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EDITORIAL

Advances in antibody-drug conjugates for urothelial carcinoma treatment

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Urothelial carcinoma (UC) is the 9th most common and the 13th most deadly cancer worldwide[1]. Despite the availability of platinum-based chemotherapy and immune checkpoint inhibitors (ICIs), the 5-year survival rate of patients with metastatic UC (mUC) remains poor (10–15%)[2]. Antibody-drug conjugates (ADCs), which combine tumor-specific monoclonal antibodies with cytotoxic agents, have emerged as a promising breakthrough. By targeting cancer cells and sparing healthy tissues, ADCs can overcome the key limitations of conventional treatments. Since the U.S. food & drug administration (FDA) approved the first ADC for solid tumors, trastuzumab emtansine (T-DM1), for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer in 2013, ADCs have significantly improved patient outcomes in various cancers. However, subsequent basket studies evaluating T-DM1 in advanced solid tumors have not demonstrated its clinical benefits in mUC[3]. The recent success of enfortumab vedotin (EV), both as a monotherapy for previously treating mUC and in combination with pembrolizumab as a first-line treatment, has reinvigorated the exploration of ADCs in UC, and further breakthroughs are anticipated. Herein, we explore the evolving role of ADCs in UC, focusing on the current therapeutic landscape, persistent clinical challenges, and promising future developments.

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Current ADCs in UC

Nectin-4-targeted ADCs

EV

Nectin-4, which is overexpressed in various cancers including UC, is targeted by EV, an anti-Nectin-4 ADC comprising a human IgG1 antibody linked to monomethyl auristatin E (MMAE) *via* a protease-cleavable linker[4]. MMAE is a potent microtubule-disrupting agent that, after internalization and payload release within tumor cells, inhibits cell division and induces apoptosis. EV has markedly reshaped the mUC treatment landscape (**Table 1**).

In December 2019, the FDA granted accelerated approval for EV as the first ADC for locally advanced or metastatic UC (la/mUC), on the basis of the phase II EV-201 trial (NCT03219333). In platinum- and ICI-pretreated patients (cohort 1, n = 125), the objective response rate (ORR) was 44%, and the complete response (CR) rate was 12%, whereas in cisplatin-ineligible patients (cohort 2, n = 89), the ORR was 52%, and the CR was 20%[4]. Before EV-201, single-agent chemotherapy was the standard third-line treatment; however, it resulted in poor outcomes. Despite comorbidities (12% Eastern Cooperative Oncology Group Performance Status 2, 13% hearing loss, and 69% creatinine clearance < 60 mL/min), EV-201 showed the highest ORR among monotherapy trials for locally advanced/metastatic UC (la/mUC).

The phase III EV-301 trial (NCT03474107) led to full FDA approval in 2021. EV, compared with chemotherapy, significantly increased overall survival (OS) (median 12.9 *vs.* 8.9 months; hazard ratio 0.70, P = 0.00015) and progression-free survival (PFS). The ORRs were 41.3% for EV and 18.6% for

