Clinical and Experimental Medicine (2025) 25:139
https://doi.org/10.1007/s10238-025-01655-6

REVIEW

Mechanism of action and future perspectives of ADCs in combination with immune checkpoint inhibitors for solid tumors

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Received: 12 February 2025 / Accepted: 26 March 2025

Abstract

Antibody–drug conjugates (ADCs) are a promising cancer therapy for targeted delivery of drugs to tumor cells. However, resistance to ADCs remains a challenge, necessitating the exploration of combination therapies. A strong biological theory suggests that ADCs interact with cancer cells and immune cells by triggering mechanisms such as immunogenic cell death, dendritic cell activation, and memory T-cell activation, resulting in long-term anti-tumor immunity and ultimately potential synergistic effects with immunotherapy. Based on extensive and reliable preclinical data, several clinical trials are currently combining ADCs with immune checkpoint inhibitors (ICIs) for the treatment of various cancers, including breast, gastric, and non-small-cell lung cancers, to evaluate the safety and anti-tumor activity of the combination therapy. Preliminary evidence from early clinical trials has reported more effective efficacy data. This paper reviews the combination of ADCs and immunotherapy, highlights the key mechanisms by which the two act synergistically, and summarizes the available clinical evidence against different ADCs targets. The paper also explores the re-challenges used for combination therapies and optimized design options for ADCs drugs.

Keywords Antibody-drug conjugates · Immunotherapy · Immune checkpoint inhibitors · Solid tumor

Introduction

ICIs, represented by PD-1/PD-L1 inhibitors, are a class of drugs that activate immune cells to exert anti-tumor effects by blocking the binding of immune checkpoints to their ligands and relieving immune suppression caused by immune checkpoints [1]. Unfortunately, however, only a fraction of patients could be able to achieve clinical benefit, and there is still a need to explore combination therapy with other drugs or different therapeutic strategies to overcome their resistance and expand their clinical utility [2, 3]. In recent years, novel antibody-based macromolecular complexes represented by ADCs have attracted increasing attention. The drug is composed of an antibody, a payload (a highly potent cytotoxic drug molecule) and a linker connecting the two [4]. The mechanism of action utilizes the binding of antibodies to antigens on the surface of target cells, where ADCs are internalized and release their payloads, thus exerting cytotoxic effects [5], providing an efficient and precise therapeutic strategy for a wide range of solid tumors [6]. Since the first approval of ADCs for the treatment of solid tumors in 2013 [7], nine ADCs have been approved for advanced solid tumors with different indications, which was showed in the Fig. 1. However, drug resistance is still difficult to avoid [8]. Relevant studies have shown that ADCs not only trigger tumor cell death by targeting antigens and releasing payloads, but also induce immunogenic cell death (ICD), which alters the tumor microenvironment and enhances the anti-tumor immune response. ICIs could release immunosuppression and further exert synergistic effects by activating T cells [9, 10], and the combined application of the two has become a research hotspot in the field of cancer therapy. This combination therapy has demonstrated significant efficacy against refractory solid tumors in several clinical trials, along with a favorable safety profile. This review will focus on the research progress of ADCs in combination with immunotherapy, focusing on its mechanism of action, clinical trial results and future development direction, providing new ideas for individualized cancer treatment.

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Published online: 04 May 2025

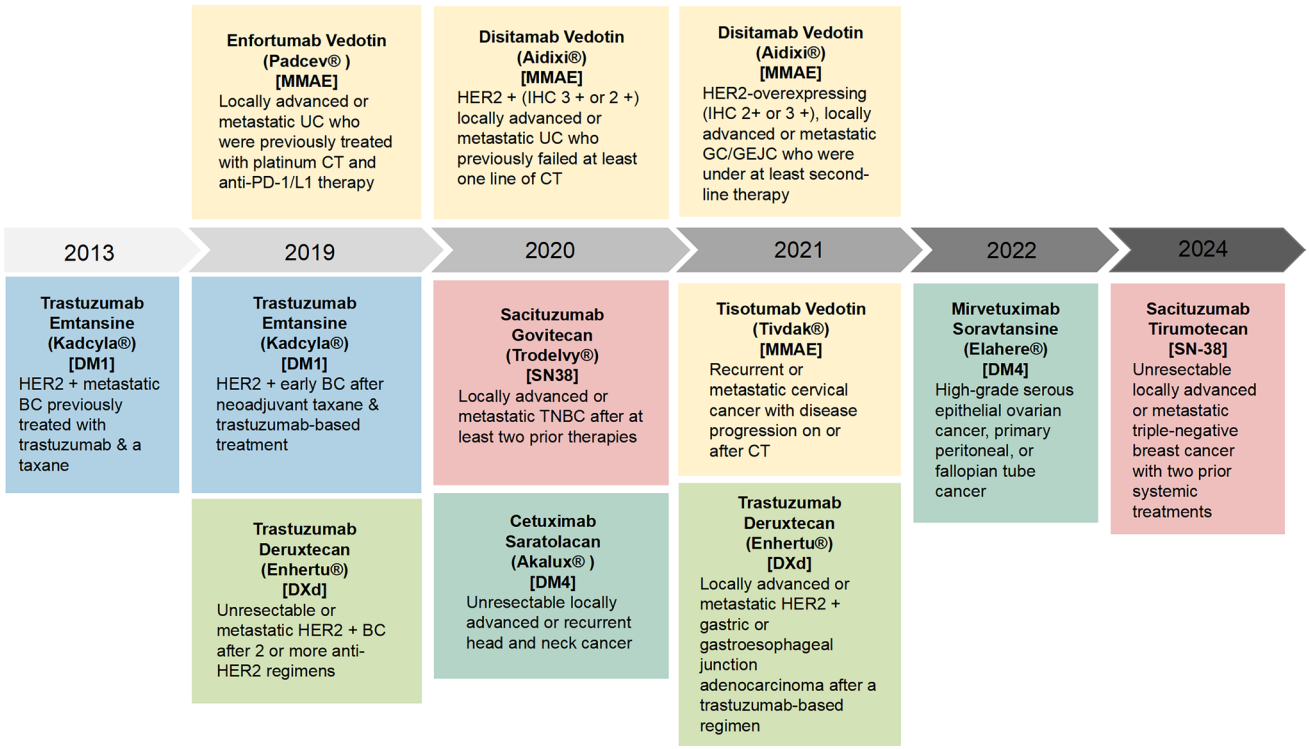

Fig.1 ADC drugs approved for solid tumors

Biological mechanisms of ADCs combined with ICIs

As shown in the Fig. 2, ADCs are internalized by recognizing and binding to specifc antigens on tumor cells. Subsequently, the linkers of ADCs are degraded, releasing ADCs payloads that trigger apoptosis [11]. Still other payloads are also capable of killing nearby non-targeted cells through a paracrine effect, a process that is not dependent on the expression of target antigens on the cell surface. It follows that payloads are the ultimate effector components of ADCs, which mainly include: microtubule inhibitors (MMAE, MMAF, DM1, DM4), DNA damaging agents (Calicheamicin, PBD, Duocarmycin), and topoisomerase inhibitors (SN38, DXd). In addition, ADCs can further enhance tumor cell killing through mAb-partially mediated effector functions such as antibody-dependent cytotoxicity (ADCC), antibody-dependent cell phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC) [12].

ADCs kill tumor cells while minimizing damage to other normal organs. This strategy not only enhances the therapeutic efficacy of the drug, but also improves the immunogenicity of the tumor [13]. One of the key mechanisms by which ADCs enhance the effectiveness of ICIs is the induction of ICD. ICD is a type of programmed cell death, which differs from conventional apoptosis in that ICD occurs with the ability to release both tumor-associated antigens (TAA) and damage-associated molecular pattern (DAMP). DAMP includes exposed cell surface calreticulin (CRT) and heat shock proteins (HSP70 and HSP90), which contribute to phagocytosis to take up dying cells, as well as extracellularly released immunostimulatory factors, such as adenosine triphosphate (ATP), high mobility group box-1 (HMGB1), and cytokines [14, 15]. Tumor cells with aberrant DAMP-release pathways (e.g., autophagy and unfolded protein response) tumor cells do not respond to stimuli that trigger immunogenic cell death. Therefore, increasing the availability of specific DAMP could convert non-immunogenic cell death into ICD [16]. These molecules are recognized, taken up and processed by dendritic cells (DCs), which subsequently present them to major histocompatibility complex (MHC II) molecules, thereby activating $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells [17, 18].

