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REVIEW

Development of antibody-drug conjugates in cancer: Overview and prospects

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Abstract

In recent years, remarkable breakthroughs have been reported on antibody-drug conjugates (ADCs), with 15 ADCs successfully entering the market over the past decade. This substantial development has positioned ADCs as one of the fastest-growing domains in the realm of anticancer drugs, demonstrating their efficacy in treating a wide array of malignancies. Nonetheless, there is still an unmet clinical need for wider application, better efficacy, and fewer side effects of ADCs. An ADC generally comprises an antibody, a linker and a payload, and the combination has profound effects on drug structure, pharmacokinetic profile and efficacy. Hence, optimization of the key components provides an opportunity to develop ADCs with higher potency and fewer side effects. In this review, we comprehensively reviewed the current development and the prospects of ADC, provided

Abbreviations: AAC, antibody-antibiotic conjugate; ADC, antibody-drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ApDC, aptamer-drug conjugate; Bcl-xL, B-cell lymphoma-extra large; CDC, complement-dependent cytotoxicity; CMCs, chemistry manufacturing and controls; ctDNA, circulating-tumor DNA; CT, computed tomography; DAR, drug-to-antibody ratio; DM1, emtansine; DM4, ravtansine; Dxd, deruxtecan; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; EDB-FN, extra domain B of fibronectin; FcγR, Fcγ receptor; G/GEJ, gastric/gastroesophageal junction; GGFG, Gly-Gly-Phe-Gly; HER2, human epidermal growth factor receptor 2; HNSCC, head and neck squamous cell carcinomas; IND, investigational new drug; mAb, monoclonal antibody; NDC, nanoparticle-drug conjugate; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; NIR, near-infrared; NMPA, National Medical Products Administration; NSCLC, non-small cell lung cancer; NK, natural killer; ORR, objective response rate; PDC, peptide-drug conjugate; PDX, patient-derived xenografts; PET, positron emission tomography; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; R&D, research and development; siRNA, small interfering RNA; SMDC, small molecule-drug conjugate; SMCC, 4-(N-Maleimidomethyl) cyclohexanecarboxylic acid N-hydroxysuccinimide ester; SPP, N-succinimidyl-4-(2-pyridyldithio) pentanoate; SPDB, N-succinimidyl-4-(2-pyridyldithio) butanoate; T-Dxd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitors; Top, topoisomerase; TROP2, trophoblast cell-surface antigen 2; U.S. FDA, United States Food and Drug Administration; UV, ultraviolet.

Dan-Yun Ruan, Hao-Xiang Wu and Qi Meng contributed equally to this work.

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an analysis of marketed ADCs and the ongoing pipelines globally as well as in China, highlighted several ADC platforms and technologies specific to different pharmaceutical enterprises and biotech companies, and also discussed the new related technologies, possibility of next-generation ADCs and the directions of clinical research.

1 | BACKGROUND

Innovations in biopharmaceutical technology have enabled the development of antibody-drug conjugates (ADCs), a new class of anticancer drugs, and opened a new era of cancer treatment with remarkable achievements [1, 2]. An ADC comprises an antibody, a payload (toxic pharmaceutical molecules with high efficiency), and the linker connecting the two [3]. Based on this structure, ADCs act as combinations of targeted drugs and chemotherapeutic drugs through the specific recognition of target antigens by antibodies and the release of payloads to eliminate target cells [4, 5]. The small molecules of some ADCs can penetrate the cell membrane to further kill surrounding tumor cells, which is termed the bystander killing effect [6]. In addition, some ADCs have antibody immune effects, such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) [7, 8].

The differences between ADC and common targeted drugs or chemotherapeutic drugs are as follows. First, traditional antibodies work by inhibiting certain signaling pathways or physiological processes that promote tumor growth [9, 10]. For an ADC, after the antibody component binds to the target antigen on tumor cells, the cytotoxic payload exerts its anti-tumor effects by directly inhibiting tumor cell mitosis or destroying the DNA structure [11], so theoretically, ADCs have stronger killing efficiency than antibodies, and due to their target specificity, the systemic toxicity of ADCs would be lower than that of common chemotherapeutic drugs, providing a better safety profile [12]. Second, for patients who have developed resistance to existing targeted treatments, ADCs acting on the same target may still be effective, which will further expand their indications for anti-tumor treatment [13, 14]. For example, human epidermal growth factor receptor 2 (HER2) is an important target for breast cancer. Metastatic breast cancer patients who failed anti-HER2 treatments still achieved sustained benefits with trastuzumab deruxtecan (Enhertu, DS-8201), an anti-HER2 ADC [15]. Most strikingly, due to bystander killing effects, Enhertu was also effective in breast cancer patients with low HER2 expression, redefining the classification of HER2-positive breast cancer [16, 17]. Last but not least, ADCs can also attack new therapeutic targets; for instance, sacituzumab govitecan (Trodelvy, IMMU-132), which targets trophoblast cell-surface antigen 2 (TROP2), offers new avenues for advanced triple-negative breast cancer treatments [18]. TROP2 is expected to become a new therapeutic target for various solid tumors [19-21].

The first concept of drug conjugates dates back to Paul Ehrlich's "magic bullet" in 1913 [22], after almost 90 years, the optimization of the components and technology finally allowed the first ADC, gemtuzumab ozogamicin (Mylotarg), to be marketed and clinically applied [23]. To date, 15 ADCs have been approved, and more than 200 had been evaluated in clinical trials. ADCs have been among the most rapidly growing areas of anticancer drugs in the past decade. Although the advent of ADCs is a major advance, it also poses a new dilemma: how to design and combine the individual components of an ADC to gain the best responses. Regarding the in vivo effect and the metabolic processes, target selection, drug structure, recognition sites and types of linkers, etc., any variance can lead to marked differences in drug efficacy, toxicity, pharmacokinetics, and precision release [24]. All these factors pose serious challenges to chemistry manufacturing and controls (CMCs), preclinical research, and subsequent clinical trials. As a result, antibody design, linker technology, payloads, and linkage processes, as well as the technology platforms of various biotech and pharmaceutical companies, have become major barriers to the development of ADCs [25].

As numerous reference materials have reviewed the development history, mechanism of action, molecular aspects of key components, and clinical applications of ADCs [1, 3, 26, 27], few have systematically summarized the research and development (R&D) and platform technology of ADC in the world, especially in China. In this review, we focused on the current development and the prospects of ADC. We provided an analysis of marketed ADCs and the ongoing pipelines globally as well as in China, highlighting several ADC platforms and technologies that are specific to different pharmaceutical enterprises and biotech companies. We also reviewed the new technologies and discussed the possibility of next-generation ADCs and the directions of clinical research.

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2 | APPROVAL AND CLINICAL APPLICATIONS OF ADCS

Since the United States Food and Drug Administration (U.S. FDA) approval of Mylotarg in 2000, there have been 15 approved ADCs worldwide to date, of which 13 ADCs are still currently marketed (Table 1). Among them, belantamab mafodotin (Blenrep) was withdrawn due to the failure of the phase III confirmatory trial [28], while moxetumomab pasudotox (Lumoxiti) was voluntarily withdrawn because of disappointing sales. Mylotarg was also removed from most major markets due to severe veno-occlusive disease and reapproved in 2017 after dose fractionation [23].

While the initial approval of the first two ADCs primarily targeted hematological malignancies, such as leukemia and Hodgkin lymphoma, the subsequent years witnessed a burgeoning interest in the development of ADCs for solid tumors. Selective subtypes of solid tumors, such as breast, lung and gastric cancer, could also benefit from ADCs (Table 1). Moreover, among 189 ADCs that are now under active clinical evaluation worldwide, more than 80% (156 ADCs) have been implemented in solid tumors.