Table 1 Trials of ADC in la/mUC

Drug	Target antigen	Payload	Study	Phase	Population	*n*	ORR	mPFS (mo)	mOS (mo)	Intervention	Ref.
EV	Nectin-4	MMAE	EV-101	I	Patients with Nectin-4-expressing mUC whose disease progressed on ≥1 chemotherapy and/or PD-1/PD-L1 inhibitors	112	43%	5.4	12.3	EV	[5]
			EV-201	II	Cohort 1: cisplatin-eligible patients progressing after both platinum-based chemotherapy and PD-1/PD-L1 inhibitors	125	44%	5.8	11.7	EV	[4]
					Cohort 2: cisplatin-ineligible patients progressing after prior PD-1/PD-L1 inhibitors	89	52%	5.8	14.7	EV	
			EV-301	III	Patients with la/mUC after disease progression with platinum and PD-1/PD-L1 inhibitors	301	41.3%	5.55	12.91	EV	[6]
			EV-103	Ib/II	Cohort K: cisplatin-ineligible patients with previously untreated la/mUC	77 (EV+P)	64.5%	NR	22.3	EV+P	[7]
						74 (EV)	45.2%	8.0	21.7	EV	
			EV-302	III	Previously untreated patients with mUC	442	67.5%	12.5	33.8	EV+P	[8]
9MW2821	Nectin-4	MMAE	9MW2821-2021-CP102	I/II	Patients with mUC	37	62.2%	8.8	NR	9MW2821	[9]
SHR-A2102	Nectin-4	Topo1i	SHR-A2102-I-101	I	Patients with mUC	31 (6 mg/kg)	32.3%	5.8	UN	SHR-A2102	[10]
SG	TROP-2	SN38	IMMU-132-01	I/II	Patients with previously treated mUC	45	28.9%	6.8	16.8	SG	[11]
			TROPHY-U-01	II	Cohort 1: patients who progressed after prior treatment with ICIs and platinum-based chemotherapy	113	28%	5.4	10.9	SG	[12]
					Cohort 2: cisplatin-ineligible patients whose disease progressed after ICIs	38	32%	5.6	13.5	SG	
					Cohort 3: patients whose disease progressed after platinum-based chemotherapy	41	41%	5.3	12.7	SG	
			TROPiCS-04	III	Patients with mUC who progressed on prior platinum-based chemotherapy and ICIs	355	23%	4.2	10.3	SG	[13]
Dato-DXd	TROP-2	DXd (Topo1i)	TROPION-PanTumor01	I	Patients with mUC treated with ≥1 prior line of therapy	40	25.0%	6.9	UN	Dato-DXd	[14]
Sac-TMT	TROP-2	KL610023 (Topo1i)	MK-2870-001	I/II	Patients with mUC treated with ≥1 prior line of therapy	11 (Sac-TMT as 2L)	45.5%	5.78	NR	Sac-TMT	[15]
						38 (Sac-TMT as 3+L)	26.3%	5.03	11.5	Sac-TMT	

Table 1 Continued

Drug	Target antigen	Payload	Study	Phase	Population	*n*	ORR	mPFS (mo)	mOS (mo)	Intervention	Ref.
DV	HER2	MMAE	RC48-C005/ C009	Ⅱ	Patients with HER2-positive unresectable, la/ mUC in whom previous chemotherapy failed	107	50.5%	5.9	14.2	DV	16
			RC48-C011	Ⅱ	HER2-negative patients with la/mUC treated with ≥1 prior systemic treatment	19	26.3%	5.5	16.4	DV	17
			RC48-C014	Ib/II	Patients with untreated or chemo-refractory la/mUC	41	73.2%	9.3	33.1	DV+toripalimab	18
MRG002	HER2	MMAE	MRG002-006	Ⅱ	Patients with la/mUC with HER2 IHC 2 + or 3 + UC who previously received ≥ 1 standard treatment	43	53.0%	7.0	14.9	MRG002	19
T-DXd	HER2	DX-8951f (Topo1i)	DESTINY-PanTumor01	Ⅱ	Patients with HER2-mutated mUC whose disease progressed after prior therapy or lacked satisfactory alternatives	40	27.5%	6.9	NR	T-DXd	20
			DESTINY-PanTumor02	Ⅱ	Pretreated patients with HER2-expressing mUC	41	39%	7.0	12.8	T-DXd	21
Sirtratumab vedotin	SLITRK6	MMAE	AGS15E-13-1	I	Patients with la/mUC	14 (dose at RP2D)	35.7%	4.0	UN	Sirtratumab vedotin	22
						93 (overall population)	18.3%	4.0	UN	Sirtratumab vedotin	
						33 (previously treated with ICIs)	27.3%	5.0	UN	Sirtratumab vedotin	
Tisotumab vedotin	Tissue factor	MMAE	InnovaTV 201	I/II	Pretreated patients with mUC	15	26.7%	UN	UN	Tisotumab vedotin	23
EV+SG	EV: Nectin-4; SG: TROP-2	EV: MMAE; SG: SN38	DAD	I	Patients with mUC whose disease progressed after platinum-based chemotherapy and/or immunotherapy	24	70%	NR	NR	EV+SG	24

ADCs, antibody-drug conjugates; Dato-DXd, datopotamab deruxtecan; DV, disitamab vedotin; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; la/mUC, locally advanced/metastatic urothelial carcinoma; mo, month; MMAE, monomethyl auristatin E; mOS, median overall survival; mPFS, median progression-free survival; mUC, metastatic urothelial carcinoma; NR, not reached; ORR, objective response rate; P, pembrolizumab; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; ref, reference; RP2D, recommended phase II dose; Sac-TMT, sacituzumab tirumotecan; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; Topo1i, topoisomerase I inhibitor; UN, unknown.