Previous studies have shown that microtubule destabilizing compounds (e.g., vincristine) are effective in inducing phenotypic and functional maturation of DCs, whereas microtubule stabilizers, such as paclitaxel, do not have this effect. Moreover, the antitumor effects of these drugs are dependent on an intact immune system and are significantly attenuated in immunodeficient mice. Importantly, these effects were observed even in the absence of tumor cell death. As previously mentioned, DCs activate $CD8^+$ cytotoxic T cells, and the function of

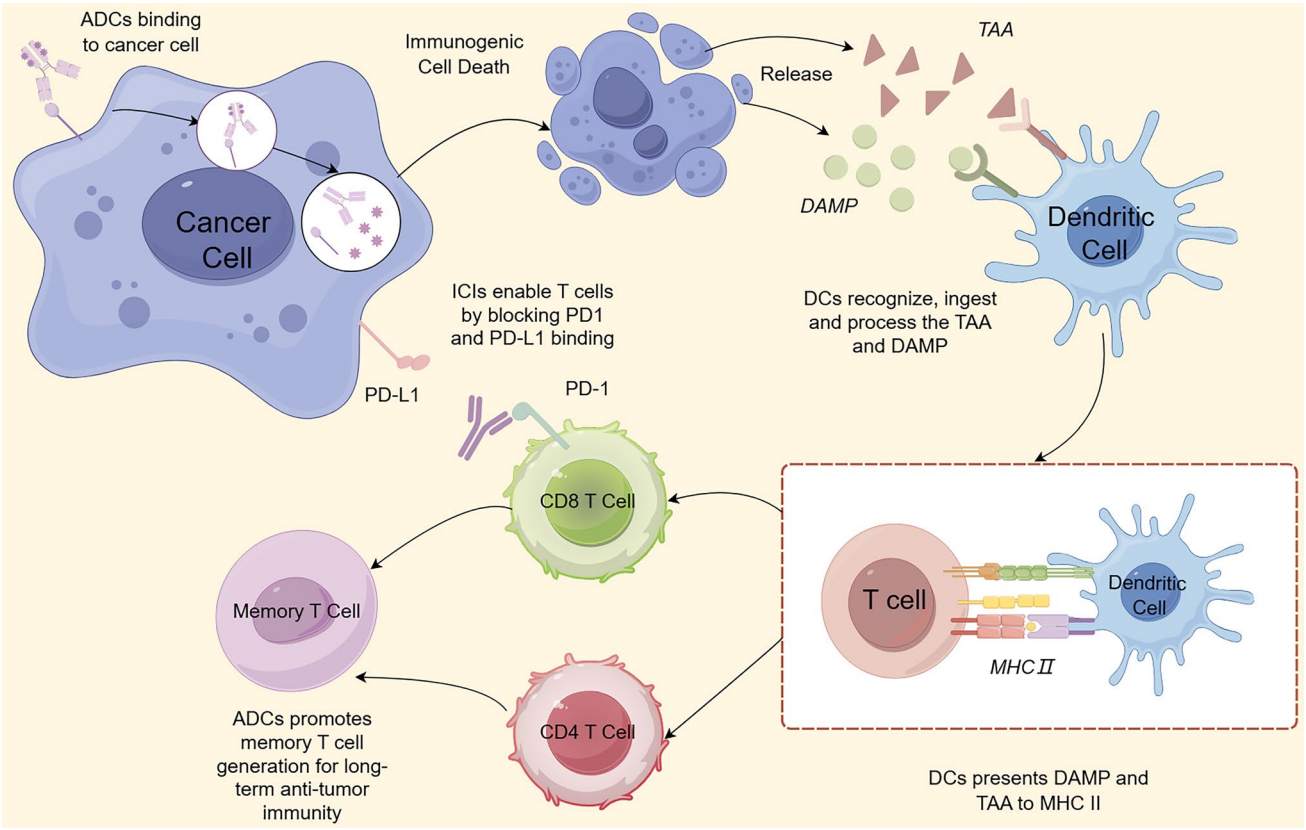

Fig. 2 Rationale for combination immunotherapy and antibody–drug concatenates (ADCs)

infiltrating $CD8^+$ T cells is inhibited by the involvement of the immune checkpoint molecules PD-1 and CTLA-4, so that the use of ICIs effectively releases and maintains T cell responses against tumors [14, 19, 20]. The synergistic effect of ADCs in combination with immunotherapy for antitumor therapy has also been demonstrated in relevant preclinical trials. Among them, in the clinical trials regarding ADCs with microtubule depolymerizing agents as payloads combined with ICIs for the treatment of mice that had been inoculated with MC38 tumors, 12 mice were used in each group, and a greater number of mice in the combination group (7) achieved complete tumor rejection compared to the ADCs (1) and ICIs (3) monotherapy groups [21, 22]. This largely demonstrates that treatment with ADCs in combination with ICIs is significantly more effective than monotherapy. Similarly, topoisomerase I inhibitors such as Trastuzumab deruxtecan (T-DXd) have shown the same effect [23, 24]. Previous studies have shown that three different topoisomerase I inhibitors (cisplatin, topotecan, and irinotecan) are able to enhance the tumor killing activity of T cells, and data from relevant preclinical mouse model experiments with T-DXd may also demonstrate the superiority of combination therapy [25, 26].

There are preclinical studies suggesting that ADCs can achieve long-term anti-tumor immunity by promoting the generation of memory T cells, a phenomenon supported by some in vivo findings.D'Amico et al. used HER-2-targeted ADCs with anthracycline derivatives as potent loads to treat humanized HER-2-expressing (HER-2 +) homozygous mice. The fully cured mice were subsequently reinoculated with either the original HER-2 + cancer cells or other tumor cells of a different lineage. The results showed that mice that received reinoculation of the original HER-2 + cancer cells remained in complete remission, whereas mice inoculated with tumor cells of a different lineage rapidly developed tumors [27]. Similarly, Iwata et al. observed that a homozygous mouse model that was fully responsive to T-DXd was able to completely reject the reinoculated cancer cells. In contrast, these same tumor cells grew rapidly in control mice without any pretreatment [25]. This was also demonstrated in another preclinical study of Disitamab vedotin (RC48) in combination with an immune checkpoint inhibitor. In conclusion, there is growing evidence that ADCs may produce adaptive immunity to exert anti-tumor effects [28].

Data from clinical studies of different ADCs in combination with ICIs

In conjunction with the strong preclinical rationale for the use of ADCs and ICIs agents in the treatment of cancer, many clinical studies have been conducted aimed at evaluating the clinical feasibility, safety, and efficacy of ADCs/ICIs combinations. Table 1 summarizes the current status of clinical trials conducted on the combination of ADCs and ICIs for the treatment of solid tumors, while Table 2 includes clinical trials for which all or part of the efficacy data have been published to date.