Substantial diversity was observed in the key components of these approved ADCs. CD33 was the first receptor to be targeted by an ADC, while HER2 has been the most targeted receptor with 3 HER2-targeting ADCs currently approved for clinical use in 4 tumor types (Table 1). The major IgG isotype of the antibody employed in these approved ADCs was IgG1, with 2 exceptions (IgG4). IgG1 antibodies have a longer serum half-life, higher Fcγ receptor (FcγR) binding efficiency, stronger ADCC and CDC effects, and are less likely to form polymers [29, 30]. Accordingly, IgG1 is the most commonly used ADC antibody. IgG4 has a lower immune activating effect and is suitable in cases where antibody-mediated cytotoxicity is not desired [31], which was employed in Pfizer's Mylotarg and inotuzumab ozogamicin (Besponsa). Although 2 ADCs employed non-cleavable linkers to restrain off-target toxicity, most of the approved ADCs (13/15; 87%) still included cleavable linkers to allow better bystander-killing effects [31]. In terms of payload, 60% of these ADCs contained a tubulin binder, and 20% of them were DNA-targeting agents, both of which were highly potent cytotoxins as only 1%-2% of cytotoxic molecules could enter the target tissue, and the amount of toxin that can be internalized is even smaller [32]. Meanwhile, ADCs with a payload of topoisomerase (Top) I inhibitors possessed higher drug-to-antibody ratio (DAR) and showed great potential, as exemplified by the better performance of trastuzumab deruxtecan (Enhertu) to trastuzumab emtansine (Kadcyla) [33].

3 | CURRENT STATUS OF ADC R&D

Apart from the 15 approved ADCs, there are now 189 ADCs actively under clinical evaluation worldwide. However, after the approval of the first ADC in 2000, only 0 to 3 new ADCs entered the clinical trial per year from the early 2010s until 2016, after which the development of ADCs flourished (Figure 1A). In 2022, 46 new ADCs entered the clinical trial worldwide. In China, although the first ADC did not enter the clinical trial until 2014, the number of new ADCs increased drastically thereafter, especially in the past 3 years with 9, 23, and 34 new ADCs entering the clinical trial.

As shown in Figure 1B, most (> 80%) of the new ADCs are still in the early stage (investigational new drug [IND], phase I and I/II) both worldwide and in China. However, 33 new ADCs have reached mid to late-stage clinical studies (Table 2), which may potentially be approved and marketed in the next few years and provide us with more options for treating refractory disease. HER2-ADC, TROP2-ADC, and epidermal growth factor receptor (EGFR)-ADC are still the top 3 most common types, and more than one such ADC has reached phase III clinical trials and beyond (Table 2). In China, apart from the National Medical Products Administration (NMPA)-approved HER2-ADC disitamab vedotin (Aidixi), both the TROP2-ADC SKB264 and EGFR-ADC MRG003 have reached phase III clinical trials and showed promising anti-tumor response in the phase I/II trial with an objective response rate (ORR) of 44% in patients with non-small cell lung cancer (NSCLC) [34] and 40% in patients with head and neck squamous cell carcinomas (HNSCC) [35], respectively. Claudin 18.2 is also a promising target, with 12 new ADCs under clinical evaluation, ranking second to HER2 (Figure 2A). The first-in-class Claudin 18.2-ADC, CMG901, demonstrated favorable activity in a heavily pretreated population of patients with gastric/gastroesophageal junction (G/GEJ) cancer, along with a manageable safety profile, which laid the foundation for further clinical development of Claudin 18.2-ADC [36]. c-Met-ADC also has 8 new agents being investigated and 1 reaching phase III clinical trial. In contrast, although 2 CD22-ADCs have been approved, only 3 new CD22-ADCs are under active clinical evaluation, ranking the least among the top 10 ADC targets (Figure 2A). Besides, one of the two approved CD22-ADCs, moxetumomab pasudotox (Lumoxiti), was voluntarily withdrawn recently by AstraZeneca.

ADCs targeting the top 10 entities contribute to nearly half (48%) of the global new ADCs landscape (Figure 2B). This trend is notably more pronounced in China, where 63% of the newly developed ADCs are concentrated on these top 10 targets (Figure 2B). Moreover, almost a quarter (23%) of new ADCs in China are targeting HER2,

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TABLE 1 ADCs approved for marketing as of March 2023

API	Trade name	Approval time (agency); withdrawal time	Developer	Target	Antibody type	Linker type	Payload	DAR	Approved indications
Gemtuzumab ozogamicin	Mylotarg	May 2000 (U.S. FDA); May 2010 withdraw; September 2017 (U.S. FDA)	Wyeth/ Pfizer	CD33	IgG4	Acetyl Butyrate	Ozoganmicin (DNA-targeting)	4.0	R/R $CD33^+$ AML
Brentuximab vedotin	Adcetris	August 2011 (U.S. FDA); May 2020 (NMPA)	Seagen/ Takeda	CD30	IgG1	mc-val-cit-PABC	MMAE (tubulin binder)	4.0	R/R HL; sALCL; pcALCL; $CD30^+$ MF; $CD30^+$ PTCL
Trastuzumab emtansine	Kadcyla	February 2013 (U.S. FDA); January 2020 (NMPA)	Genentech/ Roche	HER2	IgG1	SMCC	DM1 (tubulin binder)	3.8	$HER2^+$ mBC; $HER2^+$ eBC
Inotuzumab ozogamicin	Besponsa	August 2017 (U.S. FDA); December 2021 (NMPA)	Wyeth/ Pfizer	CD22	IgG4	Acetyl Butyrate	Ozoganmicin (DNA-targeting)	6.0	R/R B-cell precursor ALL
Moxetumomab pasudotox	Lumoxiti	September 2018 (U.S. FDA); August 2023 withdraw	AstraZeneca	CD22	IgG1	mc-val-cit-PABC	PE38 (Pseudomonas exotoxin)	1.0	R/R Hairy cell leukemia
Polatuzumab vedotin	Polivy	June 2019 (U.S. FDA); January 2023 (NMPA)	Genentech	CD79b	IgG1	mc-val-cit-PABC	MMAE (tubulin binder)	3.5	R/R DLBCL
Enfortumab vedotin	Padcev	December 2019 (U.S. FDA)	Astellas/ Seagen	Nectin-4	IgG1	mc-val-cit-PABC	MMAE (tubulin binder)	4.0	Locally advanced or metastasis UC
Trastuzumab deruxtecan	Enhertu	December 2019 (U.S. FDA); February 2023 (NMPA)	Daichi Sankyo/ AstraZeneca	HER2	IgG1	Maleimide GGFG peptide	Dxd (TOP1 inhibitor)	7.8	$HER2^+$ BC; $HER2^+$ GC/GEJC; HER^{low} BC; $HER2^{Mut}$ NSCLC
Sacituzumab govitecan	Trodelvy	April 2020 (U.S. FDA); June 2022 (NMPA)	Immunomedics/ Gilead	TROP2	IgG1	CL2A	SN-38 (TOP1 inhibitor)	7.6	Locally advanced or metastasis TNBC; UC; HR^+ BC

(Continues)

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TABLE 1 (Continued)

API	Trade name	Approval time (agency); withdrawal time	Developer	Target	Antibody type	Linker type	Payload	DAR	Approved indications
Belantamab mafodotin	Blenrep	August 2020 (U.S. FDA); November 2022 withdraw	GlaxoSmithKline (GSK)	BCMA	IgG1	Mc linker	MMAF (tubulin binder)	4.0	R/R multiple myeloma
Cetuximab sarotalocan	Akalux	September 2020 (PMDA)	Rakuten Medical	EGFR	IgG1	/	IRDye® 700DX (light activatable dye)	2.0 to 3.0	Unresectable locally advanced or recurrent head and neck cancer
loncastuximab tesirine	Zynlonta	April 2021 (U.S. FDA)	ADC Therapeutics	CD19	IgG1	PEG-Val-Ala-PABC	SG3199 (PBD dimer)	2.3	R/R DLBCL
Disitamab Vedotin	Aidixi	June 2021 (NMPA)	RemeGen	HER2	IgG1	mc-val-cit-PABC	MMAE (tubulin binder)	4.0	$HER2^+$ advanced GC/GEJC; $HER2^+$ UC
Tisotumab vedotin	Tivdak	September 2021 (U.S. FDA)	Seagen/ Genmab	TF	IgG1	mc-val-cit-PABC	MMAE (tubulin binder)	4.0	Recurrent or metastatic cervical cancer
Mirvetuximab soravtansine	Elahere	November 2022 (U.S. FDA)	ImmunoGen	FRα	IgG1	sulfo-SPDB linker	DM4 (tubulin binder)	3.4	$FR\alpha^+$ platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

Abbreviations: API, active pharmaceutical ingredient; DAR, drug-to-antibody ratio; U.S., United States; FDA, Food and Drug Administration; NMPA, National Medical Products Administration; PMDA, Pharmaceuticals and Medical Devices Agency; HER2, human epidermal growth factor receptor-2; TROP2, trophoblast cell surface antigen 2; BCMA, B cell maturation antigen; EGFR, epidermal growth factor receptor; TF, tissue factor; FRα, folate receptor alpha; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; DM1, emtansine; DM4, ravtansine; R/R, relapsed or refractory; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; sALCL, systemic anaplastic large cell lymphoma; pcALCL, primary cutaneous anaplastic large cell lymphoma; MF, mycosis fungoides; PTCL, peripheral T-cell lymphomas; mBC, metastatic breast cancer; eBC, early-stage breast cancer; GC, gastric cancer; GEJC, gastro esophageal junction cancer; ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; UC, urothelial cancer; $HER2^+$, HER2-positive; HER^{low}, low HER2 expression; $HER2^{Mut}$, activating HER2 mutations; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer; HR, hormone receptor.