chemotherapy. All-grade and grade ≥3 treatment-related adverse events (TRAEs) were similar between groups, although EV was associated with distinct toxicities, including alopecia (45.6%), peripheral sensory neuropathy (34.8%), pruritus (32.4%), and fatigue (31.4%), and the most common grade ≥3 events were maculopapular rash (7.4%) and fatigue (6.8%)[6]. Notably, EV carries risks of severe and occasionally fatal skin-associated TRAEs, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

In 2023, on the basis of EV-103 cohort K (NCT03288545), the FDA granted accelerated approval for EV plus pembrolizumab (EV+P) in cisplatin-ineligible patients[7]. The confirmatory phase III EV-302 trial (NCT04223856) demonstrated that EV+P, compared with chemotherapy, significantly increased OS (33.8 *vs.* 15.9 months; hazard ratio 0.51, $P < 0.00001$) and PFS. The benefits were consistent across cisplatin-eligible and cisplatin-ineligible patients, and in subgroups with visceral or lymph node metastases. The ORRs were 67.5% and 44.2%, and the CR rates were 30.4% and 14.5%, respectively. EV+P was well tolerated, with peripheral sensory neuropathy (50%), pruritus (39.8%), and alopecia (33.2%) as the most common TRAEs, whereas chemotherapy was most frequently associated with anemia and neutropenia. Grade ≥3 AEs occurred in 55.9% of the EV+P group and 69.5% of the chemotherapy group[8]. EV+P demonstrated remarkable efficacy: with respect to chemotherapy, this treatment achieved a doubled OS and the highest ORR, with a manageable safety profile. On the basis of these results, the FDA granted full approval in 2023 for EV+P as a first-line therapy for la/mUC, and this treatment was rapidly integrated into clinical practice.

SHR-A2102

SHR-A2102 is a novel Nectin-4-targeted ADC composed of a fully human IgG1 antibody, a cleavable linker, and a topoisomerase I inhibitor. In a phase I trial (NCT05735275) in 81 patients with la/mUC, 57.5% had received ≥2 prior systemic therapies, and 42.5% had prior exposure to disitamab vedotin (DV), a HER2-directed ADC delivering MMAE. On the basis of safety, 6 mg/kg and 8 mg/kg were selected for dose expansion. The ORR was 38.3%, and the response was greater at 8 mg/kg (50.0%) than 6 mg/kg (41.9%). The mPFS was 5.8 months. These findings suggested that SHR-A2102 induced rapid tumor regression with durable responses. Notably, SHR-A2102 demonstrated activity (ORR, 36.1%) in patients previously treated with DV, an ADC with a distinct target and payload, thereby suggesting limited cross-resistance. In the 6 mg/kg cohort, the ORR reached 54.5%, thereby exceeding the 41.3% reported in the critical EV-301 trial, whereas the 8 mg/kg group achieved an ORR of 42.9%. In terms of safety, grade ≥3 TRAEs occurred in 44.4% of patients overall, primarily anemia (23.3%) and neutropenia (19.2%); the incidence was lower in the 6 mg/kg cohort (38.7%). On the basis of its efficacy and safety, the lower dose of 6 mg/kg Q3W was selected as the recommended dose, because of its favorable safety profile[10]. Given its encouraging activity and manageable safety profile in heavily pretreated patients, SHR-A2102 was granted a Breakthrough Therapy Designation by the Center for Drug Evaluation of National Medical Products Administration (China) in December 2024.

Nectin-4 remains a well-validated and highly effective target in UCs. EV has been established as a standard of care across both pretreated and cisplatin-ineligible populations, because of its consistent clinical benefits and broad regulatory endorsement. SHR-A2102, a topoisomerase I-based ADC, has promising activity, even after prior ADC exposure, and therefore has potential for sequential use. Early clinical data on other Nectin-4 ADCs, such as 9MW2821, have been promising (**Table 1**), thus reinforcing the clinical relevance of this target class. Ongoing studies are essential to define the optimal agent selection, sequencing, and combination strategies.

HER2-targeted ADCs

Disitamab vedotin

HER2 is a growth-promoting tyrosine kinase receptor involved in cell proliferation and tumorigenesis[25]. UC is the third most common HER2-expressing malignancy after breast and gastric cancers, and the presence of HER2 overexpression in approximately 10–30% of bladder cancers highlights its potential as a therapeutic target. DV, a HER2-targeted ADC composed of hertuzumab associated with MMAE, has shown robust preliminary activity in UC (**Table 1**)[25].

