May 2025, the U.S. FDA granted accelerated approval to Teliso-V for adult patients with locally advanced or metastatic non-squamous NSCLC. Eligible candidates had prior systemic treatment and high c-MET protein expression levels (157).

Trastuzumab rezetecan

Trastuzumab Rzetecan (SHR-A1811), an ADC targeting HER2, consists of a humanized anti-HER2 monoclonal antibody, a cleavable linker, and a potent Topo I inhibitor as the cytotoxic payload. According to available clinical data, SHR-A1811 has demonstrated significant efficacy in HER2-positive breast cancer (post-multiline therapy) and HER2-mutant NSCLC, achieving ORRs of 50-70%. Ongoing studies are exploring broader populations, including those with low HER2 expression. In neoadjuvant treatment for HER2-positive breast cancer, the pathological complete response (pCR) rate reached 63.2% with SHR-A1811 monotherapy (50% in HR⁺ and 74.5% in HR⁻ subgroups) (158). For patients with advanced HER2-mutant NSCLC, the independent review committee-determined ORR was 73.4%, the disease control rate (DCR) was 98.9%, and the median PFS was 11.5 months (159). In May 2025, SHR-A1811 received regulatory approval in China for the treatment of adult patients with unresectable locally advanced or metastatic NSCLC harboring HER2-activating mutations who had received at least 1 prior systemic therapy.

4.2 Combination Clinical Application

In recent years, an increasing number of preclinical and clinical studies have investigated combination therapies involving ADCs, primarily by combining conventional chemotherapy, targeted therapy, immunotherapy, and other modalities. These methods aim to improve treatment effectiveness across different tumor types through potential synergistic effects.

4.2.1 In combination with chemotherapy

Combining GO with standard chemotherapy regimens (e.g., daunorubicin and cytarabine) in newly diagnosed AML significantly increases the complete remission rate and extends event-free survival (EFS), making it a key component of current standard therapy. In the ALFA-0701 trial, patients aged 50-70 with newly diagnosed, de novo AML who received the combination of daunorubicin, cytarabine, and GO had a median EFS of 17.3 months, significantly longer than the 9.5 months observed in those treated with chemotherapy alone (160). Clinical evidence shows that the BV combination therapeutic strategy outperforms monotherapy with chemotherapeutic agents in improving survival among patients with HL. Replacing bleomycin with BV in the traditional ABVD protocol results in the BV-AVD regimen. Multiple phase III trials (NCT01712490, NCT02292979) (161, 162) have demonstrated its superior efficacy and safety profile across disease stages, as well as a reduced risk of bleomycin-induced pulmonary complications. These findings highlight the role of BV-AVD as a preferred first-line treatment option, especially for high-risk Hodgkin lymphoma patients. In relapsed or refractory DLBCL, the pivotal ECHELON-3 clinical trial (NCT04404283) showed that the triple combination of BV, lenalidomide, and rituximab outperformed the control regimen. The combination significantly extended median OS (13.8 vs. 8.5 months) and PFS (4.2 vs. 2.6 months), achieving an ORR of 64.3%. In February 2025, the U.S. FDA approved this therapeutic approach for adult patients with

relapsed/refractory DLBCL who had received at least 2 prior systemic treatments and were not candidates for autologous hematopoietic stem cell transplantation or chimeric antigen receptor T-cell therapy (118).

4.2.2 In combination with immunotherapy

ADCs not only enable targeted elimination of neoplastic cells but also induce ICD, which releases tumor-associated antigens that activate the host immune system. When combined with immune checkpoint blockade, this approach reduces T-cell suppression, boosts antitumor immune responses, and shifts the TME from immunosuppressive to immunostimulatory. The ADC plus immunotherapy (IO + ADC) strategy has the potential to create synergistic antitumor effects, improve immunotherapy outcomes, and avoid drug resistance, as previously reported (163). Results from a Phase Ib, open-label study (NCT04042701) were presented at the 2024 ESMO Immuno-Oncology Congress. The study evaluated the safety profile and therapeutic efficacy of T-DXd combined with the PD-1 inhibitor pembrolizumab (PEM) in immunotherapy-naïve patients with HER2-positive or HER2-mutated NSCLC. Significant anti-tumor activity was seen in both groups, with an ORR over 50% and a median DOR over 15 months, regardless of HER2 status. The treatment combination was well tolerated (164).