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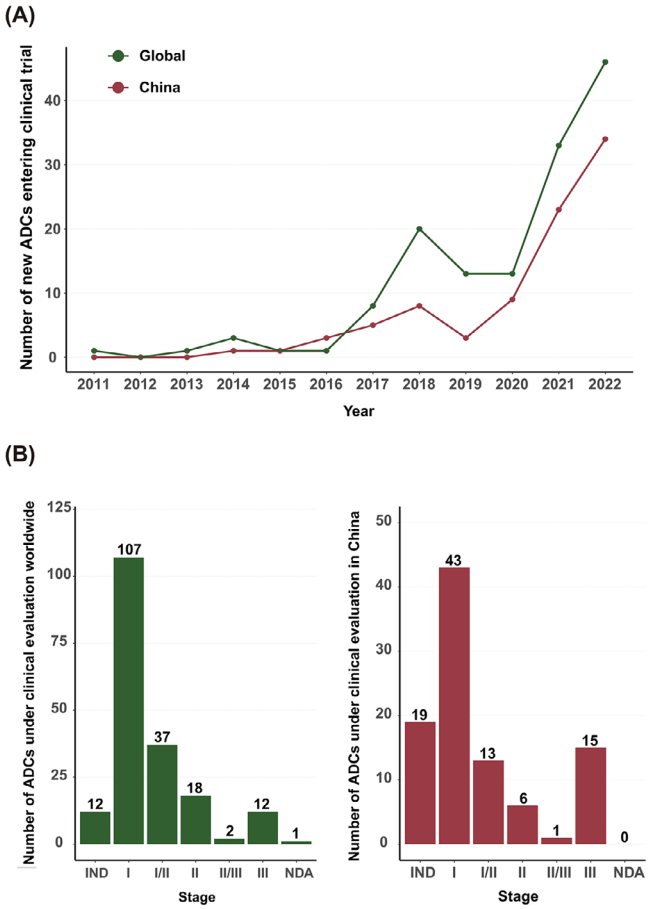

FIGURE 1 The developing landscape of ADCs. (A) Number of new ADCs entering clinical trials from 2011 to 2022 worldwide and in China, respectively. (B) Number of ADCs under clinical evaluation in different stages worldwide (left panel) and in China (right panel). Abbreviations: ADCs, antibody-drug conjugates; IND, investigational new drug; NDA, new drug application.

indicating a crowded competition in the development of HER2-ADCs.

In terms of payload, tubulin binders are still the most commonly adopted payload of new ADCs, representing 45% worldwide and 49% in China (Figure 2C). Interestingly, new ADCs with Top I inhibitors (20%) constitute a rapidly growing fraction of investigational drugs and are much more abundant than those with DNA-targeting agents (9%) (Figure 2C). In addition, ADCs with novel payloads, such as photosensitizers, immunomodulators, and RNA pol II inhibitors, are under active clinical evaluation.

It took 11 years from the approval of the first ADC Mylotarg in 2000 to the second ADC brentuximab vedotin (Adcetris) in 2011; furthermore, the first ADC Mylotarg was withdrawn in 2010, all suggesting the technical barrier to ADC development. However, in light of the diversity of targets, antibodies, linkers, conjugation methods and payloads, as well as the various combinations of these components, distinctive ADC platforms have been established to enhance the rapid exploration and verification of new ADCs (Table 3).

The Seagen ADC platform distinguishes itself through the utilization of tubulin binder monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF) as its primary payloads. MMAE exhibits high permeability, enabling a robust bystander-killing effect [37], while MMAF is more hydrophilic, with a lower tendency to aggregate and lower systemic toxicity [38]. Notably, these two payloads constitute 40% of the 15 approved ADCs and are prominently featured in the ongoing development of novel ADCs. Additionally, Seagen has innovated a cleavable linker, MC-Val-Cit, which also facilitates a bystander killing effect [39]. This linker is extensively integrated into both approved ADCs and those currently in development.

The Immunogen platform has been dedicated to ADC development for over 40 years and is renowned for its expertise in utilizing another class of tubulin binder, namely emtansine (DM1) and ravtansine (DM4). These payloads have been employed in approved ADCs trastuzumab emtansine (Kadcyla) [40] and mirvetuximab soravtansine (Elahere) [40], respectively. Immunogen excels not only in payloads but also in target selection, antibody development, and linker development. The platform boasts a diverse range of cleavable and non-cleavable linkers, including the 4-(N-Maleimidomethyl) cyclohexanecarboxylic acid N-hydroxysuccinimide ester (SMCC) linker, N-succinimidyl-4-(2-pyridyldithio) pentanoate (SPP) linker, sulfo- N-succinimidyl-4-(2-pyridyldithio) butanoate (SPDB) linker, and tri-peptide cleavable linker [41].

The pioneering deruxtecan (Dxd) technology has positioned Daichi Sankyo at the forefront of the ADC platform. The Dxd payload demonstrates the ability to overcome resistance to traditional tubulin-binding chemotherapeutic drugs like paclitaxel [42-44]. Additionally, it exhibits high permeability, enabling a potent bystander-killing effect, as evidenced by the results of the DESTINY-Breast04 study, where trastuzumab deruxtecan (T-Dxd) proved effective in patients with "HER2-low" breast cancer [45]. Daichi Sankyo further distinguishes itself with the introduction of the Gly-Gly-Phe-Gly (GGFG) linker, designed to reduce the hydrophobicity of the ADC, which results in an exceptionally stable ADC in plasma with minimal clearance, as well as allowing for a high DAR [46, 47].

In China, the RemeGen platform leads the way in ADC development. Distinguished by its exclusive conjugation method, ThioBridge technology, RemeGen offers innovative compositions featuring linkers capable of covalently coupling one or more free thiols of an antibody [48]. A noteworthy achievement of the RemeGen platform is

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TABLE 2 Promising targets of ADCs that reached mid to late-stage clinical studies and beyond.