The phase II RC48-C005/C009 study (NCT03507166/NCT03809013) enrolled 107 previously treated patients with mUC expressing HER2 immunohistochemistry (IHC) 2+ or 3+, and reported an ORR of 50.5%, mPFS of 5.9 months, and mOS of 14.2 months. Patients with high HER2 expression (IHC 3+ or IHC 2+/FISH-positive) achieved an ORR of 62.2%. The common TRAEs included peripheral sensory neuropathy (68.2%), leukopenia (50.5%), and neutropenia (42.1%). Although approximately 50% of patients had upper tract UC carcinoma, the outcomes were comparable between

upper tract UC and urothelial bladder carcinoma, including similar ORR (50.0%), mPFS (5.3 months *vs.* 6.2 months), and mOS (14.9 months *vs.* 15.2 months). Further analysis revealed an ORR of 39.6% in HER2 IHC 2+/FISH-negative tumors, thereby indicating activity even in low HER2-expressing disease[16]. Subsequently, the RC48-C011 study (NCT04073602) evaluated DV monotherapy in patients with mUC and HER2 IHC 0 or 1+. Among the 19 patients, the ORR was 26.3%, and the mPFS and mOS were 5.5 months and 16.4 months, respectively. All 6 patients with IHC 0 achieved stable disease, whereas the ORR in patients with IHC 1+ was 38.5%. This activity in low HER2-expressing tumors might be attributable to the bystander effect of MMAE, high antibody affinity, and intratumoral HER2 heterogeneity. These findings led to the FDA's granting of a breakthrough therapy designation to DV for HER2-overexpressing UC in September 2020.

DV was also evaluated in a phase Ib/II trial (RC48-C014, NCT04264936) in combination with toripalimab, in which an ORR of 73.2%, mPFS of 9.3 months, and mOS of 33.1 months were achieved in 41 patients with mUC. Moreover, HER2 overexpression (IHC 2+ or 3+) was observed in 58.5% of patients. Subgroup analyses showed consistent efficacy across treatment history (ORR: 76.0% in untreated patients *vs.* 68.8% in chemo-refractory patients) and HER2 expression levels (ORR: 80.0%, 84.2%, 64.3%, and 33.3% for IHC 3+, 2+, 1+, and 0, respectively). The most common TRAEs were elevated liver enzymes and peripheral sensory neuropathy, and grade ≥3 TRAEs occurred in 51.2% of patients[18]. Overall, DV plus toripalimab demonstrated an ORR and OS comparable to those of EV+P in EV-302 and a manageable safety profile. An ongoing phase III trial (RC48-C016, NCT05302284) is comparing DV plus toripalimab with chemotherapy in patients with untreated HER2-expressing la/mUC. If positive, the results could establish a stronger evidence base to inform clinical decision-making.

Trastuzumab deruxtecan (T-DXd, DS-8201)

T-DXd is an anti-HER2 ADC composed of a trastuzumab-derived antibody, cleavable linker, and topoisomerase I inhibitor DX-8951f. DX-8951f induces DNA damage by interfering with DNA replication and transcription, thus leading to tumor cell apoptosis. T-DXd has been approved for the treatment of metastatic HER2-positive (IHC 3+ or ISH-positive) or HER2-low (IHC 1+ or IHC 2+/ISH-negative) breast cancer, HER2-positive gastric cancer, HER2-mutant non-small cell lung cancer, and HER2-overexpressing solid tumors. However, its role in UC remains unclear. The DESTINY-PanTumor01 trial (NCT04639219), a phase II basket study, evaluated T-DXd in HER2-mutant solid tumors. Among the 7 patients with mUC, 2 achieved partial response. The DESTINY-PanTumor02 study (NCT04482309) evaluated the efficacy and safety of T-DXd in previously treated patients with HER2-expressing (IHC 2+/3+) solid tumors. Among the 41 patients with mUC, T-DXd demonstrated an ORR of 39% overall, with a higher ORR of 56.3% observed in patients with HER2 IHC 3+ tumors. The mPFS and mOS were 7.0 months and 12.8 months, respectively. The patient safety profile was manageable[21]. These results suggest that T-DXd might offer a promising treatment option for patients previously treated for HER2-mutant or HER2-overexpressing la/mUC. Confirmatory data will be critical to define the optimal role of this therapy in this population. On the basis of these findings, T-DXd received accelerated FDA approval for metastatic HER2-overexpressing tumors in April 2024.

