Antibody–drug conjugates in urothelial carcinoma: current status and future

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Purpose of review
Antibody–drug conjugates (ADCs) are quickly becoming frontline standard of care in many tumor types, including urothelial carcinoma. This review summarizes recent clinical investigations into the use of ADCs targeting nectin-4, trophoblast cell surface antigen-2 (Trop-2), human epidermal growth factor receptor 2 (HER-2), and other antigens in urothelial carcinoma.

Recent findings
This review covers efficacy and toxicity data of ADCs alone and in combination with immunotherapy; mechanisms of resistance; and preclinical studies that provide biological basis for clinical approaches.

Summary
Enfortumab vedotin and sacituzumab govitecan can be used in an unselected group of patients with urothelial carcinoma whereas HER-2 ADCs have only been administered in those with high expression or amplification. Most are being studied in combination with immune checkpoint inhibitors. Data supports use of enfortumab vedotin in combination with pembrolizumab as first-line therapy in metastatic/unresectable locally advanced urothelial carcinoma. Sacituzumab govitecan may be used as later-line option in these patients. HER-2 therapy is still under investigation but has many recent promising results.

Keywords
antibody–drug conjugate, enfortumab vedotin, human epidermal growth factor receptor 2, nectin-4, TROP-2

INTRODUCTION

There will be an estimated nearly 90 000 new cases and 18 000 deaths due to urothelial and bladder cancer in 2024 [1]. Historically, platinum-based chemotherapies have been the first-line therapy for advanced urothelial carcinoma (UC). However, these regimens are frequently associated with significant toxicities and a poor median overall survival. Moreover, a large portion of patients are ineligible to receive cisplatin due to poor performance status and decreased renal function [2,3]. Immune checkpoint inhibitors (ICIs) have been effective for a subset of patients [4–6]. Recent advances in the use of antibody–drug conjugates (ADCs) in urothelial and bladder cancer have expanded treatment options for patients with metastatic disease.

ADCs are a novel class of drugs that consist of a monoclonal antibody (mAb) carrying a cytotoxic drug via a linker [7]. In effect, the targeted action of antibodies is combined with the potency of chemotherapy (Fig. 1). Ideally, the target antigen is predominantly expressed on tumor cells while having minimal to no presence on healthy cells [8].

Recent clinical trials have demonstrated the significant potential of these agents for use in many tumor types, including urothelial and bladder cancer. This review focuses on ADCs targeting the cell-surface antigens Nectin-4, trophoblast cell surface antigen-2 (Trop-2), and HER2, covering primarily prospective clinical research (Table 1). We will discuss the current status and future prospects of ADC therapies and explore their potential to transform the therapeutic landscape for urothelial carcinoma.

Nectin-4

Nectin-4 is a type I transmembrane polypeptide involved with adhesion of cell junctions within

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KEY POINTS

- Enfortumab vedotin (EV) and pembrolizumab combination therapy is a new first-line standard of care for locally advanced/metastatic urothelial carcinoma.
- Sacituzumab govetican is currently approved for locally advanced/metastatic urothelial carcinoma and other promising trophoblast cell surface antigen-2 (Trop-2) directed antibody–drug conjugates (ADCs) are in development.
- Human epidermal growth factor receptor 2 (HER-2) targeted ADCs T-DXd and RC48 have demonstrated efficacy in HER-2 2–4+ or amplified locally advanced/metastatic urothelial carcinoma.
- Resistance mechanisms to ADCs include changes in target expression, drug efflux, or payload metabolism/engagement.

placental or embryonic tissues. It is widely expressed in metastatic urothelial carcinoma (mUC). Overexpression of nectin-4 is associated with metastasis via the WNT beta-catenin and PI3K-AKT-mTOR signaling pathways as well as interaction with the ERBB2 tyrosine kinase receptor [9].

Developed to target nectin-4, enfortumab vedotin (EV) was the first ADC approved by the FDA to treat locally advanced or metastatic UC (LA/mUC). The payload of EV is monomethyl auristatin E (MMAE). After endocytosis of the EV and nectin-4 complex, MMAE is released via proteolytic cleavage of the linker protein, leading to cell cycle arrest and apoptosis (Fig. 1).