Table 1 Summary of clinical trials of ADCs in Combination with Immune Checkpoint Inhibitors

Target	ADC	Cytotoxic payload	NCT number	Phase	ICI
HER-2	Trastuzumab emtansine	DM1	NCT02924883(KATE2)	II	Atezolizumab
			NCT03032107	Ib	Pembrolizumab
			NCT04873362 (ASTEFANIA)	III	Atezolizumab
			NCT04740918 (KATE3)	III	Atezolizumab
			NCT04632992 (MyTACTIC)	II	Atezolizumab
			NCT02605915	Ib	Atezolizumab
	Trastuzumab deruxtecan	Dxd	NCT04686305 (DESTINY-Lung03)	Ib	Durvalumab
			NCT04556773 (DESTINY-Breast08)	Ib	Durvalumab
			NCT04538742 (DESTINY-Breast07)	Ib/II	Durvalumab
			NCT04379596 (DESTINY-Gastric03)	Ib/II	Durvalumab or Pembrolizumab
			NCT04042701(DS8201-A-U106)	Ib	Pembrolizumab
			NCT03742102(Begonia)	Ib/II	Durvalumab
			NCT03523572(DS8201-A-U105)	Ib	Nivolumab
			NCT03334617(HUDSON)	II	Durvalumab
			NCT04784715 (DESTINY-Breast09)	III	Pertuzumab
	Disitamab vedotin	MMAE	NCT04280341(RC48-C013)	I	Toripalimab
			NCT04264936(RC48-C014)	Ib/II	Toripalimab
			NCT05113459(RC48-C018)	II	Sintilimab
			NCT05297552(RC48-C017)	II	Toripalimab
TROP2	Sacituzumab govitecan	SN-38	NCT04863885	I/II	Ipilimumab and Nivolumab
			NCT04468061	II	Pembrolizumab
			NCT04448886(Saci-IO HR +)	II	Pembrolizumab
			NCT04434040(ASPRIA)	II	Atezolizumab
			NCT04230109(NeoSTAR)	II	Pembrolizumab
			NCT03971409(InCITe)	II	Avelumab
			NCT03547973(TROPHY U-01)	II	Pembrolizumab
			NCT03424005(Morpheus-TNBC)	Ib/II	Atezolizumab
			NCT03337698(Morpheus Lung)	Ib/II	Atezolizumab
			NCT03869190(Morpheus-UC)	Ib/II	Atezolizumab
			NCT05186974(EVOKE-02)	II	Pembrolizumab
			NCT05609968(EVOKE-03)	III	Pembrolizumab
			NCT05633667(VELOCI-TY-Lung)	II	Zimberelimab

Table 1 (continued)

Target	ADC	Cytotoxic payload	NCT number	Phase	ICI
	Datopotomab deruxtecan	Dxd	NCT04612751(TROPION-Lung04)	Ib	Durvalumab
			NCT04526691(TROPION-Lung02)	Ib	Pembrolizumab
			NCT03742102(Begonia)	Ib/II	Durvalumab
			NCT05215340(TROPION-Lung08)	III	Pembrolizumab
			NCT05687266(AVANZAR)	III	Durvalumab and Pembrolizumab
			NCT05555732(TROPION-Lung07)	III	Pembrolizumab
	SKB264	SN-38	NCT06448312	III	Pembrolizumab
			NCT06706219	III	Pembrolizumab
			NCT06711900	III	Pembrolizumab
			NCT05351788	II	KL-A167
Nectin-4	Enfortumab vedotin	MMAE	NCT04960709(VOLGA)	III	Durvalumab
			NCT04700124(KEYNOTE-B15)	III	Pembrolizumab
			NCT04223856(EV-302)	III	Pembrolizumab
			NCT03924895(KEYNOTE-905/EV-303)	III	Pembrolizumab
			NCT03606174	II	Pembrolizumab and Nivolumab
			NCT03288545(EV-103)	I/II	Pembrolizumab
			NCT03869190(Morpheus-UC)	Ib/II	Atezolizumab
			NCT05239624(EV-ECLIPSE)	II	Pembrolizumab
			NCT04225117(EV-202)	II	Pembrolizumab
FLOR1 (FRα)	Mirvetuximab soravtansine	DM4	NCT03835819	II	Pembrolizumab
			NCT02606305	Ib/II	Pembrolizumab
TF	Tisotumab vedotin	MMAE	NCT03786081	Ib/II	Pembrolizumab
			NCT03485209(innovaTV 207)	II	Pembrolizumab
B7-H3	Vobramitamab duocarmazine(MGC018)		NCT03729596	I/II	Retifanlimab
	Enoblituzumab		NCT02475213	I	Pembrolizumab
LIV-1	Ladiratuzumab vedotin	MMAE	NCT03310957(SGNLVA-002)	Ib/II	Pembrolizumab
			NCT03424005 (Morpheus-TNBC)	Ib/II	Atezolizumab
			NCT02099058	I/Ib	Nivolumab
CEACAM5	Tusamitamab ravtansine	DM4	NCT04524689 (CARMEN-LC05)	II	Pembrolizumab
			NCT04394624 (CARMEN-LC04)	II	Pembrolizumab
Claudin18.2	LaNova Medicines-302	MMAF	NCT05188664	I/II	Toripalimab
			NCT05934331	II	Toripalimab
			NCT05994001	Ib/II	Cardonilizumab

Target	ICI type	Condition	Setting	Primary endpoint	Status
HER-2	PD-L1 inhibitor	HER2-positive Breast Cancer	Locally Advanced or Metastatic	PFS,AEs	Completed
	PD-1 inhibitor	HER2-positive Breast Cancer	Metastatic	AEs	Completed

Table 1 (continued)

Target	ICI type	Condition	Setting	Primary endpoint	Status
	PD-L1 inhibitor	HER2-positive Breast Cancer	High Risk of Recurrence Following Preoperative Therapy	IDFS	Active, not recruiting
	PD-L1 inhibitor	HER2-positive and PD-L1-positive Breast Cancer	Locally Advanced or Metastatic	PFS,OS	Terminated
	PD-L1 inhibitor	HER2-positive Solid Tumors	Advanced Unresectable or Metastatic	ORR	Completed
	PD-L1 inhibitor	HER2-positive Breast Cancer	Locally Advanced or Metastatic	DLT,AEs	Completed
	PD-L1 inhibitor	HER2-oe Non-Small Cell Lung Cancer	Locally Advanced or Metastatic	AEs,SAEs	Recruiting
	PD-L1 inhibitor	HER2-low Breast Cancer	Metastatic	AEs,SAEs	Active, not recruiting
	PD-L1 inhibitor	HER2-positive Breast Cancer	Advanced or Metastatic	AEs,SAEs	Active, not recruiting
	PD-L1 inhibitor or PD-1 inhibitor	HER2-positive esophageal/gastric/Gastric and Esophagogastric Junction Adenocarcinoma	Advanced or Metastatic	AEs,SAEs,DLT,ORR	Recruiting
	PD-1 inhibitor	HER2-expressing Breast Cancer and HER2-expressing or HER2-mutant Non-Small Cell Lung Cancer	Advanced or Metastatic	DLT,ORR	Active, not recruiting
	PD-L1 inhibitor	Triple-Negative Breast Cancer	Advanced Unresectable or Metastatic	AEs,ORR	Active, not recruiting
	PD-1 inhibitor	HER2-expressing Breast Cancer and Urothelial Cancer	Advanced or Metastatic	ORR	Completed
	PD-L1 inhibitor	Non-Small Cell Lung Cancer	Metastatic	ORR	Active, not recruiting
		HER2-positive Breast Cancer	Metastatic	PFS	Active, not recruiting
	PD-1 inhibitor	HER2-positive Solid tumors	Advanced or Metastatic	DLT,AEs	Recruiting
	PD-1 inhibitor	Urothelial Cancer	Advanced or Metastatic	AEs	Unknown status
		HER2-positive Gastric and Esophagogastric Junction Adenocarcinoma	Locally Advanced	PCR	Unknown status
	PD-1 inhibitor	Muscle Invasive Bladder Cancer		PCR	Recruiting
TROP2	CTLA-4 inhibitor and PD-1 inhibitor	Urothelial Cancer	Metastatic	MTD,ORR	Active, not recruiting
	PD-1 inhibitor	Triple-Negative Breast Cancer	Metastatic	PFS	Recruiting
	PD-1 inhibitor	HR + /HER2- Breast Cancer	Invasive or Metastatic	PFS	Active, not recruiting
	PD-L1 inhibitor	Triple-Negative Breast Cancer		Rate of undetectable circulating tumor cfDNA-6 Cycles	Active, not recruiting
	PD-1 inhibitor	Triple-Negative Breast Cancer	Localized	PCR	Recruiting
	PD-L1 inhibitor	Triple-Negative Breast Cancer	Stage IV or Unresectable, Recurrent	BORR	Recruiting
	PD-1 inhibitor	Urothelial Cancer	Unresectable Locally Advanced/Metastatic	ORR,PFS,TEAEs	Recruiting
	PD-L1 inhibitor	Breast Cancer	Metastatic	ORR	Recruiting
	PD-L1 inhibitor	Non-Small Cell Lung Cancer	Metastatic	ORR	Active, not recruiting
	PD-L1 inhibitor	Urothelial Cancer and Bladder Cancer	Advanced or Metastatic	ORR,PCR	Active, not recruiting
	PD-1 inhibitor	Non-Small Cell Lung Cancer	Advanced or Metastatic	ORR,DLT	Active, not recruiting
	PD-1 inhibitor	Non-Small Cell Lung Cancer	Metastatic	PFS,OS	Recruiting
	PD-1 inhibitor	Non-Small Cell Lung Cancer	Resectable,Advanced or Metastatic	ORR	Recruiting