Collectively, DV and T-DXd are the leading HER2-directed ADCs under clinical evaluation for UC. DV has shown high response rates both as a monotherapy and in combination with ICIs, and its activity extends to tumors with low HER2 expression. Building on its success in breast and gastric cancers, T-DXd has demonstrated meaningful activity in IHC 3+ UC. Agents such as MRG002 are under investigation but have shown early signals of efficacy and tolerability. Further studies are needed to clarify their roles in HER2-expressing UC and to inform treatment sequencing (**Table 1**).

TROP-2-targeted ADCs

Sacituzumab govitecan (SG)

SG is a humanized IgG1 antibody targeting trophoblast cell-surface antigen 2 (TROP-2), conjugated *via* a cleavable linker to SN-38, a topoisomerase I inhibitor. Its mechanism is similar to that of DX-8951f described above. TROP-2 is overexpressed in several epithelial cancers, including breast cancer, and is involved in cell migration and growth[26]. SG was initially approved for the treatment of triple-negative breast cancer but has demonstrated activity against UC. The phase II TROPHY-U-01 study (NCT03547973) has reported an ORR of 28%, mPFS of 5.4 months, and mOS of 10.9 months after prior ICI and platinum therapy. Key grade ≥3 TRAEs included neutropenia (35%) and anemia (14%). Subsequent cohorts showed ORRs of 32% and 41% in the cisplatin-ineligible and pembrolizumab combination settings, respectively[12]. On the

basis of these results, SG received accelerated FDA approval in April 2021 for previously treated mUC. However, the phase III TROPiCS-04 trial (NCT04527991) did not meet its primary endpoint (mOS, 10.3 months with SG *vs.* 9.0 months with chemotherapy; HR, 0.86; $P = 0.087$), although SG achieved a higher ORR (23% with SG *vs.* 14% with chemotherapy). Several factors might have contributed to the negative outcome, including the lack of mandatory granulocyte colony-stimulating factor prophylaxis, which led to a high rate of neutropenia (56%), as well as the inclusion of heavily pretreated patients with substantial comorbidities[13]. These safety issues might have decreased treatment adherence or led to early discontinuation. Although SG did not demonstrate an OS benefit over chemotherapy, the higher ORR with SG (23% *vs.* 14% with chemotherapy) consistent with the TROPHY-U-01 findings suggested retained antitumor activity. These findings underscore the importance of patient selection, supportive care, and biomarker development in future ADC trials for UC. The FDA subsequently withdrew approval for SG for mUC.

Sacituzumab tirumotecan (Sac-TMT)

Sac-TMT, a TROP-2-targeted ADC carrying KL610023, a topoisomerase I inhibitor payload, has shown efficacy in triple-negative breast cancer and advanced non-small cell lung cancer. In a phase I/II MK-2870-001 study (NCT04152499), Sac-TMT monotherapy was evaluated in patients with la/mUC who had progressed during or after prior anticancer therapy (cohort 9). The ORR was 45.5% in the second-line setting and 26.3% in the later-line setting, the mPFS was 5.78 and 5.03 months, respectively, and the mOS was not reached and 11.5 months, respectively. Grade ≥3 TRAEs occurred in 59.2% of patients, and primarily comprised anemia (38.8%) and neutropenia (28.6%)[15]. Sac-TMT maintained a relatively high ORR and favorable safety profile in the later-line treatment setting. The ongoing KEYMAKER-U04 trial (NCT06483334) is evaluating Sac-TMT combined with EV, with or without pembrolizumab, in previously treated or treatment-naïve patients with mUC.

Currently, SG and Sac-TMT are the most clinically advanced TROP-2-targeted ADCs for UC. SG initially gained accelerated approval on the basis of early phase activity; however, its withdrawal after a negative phase III result highlights the challenges in translating response into survival benefits. Sac-TMT, which demonstrated encouraging results in later-line settings, is under active evaluation and includes novel combinations. Dato-DXd, which remains under investigation, has shown early signs of activity and is currently being studied in tumor-agnostic trials. Further studies are required to determine whether TROP-2 ADCs can be refined to achieve broader and more durable benefits in patients with mUC (**Table 1**).