The safety/tolerability and pharmacokinetics of single-agent EV in patients with nectin-4 expressing mUC was first evaluated in the phase I dose-escalation basket trial EV-101 [10]. These were patients who had progressed on prior chemotherapy and/or

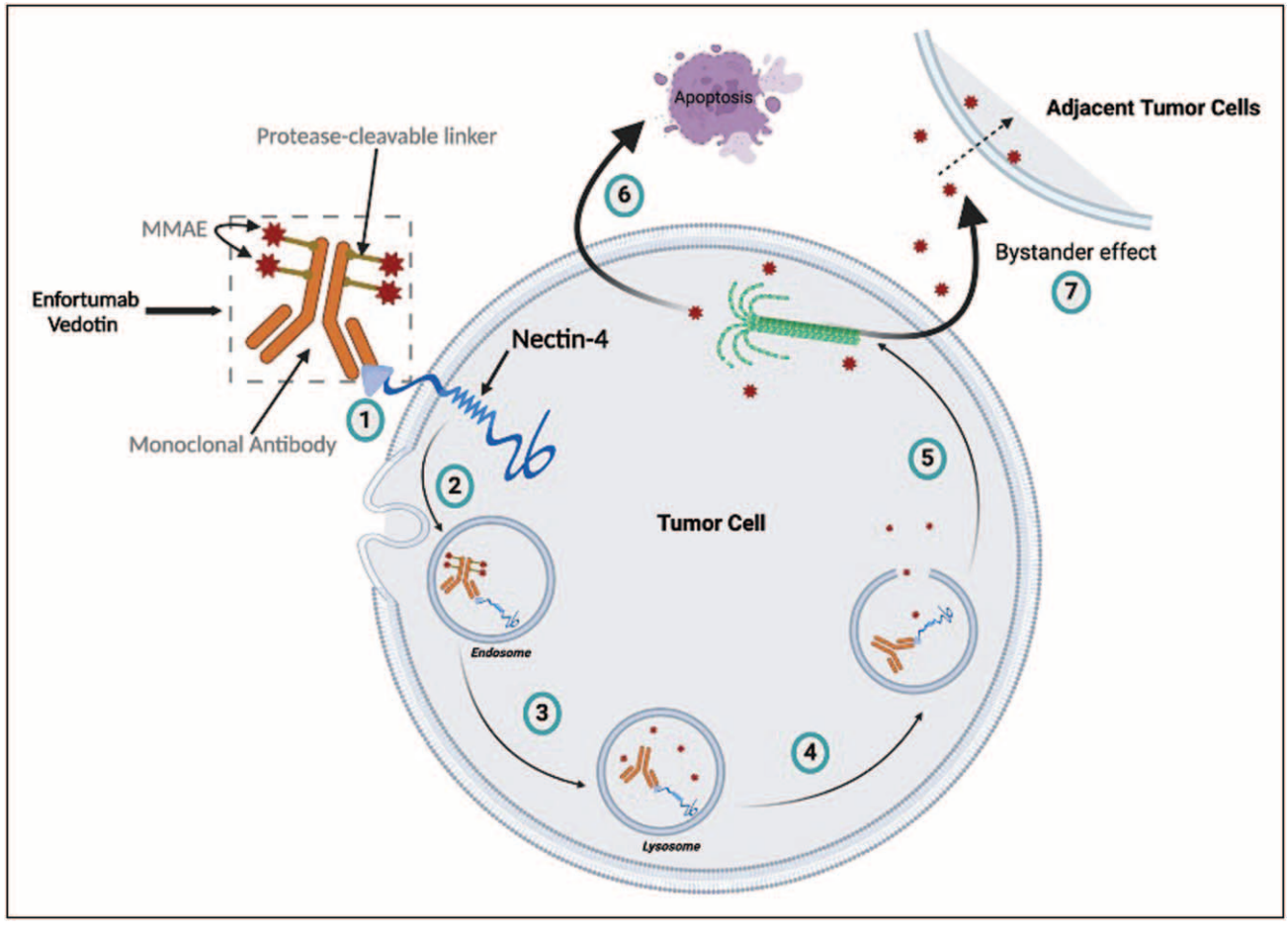

FIGURE 1. Enfortumab vedotin mechanism of action. (1) Target binding: EV selectively binds to cells that express nectin-4. (2) Internalization: EV-nectin-4 complex is internalized via receptor-mediated endocytosis. (3) Proteolytic cleavage: the complex travels to the lysosomes where the linker between the mAB and the is cleaved. (4) MMAE is released into the cytosol. (5) Microtubule disruption: MMAE binds to tubulin causing microtubule disruption. (6) Cell cycle arrest and apoptosis. (7) Bystander effect: passive toxin diffusion into adjacent tumor cells. ∗Created with BioRender.com.