Target	Drug	Global status[a]	Status in China[b]	MOA	Payload
HER2	Trastuzumab emtansine	Approved	Approved	Tubulin binders	DM1
	Trastuzumab deruxtecan	Approved	Approved	Top I inhibitors	DX-8951
	Disitamab vedotin	Approved	Approved	Tubulin binders	MMAE
	Trastuzumab duocarmazine	NDA	/	DNA-targeting	Duocarmycin
	TAA013	III	III	Tubulin binders	DM1
	SHR-A1811	III	III	Top I inhibitors	Rezetecan
	MRG002	III	III	Tubulin binders	MMAE
	LCB14-0110	III	III	Tubulin binders	MMAF
	ARX788	II/III	II/III	Tubulin binders	MMAF
	DX126-262	III	III	Tubulin binders	Tub114
	DP303c	III	III	Tubulin binders	MMAE
	A166	II	II	Tubulin binders	MMAF
TROP2	Sacituzumab govitecan	Approved	Approved	Top I inhibitors	SN-38
	SKB264	III	III	Top I inhibitors	Belotecan
	Datopotamab deruxtecan	III	III	Top I inhibitors	DX-8951
EGFR	Cetuximab saratolacan	Approved	/	Photosensitizer	IR700
	MRG003	III	III	Tubulin binders	MMAE
	AVID100	II	/	Tubulin binders	DM1
c-Met	Telisotuzumab vedotin	III	III	Tubulin binders	MMAE
	RC108	II	II	Tubulin binders	MMAE
CD22	Moxetumomab pasudotox	Approved	Approved	Protein synthesis inhibitor	PE38
	Inotuzumab ozogamicin	Approved	/	DNA-targeting	Calicheamicin
CD276	Vobramitamab duocarmazine	II/III	/	Top I inhibitors	Doxorubicin
	Ifinatamab deruxtecan	II	II	Top I inhibitors	DX-8951
CEA	Tusamitamab ravtansine	III	III	Tubulin binders	DM4
	Labetuzumab govitecan	II	/	Top I inhibitors	SN-38
FRα	Mirvetuximab soravtansine	Approved	III	Tubulin binders	DM4
	Farletuzumab ecteribulin	II	/	Tubulin binders	Eribulin
AXL	Mecbotamab vedotin	II	/	Tubulin binders	MMAE
BCMA	Belantamab mafodotin	Approved	III	Tubulin binders	MMAF
CD123	Pivekimab sunirine	II	/	DNA-targeting	DGN549
CD138	Indatuximab ravtansine	II	/	Tubulin binders	DM4
CD19	Loncastuximab tesirine	Approved	III	DNA-targeting	PBD
CD20	Eramkafusp alfa	II	/	Cytokine	IFNα
CD25	Camidanlumab tesirine	II	/	DNA-targeting	PBD
CD30	Brentuximab vedotin	Approved	Approved	Tubulin binders	MMAE
CD33	Gemtuzumab ozogamicin	Approved	/	DNA-targeting	Calicheamicin
CD37	Naratuximab emtansine	II	/	Tubulin binders	DM1
CD79b	Polatuzumab vedotin	Approved	Approved	Tubulin binders	MMAE
CEACAM6	L-DOS47	II	/	Enzyme	DOS47
Globo H	OBI-999	II	/	Tubulin binders	MMAE
HER3	Patritumab deruxtecan	III	III	Top I inhibitors	DX-8951
LIV-1	Ladiratuzumab vedotin	II	/	Tubulin binders	MMAE
NaPi-2b	Upifitamab rilsodotin	III	/	Tubulin binders	MMAF
Nectin-4	Enfortumab vedotin	Approval	III	Tubulin binders	MMAE

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TABLE 2 (Continued)

Target	Drug	Global status[a]	Status in China[b]	MOA	Payload
ROR1	Zilovertamab vedotin	III	II	Tubulin binders	MMAE
ROR2	Ozuriftamab vedotin	II	IND	Tubulin binders	MMAE
Tissue factor	Tisotumab vedotin	Approval	III	Tubulin binders	MMAE

Abbreviations: HER2, human epidermal growth factor receptor 2; TROP2, tumor-associated calcium signal transducer 2; EGFR, epidermal growth factor receptor; CEA, Carcinoembryonic antigen; FRα, folate receptor alpha; BCMA, B cell maturation antigen; CEACAM6, CEA cell adhesion molecule 6; HER3, erb-b2 receptor tyrosine kinase 3; ROR1/2, receptor tyrosine kinase-like orphan receptor 1/2; NDA, new drug application; MOA, mechanism of action; IND, investigational new drug; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; DM1, emtansine; DM4, ravtansine; PBD, pyrrolobenzodiazepine; IFNα, interferon alpha.

[a]Denoted the development stage of the drugs worldwide, such as in the stage of investigational new drug (IND), phase II clinical trial, phase III clinical trial, the stage of new drug application (NDA), and approved.

[b]Denoted the development stage of the drugs in China, such as in the stage of investigational new drug (IND), phase II clinical trial, phase III clinical trial, the stage of new drug application (NDA), and approved. "/" indicated that the drug is not under active clinical evaluation in China.

the development of disitamab vedotin (Aidixi), which stands as the sole approved ADC originating from a domestic biotechnology institute in China [49]. KELUN-BIOTECH is another prominent ADC platform in China and renowned for its OptiDC technology, which allows for the tailored design of ADCs, optimizing them for various biological targets.

Each of these ADC platforms has its own distinctive features, focusing on the development of differentiated ADC products based on their respective core technologies. This has significantly propelled the research and development of ADCs. In the near future, we can expect to witness the emergence of even more advanced and improved ADC medications.

4 | FUTURE DEVELOPMENTS ON ADCS

ADCs have started to change cancer treatment in recent years. Since 15 ADCs have entered the market and 189 ADCs are actively under clinical evaluation worldwide up to date, how to meet the clinical needs and improve drug designs have become the main challenges for ADC development, which will also affect the pattern of exploitation and strategy of ADC products. This section summarized the major innovations and discussed the future directions and new possibilities of next-generation ADCs. In general, it is mainly a pioneering exploration based on the drug composition and the optimal mode of clinical applications (Figure 3).

4.1 | Selection of target antigen

Appropriate targets play decisive roles in the pharmacological properties of ADCs. Currently, the target antigens of approved ADC drugs are specific proteins overexpressed in typical tumor cells, such as HER2, TROP2, and Nectin4 in solid tumors and CD19, CD22, CD33, and CD30 in hematological malignancies. Recently, the R&D of new ADC targets has been fully underway, and the novel selection strategy of target antigens is also constantly being updated. One promising way is to find mutant proteins in tumors because they usually have higher levels of ubiquitination modification and are easier to internalize and degrade than wild-type proteins. Targeting ADCs carrying oncogenic mutant proteins can maximize the specificity of treatment [50]. With the promotion of basic research on tumor immunity, the target development of ADC has gradually expanded from traditional tumor antigens to the microenvironment and cancer stem cell antigens in recent years [51, 52]. A growing number of ADCs based on this concept could enter preclinical and clinical research in the future. In addition, the progress of bioinformatics and computer-aided drug screening technology has greatly accelerated the development of antigen selection [53]. Given the desirable antigen characteristics, including differential expression between tumor and normal tissues, surface localization, and internalization after ligand interaction, researchers are also attempting to integrate multi-omics sequencing data to predict and develop new ADC antigens that are most suitable for targeting [54]. The discovery of these new targets will greatly expand the indications for ADC therapy in the future.

4.2 | Design of antibody/new delivery tools

Currently, numerous technical platforms are devoted to optimizing ADC antibodies. The future directions to upgrade ADC antibodies include selecting antibody serotypes, increasing antibody humanization, adjusting and optimizing antibody structures, etc [55, 56]. Some new

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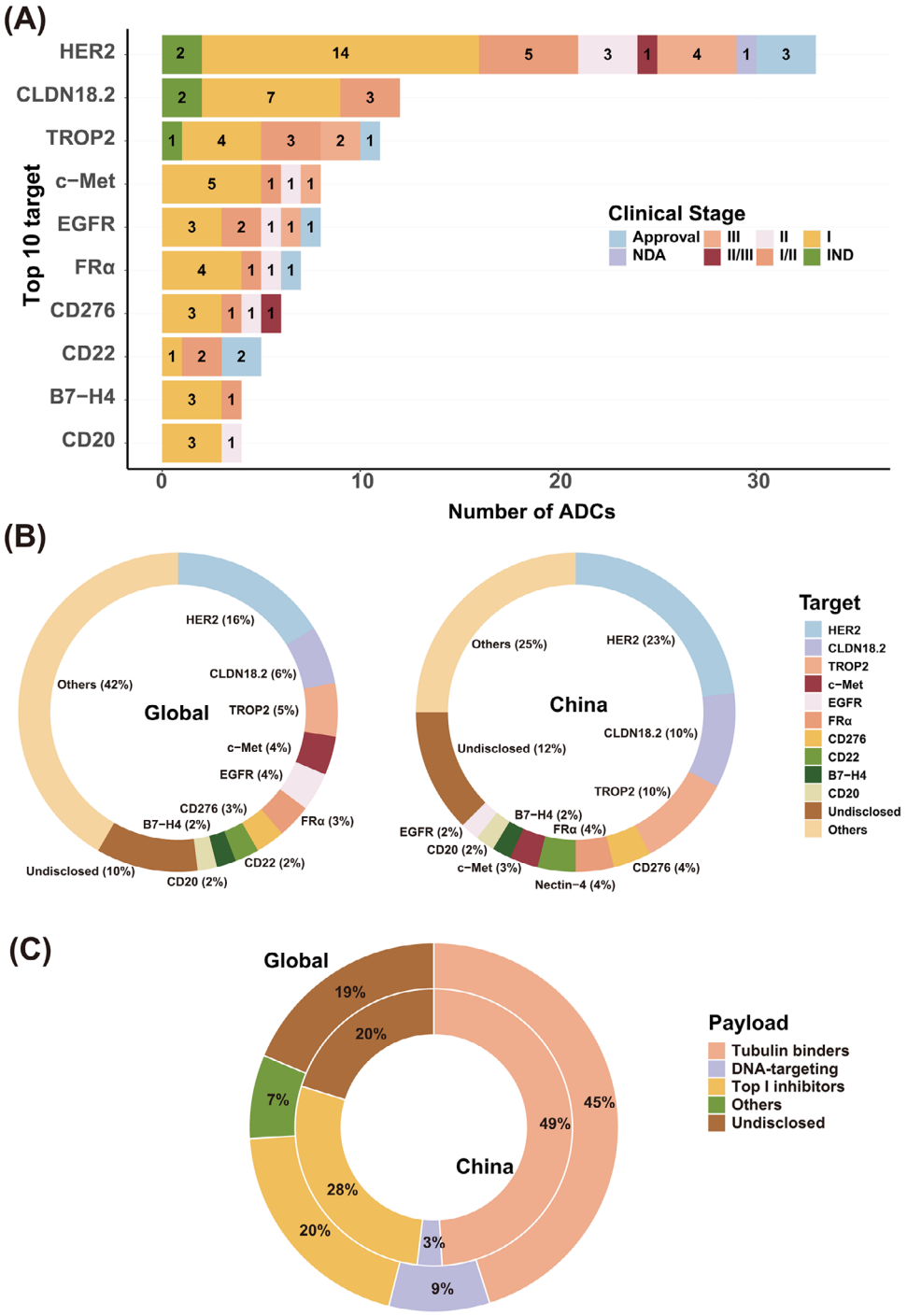