Table 1 (continued)

Target	ICI type	Condition	Setting	Primary endpoint	Status
	PD-L1 inhibitor	Non-Small Cell Lung Cancer	Advanced or Metastatic	DLT,TEAEs	Recruiting
	PD-1 inhibitor	Non-Small Cell Lung Cancer	Advanced or Metastatic	DLT,TEAEs	Active, not recruiting
	PD-L1 inhibitor	Triple-Negative Breast Cancer	Advanced or Metastatic	AEs,ORR	Active, not recruiting
	PD-1 inhibitor	Non-Small Cell Lung Cancer	Metastatic	PFS,OS	Recruiting
	PD-L1 inhibitor and PD-1 inhibitor	Non-Small Cell Lung Cancer	Advanced or Metastatic	PFS,OS	Active, not recruiting
	PD-1 inhibitor	PD-L1 TPS < 50% Non-Small Cell Lung Cancer	Advanced or Metastatic	PFS,OS	Recruiting
	PD-1 inhibitor	PD-L1 Positive Non-Small Cell Lung Cancer	Advanced or Metastatic	PFS	Recruiting
	PD-1 inhibitor	Non-Small Cell Lung Cancer	Unresectable stage III	18 m EFS rate	Not yet recruiting
	PD-1 inhibitor	Non-Squamous Non-Small Cell Lung Cancer	Advanced or Metastatic	PFS	Recruiting
	CD47 inhibitor	Non-Small Cell Lung Cancer	Advanced or Metastatic	AEs,ORR	Recruiting
Nectin-4	PD-L1 inhibitor	Muscle Invasive Bladder Cancer		AEs	Active, not recruiting
	PD-1 inhibitor	Muscle Invasive Bladder Cancer		EFS	Active, not recruiting
	PD-1 inhibitor	Urothelial Cancer	Advanced or Metastatic	PFS,OS	Active, not recruiting
	PD-1 inhibitor	Muscle Invasive Bladder Cancer		EFS between groups C and B	Active, not recruiting
	PD-1 inhibitor	Urothelial Cancer	Advanced or Metastatic	ORR	Terminated
	PD-1 inhibitor	Urothelial Cancer	Advanced or Metastatic	AEs,ORR,PCR	Active, not recruiting
	PD-L1 inhibitor	Urothelial Cancer	Advanced or Metastatic	ORR,PCR	Active, not recruiting
	PD-1 inhibitor	Urothelial Cancer	Neoadjuvant	PCR	Recruiting
	PD-1 inhibitor	Malignant Solid tumors	Advanced or Metastatic	ORR	Active, not recruiting
FLOR1 (FRα)	PD-1 inhibitor	FRα positive,MSS Endometrial cancer	Recurrent or Persistent	ORR,PFS	Active, not recruiting
	PD-1 inhibitor	FRα positive Epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer	Advanced	TEAEs,ORR	Completed
TF	PD-1 inhibitor	Cervical Cancer	Recurrent or Stage IVB	DLT,ORR	Active, not recruiting
	PD-1 inhibitor	Solid tumors	Advanced or Metastatic	ORR	Active, not recruiting
B7-H3	PD-1 inhibitor	Solid tumors	Advanced or Metastatic	DLT,AEs,SAEs	Terminated
	PD-1 inhibitor	Solid tumors	Advanced	AEs,SAEs	Completed
LIV-1	PD-1 inhibitor	Triple-Negative Breast Cancer	Locally Advanced or Metastatic	ORR,DLT,AEs	Completed
	PD-L1 inhibitor	Breast Cancer	Metastatic	ORR	Recruiting
	PD-1 inhibitor	Solid tumors	Advanced	AEs,RPTD,AUC,Cmax,Tmax	Active, not recruiting
CEACAM5	PD-1 inhibitor	CEACAM5-positive Non-Small Cell Lung Cancer	Advanced or Metastatic	DLT,ORR	Terminated
	PD-1 inhibitor	CEACAM5-positive Non-Small Cell Lung Cancer	Metastatic	DLT,ORR	Terminated
Claudin18.2	PD-1 inhibitor	Solid tumors	Advanced	DLT,RP2D,OBD,MTD	Completed
	PD-1 inhibitor	Gastro-Intestinal Cancer	Advanced	PFS	Recruiting
	TIGIT inhibitor	Claudin 18.2 Positive Bile Duct Cancer	Advanced	ORR,AEs	Recruiting

HER-2

HER-2 is a key member overexpressed in a variety of cancers, including breast cancer, urothelial carcinoma [29], colorectal cancer [30], and non-small cell lung cancer [31], etc. Activated HER-2 promotes tumor growth and spread [32]. Therefore, HER-2 is a promising therapeutic target for the treatment of many HER-2-positive tumors [33, 34].

Trastuzumab emtansine (T-DM1) was the first ADC approved for solid tumors. Results from a number of

previous combination trials have shown higher objective remission rates (ORR) in PD-L1-positive patients, as well as a more significant efficacy advantage [18, 35, 36]. However, it is worth noting that T-DM1 combination immunotherapy did not show significant clinical significance in a trial in which all patients were PD-L1 negative [37].

T-DXd is currently a hot research topic for the treatment of HER-2-positive solid tumors. Several trials are exploring the feasibility and potential efficacy of combining this ADC with immunotherapy. In the breast cancer (BC) portion of the phase Ib DS8201-A-U105 trial, 45 HER-2-positive BC patients were treated with T-DXd in combination with Nivolumab. Interim analysis showed that HER-2-positive patients had an ORR of 65.6% and an mPFS of 11.6 m, while patients with low HER-2 expression had an ORR of 50.0% and an mPFS of 7.0 m. Patients with HER-2 high-expression (IHC 3 + /2 +) mUC who received the combination treatment in the uroepithelial carcinoma (UC) portion of the same trial achieved ORR of 36.7%, mPFS of 6.9 m and mOS of 11.0 m. The results demonstrated that the recommended extended dose (RDE) was well tolerated and showed significant antitumor activity in patients with HER-2-positive mBC and HER-2-overexpressing mUC who had received extensive pretreatment. This antitumor activity is consistent with previous studies of T-DXd monotherapy [38–42]. The ongoing HUDSON trial evaluated the antitumor efficacy of Durvalumab in combination with T-DXd for the treatment of patients with HER-2 overexpressing (HER-2e) or HER-2-mutant (HER-2m) NSCLC. Patients with HER-2 m demonstrated significant antitumor activity in terms of ORR (35.0% vs. 26.1%), PFS (5.7 vs 2.8 m), and OS (10.6 vs 9.5 m) were superior to HER-2e patients, suggesting that combination therapy demonstrated a trend toward more significant efficacy in HER-2m patients [43]. In addition, the DS8201-A-U106 study evaluated the anti-tumor effects of Pembrolizumab in combination with T-DXd in HER-2e and HER-2m NSCLC patients. The latest interim analysis showed that patients in both cohorts demonstrated significant antitumor activity (ORR: 54.5% vs 66.7%; mPFS: 15.1 vs 11.3 m) [44]. A comparison of the results of the HUDSON trial and the DS8201-A-U106 study reveals that the efficacy of T-DXd in combination with a PD-1 inhibitor is significantly more prominent in the same treatment population. Trials are also evaluating the efficacy of T-DXd in combination with immunotherapy (Module 1 of DESTINY-Breast07) as well as triple therapy with T-DXd, immunotherapy and chemotherapy (Module 4 of DESTINY-Breast07) in patients with HER-2-positive mBC [45]. The DESTINY-Gastric03 trial on the treatment of patients with advanced/metastatic HER-2 + esophageal, gastric or gastroesophageal junction adenocarcinoma (GEJA) is also ongoing [46].