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Table 1. Overview of currently available/investigational antibody–drug conjugates for urothelial cancer

ADC agent	Target	Payload	Linker	FDA approval/indication
Enfortumab Vedotin (Padcev)	Nectin-4	MMAE	Cleavable	FDA approved for: - EV in combination with Pembrolizumab as 1st line systemic therapy for LA or mUC (Stage IV) for both cis-eligible and cis-ineligible patients. - EV monotherapy as 2nd line systemic therapy for LA or mUC postplatinum or other chemotherapy. - EV monotherapy as 2nd line systemic therapy for LA or mUC for cis-ineligible patients postcheckpoint inhibitor and/or other chemotherapy.
Sacituzumab Govitecan (Trodelvy)	Trop-2	SN-38	Cleavable	- FDA approved for LA or mUC who previously received a platinum-based chemotherapy and either a PD-1 or a PD-L1 inhibitor.
Datopotamab deruxtecan (Dato-DXd)	Trop-2	DXd	Cleavable	- Investigational for heavily treated solid tumors including mUC - Ongoing studies: TROPION-PanTumor02 (NCT05460273) and TROPION-PanTumor03 (NCT05489211).
Trastuzumab Emtansine (T-DM1)	HER-2	DM1	Noncleavable	- FDA approved for HER2-positive breast cancer. - Investigational for other HER-2 overexpressing solid tumors (basket study).
Trastuzumab Deruxtecan (T-DXd)	HER-2	DXd	Cleavable	- FDA approved for unresectable or metastatic HER2-positive solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options (DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02).
Disitamab Vedotin (RC48-ADC)	HER-2	MMAE	Cleavable	- Ongoing investigations: NCT03809013, NCT04879329, ChiECRCT20210564
ASG-15ME	SLITRK6	MMAE	Cleavable	
Tisotumab Vedotin	TF	MMAE	Cleavable	- FDA approved for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy - Investigational for UC
Oportuzumab Monatox (Vicineum)	EpCAM	Pseudomonas exotoxin (ETA252–608)	Cleavable	

DM1, emtansine; DXd, Deruxtecan; EpCAM, epithelial cell adhesion molecule; LA, locally advanced; MMAE, monomethyl auristatin E; mUC, metastatic urothelial cancer; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1; UC, urothelial cancer.

immune checkpoint (anti PD1/PDL1) inhibitors (ICIs). Initially patients were screened based on nectin-4 expression on immunohistochemistry (IHC) of biopsy tissue, however, this prerequisite was removed after the majority of patients were found to have high expression. The recommended phase II dose was determined to be 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle. At that dose, the objective response rate (ORR) was 43% with duration of response lasting 7.4 months. Median overall survival (OS) was 12.3 months, and at 1 year the OS rate was 51.8%. The most common treatment-related adverse events (TRAEs) included fatigue, rash, alopecia, nausea, and peripheral neuropathy, typically grade 1–2 in severity. It is thought that peripheral neuropathy is mediated through the microtubule destabilization associated with MMAE.

EV-201 specifically evaluated EV monotherapy in patients with la/mUC in the post-ICI setting. EV-201 cohort 1 enrolled patients with prior ICI and prior platinum, while cohort 2 enrolled patient who were post-ICI and platinum ineligible. Both cohorts demonstrated efficacy in their respective cohort [11,12], leading to FDA approval of enfortumab vedotin monotherapy in patients with la/mUC who had progressed on ICI and platinum, or who were platinum ineligible after progression on ICI. The most common adverse effects leading to discontinuation of EV were peripheral neuropathy, rash, and fatigue, while sequela of other AEs, such

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as lymphopenia leading to pulmonary infection and hyperglycemia leading to DKA, led to treatment-related death in 1 patient in cohort 1 (<1%) and 3 (3%) in cohort 2.