FIGURE 2 The diversity in target and mechanism of action of ADCs pipeline currently under clinical evaluation. (A) The top 10 targets of ADCs pipeline currently under clinical evaluation. (B) Comparison of target diversity of ADCs worldwide and in China. (C) Payload diversity in ADC pipeline of both worldwide and in China. Abbreviations: ADCs, antibody-drug conjugates; CLDN 18.2, claudin 18 isoform 2; c-Met, hepatocyte growth factor receptor; EGFR, epidermal growth factor receptor; FRα, folate receptor alpha; HER2, human epidermal growth factor receptor-2; IND, investigational new drug; NDA, new drug application; TROP2, trophoblast cell surface antigen 2.

design ideas for ADC antibodies have been proposed, such as conditional antibody ADCs [57], bispecific ADCs [58], noninternalized ADCs [59], and vehicles that replace antibodies with other types of molecules [27, 60], which will lead the future R&D trend of ADCs.

Conditional antibody ADCs, activated only in the tumor microenvironment, are expected to increase the therapeutic window, significantly enhance the on-target effects, and reduce the off-tumor toxicity [57]. The "probody" concept, proposed by Cytomx Company, does not function

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TABLE 3 ADC developers and technology platforms[a].

Developer	Platform	Major technologies	Pipelines
Seagen	ADC technology	MMAE-based, novel dipeptide linker	CD30, Nectin-4, TF, LIV-1, CD228, ITGB6, STn
ImmunoGen	ADC platforms	Target selection, antibody development, portfolio of toxins and engineered linkers	FRα, CD37
Genentech/Roche	THIOMAB™ antibody technology	Uses protein chemistry to link a specific number of drug molecules with each antibody	HER2, CD79B
Daichi Sankyo	Dxd ADC technology	Innovative payload and linker	HER2, TROP2, HER3
Spirogen/AstraZeneca	PBD technology	Unique dimeric cytotoxins with highly potent at sub-picomolar concentrations.	/
ADC Therapeutics	PBD technology (Introduced from Spirogen)	PBD-based ADC, potent and flexible class of payloads	CD19, CD25, CD22, AXL, KAAG1
Synaffix	GlycoConnect™	Exploits the native antibody glycan for site-specific conjugation	AXL, DLK-1, B7-H4, TF
	HydraSpace™	Highly polar sulfonamide spacer technology, further enhances therapeutic index	
	toxSYN™	A linker-payload platform that spans key, validated MOAs for ADC product development	
Mersana	DolaLock Technology	Locks the drug inside the cells and controls the bystander effect	HER2, NaPi2b, B7-H4, 5T4
	Dolaflexin	Proprietary payload with higher DAR	
	Dolasynthen	Precise control DAR, site-specific bioconjugation, homogeneous ADC development	
	Immunosynthen	Proprietary STING agonist platform	
Tubulis	P5 conjugation platform	Rapidly generates ultra-stable ADCs with unprecedented linker stability and chemical flexibility	CD30
	Tubutecan-topo-I payload platform	Offers optimized on-target delivery of potent topoisomerase-I inhibitors, increasing the therapeutic window	
	Tub-tag ® platform	Modulating the antibody to provide a beneficial microenvironment for the payload, increasing drug stability	
Ambrx	Expanded genetic code technology platform	Precisely incorporate novel SAAs in proteins within a living cell	HER2, CD70, PSMA
NBE Therapeutics	Transpo-mAb Display technology	Develop the highest quality therapeutic antibodies against any target of choice	ROR1
	SMAC-Technology	Sortase-enzyme-mediated site-specific coupling	
	A novel anthracycline-based toxin platform	Highly potent anthracycline-based DNA damaging intercalating toxin with immune-activated function	

(Continues)

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TABLE 3 (Continued)

Developer	Platform	Major technologies	Pipelines
Zymeworks	ZymeLink™ Auristatin	Auristatin-based drug-linker with favorable pharmacokinetics and drug exposure	HER2, FRα
	Topoisomerase 1 Inhibitor	Novel camptothecin payload with strong bystander activity. Traceless and plasma-stable cleavable peptide linker	
	ZymeLink™ Hemiasterlin	Traceless cleavable dipeptide linkers, sufficiently hydrophilic to enable DAR 8 ADCs	
	Site-Specific Conjugation	Cysteine-insertion conjugation technique to generate homogeneous ADCs	
	TLR7 Immune-Stimulating Antibody Conjugates	Tumor-specific antibodies were conjugated to a TLR7a immunostimulatory small molecule via a peptide cleavable linker	
Sutro	XpressCF+®	Manufacturing proteins and antibodies with site-specific incorporation of non-natural amino acids	FRα, CD74, BCMA, ROR1, TF
Immunomedics/GILEAD	A novel ADC platform	Specialized hydrolysable linker	TROP2
Byondis	ByonZine®	Proprietary duocarmazine linker-drug technology.	HER2, c-Met, CD123
	ByonShieLD ®	Site-specific conjugation technology	
Alteogen	NextMab™ADC	Metal ion binding motif is used for site-specific conjugation	HER2, FRα
CytomX Therapeutics	Probody® Therapeutic Platform	A pioneering antibody prodrug technology	CD166, CD71, EpCAM
Debiopharm	Multilink™	A new linker-drug-conjugate suited for multidrug attachment	CD37
Pyxis oncology	FACT technology platform	Flexible site-specific conjugation technology	ED-B, DLK-1, CD123
	ADC target selection	Offer a new approach for non-internalizing targets	
RemeGen	ADC platform	Screening platform	HER2, MSLN, c-Met, CLDN18.2
		Proprietary Thiel-bridge conjugation technology	
		GMP syntheses of linker, payload and link-payload	
		GMP manufacturing of ADC DS and DP	
MediLink Therapeutics	Tumor Microenvironment Activable LINker-payload (TMALIN™)	Unique enzymatic digestion characteristics, cleaved in TME, enable ADC to be enriched in the TME	B7H3, HER3
KELUN-BIOTECH	OptiDC platform	Design of customized ADCs optimized for different biological targets	HER2, TROP2, CLDN18.2
DualityBio	DITAC platform	Duality Immune Toxin Antibody Conjugate	HER2, TROP2, HER3, CD276
	DIMAC platform	Duality Immune Modulating Antibody Conjugate	

Abbreviations: ADC, antibody-drug conjugates; DAR, drug-to-Antibody Ratio; MOA, mechanism of action; ITB6, integrin beta 6; STn, Sialyl-Thomsen-nouveau antigen; TF, tissue factor; HER2, human epidermal growth factor receptor 2; TROP2, tumor-associated calcium signal transducer 2; HER3, erb-b2 receptor tyrosine kinase 3; KAAG1, kidney associated antigen 1; ROR1, receptor tyrosine kinase-like orphan receptor 1; FRα, folate receptor alpha; BCMA, B cell maturation antigen; PSMA, prostate-specific membrane antigen; MSLN, mesothelin; STING, stimulator of interferon genes; SAA, synthetic amino acids; TLR7a, toll-like receptor 7 agonist; GMP, good manufacturing practice; DS, drug substance; DP, drug product; TME, tumor microenvironment.