RC48-C013, a evaluating RC48 in combination with Phase I trial for the treatment of HER-2-positive advanced gastric cancer or gastroesophageal junction (G/GEJ) and other solid tumors, achieved an ORR of 50.0% in patients receiving the recommended Phase II dose (RP2D), which was significantly higher than that of the 24.8% in patients treated with RC48 alone. Even in G/GEJ patients with low HER-2 expression, the ORR reached 46.0%. Further analysis showed that the efficacy of primary patients was superior to that of patients who had received prior anti-HER-2 therapy, with significant improvements in ORR (53% vs 43%), mPFS (6.1 vs 4.2 m) and mOS (24.7 vs 11.9 m). In addition, patients who received RP2D with PD-L1 CPS ≥ 1 demonstrated higher ORR and longer PFS and OS. This suggests that RC48 combination immunotherapy could improve the efficacy of some G/GEJ patients, which is clinically important ICIs [47, 48]. RC48-C014 is another phase Ib/II trial for la/mUC, and the most recent analysis of the data showed that, using the same treatment combination The mOS of patients was 33.1 m, mPFS was 9.3 m and ORR was as high as 73.0%, demonstrating significant efficacy and OS advantage in long-term follow-up [49].

Trop-2

In recent years, it has been found that the expression level of (Trop-2) is significantly increased in a variety of solid tumors. This upregulation not only promotes the proliferation, growth and spread of tumor cells, but is also closely associated with poorer prognosis and higher risk of metastasis human trophoblast surface antigen [50, 51].

Sacituzumab govitecan (SG) is the first Trop 2-targeted ADC. Previously treated triple-negative and hormone receptor-positive/HER-2-negative (HR + /HER-2-) mBC patients were evaluated in the Saci-IO HR + trial on SG. In PD-L1-positive (CPS ≥ 1) HR + /HER-2- patients, SG in combination with Pembrolizumab (Group A) showed superiority over single agent (Group B): median PFS was prolonged by 4.4 m (11.1 vs 6.7 m) and median OS was prolonged by 6 m (18.5 vs 12.5 m), and the experimental results were more supportive of the combination, however, the results of the trial were more favorable to the combination, however, the different PD -L1 expression tiers (CPS ≥ 1 vs CPS < 1) showed no significant difference in PFS and OS [52]. In addition, in the Morpheus-TNBC trial, SG in combination with Atezolizumab showed a trend toward benefit (12.2 vs 5.9 m) despite immature PFS data [53]. Comparison of the efficacy data in the combination therapy portion of the above two trials showed that the antitumor activity of SG combined with Atezolizumab was significantly better than that of SG combined with Pembrolizumab, with ORR of 76.7 and 21.2%, respectively. In addition, SG in combination with Atezolizumab also demonstrated superior efficacy in terms of median PFS (12.2 vs 8.4 m). The most recent data from the Phase II

Table 2 Clinical efficacy of ADCs in Combination with Immune Checkpoint Inhibitors

Target	ADC	NCT number	Phase	ICIs	whether arrived primary endpoints
HER-2	Trastuzumab emtansine	NCT02924883(KATE2)	II	Atezolizumab	Yes
		NCT03032107	Ib	Pembrolizumab	Yes
		NCT02605915	Ib	Atezolizumab	Yes
	Trastuzumab deruxtecan	NCT04379596 (DESTINY-Gastric03)	Ib/II	Durvalumab or Pembrolizumab	Yes
		NCT04042701 (DS8201-A-U106)	Ib	Pembrolizumab	Yes
		NCT03523572 (DS8201-A-U105)	Ib	Nivolumab	Yes
		NCT03334617 (HUDSON)	II	Durvalumab	Yes
	Disitamab vedotin	NCT04280341 (RC48-C013)	I	Toripalimab	Yes
		NCT04264936(RC48-C014)	Ib/II	Toripalimab	Yes
Trop2	Sacituzumab govitecan	NCT04448886 (Saci-IO HR +)	II	Pembrolizumab	Yes
		NCT03424005 (Morpheus-TNBC)	Ib/II	Atezolizumab	Yes
		NCT05186974 (EVOKE-02)	II	Pembrolizumab	Yes
	Datopotomab deruxtecan	NCT04526691(TROPION-Lung02)	Ib	Pembrolizumab	Yes
		NCT03742102(Begonia)	Ib/II	Durvalumab	Yes
	SKB264	NCT05351788	II	KL-A167	Yes
Nectin-4	Enfortumab vedotin	NCT04223856(EV-302)	III	Pembrolizumab	Yes
		NCT03288545(EV-103)	I/II	Pembrolizumab	Yes
		NCT04225117(EV-202)	II	Pembrolizumab	Yes
FLOR1 (FRα)	Mirvetuximab soravtansine	NCT03835819	II	Pembrolizumab	No
TF	Tisotumab vedotin	NCT03786081	Ib/II	Pembrolizumab	Yes
B7-H3	Enoblituzumab	NCT02475213	I	Pembrolizumab	Yes
LIV-1	Ladiratuzumab vedotin	NCT02099058	I/Ib	Nivolumab	Yes
CEACAM5	Tusamitamab ravtansine	NCT04524689 (CARMEN-LC05)	II	Pembrolizumab	Yes
Claudin18.2	LaNova Medicines-302	NCT05994001	Ib/II	Cardonilizumab	No

Target	Efficacy data				
	ORR, %	mOS, months	mPFS, months	mDOR, months	DCR(%)
HER-2	Atezolizumab:45 Placebo:43	NA	Atezolizumab:8.2 Placebo:6.8	NA	NA
	20	NA	9.6	10.1	60
	Triple:14 Duplex:35 Quadruple:100	NA	NA	NA	NA
	GroupD:58 GroupE:63 GroupF:13	NA	NA	NA	NA
	HER2 e:54.5 HER2 m:66.7	NA	HER2 e:15.1 HER2 m:11.3	HER2 e:20.2 HER2 m:15.1	NA
	mBC:HER2 + :65.6; HER2 low:50.0 mUC:HER2 high:36.7; HER2 low:NA	mBC:HER2 + :NA; HER2 low:19.5 mUC:HER2 high:11.0; HER2 low:NA	mBC:HER2 + :11.6; HER2 low:7.0 mUC:HER2 high:6.9; HER2 low:NA	mBC:HER2 + :N; HER2 low:5.5 mUC:HER2 high:13.1; HER2 low:NA	NA
	HER2 e:26.1 HER2 m:35	HER2 e:9.5 HER2 m:10.6	HER2 e:2.8 HER2 m:5.7	NA	NA
	G/GEJ:43 Other solid tumor:25	G/GEJ:16.8 Other solid tumor:10.5	G/GEJ:6.2 Other solid tumor:4.9	G/GEJ:5.1 Other solid tumor:8.2	G/GEJ:75 Other solid tumor:75
	73.2	33.1	9.3	8.6	90.2