The utility of EV monotherapy in la/mUC post-platinum and post-ICI was further characterized in the phase III trial, EV-301. In this study, patients were randomized to receive EV monotherapy or standard chemotherapy (docetaxel, paclitaxel, or vinflunine) [13]. The mOS in the EV group was 12.9 months, compared to 9.0 months in the chemotherapy group. The EV group also had a longer median progression-free survival (mPFS) of 5.5 months, compared to 3.7 months in the chemotherapy group. Incidence of TRAEs was similar in the two groups. These results were consistent in follow-up analyses [14▪].

The efficacy of combining of EV with immunotherapy was suggested by preclinical studies describing immunogenic cell death and neoantigen generation following treatment with cytotoxic therapy [15]. EV and pembrolizumab were first tested in combination in the phase Ib/II trial EV-103 [16]. Patients with la/mUC who were ineligible for cisplatin received EV on days 1 and 8 and pembrolizumab on day 1 in 3-week cycles. The results were promising, with an ORR of 73.3% and mOS of 26.1 months. A cohort of patients was randomized to receive EV and pembrolizumab or EV alone. The ORR was 64.5% for the combination group compared to 45.2% for EV alone [17▪].

EV-302 compared the combination of EV and pembrolizumab to the well established combination chemotherapy regimen of gemcitabine with cisplatin or carboplatin [18▪▪]. The mPFS was 12.5 months in the EV-pembrolizumab group compared to 6.3 months in the chemotherapy group, and mOS was 31.5 months in the EV-pembrolizumab group compared to 16.1 months in the chemotherapy group. 55.9% of patients in the EV-pembrolizumab group experienced grade 3 or higher TRAEs, compared to 69.5% in the chemotherapy group (more details on TRAEs in Table 2).

These results heralded EV and pembrolizumab combination therapy as the new first-line standard of care for la/mUC. There are also many ongoing trials investigating the use of EV and immunotherapy in the perioperative setting, outlined in Table 3. These include use of the EV and pembrolizumab combination as neoadjuvant therapy (EV-303, EV-304) and use of alternative immunotherapeutics such as durvalumab and trememlimumab (VOLGA). Novel trials in the metastatic space include the double antibody–drug conjugate (DAD) trial, which combines EV with the Trop-2 targeted ADC, sacituzumab govitecan (SG) [19]. The combination was determined to be safe in phase I trials and is being investigated further in a phase 2 trial (NCT04724018) that include an arm in which patients with receive EV + SG combined with pembrolizumab. Alternative nectin-4 targeting ADCs are in development [20,21], and a novel bicycle toxin conjugate BT8009, predicted to have less off-tumor toxicity compared to ADCs, has been studied in a phase 1/2 study called Duravelo-1 (NCT04561362) [22].

Resistance to EV is an active area of research, especially as the use of EV migrates to earlier lines of therapy. It is not entirely clear that nectin-4 expression is as uniformly positive as previously thought. One study by Klümper et al. identified decreased nectin-4 expression in metastatic tumors that were matched with primary tumors [23].

Table 2. Treatment-related adverse events in representative clinical trials for various ADC

Drug	Trial	Number of participants (*N*)	Most common AEs±any grade (%)	Most common ≥3 grade AEs (%)	Deaths due to treatment (#/underlying cause)
Enfortumab Vedotin (Padcev)	NCT0347410 (EV-301)	296	Alopecia (45.3), peripheral neuropathy (33.8), pruritus (32.1)	Maculopapular rash (7.4), Fatigue (6.4), neutropenia (6.1)	7 patients. Underlying cause: multiorgan dysfunction syndrome (2 patients) and abnormal hepatic function, hyperglycemia, pelvic abscess, pneumonia, and septic shock (each in 1 patient)
Sacituzumab Govitecan (Trodelvy)	NCT03547973 (TROPHY-U-01)	113	Diarrhea (65), nausea (60), fatigue (52)	Neutropenia (35), leukopenia (18), anemia (14)	1 patient. Underlying cause: sepsis due to febrile neutropenia
Trastuzumab Deruxtecan (T-DXd)	(NCT04482309) (DESTINY-PanTumor02)	267	Nausea (55.1), anemia (27.7), diarrhea (25.8)	Neutropenia (10.9), anemia (10.9)	3 patients. Underlying cause: ILD/ pneumonitis

ADC, antibody–drug conjugate.