EV, combined with immunotherapy, has transformed the treatment of advanced UC. Based on results from the Phase Ib/II EV-103 trial (NCT03288545), the U.S. FDA granted Breakthrough Therapy designation in February 2020 for this regimen (with PEM) as a first-line treatment for cisplatin-ineligible patients with locally advanced or metastatic UC (165). Guo et al. reported the final results of the Phase Ib/II RC48-C014 trial, an investigator-initiated study assessing the combination of DV and toripalimab in patients with advanced UC. As of March 1, 2024, the confirmed ORR was 73.2%, with a median PFS of 9.3 months and OS of 33.1 months. The DV and toripalimab combination showed significant efficacy and manageable safety, especially in HER2-expressing patients. These results support further research into this regimen for advanced UC (166). OptiTROP-Lung01 (NCT05351788) is a multicenter, multicohort, open-label Phase II trial evaluating the combination of sac-TMT and tagitanlimab (an anti-PD-L1 antibody) as first-line treatment for patients with advanced or metastatic NSCLC lacking actionable genomic alterations. In this trial, Cohort 1A patients received sac-TMT at 5 mg/kg every 3 weeks, along with tagitanlimab at 1200 mg every 3 weeks. Conversely, Cohort 1B received sac-TMT (5 mg/kg biweekly) and tagitanlimab (900 mg biweekly). The confirmed ORR was 40.0% in Cohort 1A and 66.7% in Cohort 1B, with median PFS of 15.4 months and not yet reached, respectively. Both cohorts showed low discontinuation rates due to adverse events, indicating good tolerability, and no treatment-related deaths occurred. These findings suggest the combination's effectiveness and manageable safety in NSCLC patients, warranting further study (24).

4.2.3 In combination with targeted drugs

The combination of ADCs and targeted agents is a very active area in oncology, focusing on improving effectiveness by blocking multiple cancer-driving pathways simultaneously or leveraging synergistic mechanisms. For instance, T-DXd is a HER2-targeting ADC, while pertuzumab is a monoclonal antibody that binds to a different HER2 epitope; their combined use allows for more thorough suppression of HER2 signaling. The important Phase III DESTINY-Breast09 trial showed that the “T-DXd + pertuzumab” combo performed better than the traditional “taxane + trastuzumab + pertuzumab (THP)” treatment in patients with unresectable or metastatic HER2⁺ breast cancer. It significantly increased median PFS from 26.9 to 40.7 months, lowering the risk of disease progression or death by 44% (167). With the FDA's approval of its supplemental New Drug Application (sBLA) for priority review, this combo could soon become a new first-line standard.

In a single-arm, open-label Phase IIa clinical trial (NCT00875979), Miller KD et al. studied the combination of T-DM1 and pertuzumab in patients with HER2⁺ locally advanced or metastatic breast cancer. The overall ORR was 41%, with first-line therapy showing higher effectiveness (57% vs. 33% for second-line and beyond). The median PFS was 6.6 months, indicating sustained antitumor activity (168). Unlike conventional monospecific ADCs, bispecific ADCs demonstrate improved target selectivity by recognizing either two different antigens or different epitopes of the same antigen. This mechanism enhances therapeutic efficacy while reducing systemic toxicity. Izalontamab brengitecan (BL-B01D1), a new bispecific ADC targeting EGFR and HER3, marks a significant progress in the field (28). Osimertinib, a well-established third-generation EGFR tyrosine kinase inhibitor, works synergistically with the bispecific ADC BL-B01D1. This combination targets EGFR-mutant signaling and kills EGFR/HER3-positive tumor cells, potentially overcoming resistance to osimertinib. Phase II data from WCLC 2025 showed a 100% ORR as first-line therapy for NSCLC, leading to an ongoing Phase III trial (169).