Bispecific ADC

BL-B01D1

Epidermal growth factor receptor (EGFR, also known as ERBB1 or HER1) and human epidermal growth factor receptor 3 (HER3, also known as ERBB3) are ERBB-family receptor tyrosine kinases implicated in tumorigenesis through ligand-independent signaling. Both are attractive targets because they are highly expressed in multiple solid tumors. BL-B01D1 is a first-in-class bispecific ADC targeting EGFR and HER3 conjugated to a novel topoisomerase I inhibitor (Ed-04) *via* a cleavable linker. In a phase I study of BL-B01D1 in advanced solid tumors, the ORR reached 52.5%, and the disease control rate was 87.5% among heavily pretreated patients with EGFR-mutant non-small cell lung cancer resistant to third-generation tyrosine kinase inhibitors, thus markedly outperforming historical standards. In another ongoing phase Ib/II study (NCT05785039), BL-B01D1 was evaluated in patients with la/mUC. The patients had received a median of 2 prior frontline therapies. Among the 23 evaluable patients treated with 2.2 mg/kg, the ORR of 34.8% and the mPFS of 5.5 months indicated that BL-B01D1 retained moderate efficacy even in heavily pretreated patients. Among patients who received only prior first-line chemotherapy, the ORR was 80%, and mPFS was not reached. Common TRAEs (≥20% all-grade/≥grade 3) included anemia (74%/17%), leukopenia (65%/26%), thrombocytopenia (65%/26%), and neutropenia (44%/22%). These findings suggest that BL-B01D1 exhibits encouraging antitumor activity and has a manageable safety profile in patients with la/mUC. However, larger studies are required to confirm these results[27].

ADCs in localized disease

ADCs are being investigated as therapeutic strategies for localized UCs, including non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Oportuzumab monatox (OM), an EpCAM-targeted ADC administered intravesically, has shown efficacy in patients with Bacillus Calmette-Guérin (BCG)-unresponsive NMIBC. In a phase II trial (NCT00462488), patients with OM achieved a 44% CR rate, and in a phase III trial (NCT02449239), a CR of

40% at 3 months and 52% at 12 months was achieved[28]. When administered in combination with durvalumab, OM achieved a 47% CR at 3 months in a phase I trial (NCT03258593)[29]. Overall, the TRAEs were primarily grade 1–2 bladder-related symptoms and occurred in approximately half the patients.

The previously described ADCs are also being explored in NMIBC. Ongoing studies include the phase I EV-104 trial of intravesical EV[30], a prospective study evaluating DV plus BCG in HER2-positive high-risk NMIBC[31], and the TRUCE-04 phase II trial of DV monotherapy in high-risk NMIBC[32]. These early-phase trials reflect growing interest in extending ADC use to earlier-stage bladder cancer, although further data are awaited.

Given the remarkable efficacy of EV and DV in la/mUC, ADCs are also gaining attention in bladder-sparing strategies for localized MIBC. In the EV-103 study (NCT03288545), neoadjuvant EV led to pathological complete response (pCR) and pathologic downstaging rates of 36.4% and 50.0% in cisplatin-ineligible patients (cohort H), the 24-month event-free survival (EFS) was 62.0%, and median EFS was not reached[33]. In cohort L, EV administered before and after cystectomy yielded pCR and pathologic downstaging rates of 34.0% and 42.0%, respectively, and fatigue was the most common TRAE[34]. The ongoing phase III trials EV-303 and EV-304 are evaluating EV plus pembrolizumab in MIBC. DV is also being investigated in this setting. In the phase II RC48-C017 trial (NCT05297552), DV plus toripalimab achieved a 63.6% pCR rate in HER2-positive MIBC. In the IHC 3+ subgroup, the pCR rate was 84.6%, and the 1-year EFS was 89.5%[35]. The HOPE-03 trial similarly reported a 56.5% pCR rate with neoadjuvant DV plus tislelizumab[36]. These findings support potential roles of ADCs in bladder-sparing strategies. However, several questions remain, including the optimal duration of perioperative ADC ± immunotherapy, whether monotherapy or dual-agent regimens should be used, and how to select patients and monitor recurrence[37]. Further research is warranted to optimize these approaches and clarify the role of ADCs in bladder preservation.

Current hot topics on ADCs

Uncertainty in target antigen testing

Despite growing enthusiasm for ADCs in UC, HER2 testing remains a major challenge. Unlike breast or gastric cancers, UC lacks a validated tumor-specific HER2 scoring system. Most trials have applied modified breast cancer criteria that do not capture the distinct biology of UC. DV has demonstrated a moderate ORR in HER2 IHC 2+/FISH-negative tumors[16], thus suggesting that HER2 protein expression, independently of gene amplification, might confer therapeutic benefits. These findings challenge the binary HER2 classification and prompt questions regarding how HER2-low or HER2-ultralow expression should be defined and assessed. HER2 expression is also highly heterogeneous in UC, and intratumoral variability is observed in more than 55% of tumors[38]. Because conventional IHC lacks the sensitivity and dynamic range required to detect low-level expression or to capture spatial heterogeneity, its utility in patient selection is limited. Emerging technologies aimed at improving HER2 quantification, such as quantitative immunofluorescence, RNA-based profiling, and artificial intelligence-assisted pathology, are not yet in clinical use. Defining and validating clinically meaningful thresholds in prospective ADC trials remain urgent priorities[39].

