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doi.org/10.58931/cot.2024.1329

Antibody-drug Conjugates in The Management of Advanced Urothelial Carcinoma

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Introduction

For decades, the cornerstone for treatment of advanced urothelial carcinoma (aUC) has consisted of platinum-based chemotherapy regimens, such as GC (gemcitabine plus cisplatin/carboplatin) or MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin).[1] Thereafter, immune checkpoint inhibitors (ICI) were incorporated into the standard of care, initially as monotherapy in subsequent-line settings and more recently as maintenance treatment with chemotherapy in the first-line setting.[2-5] Recently, the development of antibody-drug conjugates (ADCs) has dramatically shifted the treatment landscape for aUC.

ADCs are engineered to function as a biologic *"honing missile"*,[6] with the aim of delivering its cytotoxic payload to the target cancer cell while remaining stable in circulation and minimizing off-target toxicity. Enfortumab vedotin was the first to demonstrate efficacy in urothelial carcinoma (UC),[7] initially as monotherapy and later in combination with ICI, surpassing the decades-old standard of first-line chemotherapy.[8] The aim of this review is to discuss the evolving field of ADCs in aUC, highlighting the main targets, clinical data, toxicities, and future opportunities.

The "ABCs" of ADCs

An ADC is composed of three primary elements: A) a target-specific antibody, B) a cytotoxic payload, and C) a linker molecule that conjugates the two. The antibody's target determines its tissue specificity. Ideally, the target is an antigen preferentially expressed on tumour tissue and minimally expressed on non-malignant tissue to reduce off-target side effects.[9] Moreover, the antibody should have minimal immunogenicity to avoid neutralization and/or hypersensitive reactions from the host's immune system.[10]
In the UC context, ADC research to date has concentrated on targeting three highly expressed cell-surface proteins: nectin-4, trophoblast cell surface antigen-2 (trop-2), and the ErbB family of receptors **(Figure 1)**.

The cytotoxic payloads currently employed in UC are classified into microtubule destabilizers (e.g. auristatins) and topoisomerase inhibitors (e.g. deruxtecan, SN-38). Due to their high potency, these agents are typically unsuitable for direct administration; however, when conjugated to antibodies, they can be delivered systemically with reduced toxicity.[11] The *drug-antibody ratio* (DAR) is the number of cytotoxic molecules bound to each antibody, and higher DARs can increase the efficacy of ADCs.

Linkers maintain the stability of ADCs in systemic circulation and control the payload delivery to target cells. Cleavable linkers facilitate payload release via enzymatic or pH-triggered degradation, delivering the payload to not only target cells but also the surrounding tumour microenvironment, termed the *bystander effect*. While the bystander effect can be beneficial in therapy, cleavable linkers also carry the risk of premature payload release and potential systemic toxicity. In contrast, ADCs with non-cleavable linkers release their payload only after the ADC is internalized and degraded inside the target cell, which can reduce systemic toxicity. This, however, can also increase an ADC's half-life, which may lead to distinct delayed toxicities. Therefore, the engineering of linkers plays a vital role in balancing toxicity and efficacy.[11]

ADCs by target

Nectin 4

Nectin-4 is a transmembrane cell-adhesion molecule expressed at low levels in healthy tissues of the aerodigestive tract, skin, and placenta.[12] Aberrant expression has been observed in several