5. Exploration of ADC Safety

5.1 Systemic Pharmacokinetics

ADCs have pharmacokinetic properties that differ from those of traditional chemotherapy and monoclonal antibodies due to their modular structure (antibody, linker, payload) and their processing in the body. These principles control exposure to intact ADCs, free payloads, and metabolites, which influence toxicity. Understanding how ADC pharmacokinetics affect exposure and toxicity is essential for optimizing dosing, reducing side effects, and ensuring patient safety (83). After an IV injection, ADCs first circulate in the blood, exit blood vessels, enter tumor tissues, diffuse through the tumor microenvironment (TME), bind to surface antigens on tumor cells, and are taken up by endocytosis. Inside lysosomes, the linker breaks, releasing the toxin, which then enters the cytoplasm or nucleus to kill the cell. Any failure here can lower treatment success (170). A key overlooked fact is that most ADCs administered never reach the tumor; instead, they are taken up and broken down by healthy tissues. The safety of ADCs mainly depends on their unique pharmacokinetics, since an ADC is basically a "three-part system": the antibody, the linker, and the payload. The combined behavior of these parts determines how much of the drug is in the body, where it goes, how it is released, and the potential for toxicity (171).

The stability of the linker is a key factor influencing pharmacokinetic properties, as the rate and extent of payload release depend on both the linker type and the tissue microenvironment. Cleavable linkers, such as those made from peptides or hydrazones, release their payload within acidic lysosomal compartments (pH 4.5–5.0) or through tumor-specific proteases, while non-cleavable linkers require complete antibody degradation to release the payload-linker-amino acid conjugate (29). Premature cleavage of cleavable linkers in circulation increases exposure to free payload, thereby amplifying off-target toxicity (172). Conversely, non-cleavable linkers rely on lysosomal degradation after internalization; although this improves plasma stability, it may reduce payload-release efficiency (44). An important factor in assessing ADC efficiency is the DAR, which measures the number of drug molecules attached to each mAb. DAR values can affect drug effectiveness, as low drug loading may decrease potency, while high drug loading can influence toxicity and pharmacokinetics (173). Therefore, many clinical ADCs use a compromise with a DAR of approximately 4, followed by adjustments to pharmacokinetics and stability via hydrophilic linkers and site-specific conjugation (174). From a molecular weight and spatial volume perspective, the main component of an ADC is the antibody, resulting in pharmacokinetic profiles that are largely similar to those of the unmodified

antibody. The tissue distribution of ADCs depends on both antibody-mediated targeted delivery and nonspecific uptake mechanisms, including Fc γ receptor-mediated endocytosis, macropinocytosis, and charge-based interactions (175, 176). These processes can result in both on-target and off-target toxicity.

The target antigens for ADCs are often proteins highly expressed on tumor cells, although they may also be expressed at varying levels in normal tissues. Therefore, while ADCs are designed to selectively bind to and eliminate tumor cells, they can also bind to and destroy normal cells that express the target antigen. This accidental binding can cause damage to healthy tissues and organs, a phenomenon known as on-target toxicity (177). As a result, ADCs may harm normal cells expressing the same antigen during cancer treatment, creating a significant challenge for target selection (178). For example, Trop2, which is overexpressed in many tumors, is also found at low levels in normal ocular surface and oral mucosal cells. Trop2-targeted ADCs, such as SG, sac-TMT, and Dato-DXd, can cause ocular toxicity and oral mucositis by binding to Trop2 on these cells. Reported incidences include 5% ocular toxicity (179) and 10% oral mucositis (139) for SG, 49.2% oral mucositis for sac-TMT (150), and 36.4% ocular toxicity with 72.7% oral mucositis for Dato-DXd (180). Interestingly, when researchers analyzed data from over 100 clinical ADC trials (181), they discovered that ADCs within the same payload class showed very similar toxicity profiles, regardless of the specific target. This indicates that toxicity is often "payload-driven" rather than solely determined by the antibody's localization. Off-target toxicity can result from premature payload release into the bloodstream due to linker instability (172), nonspecific uptake of the ADC by normal cells, and nonspecific binding of the ADC's antibody to normal cells (182). Additionally, ADCs undergo recycling via the neonatal Fc receptor (FcRn), which extends the half-life of the antibody component and may increase exposure to the payload (183).