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Table 3. Ongoing clinical trials of enfortumab vedotin in perioperative setting

ADC agent	NCT/trial name	Phase/study type	Patient population/ setting	Combination agent/ comparator	Intervention
Enfortumab Vedotin	NCT05239624/ EV-ECLIPSE	Phase II Single arm	-Untreated MIBC -Both cis-eligible and ineligible patients	EV + Pembro[a]	-Preoperative EV plus Pembro followed by cystectomy followed by Pembro monotherapy
	NCT06356155/ NEPTUNE	Phase II Single arm	-High-grade localized/ locally advanced upper tract UC -Eligible for curative-intent surgery[g] -Cis-eligible patients	EV + Pembro[a]+ surgery[g]	-Preoperative EV plus Pembro followed by surgery[g] followed by Pembro monotherapy
	NCT05014139	Phase I Single arm	-NMIBC with high-risk BCG-unresponsive disease -Ineligible for RC	EV alone	-Weekly EV during induction, followed by monthly EV during maintenance phase.
	NCT04960709/ VOLGA	Phase III Randomized	-Untreated MIBC -Cis-ineligible	Arm 1: EV + Durvalumab[b] + Tremelimumab[c] + RC Arm 2: EV + Durvalumab[b] + RC Comparator: SOC (RC +/- adjuvant therapy[d])	Arm 1: preoperative EV plus Durvalumab plus Tremelimumab, followed by RC, followed by postoperative Tremelimumab and Durvalumab. Arm 2: preoperative EV plus Durvalumab, followed by RC, followed by postoperative Durvalumab.
	NCT03924895/ KEYNOTE-905/EV-303	Phase III Randomized	-Untreated MIBC -Cis-ineligible -Neoadjuvant and adjuvant EV	Arm A: Pembro[a] + Surgery[e] Arm B: EV + Pembro[a] + Surgery[e] Comparator: Surgery[e] alone	Arm A: preoperative Pembro, followed by surgery[e], followed by postoperative Pembro. Arm B: preoperative EV plus Pembro, followed by surgery[e], followed by postoperative EV plus Pembro, followed by Pembro alone.
	NCT04700124/ KEYNOTE-B15/EV-304	Phase III Randomized	-Untreated MIBC -Cis-eligible -Neoadjuvant and adjuvant EV	Arm A: EV+ Pembro[a] + surgery[e] Comparator: SOC-Neoadjuvant chemotherapy[f] + surgery[e]	-Preoperative EV plus Pembro, followed by surgery[e], followed by adjuvant EV plus adjuvant Pembro.

BCG, Bacillus Calmette-Guerin; EV, enfortumab vedotin; MIBC, muscle invasive bladder cancer; NMIBC, nonmuscle invasive bladder cancer; Pembro, pembrolizumab; PLND, pelvic lymph node dissection; RC, radical cystectomy; RNU, radical nephroureterectomy; SOC, standard of care; UC, urothelial carcinoma.
[a]Anti- PD-1 antibody.
[b]Anti- PD-L1 antibody.
[c]Human IgG2 mAb.
[d]Nivolumab approved as adjuvant therapy for MIBC based on high-risk criteria.
[e]RC plus PLND.
[f]Gemcitabine plus cisplatin.
[g]RNU or distal ureterectomy.

Trop-2

Trop-2 (tumor-associated calcium signal transducer 2) is a transmembrane protein involved in calcium signaling, cell adhesion, and stem-cell self-renewal [24,25]. Trop-2 overexpression is seen not only in urothelial carcinoma but also nonsmall cell lung cancer (NSCLC), prostate adenocarcinoma, and hormone receptor positive and triple-negative breast cancer [26]. Moderate (2+) or strong (3+) expression of Trop-2 is nearly universal in both normal

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urothelial tissue as well as urothelial carcinoma [26,27]. Expression is largely preserved at sites of metastasis if highly expressed in the primary lesion [28].