[a]The information was collected from company websites.

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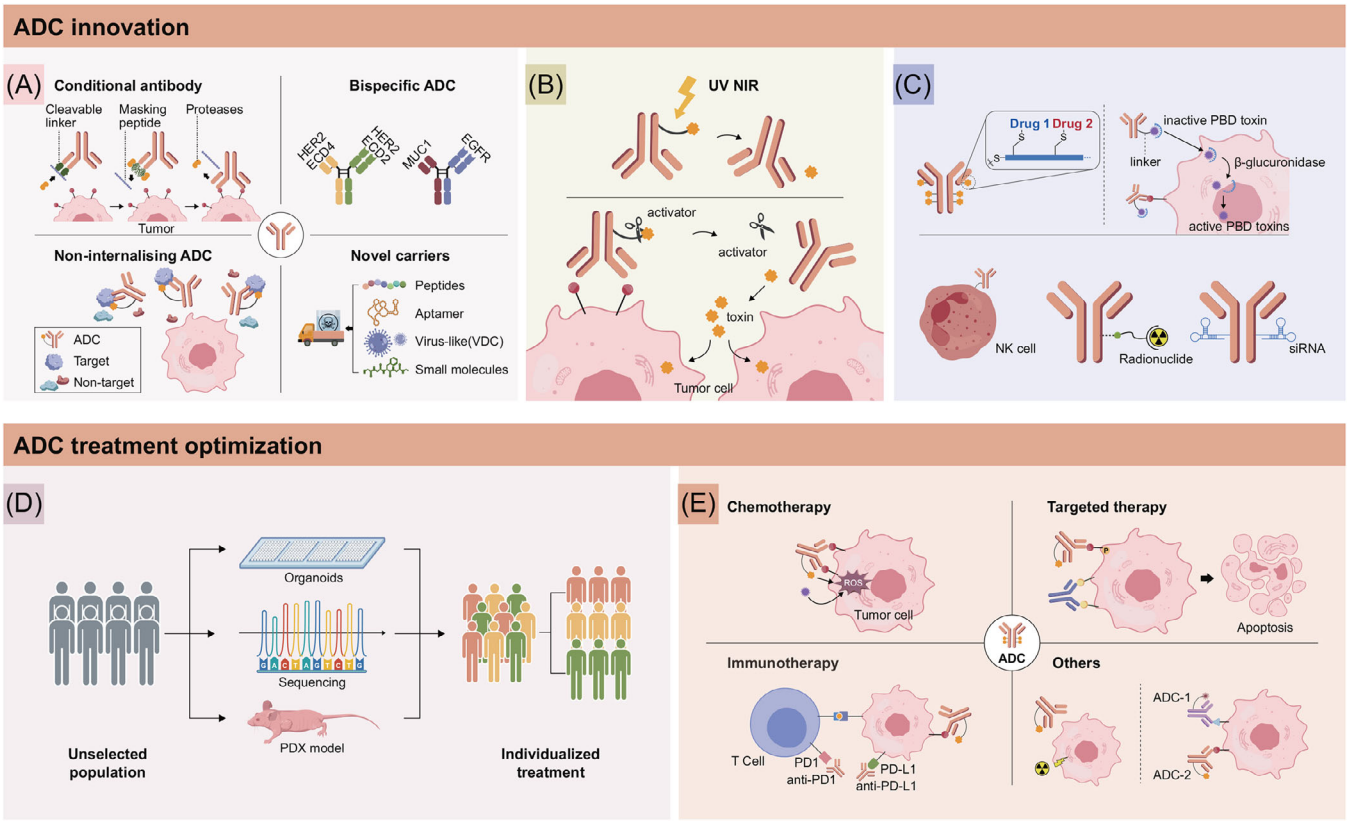

FIGURE 3 Strategies for ADC structural innovation and treatment optimization. (A) Novel antibody-designation strategies such as a conditional antibody (top left), bispecific antibody (top right; the left represented dual epitope ADC, and the right represented dual target ADC), non-internalizing antibody (bottom left) and novel drug carriers such as peptides, aptamer, virus-like, small molecules (bottom right). (B) Innovations of ADC linkers such as UV (ultraviolet) or NIR (near infrared) controlled linkers (top) and "click release" linker (bottom). (C) ADC payload-engineering approaches, including but not limited to dual-payload ADCs (top left), prodrug-ADC (top right; PBD) and ADCs carried novel payloads such as antibody-NK cell conjugate drugs, radionuclide-drug conjugates and antibody-siRNA conjugates (bottom). (D) Using methods such as pharmacogenomic profiling and organoids/PDX model-based drug screening to realize individualized treatment and tailor ADC administration accordingly. (E) Paradigms of ADC combination treatment include combination with chemotherapy (top left), targeted therapy (top right), immunotherapy (bottom left) and novel combination strategies such as combination with radiotherapy or other ADCs (bottom right). Abbreviations: ADC, antibody-drug conjugate; UV, ultraviolet; NIR, near-infrared; NK cell, natural killer cell; PBD, pyrrolobenzodiazepine; PDX, patient-derived xenograft; PD-1, programmed death-1; PD-L1, programmed death-1 ligand.

in the initial state and only becomes active after chemical reactions or enzymatic transformation in the organism. The efficacy of several drugs developed based on this concept, such as CX-2009 [61], CX-072 [62], and Pb-Tx [63], has been preliminarily confirmed in clinical trials.

Another popular design is bispecific ADC, which targets 2 different binding epitopes of the same antigen or 2 different antigens on the same tumor cell [58, 64, 65]. At present, the pipeline of bispecific ADCs under development mainly focuses on targets such as HER2, EGFR, c-Met, and TROP2. Eleven bispecific ADCs have been approved for clinical trial by the U.S. FDA or the European Medicines Agency (EMA; Table 4). Representative drugs, such as Regeneron's cMet/cMet dual antibody ADC (REGN5093-M114), is a dual-epitope ADC. BL-B01D1 is currently the only dual anti-EGFR × HER3 ADC, a phase I clinical study has recently reported its efficacy and safety on heavily treated metastatic/locally advanced solid tumors [66]. Although dual targets offer better efficacy, there may be a problem of too narrow therapeutic window, and the design of dual antibodies may also lead to greater toxicity [67]. How to design bispecific ADCs with better on-target effects and lower off-target toxicity is also a direction worth exploring.

Typical ADC needs to be internalized after binding to the target to release the payload. Non-internalizing ADC does not depend on the internalization process but rather achieves payload delivery and release by targeting non-internalized antigens on tumor cells. Pyxis Oncology's PYX-201 is the first non-internalizing ADC under clinical development. It targets extra domain B of fibronectin (EDB-FN), a protein expressed in the extracellular matrix

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TABLE 4 Pipelines of bispecific ADCs.