5.2 Payload Toxicity

As the "ammunition" of ADCs, payloads determine their toxicity profile. Each payload exhibits distinct cytotoxicity, leading to organ-specific damage. Microtubule inhibitors such as MMAE, DM1, and MMAF disrupt microtubule-dependent processes in neurons and platelets, causing neurotoxicity and thrombocytopenia (184). Clinical trials report high rates of peripheral neuropathy with MMAE-based ADCs (185), while T-DM1-induced thrombocytopenia limits its dosage (186). DNA-damaging payloads in ADCs, such as calicheamicin and PBD dimers, exhibit off-target toxicity. Because of their affinity for rapidly dividing cells, these agents mainly affect hematopoietic stem cells in the bone marrow and mucosal epithelial cells, resulting in myelosuppression and gastrointestinal toxicity (187). PBD dimers, with strong DNA crosslinking ability, can cause DNA damage in both cancerous and normal tissues. Calicheamicin payloads, which induce DNA double-strand breaks, may lead to hepatic sinusoidal obstruction syndrome if released prematurely from the ADC conjugate (188, 189). The pulmonary system, especially alveolar epithelial cells, is also at risk from these payloads, potentially causing interstitial lung disease (ILD) characterized by respiratory symptoms (190). ADCs that incorporate Topo I inhibitors (e.g., SN-38, DXd) as payloads mainly cause gastrointestinal and blood-related toxicities (191). By inducing DNA double-strand breaks, these payloads trigger apoptosis in rapidly dividing cells (192). Significant hematological side effects, such as leukopenia, anemia, and neutropenia, are observed in many Phase III trial ADCs, including YL201, HS-20093, MHB088C, and BL-B01D1 (193–196).

5.3 Strategies for Reducing Toxicity

Leveraging the unique pharmacokinetic principles of ADCs and the relationship between exposure and toxicity, multiple strategies can be used to reduce ADC-related toxicity.

The first strategy is dose optimization, which can be approached from five aspects. First, identify the optimal therapeutic dose that ensures efficacy while minimizing ADC-related toxicity. For T-DXd in HER2-positive breast cancer (BC) and HER2-mutant non-small cell lung cancer (NSCLC), randomized studies comparing 5.4 mg/kg and 6.4 mg/kg showed similar ORRs (49% vs. 56%) and overlapping PFS curves, indicating no significant difference in efficacy. However, there was a notable difference in ILD incidence: the higher-dose group reported an ILD incidence of 28%, whereas the low-dose group reported only 13% (134). Second, establish a maximum dose limit to prevent excessive drug exposure in patients with larger body sizes. For example, EV initially lacked a dose cap, leading to three treatment-related fatalities in patients with a baseline weight ≥ 100 kg. Implementing a 125 mg dose cap eliminated excessive free payload (MMAE) exposure, reducing fatal toxicities while maintaining ORR. Additionally, treatment duration can be limited. For ADCs with cumulative toxicities, such as neurotoxicity, restricting the number of treatment cycles can reduce toxicity risk (197). Furthermore, dose adjustments can be made based on treatment response. For example, InO uses a two-step dose adjustment: an initial dose of 1.8 mg/m² to induce remission, followed by a maintenance dose of 1.6 mg/m² (198). Finally, fractionated dosing can be applied. GO was initially withdrawn from the market due to excessive toxicity but was later re-approved after improving its safety profile through low-dose fractionated administration, changing from a single dose of 9 mg/m² to divided doses of 3 mg/m² on days 1, 4, and 7. This adjustment significantly reduced hepatic and hematological toxicities while maintaining therapeutic efficacy (114).

The second strategy is patient stratification. A meta-analysis of 999 subjects with UGT1A1 genotypes found that individuals carrying the UGT1A1*28/*28 genotype have an increased risk of severe SG-related toxicity. Pre-treatment UGT1A1 genotyping is recommended to identify patients who may benefit from personalized dosing, closer monitoring, or alternative therapies. Dosing adjustments or the selection of alternative treatment regimens based on genotype can help reduce toxicity risks (199).