Together, these diagnostic uncertainties pose a key barrier to effective ADC deployment and highlight the need for standardized UC-specific antigen testing strategies.

Potential resistance mechanisms

Understanding the mechanisms of drug resistance is critical for optimizing ADC therapy (**Figure 1**). The loss of target antigen expression or impaired antigen engagement can lead to resistance. Despite widespread Nectin-4 expression, the response rates to EV vary markedly[8]. Downregulation of Nectin-4 and Nectin-4 copy number variations are associated with poorer responses and worse survival outcomes[40]. Beyond antigen loss, the tumor microenvironment might impede ADC distribution, and resistance might arise through clonal evolution, impaired internalization, lysosomal dysfunction (e.g., diminished Cathepsin B expression), drug efflux *via* MDR1 (ABCB1), or loss of STING-mediated immune activation[40,41].

Cross-resistance between ADCs sharing similar payloads (e.g., EV and DV, both MMAE based) might also decrease sequential efficacy, although clinical data remain limited.

Future strategies should focus on biomarker-driven approaches, molecular profiling, and rational combination therapies to overcome drug resistance and optimize ADC-based treatments.

Future directions of ADCs

The future of ADC therapy for UC is advancing through refinements in construct design, antigen targeting, and treatment personalization[42]. Novel ADCs are being developed by using new antigens, more potent payloads, and optimized