ADC	Drug name	Target	Indication(s)	Status	Developer
Bispecific ADC	M1231	MUC1; EGFR	Solid tumor, NSCLC, ESCC	I (Terminated)	Sutro Biopharma
	AZD9592	EGFR; c-Met	Solid tumor, NSCLC, HNSCC	I	AstraZeneca
	BL-B01D1	EGFR; HER3	NSCLC	I	Biokin Pharmaceutical
	CBP-1008	FOLR; TRPV6	Breast cancer, ovarian cancer	II	Coherent Biopharma
	CBP-1018	FOLR; PSMA	Bladder cancer, lung cancer	I	Coherent Biopharma
	DM001	EGFR; TROP2	NSCLC, pancreatic cancer, cervical cancer, skin cancer	Pre-Clinic	Xadcera
	DM002	HER3; MUC1	Lung cancer, breast cancer, pancreatic cancer, ovarian cancer, endometrial cancer	Pre-Clinic	Xadcera
	DM004	5T4; MET	Lung cancer, gastric cancer	Pre-Clinic	Xadcera
	BCG022	HER3; MET	Solid tumor	Pre-Clinic	Biocytogen
	BCG033	TROP2; PTK7	Solid tumor	Pre-Clinic	Biocytogen
	BSA01	EGFR; MUC1	Gastric cancer, NSCLC, PDAC	Pre-Clinic	Biocytogen
	YH-012	HER2; TROP2	NSCLC, pancreatic cancer, breast cancer, ovarian cancer	Pre-Clinic	Biocytogen
	YH-013	EGFR; MET	NSCLC, pancreatic cancer	Pre-Clinic	Biocytogen
Dual-epitope ADC	REGN5093-M114	c-Met	NSCLC	I/II	Regeneron
	ZW49	HER2; ECD2/ECD4	$HER2^+$ solid tumor	II	Zymeworks
	JSKN-003	HER2; ECD2/ECD4	Solid tumor	I	Alphamab Oncology
	TQB2102	HER2; ECD2/ECD4	Solid tumor	I	Chiatai Tianqing
	KM501	HER2; ECD2/ECD4	Breast cancer, gastric cancer, CRC, lung cancer	I	Xuanzhu Biopharm
	MEDI4276	HER2; 39S/ECD4	Breast cancer	I (Terminated)	AstraZeneca

Abbreviations: ADC, antibody-drug conjugates; MUC1, mucin 1; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ESCC, esophageal squamous cell carcinoma; CRC: colorectal cancer; c-MET, MET proto-oncogene; HNSCC, head and neck squamous cell carcinoma; HER2, human epidermal growth factor receptor-2; HER3, erb-b2 receptor tyrosine kinase 3; FOLR, folate receptor alpha; TRPV6, transient receptor potential cation channel subfamily V member 6; PSMA, folate hydrolase 1; TROP2, tumor-associated calcium signal transducer 2; 5T4, trophoblast glycoprotein; PTK7, protein tyrosine kinase 7; ECD, extracellular domain.

(ECM), without having to penetrate the interstitial and ECM barriers commonly found in cancer, allowing toxin release outside the tumor cell. The high lipid solubility of the toxin exerts a bystander effect to kill tumor cells [59]. The phase I clinical trial of PYX-201 in solid tumors, the PYX-201-101 trial, has been officially launched (NCT05720117). The efficacy of non-internalizing ADC in clinical practice is also worth anticipating.

In addition to improving and optimizing the antibody structure, another promising approach is to remove the monoclonal antibody (mAb) delivery structure and couple the payload to a lower-molecular-weight polypeptide fragment or another type of molecular delivery tool [27]. A variety of new drugs have been developed, such as peptide-drug conjugates (PDCs), small molecule-drug conjugates (SMDCs), aptamer-drug conjugates (ApDCs) and nanoparticle-drug conjugates (NDCs) [60, 68]. The major technical challenge for such ADCs is that they may be rapidly cleared in plasma, but if this barrier can be overcome, it has the potential to be used to treat inaccessible tumors, including those with poor vascular innervation and central nervous system tumors [69]. These new drugs also greatly broaden the scope of application of ADC drugs and have broad research and development prospects.

4.3 | Linker

Linkers guarantee the controlled delivery of ADCs. In recent years, many important advances have been made in linker design, which will help to direct future linker development. The first is the emergence of photo-responsive cleavable linkers, which adopt a near-infrared (NIR) light-locking strategy. After NIR light irradiation, the ADC effectively releases the payload in the irradiated tumor region in a site-specific manner [70, 71]. A novel ultraviolet (UV) optically controlled ADC has

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also been reported. The linker introduced UV-controlled o-nitrobenzyl as a cleavage trigger, and ADCs containing o-nitrobenzyl linkers showed a significant increase in activity after irradiation with UV light, up to 50-fold higher than that of unirradiated ADCs in in vitro cytotoxicity assays [72]. Wang *et al.* [73] developed a bioorthogonal cleavable linker that uses the classical bioorthogonal cutting pair Cu(I)-BTTAA and dsProc, and this linker has been explored mainly in vitro. This type of ADC still has many issues to be solved, such as reaction efficiency, reaction rate, substrate stability, biocompatibility and ease of handling, and thus is still far from clinical application [73].

To further achieve the controlled release of drug molecules, researchers began to explore a new type of intelligent ADC, the "click to release" strategy. The first is a click chemical reaction named "Staudinger ligation" reported by Soni *et al.* [74]. Then is the tetrazine/trans-cyclooctene-based click reaction used by Tagworks researchers [75], and the click chemical reaction based on dielectric ion/cycloalkyne compounds first reported by Bernard *et al.* [76]. Researchers at Tagworks Pharmaceuticals have refined their click-and-release strategy in recent years, making it much more efficient than before [77]. The ADCs designed based on the "click to release" strategy also guarantee safety and controllability, which is very valuable in the future development of ADC drugs.

4.4 | Advances in conjugation methods

To date, most conjugations of ADC randomly occur at canonical amino acid residues, such as lysine or interchain cysteines, which lack specificity, and lead to heterogeneity of DAR and drug distribution. Site-specific conjugation technology, including engineered cysteine conjunctions, unnatural amino acid conjunctions, glycosylated conjunctions and C-terminal conjunctions of antibody light chains (or heavy chains), enables antibodies and small molecules to be fixed to a site and quantitatively conjugated, resulting in high homogeneity, good stability, and better activity, and this approach is gradually becoming the choice for the new generation of ADCs.

Besides, to address the low DAR of conventional coupling techniques, Dantari's T-HDC technology "packages" the payload by using polymer molecules and then couples the polymer-packaged payload to the antibody. This load-release system can carry more payloads, and one antibody can carry more than 60 payload molecules [78]. Dolaflexin, a multiwarhead ADC platform of Mersana, also uses polymers to develop high DAR ADC drugs. However, the multiwarhead ADC developed based on this platform has encountered major clinical setbacks, with reports of serious adverse reactions [79, 80]. New ADC drugs based on this technology are also worth exploring in future research.

4.5 | Optimization of payload

Microtubule inhibitors and DNA alkylating agents have dominated ADC payloads for many years. With the development of basic research, promising ways of payload optimization emerge in an endless stream. First of all, the development trend of payloads has gradually shifted from cytotoxic drugs to other noncytotoxic mechanistic agents, which mainly include Top 2 inhibitors, RNA polymerase inhibitors, B-cell lymphoma-extra-large (Bcl-xL) inhibitors, and immunostimulants [81-83]. Another innovative design of payload is prodrug-ADC, which can only be activated and released after entering tumor cells, further enhancing the drug specificity and therapeutic window. In addition to upgrading a single payload, a potential strategy is to carry 2 payloads with different or similar mechanisms of action. These dual-payload ADCs can deliver 2 synergistic payloads to tumor cells to achieve better efficacy and also address, to some extent, the issues of chemotherapy resistance and heterogeneity of antigen expression [84-86]. However, the development of dual-payload ADC is hindered by its high R&D cost and technical difficulty [85].

Besides, ADC payloads have become increasingly diverse, with brand-new payloads now under development. For instance, Acepodia is developing antibody-natural killer (NK) cell conjugate drugs that connect tumor-targeting antibodies directly to the surface of its proprietary NK cell line for better tumor killing (NCT04319757). Rakuten Aspyrian is developing Illuminox™, a photoimmunotherapy platform designed to pair cancer-targeting drugs (e.g., antibody drugs) with photoactivatable conjugates and then activate them for tumor killing using a light-application system [87]. Early clinical trials are also underway for additional novel-payload, radionuclide-drug conjugates designed to selectively deliver radioactive payloads [88]. Inspired by the ADC concept, antibody-small interfering RNA (siRNA) conjugates have emerged as potential vehicles for targeted siRNA drug delivery that can overcome current barriers to siRNA delivery [89]. Besides, there are ongoing studies on new payloads, including antibody-steroid conjugates (NCT05556226), antibody-antibiotic conjugates (AACs) [90] and degrader-antibody conjugates [91]. It is believed that these ADCs with novel payloads will soon open up new areas for tumor treatment with their unique advantages.