The third strategy involves developing biomarkers to predict severe toxicity. Currently, there are no diagnostic tools to manage ADC-related toxicities, although multiple development efforts are underway. One early-stage project focuses on detecting and monitoring ADC-associated ILD by measuring lung-derived cell-free DNA (cfDNA). This method relies on observations that patients treated with T-DXd show significant methylation spikes when ILD develops, which then decrease after corticosteroid treatment. By identifying specific methylation signatures in lung-derived cfDNA, this approach can provide objective criteria for grading ILD severity and guiding treatment decisions, including drug rechallenge protocols (200).

Discussion

The potential and challenges of ADCs

ADCs have become a revolutionary method in oncology, using antibody specificity to precisely target and deliver toxic payloads to tumor cells. This targeted approach has shown great therapeutic promise, but challenges in drug design, effectiveness, and safety remain. Future research should aim to optimize ADC features to enhance clinical results. The development of ADC technology has occurred in three main stages. Although the idea of ADCs was introduced in the early 20th century, technological limitations delayed their clinical use until 2000, when GO, the first approved ADC, gained regulatory approval (113). First-generation ADCs, which used murine or chimeric antibodies, random conjugation methods, unstable linkers, high immunogenicity, poor stability, and narrow therapeutic windows, have been replaced by later versions. Second-generation ADCs, such as BV and T-DM1, use humanized antibodies and random conjugation techniques, greatly reducing immunogenicity. However, attaching

drugs randomly to native amino acids (cysteine/lysine) caused product heterogeneity, affected pharmacokinetics, and increased toxicity (201). Third-generation ADCs, including Pola and EV, use site-specific conjugation methods to produce uniform products, thereby broadening therapeutic windows and marking a new chapter in precision ADC development (202).

Mechanisms of Resistance and Cross-Resistance in ADC Therapy

As formats diversify, more ADCs target the same antigens or carry similar payloads. This highlights a key issue of cross-resistance, in which resistance to one ADC can reduce the effectiveness of subsequent ADCs sharing the same molecular vulnerabilities. Understanding the mechanisms behind cross-resistance is crucial for optimizing ADC sequencing, positioning, and combination strategies to improve clinical outcomes. Since ADCs are targeted cytotoxic agents, resistance usually comes from either the antibody or the payload component. These can generally be divided into three types.

Target-centered cross-resistance: ADCs targeting the same antigen share vulnerabilities to resistance caused by target modifications, including loss or downregulation of the target antigen, expression heterogeneity, mutations, or masking (203). Under therapeutic pressure, tumor cells may reduce or even cease to express the target antigen, rendering the ADC's "guidance head" unable to find its target. For example, the DAISY trial provided additional clinical evidence that approximately 65% of HER2-positive breast cancer patients experienced a decrease in HER2 expression during treatment with T-DXd (204). Tumors are not uniform; within a single tumor, only some cells may express the antigen at high levels, while others express it at low levels or not at all. ADCs can kill only cells with high antigen levels, allowing low-expressing tumor cells to survive through clonal expansion and become a source of resistance. Studies have shown that patients with highly heterogeneous HER2 expression respond minimally to T-DM1 therapy (205).

Payload-centered cross-resistance: ADCs using the same payload class are vulnerable to resistance mechanisms that reduce payload activity (206). For microtubule inhibitors (such as MMAE and DM1), overexpression of drug efflux pumps (e.g., P-glycoprotein) can reduce intracellular accumulation or payload-binding affinity (207, 208). For Topo I inhibitors (such as DXd and SN-38), upregulation of DNA repair pathways (204) or mutations in Topo I (209) can counteract their cytotoxic effects. **Linker/transport-mediated cross-resistance:** Shared defects in internalization (e.g., increased caveolae-mediated pathways (210) or linker cleavage issues (e.g., reduced lysosomal proteolytic activity (211)) may confer cross-resistance to ADCs with similar linker designs, regardless of payload type. As previously mentioned, despite notable advancements in ADC development, challenges such as safety and drug resistance persist in clinical practice. Addressing these complex issues requires a comprehensive approach, including optimizing ADC design, personalizing treatment strategies, and developing innovative combination therapies. Currently, the field of ADC design and engineering is moving toward diversification and innovation.