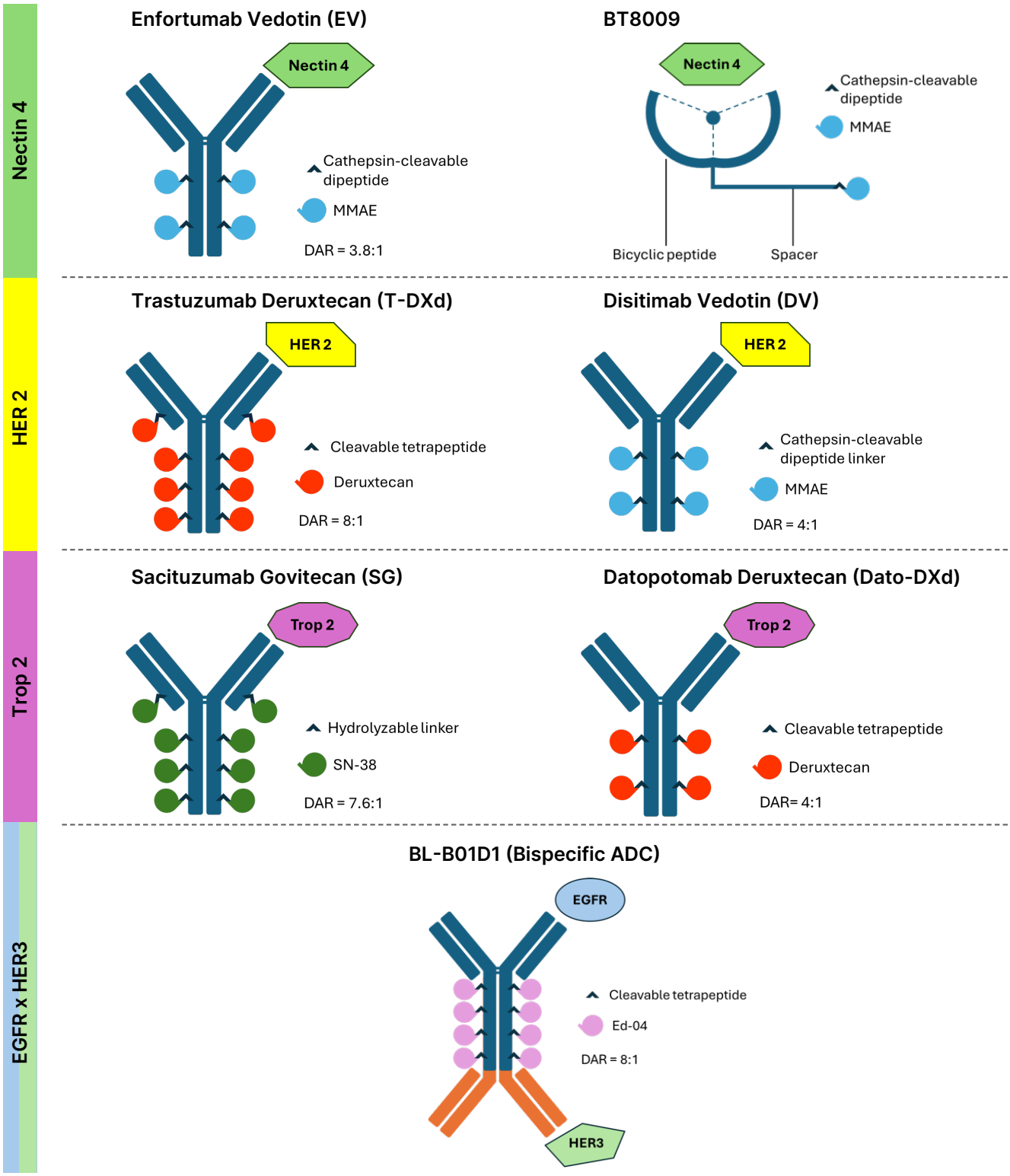

Figure 1. Structures of antibody-drug conjugates (ADC) and a bicycle toxin conjugate (BTC) used in advanced urothelial carcinoma. Each ADC consists of a target-specific antibody, linker molecule, and cytotoxic payload. A BTC uses a small molecule (0.9 kD) bicyclic peptide with a high target-affinity in lieu of an antibody; courtesy of Pooya Dibajnia, BSc (Hons), MD, FRCPC and Aly-Khan Lalani, BSc (Hons), MD, FRCPC; *courtesy of Pooya Dibajnia, BSc (Hons), MD, FRCPC and Aly-Khan Lalani, BSc (Hons), MD, FRCPC*

Abbreviations: DAR: drug-antibody ratio; **EGFR:** epidermal growth factor receptor; **HER2:** human epidermal growth factor receptor 2; **HER3:** human epidermal growth factor receptor 3; **MMAE:** monomethyl auristatin E.

tumour types, including bladder, breast, lung, pancreatic, and ovarian cancer, which makes it an ideal target for engineering ADCs for aUC.[13]

Enfortumab vedotin (EV) is the first nectin-4 targeting ADC, which contains the microtubule destabilizer monomethyl auristatin E (MMAE) as its payload. Two pivotal phase III trials have established the role of EV in the management of aUC. In the subsequent-line setting, the EV-301 trial compared EV versus chemotherapy in patients previously treated with platinum-based chemotherapy and ICI. The EV arm was associated with an improved median overall survival (mOS) of 12.9 months versus 8.9 months (hazard ratio [HR] = 0.70) in the chemotherapy arm.[7, 14] The benefit of EV in platinum-ineligible patients post-ICI therapy has also been demonstrated in the phase II setting.[15] In the first-line setting, the EV-302 trial showcased the efficacy of EV in combination with pembrolizumab (PD-1 inhibitor) compared to platinum-based chemotherapy. This trial with 886 patients demonstrated a significant improvement in mOS of 31.5 months for the EV + pembrolizumab arm versus 16.1 months for the chemotherapy arm (HR = 0.47). The overall response rate (ORR) was 67.7% with EV + pembrolizumab, compared to 44.4% with chemotherapy. These studies have led to the approval of EV by the US Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency **(Table 1)**. The use of EV in the first- and subsequent-line settings is being incorporated into guideline recommendations.[16]

Clinicians need to be mindful of several unique toxicities associated with EV. Peripheral neuropathy can be caused by the neurotoxic payload MMAE. It is observed in 30-40% of patients when EV is used as a single agent,[7, 17, 18] and potentially a higher percentage when combined with pembrolizumab.[8] Sensory neuropathy is the most commonly reported form; however, motor and autonomic neuropathy are also possible. Vigilant monitoring is critical in patients who may carry subclinical neuropathy (e.g. diabetes, older age). High-grade neuropathy, observed in 3-4% of patients, may require dose reductions or discontinuation of therapy. In addition, dermatologic toxicities occur in 30-40% of patients.[18] The presumed mechanism of dermatologic toxicities is on-target/off-tumour binding of EV to normal nectin-4 expressing tissue (e.g. epidermis, hair follicles). This can present in various forms, including maculopapular rash (typically in skin folds), stomatitis, conjunctivitis, and bullous dermatitis.[19] Finally, hyperglycemia is observed in up to 10% of patients, with approximately 6% being grade 3 or higher, necessitating caution in patients with diabetes.[20]