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4.6 | Refinement of the drug delivery scheme from preclinical research

In addition to the optimization and upgrading of ADC itself, how to use the existing ADC drugs to improve their clinical efficacy through clinical and translational research strategies is also worth exploring. One promising approach is to adopt a divided/staged dosing regimen to maintain the anti-tumor dose intensity while reducing the peak concentration. Similar to ordinary chemotherapy, this method helps to reduce the maximum toxicity caused by serum concentration and prolong the existence time of drugs, thus ensuring that more tumor cells entering the cell cycle are affected by drugs [92-94]. After ADC drugs enter the blood circulation, nontarget toxicity will inevitably occur. How to balance target and nontarget toxicity is also an urgent problem in preclinical research. As mentioned earlier, a new nuclide-conjugated drug has emerged that can make disease "visible and treatable". For example, there are studies using zirconium 89-labeled trastuzumab and positron emission tomography (PET) to assess HER2 status in different target lesions, combining imaging analysis and fluorodeoxyglucose (F18)-labeled PET/computed tomography (CT) imaging, and evaluating HER2 status in different target lesions. It can predict which patients/lesions will benefit more from HER2 ADC treatment, thus providing more possibilities for the choice of treatment regimen [95]. Besides, based on the rapid development of preclinical research models, there have been attempts to use patient-derived xenografts (PDX) models or organoids to conduct *in vivo/in vitro* drug sensitivity tests to guide treatment [96]. However, there are no studies on ADC drugs in this area at present. In conclusion, a closer combination of preclinical research and clinical practice is needed to achieve more refined drug treatment management of ADC in the future.

4.7 | Screening suitable populations using predictive markers

ADC drugs mainly rely on their antibodies to localize to the therapeutic target, so the expression of the target should be considered first when selecting the appropriate population for ADC therapy [1]. Another important component of ADC is the payload, and the mechanism of the payload may lead to differences in ADC-sensitive populations. Moreover, as a macromolecular substance with a relatively complex structure, ADCs might be quite different from simple antibody drugs and chemotherapy drugs. With the emergence of more ADCs with varying mechanisms and more combined clinical trials in the future, ADC predictive markers will also be a worthwhile direction for further research. For example, broad-spectrum markers can be studied in terms of the mechanism of ADC itself or the effects of drug metabolism. It is also possible to incorporate the analysis of multi-omics sequencing data to construct a population-specific ADC drug response prediction signature or to stratify the treatment response in the target population. Additionally, advances in the field of circulating-tumor DNA (ctDNA) and liquid biopsy have made it possible to find more generalizable hematological tumor markers for ADC. In conclusion, biomarker-guided precise population stratification and treatment will be one of the future directions for the clinical application of ADCs.

4.8 | Exploration of rational combination therapy

Increasing numbers of preclinical and clinical studies have begun to explore the combination therapy of ADCs, mainly including traditional chemotherapy, targeted therapy, immunotherapy, and other combination therapies. First of all, drug combinations are designed from the perspective of the traditional chemotherapy "1 + 1" concept by exploiting the nature of the ADC payload as a cytotoxic drug. For example, DNA damage drugs acting on the S phase and causing G2/M phase arrest can be appropriately combined with tubulin inhibitors with the greatest efficacy in the G2/M phase to increase the anti-tumor proliferation effect [97, 98]. Second, as a new type of targeted chemotherapy, the efficacy of ADCs largely depends on the degree of targeting. Therefore, combination methods that are conducive to increasing the expression of ADC target antigens can be selected to increase the therapeutic effect of ADCs [99, 100]. Moreover, the ADC payload is not limited to cytotoxic drugs. For instance, the combination of radionuclide payload and chemotherapy may play a role in the combination of radiotherapy and chemotherapy [101], and new combinations of ADC and chemotherapy, such as antibody-siRNA conjugates, antibody cell conjugates, and degrader-antibody conjugates, are also worth trying. These new drugs may solve the problems of low targeting and high off-target toxicity of traditional treatment methods and have broad development prospects.

At present, ADC combined with targeted therapy mainly focuses on the application of HER2-targeted ADC drugs in breast cancer. Several clinical trials have used trastuzumab emtansine combined with pertuzumab, an ADC targeting HER2, to try to replace the role of chemotherapy drugs, but the effect of the combination has not been satisfactory [102-104]. This suggests that there are still differences between ADC and chemotherapeutic drugs, and future studies should not simply replace the two, and more pre-clinical and clinical studies are needed to confirm.

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On the other hand, if a HER2-targeted ADC is used in combination with a tyrosine kinase inhibitors (TKI), it may achieve a dual blockade of the EGFR pathway and achieve a better therapeutic index, such as the combination of trastuzumab emtansine and neratinib [105, 106]. The mechanism is not fully understood, and it has been reported that this may be related to the ability of TKIs to change the abundance of HER2 molecules on the cell surface [107]. Additionally, some studies have reported the combination of antiangiogenic drugs and ADCs because antiangiogenic drugs may increase vascular permeability and promote the delivery of ADC drugs to the target site, thereby increasing the effect of ADCs [98, 108]. The efficacy of combining ADC drugs with more targeted therapeutic drugs is also worth further exploration. Several studies of ADC combined with immunotherapy are also being explored [100]. At present, the combination of ADC and immunotherapy mostly focuses on the immune checkpoint programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1). EV-103 cohort K, a randomized cohort study designed to evaluate enfortumab vedotin (Padcev) alone or in combination with Keytruda as first-line treatment in patients with locally advanced or metastatic urothelial carcinoma who were unable to receive cisplatin chemotherapy, showed an improvement in the ORR (ORR: 45.2% vs. 64.5%) [109]. In addition to targeting tumor cells, ADC can act on various immune cells or the ECM in the tumor microenvironment. For example, ADC targeting CD73 in preclinical studies has shown preliminary therapeutic activity [110]. In preclinical models, ADC targeting cancer-related fibroblasts can enhance the activity of $CD8^+$ T cells when combined with pembrolizumab [111].

Some issues need to be considered when ADCs are used in combination with immunotherapy, such as the comprehensive effects of ADC and immunotherapeutic drugs on patients' immune system, which places greater demands on preclinical model development, as the immune environments of animals and humans often have some differences. Based on the diversity of the types of ADCs and immunotherapy drugs and the possible mechanism of the combination, ADCs combined with immunotherapy have a very large research space, and their prospects are worth anticipating.

There are some new combination perspectives worth exploring. For instance, instead of the traditional combination of chemotherapeutic agents or chemotherapy combined with target drugs, the design and development of dual-payload ADCs can exert a combined effect directly localized to the target, which helps to reduce the problem of nontarget toxicity [85, 112]. The first study of ADC combined with radiotherapy, disitamab vedotin (Aidixi) combined with radiotherapy and immunotherapy in the treatment of HER2-positive advanced refractory solid tumors, has also reported preliminary phase II data, providing evidence for the effectiveness of ADCs combined with radiotherapy [113]. In addition, the application of ADCs in neoadjuvant therapy and the exploration of the combination of two ADCs are also very interesting research directions in the future.

5 | CONCLUSION

As an innovative form of drug treatment, ADCs possess significant market potential and clinical value in the realm of anti-tumor therapeutics. Nevertheless, they are not without challenges, difficulties, and formidable competition. In the past decade, the design of ADCs has been continuously improved, and the technology has been sequentially modernized. New antibody forms, new delivery systems, non-internalized antigen targets, novel cytotoxic payloads, and site-specific conjugation methods have been explored to facilitate the development of ADCs. Nevertheless, there are still many problems that need to be solved: better understanding of the mechanism of action; identifying effective biomarkers of treatment response; enhancing drug permeability in solid tumors; improving the efficacy while reducing toxicities; exploring the best mode of administration and overcoming drug resistance. Importantly, recent ADC products have showcased exciting possibilities, suggesting that we have entered an era where "everything can be conjugated". While numerous innovations await clinical validation, the studies conducted in this field have yielded encouraging results. It is firmly believed that ADCs hold a promising future for the next decade, poised to revolutionize the landscape of anti-tumor therapies.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Rui-Hua Xu made contributions to conception and study supervision. Dan-Yun Ruan, Hao-Xiang Wu, and Qi Meng searched data for this article. All authors contributed substantially to the discussion of the content, wrote the manuscript, and reviewed the manuscript before submission. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Rui-Hua Xu reports speaker fees from Bristol Myers Squibb, Roche, MerckSerono, Hutchison, Hengrui, Junshi, Oilu, CPPC, Henlius, and participates on advisory board for Astellas, MSD, AstraZeneca, Junshi, Hengrui, BeiGene.

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Innovent, CPPC, and Keymed. All other authors declare no competing interests.

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