Emerging ADC Platforms and Future Directions

Despite the clinical success of multiple antibody-drug conjugates, several unresolved challenges still limit their therapeutic index and broader applicability. Tumor heterogeneity, antigen downregulation, and variable internalization kinetics remain major barriers to achieving lasting responses, especially in spatially diverse solid tumors. Off-target toxicity arising from premature linker cleavage, payload diffusion, and Fc-mediated uptake by healthy tissues underscores the need for next-generation linker chemistries and conditionally activated payloads. At the same time, emerging resistance mechanisms such as antigen loss, drug efflux, lysosomal dysfunction, and adaptive changes in cell death pathways

underscore the importance of rational combination strategies that involve immune checkpoint inhibitors, DNA damage response agents, or tumor microenvironment-targeting therapies. Advances in single-cell profiling, spatial transcriptomics, and functional imaging are expected to improve patient selection and enable biomarker-guided use of ADCs, moving the field from empirical target-payload pairing toward precisely engineered conjugates optimized for specific tumor environments.

New constructs have appeared, including bispecific ADCs, probody-drug conjugates (PDCs), immune-stimulating ADCs (ISACs), protein-degrader ADCs (DACs), and dual-payload ADCs, marking an era of "universal conjugation" (212). Currently, about 10 bispecific ADCs are in clinical development worldwide. These agents target either two different epitopes of the same tumor antigen or two separate antigens. For example, BL-B01D1 by Biokin Pharmaceutical, which targets EGFR×HER3, has entered Phase III trials (213). Biparatopic ADCs mainly target established key molecules such as HER2, exemplified by JSKN003, TQB-2102, and KM-501 (214). In targeted therapy, PDCs use advanced strategies to achieve tumor specificity. The N-terminus of PDCs is either linked to a self-blocking component through a labile linker or engineered to show pH-responsive changes in the antigen-recognition domain. When reaching the TME, breaking of the masking element or local reconfiguration of the antigen-binding site restores receptor affinity, allowing payload release (215, 216). Clinical candidates CX-2051 (EpCAM-directed) and CX-2009 (ALCAM-targeted) exemplify this approach (217, 218). ISACs harness the immune system's anti-tumor potential by targeting Toll-like receptors (TLR7, TLR8, and TLR9). Activation of these receptors on APCs triggers the presentation of tumor-derived DAMPs, initiating both innate and adaptive immune responses (219). BDC-1001, a HER2-targeted ISAC with FDA orphan drug designation, is currently under clinical evaluation across multiple solid tumor types (220).

DACs employ proteolysis-targeting chimeras (PROTACs) to harness the endogenous intracellular protein-degradation machinery and selectively target proteins of interest. By simultaneously binding to a target protein ligand and an E3 ubiquitin ligase, DACs initiate targeted ubiquitination and subsequent proteasomal degradation, thereby conferring high tumor specificity (221). This approach circumvents the need for direct antagonism of the target, thereby expanding the druggable proteome. Dual-payload ADCs deliver two distinct cytotoxic payloads with synergistic mechanisms, addressing tumor resistance and heterogeneity (222). In addition to developing smarter ADC armaments through strategies such as selecting superior targets, optimizing antibody structures for enhanced targeting precision, and employing dual- or multi-payload ADCs, future advancements should also focus on integrating ADC platforms with other interventional approaches. This includes exploring novel combinations with immunotherapy and targeted agents to achieve multi-pathway tumor suppression, thereby offering more effective and personalized treatment options for cancer patients. Concurrently, leveraging precision medicine tools, including biomarker-guided therapeutic selection and AI-driven efficacy prediction models, will facilitate patient stratification for tailored treatments, optimize dosage-adjustment protocols to manage toxicity, and ultimately advance the goal of efficient and safe cancer therapy while improving therapeutic windows and clinical outcomes.

In conclusion, ADC drugs have significantly changed cancer treatment and will likely remain a main focus of research in the next decade. Their potential resides in precise targeting and powerful killing mechanisms, while challenges include inherent toxicity, tumor resistance, and complex technical barriers. Future success relies on continuous technological innovation and clinical creativity to find the best balance between effectiveness and toxicity, ultimately offering new hope to more patients. More broadly, antibody–drug conjugates represent one of the most promising platforms for next-generation targeted cancer therapy, offering a versatile framework for integrating precision targeting, potent cytotoxic agents, and immune-modulating strategies.

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Declarations

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