Table 2 (continued)

Target	Efficacy data				
	ORR, %	mOS, months	mPFS, months	mDOR, months	DCR(%)
Trop2	GroupA(combination):21.2 GroupB(SG):17.3	GroupA(combination):16.9 GroupB(SG):17.1	GroupA(combination):8.4 GroupB(SG):6.2	NA	NA
	Sacituzumab govitecan + Atezolizumab:76.7 control:66.7	NA	Sacituzumab govitecan + Atezolizumab:12.2 control:6.9	Sacituzumab govitecan + Atezolizumab:14.0 control:7.1	Sacituzumab govitecan + Atezolizumab:93.3 control:100
	squamous: CohortA:73 CorhortB:54 non-squamous: CohortA:67 CorhortB:37	NA	NA	NA	squamous: CohortA:82 CorhortB:85 non-squamous: CohortA:89 CorhortB:74
	Duplex:52 Triple:56	NA	Duplex:11.1 Triple:6.8	Duplex:NA Triple:12.9	Duplex:88 Triple:89
	79	NA	13.8	15.5	NA
	1A:48.6 1B:77.6	NA	1A:15.4 1B:NA	NA	1A:94.6 1B:100
Nectin-4	29.1	31.5	12.5	NA	NA
	73.3	26.1	12.3	25.6	93.3
	23.9	6	3.9	9.4	56.5
FLOR1 (FRα)	37.5	NA	NA	NA	NA
TF	GroupE:40.6 GroupF:35.3	GroupE:NA GroupF:15.3	GroupE:5.3 GroupF:5.6	GroupE:NA GroupF:14.1	GroupE:81.3 GroupF:73.5
B7-H3	HNSCC:33.3 NSCLC:35.7 UC:5.9 Melanoma:7.7	HNSCC:17.38 NSCLC:12.32 UC:5.72 Melanoma:14.19	HNSCC:3.48 NSCLC:4.83 UC:2.18 Melanoma:2.07	NSCLC:8.3	NA
LIV-1	30.6	NA	5.9	NA	86.1
CEACAM5	52.6	NA	11.6	12.4	NA
Claudin18.2	NA	NA	NA	NA	NA

EVOKE-02 study indicate that, regardless of histologic type (squamous or non-squamous), SG in combination with Pembrolizumab demonstrated antitumor activity in untreated mNSCLC demonstrated anti-tumor activity in [54].

Datopotomab deruxtecan (Dato) is a Trop-2-targeted ADC with a topoisomerase I inhibitor as its payload. In the BEGONIA trial, patients with metastatic triple-negative breast cancer (mTNBC) who were treated with Dato in combination with durvalumab achieved an ORR of 79.0% (6 out of 62 patients) complete remission (CR), 43 partial remission (PR)) [55]. Data from another phase Ib trial of Dato in combination with Pembrolizumab (± platinum analog) for NSCLC showed durable antitumor activity in patients in any PD-L1 expression state with both double and triple therapy [56]. Another Trop-2-targeted ADC drug, SKB264, also showed promising antitumor efficacy results (ORR of 48.6%) in patients with primary advanced NSCLC [57]. Several other Phase III clinical trials of SKB264 are ongoing and data are not yet available.

Nectin-4

Enfortumab vedotin (EV), an ADC targeting Nectin-4, has been approved as a single agent for the treatment of platinum and ICIs-refractory advanced uroepithelial cancer (aUC). In the Phase III EV-302 trial, EV in combination with Pembrolizumab demonstrated significant efficacy in patients with previously untreated a/mUC, with an mPFS of 12.5 m, which was significantly better than that of the chemotherapy group at 6.3 m, and an mOS of 31.5 m, which was almost twice that of the chemotherapy group. In addition, the ORR of the combination therapy was also significantly higher than that of the chemotherapy group (67.7% vs. 44.4%), and reduced the risk of disease progression by 55% and the risk of death by 53%. These results suggest that combination therapy with EV offers significant and clinically meaningful advantages over conventional chemotherapy in the first-line treatment of a/mUC [58]. Moreover, in the phase II EV-202 study, the confirmed ORR of EV monotherapy in patients with head and neck cancer (HNC) was 23.9%, which exceeded the prespecified threshold (17.5%) and showed good anti-tumor activity. This provides a basis for evaluating EV in combination with Pembrolizumab

in patients with HNC. Another cohort of EV-202 is currently investigating EV in combination with Pembrolizumab as a first-line treatment for patients with recurrent/metastatic head and neck squamous carcinoma (R/M HNSCC) with PD-L1 CPS ≥ 1 [59].

Other new targets

Previous studies demonstrated that Mirvetuximab soravtansine (MIRV) showed well tolerability and single-agent activity in a Phase I dose extension study in patients with FRα-positive advanced or recurrent endometrial cancer (EC). A subsequent Phase II study evaluated its efficacy in combination with Pembrolizumab. Of the 16 patients treated, the ORR was 37.5%, including 1 patient got CR and 5 patients got PR. Recent findings suggest that MIRV in combination with Pembrolizumab meets the primary endpoint in the treatment of FRα-positive recurrent microsatellite-stabilized (MSS/pMMR) plasmacytoid EC, with value for further study, and studies targeting subgroups of potential benefit are also ongoing [60]. In addition, Tisotumab vedotin (TV) is a kind of ADCs that targets tissue factor (TF). In a Phase Ib/II study in recurrent/metastatic cervical cancer (r/mCC), TV demonstrated promising anti-tumor activity when used in combination with bevacizumab, Pembrolizumab, or carboplatin for first- or second- or third-line treatment. This provides support for further exploration of TV in combination with single agents. Expansion studies of TV in combination with carboplatin, Pembrolizumab, and optionally in combination with bevacizumab for first-line treatment are currently underway [61]. Finally, the regimen of Tusamitamab ravtansine (ADC targeting CEACAM5) in combination with Pembrolizumab showed positive preliminary results in a phase I b/II trial in advanced non-squamous NSCLC, with an ORR of 47.8%, an mPFS of 11.6 m, and an mDOR of 12.4 m [62]. In addition to this, there are several drugs targeting Claudin 18.2 (mainly in GI tumors) currently in clinical trials. One of these Phase Ib/II clinical trials was announced at ASCO: out of 6 patients whose efficacy could be evaluated, 3 achieved PR, so its BOR in Phase Ib was 50% [63].

Safety and re-challenge of ADCs in combination with ICIs

Drug safety and adverse reactions

Table 3 summarizes the safety data from the clinical trials in Table 2.

In non-randomized early clinical trials of T-DM1 combination immunotherapy, the most common adverse events (AEs) included fatigue, anemia, nausea, and pneumonia. In several trials, some patients experienced grade 3 or more serious adverse events such as thrombocytopenia, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), and pneumonia. Discontinuation of treatment due to adverse events was more frequent in patients receiving T-DM1 in combination with Atezolizumab than T-DM1 alone, and one death due to phagocytosis syndrome occurred in the experimental group [35]. When T-DM1 was combined with Pembrolizumab, four patients developed after cycles 2, 3, 4, and 12 of treatment with pneumonia, all of which were suspected to be ICIs-associated pneumonia and improved after receiving steroid therapy [18]. In contrast, in the randomized KATE 2 trial, despite more discontinuations due to pneumonia in the Atezolizumab group, the incidence of all grades and grade 3 or worse pneumonia was similar in both groups, suggesting that combining Atezolizumab does not significantly increase the risk of pneumonia [35].