Sacituzumab govitecan (SG, formerly IMMU-132) is an ADC with a topoisomerase I inhibitor and cleavable linker CL2A [29,30], targeted to Trop-2 expressing tumors via the monoclonal antibody RS7. Uptake of 131I-RS7 in preclinical studies was modest [31], suggesting that the mechanism of action of SG may be primarily via drug release in the tumor microenvironment, resulting in a 'bystander effect' on adjacent cells [32,33]. After promising results were demonstrated in a subset of patients with urothelial carcinoma enrolled in the IMMU-132-01 basket trial for SG [34], the ADC was further developed for therapy in the metastatic setting.

Trophy-U-01 is a phase II multicohort study utilizing SG as monotherapy (cohorts 1 and 2) or in combination and/or sequencing with chemotherapy and immune checkpoint inhibitors (cohorts 3–6) for patients with la/mUC. Results from cohorts 1–3 have been published, and generally compare favorably with historic data for single-agent chemotherapy in this population [35–37]. Cohorts 4–6 are actively enrolling. SG received accelerated FDA approval for use in mUC in April 2021 largely based on the ORR demonstrated in Trophy-U-01 cohort 1.

In May 2024, Gilead announced that TROPiCS-04, a randomized phase 3 trial comparing SG to physician choice chemotherapy (paclitaxel, docetaxel, or vinflunine) in la/mUC, failed reach its primary endpoint of OS. It is possible that an increased rate of death in this trial was related to suboptimal growth factor support and increased rate of neutropenia and infections. This data has not yet been presented. SG is also being studied in the neoadjuvant setting (SURE-01, SURE-02), and in combination with dual immune-checkpoint inhibitors ipilimumab/nivolumab (NCT04863885). It appears that the efficacy of SG in patients with variant histology UC is similar to that of SG in urothelial carcinoma [38].

Additional Trop-2 ADCs have pharmaceutical characteristics which may prove advantageous when compared to SG. Datopotamab deruxtecan (Dato-DXd) is a Trop-2 targeting ADC with topoisomerase I inhibitor payload. In contrast to SG, dato-DXd is readily internalized and studies suggest increased linker stability and payload potency [39]. In preliminary results of the phase 1 basket trial TROPION PanTumor-01 study (NCT03401385), 18 patients with heavily pretreated la/mUC received dato-DXd and had ORR of 27.8% [40▪]. Patients with la/mUC urothelial cancer will also be included later phase TROPION-PanTumor basket trials (PanTumor02/NCT05460273, PanTumor03/NCT05489211). Another novel Trop-2 ADC is SKB264 (now MK-2870, also known as sacituzumab tirumotecan; Merck & Kelun-Biotech). This ADC also features a topo I inhibitor payload, with a unique 2-methylsulfonyl pyridine linker. Likely due to the linker, SKB264 had a longer circulating half-life than SG (56.3 h vs. 15.5 hr), resulting in nearly fivefold greater exposure to tumor [41]. First-in-human studies of SKB264 in metastatic solid tumors suggests efficacy at all dose levels (2, 4, 6 mg/kg), manageable toxicity, and an ideal dosing of every 2 weeks [42].

The most frequent toxicities observed with SG include diarrhea, nausea and fatigue. In Trophy-u-01 cohort 1, treatment-related dose reduction and dose interruptions occurred in 40% and 47% of patients, respectively [35]. In the overall population, grade 3 or higher neutropenia, leukopenia and anemia occurred frequently (35%, 18%, and 14%, respectively). The overall rate of adverse effects was higher in patients with homozygous UGT1A1∗28 alleles compared to wild-type UGT1A1. In particular, diarrhea (71% vs. 65%), leukopenia (50% vs. 26%) and peripheral neuropathy (29% vs. 5%) was more common in patients homozygous for UGT1A1∗28. Resistance to sacituzumab govitecan has been shown to be mediated by both loss of Trop-2 expression and mutations to topoisomerase I [43].

Human epidermal growth factor receptor 2

HER2 is a tyrosine kinase receptor belonging to a group of epithelial growth factor receptors that influence cell growth, survival, and mobility [44]. The portion of patients with HER2 high (2–3+) expression on IHC or HER2 amplification of FISH is estimated to be about 8–33% [45]. HER2 overexpression/amplification is associated with more aggressive tumor behavior and poorer outcomes for patients [46]. HER-2 targeted therapies have been successfully used to treat HER-2 overexpressing breast, gastric and colorectal cancers, and demonstrate increasing promised for use in urothelial carcinoma.