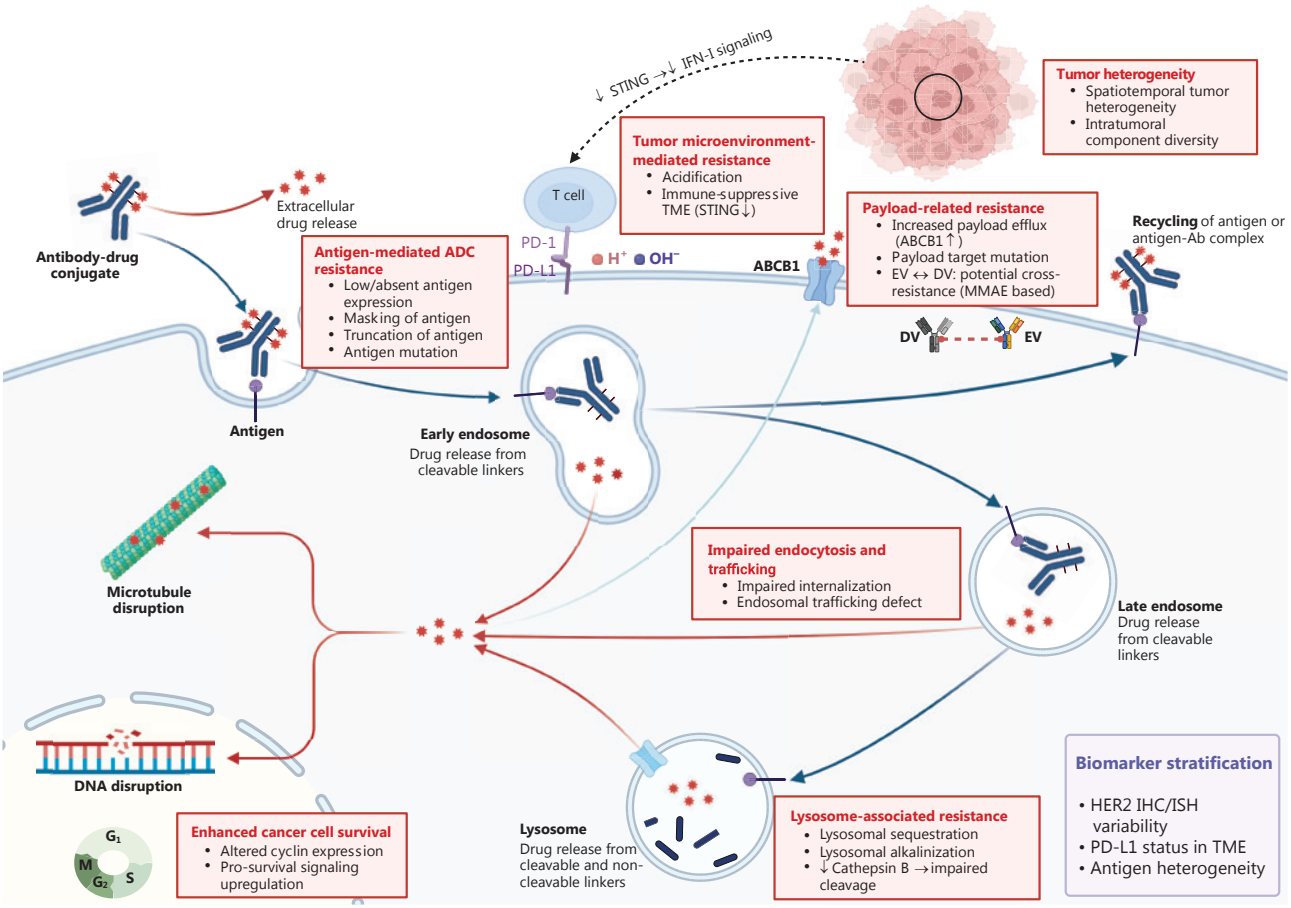


Figure 1 Representative mechanisms of resistance to ADCs and implications for biomarker-guided therapy in urothelial carcinoma. Resistance may arise from antigen downregulation or heterogeneity, impaired internalization, lysosomal dysfunction (e.g., cathepsin B deficiency), and drug efflux *via* transporters such as MDR1. STING pathway suppression may also decrease immunogenicity and limit ADC-ICI synergy. Dashed lines indicate potential cross-resistance between MMAE-based ADCs (e.g., EV and DV). The inset summarizes key challenges in biomarker-guided selection, including HER2 IHC/ISH variability and tumor microenvironment factors. ADC, antibody-drug conjugate; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; TME, tumor microenvironment; DNA, deoxyribonucleic acid; MMAE, monomethyl auristatin E; STING, stimulator of interferon genes; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; ICI, immune checkpoint inhibitors; MDR1, multidrug resistance protein 1; EV, enfortumab vedotin; DV, disitamab vedotin. The figures were created with BioRender.com, used with permission.

linkers to enhance their efficacy[43]. Refining antigen selection according to reproducible quantitative metrics is essential for aligning therapeutic targeting with tumor biology. Although antigens such as Nectin-4 and HER2 remain central to current platforms[8,18], the variability in expression and detection methods, particularly for HER2, continues to complicate patient stratification and response prediction. Therefore, companion diagnostics are needed to accurately define the relevant expression thresholds across a spectrum of UC subtypes. Emerging innovations such as site-specific conjugation platforms and dual-targeting ADCs are also under investigation to enhance tumor selectivity and the therapeutic index.

Beyond target selection, key future challenges include optimizing sequencing strategies and managing potential cross-resistance. For example, MMAE-based ADCs, such as EV and DV, might exhibit overlapping resistance, whereas switching to topoisomerase I payloads (such as SG, T-DXd) might potentially overcome such limitations. Whether ADCs with overlapping targets or payloads retain efficacy after prior ADC exposure (for example, whether DV or SHR-A2102 remains effective after EV failure) remains unclear. Resistance profiling might guide payload selection and help avoid class overlap. Dual ADC strategies with distinct mechanisms are under active investigation. Although the SG phase III trial yielded negative

findings, the combination of SG with EV achieved 70% ORR with manageable toxicity in early-phase studies[24].

Combination strategies are a major research direction in this field. According to preclinical data, ADCs synergize with ICIs through dendritic cell activation and immunogenic cell death[44]. Clinical trials in UC have shown greater efficacy of ADC–ICI combinations than monotherapy[6,8,16,18]. Whether ICIs should be reserved for first-line combination therapy or continued after ADC failure remains unclear. New combinations of agents such as cabozantinib, evorpacept, and erdafitinib are also under study, although their toxicity must be considered. As more ADCs enter clinical development, regulatory frameworks for companion diagnostics and accelerated approval pathways will be increasingly important.

Ultimately, integrating ADCs into biomarker-guided multimodal treatment frameworks stands to define the next-generation care for patients with UC.

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Conflict of interest statement

X.S. has the following potential conflicts of interest to disclose: consulting or advisory roles at Pfizer, Astellas, RemeGen, and Junshi Biosciences; speaker fees from Novartis, MSD, and BeiGene. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest or conflict with the subject matter or materials discussed herein, apart from those disclosed.

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