Several trials have shown that patients treated with T-DXd combination immunotherapy are more likely to experience serious adverse events (SAEs) compared to single-agent T-DXd. Preliminary results from the DESTINY-Gastric03 trial showed a higher incidence of Grade ≥ 3 AEs with triple therapy with T-DXd (91%) than with two-agent therapy (81%) and single-agent therapy (64%) [46]. In the mBC and mUC modules of the DS8201-A-U105 trial, the most common treatment-related adverse events (TEAEs) were nausea, fatigue, and vomiting. Compared to patients with low HER-2 expression, HER-2-positive patients had a higher incidence and severity of AEs, particularly interstitial lung disease (ILD)/pneumonia, with some patients experiencing grade 5 ILD/pneumonia, leading to discontinuation or death [38–42]. A similar situation was observed in the phase Ib trial in combination with Pembrolizumab and in the HUDSON trial. In that trial, pneumonia was the most common grade ≥ 3 AE. Management of ILD/pneumonia consisted mainly of drug discontinuation and steroid therapy, with some patients improving with treatment [43].

In the two trials testing Dato, stomatitis and nausea were the most common TEAEs, with higher rates of nausea especially in two- or three-drug combinations. The incidence of stomatitis was 57.0% in the TROPION-Lung02 trial compared with 65.0% in the Begonia trial, both of which were predominantly grade 1–2 adverse events [55, 56].

Finally, in the Enfortumab vedotin in combination with Pembrolizumab trial, peripheral sensory neuropathy (PN) was the most common TEAE, mostly mild to moderate. In contrast, in the EV-103 trial, peripheral neuropathy and skin reactions were grade ≥ 3 AEs requiring special attention [58, 64].

Table 3 Safety of Trials of ADCs in Combination with Immune Checkpoint Inhibitors

Target	ADC	NCT number	Phase	ICI	Safety
HER-2	Trastuzumab emtansine	NCT02924883(KATE2)	II	Atezolizumab	Grade ≥ 3 AEs:thrombocytopenia, increased aspartate aminotransferase, anemia, neutropenia and increased alanine aminotransferase
		NCT03032107	Ib	Pembrolizumab	All-Grade AEs:fatigue, anemia, elevated aspartate aminotransferase, constipation, nausea, and pneumonitis Any Grade 3:fatigue, elevated aspartate aminotransferase, elevated alanine aminotransferase, pneumonitis, lung infection, oral mucositis, and vomiting
		NCT02605915	Ib	Atezolizumab	The most common AEs: fatigue, diarrhea, and nausea
	Trastuzumab deruxtecan	NCT04379596 (DESTINY-Gastric03)	Ib/II	Durvalumab or Pembrolizumab	ILD/pneumonitis: GroupD:8 patients; GroupE:5 patients; Grade ≥ 3 AEs: GroupD:91%; GroupE: 81%; GroupF: 28%;
		NCT04042701(DS8201-A-U106)	Ib	Pembrolizumab	ILD/pneumonitis:11 patients Grade ≥ 3 TEAEs:38.2% Any TEAEs:94.5%
		NCT03523572(DS8201-A-U105)	Ib	Nivolumab	mBC:HER2 + :Grade ≥ 3 TEAEs: nausea,fatigue and constipation HER2-low:Grade ≥ 3 TEAEs:nausea,vomiting and anemia mUC:HER2-high:nausea, fatigue and vomiting HER2-low:nausea and fatigue TEAEs leading to discontinuation:ILD/ pneumonitis
		NCT03334617(HUDSON)	II	Durvalumab	Grade ≥ 3 TEAEs:pneumonitis,pulmonary embolism,anemia
	Disitamab vedotin	NCT04280341 (RC48-C013)	I	Toripalimab	Any TRAEs:a decreased white blood cell count,a decreased neutrophil count,asthenia,an increased AST level,and an increased ALT level Grade ≥ 3 TRAEs:a decreased neutrophil count and a decreased white blood cell count
		NCT04264936(RC48-C014)	Ib/II	Toripalimab	Grade ≥ 3 TRAEs:gamma-glutamyltransferase increased, asthenia,hypertriglyceridaemi a,and alanine aminotransferase increased,blood glucose increased,pneumonitis,aspartate aminotransferase increased,blood creatine phosphokinase increased,and neutropenia

Table 3 (continued)

Target	ADC	NCT number	Phase	ICI	Safety
Trop2	Sacituzumab govitecan	NCT04448886(Saci-IO HR +)	II	Pembrolizumab	Grade ≥ 2 AEs: GroupA:neutropenia,fatigue,alopecia,anemia,leukopenia,,diarrhea and nausea GroupB:neutropenia,alopecia,diarrhea,nausea,fatigue and anemia
		NCT03424005 (Morpheus-TNBC)	Ib/II	Atezolizumab	Grade 3–4 AEs: Sacituzumab govitecan + Atezolizumab:70% control:44.4% SAEs: Sacituzumab govitecan + Atezolizumab:23.3% control:44.4%
		NCT05186974(EVOKE-02)	II	Pembrolizumab	Grade ≥ 3 TEAEs:70%
	Datopotomab deruxtecan	NCT04526691 (TROPION-Lung02)	Ib	Pembrolizumab	All grade TEAE:stomatitis and nausea Grade ≥ 3 TEAEs:Duplex:57%,Triple:76%
		NCT03742102 (Begonia)	Ib/II	Durvalumab	The most common AEs:Nausea and stomatitis Grade 3–4 AEs:57% SAEs:23%
	SKB264	NCT05351788	II	KL-A167	Grade ≥ 3 TRAEs:neutrophil count decreased, white blood cell count decreased, anemia, rash and drug eruption
Nectin-4	Enfortumab vedotin	NCT04223856 (EV-302)	III	Pembrolizumab	Any Grade AEs:peripheral sensory neuropathy, pruritus,and alopecia; Grade ≥ 3 TRAEs:maculopapular rash, hyperglycemia,and neutropenia
		NCT03288545 (EV-103)	I/II	Pembrolizumab	The most common TRAEs:peripheral sensory neuropathy, fatigue, and alopecia Grade ≥ 3 TRAEs:asymptomatic lipase elevation, fatigue, and maculopapular rash
		NCT04225117(EV-202)	II	Pembrolizumab	The most common TRAEs:alopecia, fatigue, and peripheral sensory neuropathy Grade ≥ 3 TRAEs:anemia and decreased neutrophil count
FLOR1 (FRα)	Mirvetuximab soravtansine	NCT03835819	II	Pembrolizumab	The most common TRAEs:AST elevation, blurred vision, fatigue and diarrhea
TF	Tisotumab vedotin	NCT03786081	Ib/II	Pembrolizumab	Grade ≥ 3 TRAEs: GroupE:anemia,asthenia,hypokalemia,acute kidney injury GroupF:anemia,intetinal obstruction,weight decreased,acute kidney injury
B7-H3	Enoblituzumab	NCT02475213	I	Pembrolizumab	The most common TRAEs:infusion-related reactions (IRRs),fatigue Grade ≥ 3 TRAEs:IRRs,increased lipase

Table 3 (continued)

Target	ADC	NCT number	Phase	ICI	Safety
LIV-1	Ladiratuzumab vedotin	NCT02099058	I/Ib	Nivolumab	Any Grade AEs: peripheral sensory neuropathy, dermatitis acneiform, diarrhea,and hypoalbuminemia Grade ≥ 3 AEs:were pulmonary embolism (PE), hypokalemia,and diarrhea, malignant neoplasm progression, peripheral sensory neuropathy, and hypophosphatemia Grade ≥ 3 TRAEs:hypophosphatemia and peripheral sensory neuropathy
CEACAM5	Tusamitamab ravtansine	NCT04524689(CARMEN-LC05)	II	Pembrolizumab	SAE:36.8% Grade ≥ 3 TEAEs:64.9%
Claudin18.2	LaNova Medicines-302	NCT05994001	Ib/II	Cardonilizumab	The most common TRAEs:bilirubin increase, thrombocytopenia, neutropenia, infusion reactions (rash), leukopenia (42.9%), anemia

Re-challenge

Serious drug-related adverse reactions are a common reason for discontinuation during oncology treatment. However, most adverse reactions are usually mild and reversible, and can be alleviated by symptomatic treatment and return to normal function after discontinuation. When adverse reactions are effectively controlled, patients can continue their original treatment regimen or make dose adjustments as clinically indicated. This restarting of the original regimen after discontinuation is known as "rechallenge."