Trastuzumab-based ADCs have been studied in urothelial carcinoma. Trastuzumab emtansine (T-DM1), FDA-approved for use in HER-2 positive breast cancer, consists of an antimicrotubule payload linked to the monoclonal antibody trastuzumab via a noncleavable linker. A phase II study (KAMELEON) of T-DM1 in advanced or metastatic UC enrolled 13 patients with selection for HER2 overexpression on IHC and achieved an ORR of 38.5% [44]. Patients with HER2 expressing urothelial carcinoma were also enrolled in a phase 1 basket trial of trastuzumab duocarmazine [47]. Of the 16

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patients with la/mUC, there was a 25% ORR with mPFS of 4.0 months. Trastuzumab deruxtecan (T-DXd), which differs from T-DM1 primarily in that it features a higher drug-to-antibody ratio and a cleavable linker design. In DESTINY-PanTumor02, a phase 2 basket trial using T-Dxd in patients with HER-2 overexpressing solid tumors, demonstrated favorable responses in the overall cohort, leading to FDA approval for use of T-Dxd in all patients with unresectable/metastatic solid tumors with HER2 3+ expression on IHC. Within the larger cohort, 41 patients with urothelial cancer were enrolled [4]. These patients benefited from an ORR of 39% and median duration of response of 8.7 months. T-DXd has also been studied in combination with nivolumab, with similar response rates [48].

Disitamab vedotin (DV, or RC48), which consists of an anti-HER2 monoclonal antibody and MMAE payload with cleavable linker, has demonstrated promising efficacy as a 2nd line therapeutic in HER-2 overexpressing la/mUC. For patients with HER-2 $\geq$2+ by IHC receiving DV as monotherapy, ORR was 50.5% with mPFS was 5.9 months and mOS 14.2 months [49]. Even patients with HER-2 low (0–1+) by IHC derived some benefit [50]. In combination with the PD-1 inhibitor toripalamab, ORR was 71.8% in a cohort of 41 patients [51]. In a phase 3 study combining DV and pembrolizumab, similar response rates were achieved in a safety run-in cohort of 20 patients (ORR 75%) [52]. Common adverse effects associated with DV monotherapy or in combination with ICI include sensory neuropathy, diarrhea, alopecia, fatigue, and neutropenia [51,52].

The optimal clinical application of HER2-targeted ADCs is still to be determined. There is significant co-expression of Her-2 and nectin-4 [53], thus, determination of sequencing in ADCs targeting these respective antigens will need to be studied. Regarding sequencing MMAE-payload ADCs such as DV and EV, it remains to be seen whether patients can tolerate repeat exposure to this toxic payload.

OTHER TARGETS

There are other antigen targets in urothelial carcinoma for which ADCs have been created but are less mature in their development process than nectin-4, Trop-2 and HER2. Oportuzumab monatox is a EpCAM-targeting antibody fragment with exotoxin payload that was studied as an intravesicular drug in patients with BCG-unresponsive urothelial carcinoma in situ of the bladder which failed to receive FDA-approval following a phase 3 study [54]. Sirtratumab vedotin and tisotumab vedotin are ADCs targeting SLITRK6 and tissue factor, respectively, which demonstrated responses in mUC but have not been developed further [55,56]. BL-B01D1 is an EGFRxHER3 bispecific antibody with topo-1 inhibitor payload which was studied in la/mUC with promising phase I/II data published in the September 2024 ESMO annual meeting [57].

CONCLUSION

In conclusion, the latest advancements in ADCs represent a pivotal shift in the treatment paradigm of advanced urothelial carcinoma. Enfortumab vedotin in combination with pembrolizumab has replaced platinum-containing chemotherapy regimens as first line therapy in mUC for most patients. Trop-2 targeting ADCs show promise in all-comers as well, while HER-2 targeted ADCs are being developed for patients with HER-2 overexpression and amplifications. The next generation of ADCs in locally advanced and metastatic UC promise to redefine standards of care and extend survival for UC patients.

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