ILD/pneumonia is a common discontinuation-related adverse event in many cancer therapies, and ADCs are no exception. In the DESTINY clinical program, T-DXd demonstrated an overall manageable safety profile, with hematologic and gastrointestinal AEs being the most common, but ILD/pneumonia being the AE of particular concern [65–69]. Grade 2 or higher ILD/pneumonia requiring permanent discontinuation of the drug and treatment with high-dose steroids. The 2024 ESMO Congress reported a retrospective analysis of T-DXd retreatment, with data from nine clinical trials covering patients with HER-2-altered breast, gastric, colorectal, and non-small-cell lung cancers who had received at least one dose of T-DXd. Of the 2,145 patients 193 developed grade 1 ILD, of which 97 were relieved by hormone therapy and 45 patients were re-treated with T-DXd after recovery. And of these 45 patients, 15 patients had recurrent ILD due to the rechallenge dose being consistent with the original dose (both grade 1 and 2). Of all the patients with recurrent ILD, only eight recovered completely. In addition, two patients were retreated before they had fully recovered from grade 1 ILD, resulting in progression of ILD to grades 2 and 3, respectively [70].

In addition, there is a case report describing a patient who underwent T-DXd rechallenge after failure of multiple lines of therapy. The patient was diagnosed with grade 3 ILD after two cycles of therapy and was treated with steroids and antibiotics. After symptoms resolved and returned to grade 1 ILD, the patient underwent T-Dxd rechallenge, but at a reduced dose, while maintaining low-dose steroid therapy. During the rechallenge period, the patient efficacy reached PR and no exacerbation or recurrence of ILD was observed [71]. In addition, in the phase 1b trial of T-DM1 in combination with Pembrolizumab, four patients with suspected ICIs-associated pneumonia improved after steroid treatment. Three of these patients permanently discontinued Pembrolizumab but continued to use T-DM1 and no significant increase in pulmonary abnormalities was observed [18].

ADCs development and future prospects

In recent years, the rapid development of ADCs has opened up new avenues for tumor therapy. Classical ADCs targets (e.g., HER-2, CD30, and CD79b) have achieved remarkable results in the treatment of a variety of tumors. However, the problems of drug resistance and heterogeneity of these traditional targets have gradually emerged [72, 73]. And tumor resistance is usually associated with downregulation of the expression of therapeutic targets or off-target effects. For this reason, researchers have used combination target strategies or target epitope optimization to enhance tumor efficacy and delay the onset of drug resistance.

Antibody and target selection

The ideal backbone for constructing ADCs is the ability to recognize antigens that are specifically expressed only on the surface of cancer cells and are completely absent from noncancerous tissues, thus enabling tumor-specific payload delivery. However, most ADCs targets (e.g., HER-2 and TROP-2) are also expressed to some extent in noncancerous tissues, which may lead to the development of target-dependent and non-dependent toxicity. To enhance tumor specificity, antibodies that recognize tumor-specific antigens with structural variants such as truncation, cleavage or post-translational modifications are being explored [73–75]. Among them, bispecific ADCs can significantly improve payload delivery and cytotoxicity by combining antibodies to both targets and conventional payloads. In addition, nano-antibody–drug couplings (NDCs) developed to address the permeability problem caused by the oversized molecules of conventional ADCs have demonstrated enhanced permeability and anticancer potential in solid tumors [76]. Some ADCs can also effectively address the problem of epigenetic heterogeneity by stimulating antitumor activity against cancer cells surrounding target antigen-expressing cells through a bystander effect. Several studies have shown that cleavable junctions and hydrophobic payloads are key to the realization of the bystander effect, which will be an important direction for the development of novel ADCs [77, 78].

Linker optimization

Linkers are important components of ADCs, which play a key role in ADCs stability, efficacy, and safety by covalently linking monoclonal antibodies to cytotoxic payloads [79, 80]. Two main types of linkers exist: cleavable and non-cleavable linkers, while cleavable linkers include chemically unstable and enzyme-sensitive linkers. Among them, chemically unstable linkers can undergo cleavage in the acidic environment of tumors to release drugs efficiently, but their stability in the blood circulation is relatively poor, which usually leads to premature drug delivery [73, 81, 82]. The emergence of enzyme-sensitive linkers has solved this problem by improving stability and delivery efficiency through specific cleavage using specific enzymes overexpressed in tumors [83, 84]. Non-cleavable linkers release the drug by enzymatic complete degradation within the lysosome, which has the advantage of high stability and low off-target toxicity, but their low release efficiency and inability to produce a bystander effect need to be optimized by optimizing the payload structure to improve the efficacy [85].

Payload optimization

Payloads improvement is a key component in the ADCs optimization process. Traditional payloads, such as microtubule inhibitors and DNA-targeting agents, have faced challenges due to their toxicity and dose limitations [76, 86]. In recent years, the successful application of topoisomerase I inhibitors as novel payloads has significantly enhanced the efficacy of ADCs including T-Dxd and SG, which achieve higher efficacy through a high drug-antibody ratio (DAR) [87–89]. Meanwhile, the introduction of low-toxicity molecules and improvements in linker technology have enhanced the stability and therapeutic window of ADCs [86]. In addition, to meet the need for tumor specificity and high potency, the selection of payloads usually favors molecules with efficient activity that can act at low concentrations, usually with IC50 values in the nanomolar to picomolar range [90].

The therapeutic regimen of ADCs in combination with ICIs has shown a remarkable trend in solid tumor treatment in recent years. This combination therapy has shown promising results in several solid tumor types (e.g., NSCLC, BC, gastric cancer, etc.), especially in refractory tumors and tumors with high immune tolerance, where the combination therapy has demonstrated enhanced anti-tumor activity. However, there are still some limitations that need to be addressed in order to achieve optimal results. Although preclinical and early clinical data suggest significant synergistic effects of this combination therapy, particularly in reducing tumor growth and enhancing immune response, the issue of drug resistance remains. Although some early clinical trials have demonstrated the potential of combination therapy with ADCs and ICIs in cancers such as HER-2-positive breast cancer and non-small-cell lung cancer, the inconsistency of effects between different tumor types, as well as the potential for serious adverse events, highlight the need for further optimization of treatment regimens. Future studies should focus on optimizing dosing regimens, selecting appropriate biomarkers, and exploring the safety of these combination therapies in a broader patient population to ensure more sustainable and effective treatment options.

Conclusion

In summary, the combination of ADC and immunotherapy demonstrates significant synergistic potential, not only directly killing tumor cells through targeted delivery of cytotoxic drugs, but also inducing ICD and enhancing immune responses in the tumor microenvironment. Both preclinical and clinical studies have demonstrated that this synergistic effect helps to overcome tumor heterogeneity, reduce treatment resistance and improve patient prognosis

[91]. Early clinical trials have shown that this combination strategy has demonstrated excellent anti-tumor activity and overall manageable toxicity in a variety of solid tumors. However, there is still a need to be vigilant about possible overlapping toxicity issues and to enhance monitoring of treatment safety and long-term outcomes. As relevant data are currently limited, support for optimizing clinical practice and improving patient care through continued pharmacovigilance and the accumulation of real-world evidence is still needed. In conclusion, the combination of ADCs and immunotherapy provides an exciting new direction for cancer treatment and is expected to become an important component of individualized therapy and drive overall progress in the treatment of refractory cancers (Figs. 1 and 2).

Author contributions Conceptualization and design: WANG A, LI T, and LV YH; data collection and analysis: WANG A, LIU C, and CUI XR; manuscript drafting: LI T, WANG A and ZHOU X; critical revision of the article for important intellectual content: WANG T and ZHANG F; study supervision: HU Y and LIU ZF. All authors have approved the final version of the article.

Funding This review article did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability All data generated or analyzed during this study are included in this published article. Data are available upon reasonable request. The data supporting this study's findings are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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