Ongoing studies of other nectin-4-based therapies use various combinations of antibodies, payloads and/or linker molecules.[21, 22] Bicycle toxin conjugates (BTC) are a novel class of therapeutic that have evolved from the design principles of ADCs. BTCs employ a small molecule bicyclic peptide with a high target affinity in lieu of an antibody. The theoretical advantage of BTCs is that the small size allows better infiltration of tumour tissue and improves systemic clearance, thereby improving outcomes and reducing toxicities. BT8009 is a nectin-4-based BTC that has demonstrated an ORR of 50% in early phase trials,[23] and is currently being explored in the phase II/III Duravelo-2 trial for aUC **(Table 1)**.[24]

ErbB family

The ErbB family of cell-surface receptors are highly expressed in urothelial carcinomas,[25, 26] and are implicated in oncogenesis. ADC development in aUC has thus far focused on ErbB1 (EGFR), ErbB2 (HER2), and ErbB3 (HER3).

The HER2-targeting ADC trastuzumab deruxtecan (T-DXd) is already an established therapy in breast cancer and is being investigated in aUC.[27] T-DXd has recently garnered FDA approval for all tumour types with high HER2 expression by immunohistochemistry (IHC 3+). T-DXd combines trastuzumab (HER2-targeting monoclonal antibody) to deruxtecan, a topoisomerase I inhibitor more potent than SN-38 (the active metabolite of irinotecan) with a DAR of 8:1.[28] DESTINY-PanTumour2 was a phase II basket trial that assessed T-DXd in patients with a variety of HER2-expressing tumours after prior lines of therapy. In the UC cohort (n=41), an ORR of 39% was observed, with a median progression-free survival (mPFS) of 7.0 months, and mOS of 12.8 months **(Table 1)**. Notably, the IHC 3+ subgroup (n=16) had a higher ORR of 56.3%, mPFS of 7.4 months, and mOS of 13.4 months. With respect to toxicity, T-DXd carries the unique risk of pneumonitis/interstitial lung disease, observed in 10.5% of the study population. T-DXd holds promise for aUC with high HER2 expression, and larger trials and/or real-world evidence are needed to better understand the safety and efficacy of this agent.

ADC	Target	Payload	Phase	Study and Design	Primary Outcomes	Approvals
Enfortumab vedotin	Nectin-4	MMAE	Phase III	EV 302 – 1L EV + Pembro vs chemo	mOS: 31.5 mo vs 16.1 mo (HR 0.47; 95% CI 0.38 - 0.58) mPFS: 12.5 mo vs 6.3 mo (HR 0.45; 95% CI 0.38 – 0.54)	FDA Health Canada EMA
				EV 301 – 3L EV vs chemo (post ICI and platinum-based chemo)	mOS: 12.9 mo vs 8.9 mo (HR 0.70; 95% CI 0.58 - 0.85)	
				EV 303 – Peri-operative EV + Pembro vs chemo (Cisplatin-ineligible)	Ongoing (NCT03924895)	
				EV 304 - Peri-operative EV + Pembro vs chemo(Cisplatin-ineligible)	Ongoing (NCT04700124)	
			Phase II	EV 201 – 2L EV post-ICI in platinum-ineligible	ORR = 52%	
BT8009 (BTC)	Nectin-4	MMAE	Phase II/III	Duravelo-2	Ongoing	
			Phase I/II	BT8009-100	ORR = 50%	
Trastuzumab deruxtecan	HER2	Dxd	Phase II	DESTINY-PanTumor02	ORR = 39.9% (56.3% for IH3+)	FDA (IHC3+)
Disitamab vedotin	HER2	MMAE	Phase III	DV-001 – DV + pembro vs chemo	Ongoing	
			Phase II	RC48-C005 – 2L DV in IHC 2+ or 3+ RC48-C009 – 3L DV in IHC 2+ or 3+ RC48-C011 – 2L DV in HER2 negative	ORR = 51.2% ORR = 46.9% ORR = 26.3%	
Sacituzumab govitecan	Trop-2	SN-38	Phase III	TROPiCS-04	Did not meet primary endpoint of OS	FDA
			Phase II	TROPHY-U-01 - Cohort 1 – 3L SG post ICI and chemo - Cohort 2 – 2L SG post ICI (platinum-ineligible) - Cohort 3 – 2L SG + pembrolizumab post chemo	 ORR = 28% ORR = 32% ORR = 41%	
Datopotamab deruxtecan	Trop-2	Dxd	Phase II	TROPION-PanTumor03	Ongoing	
			Phase I	TROPION-PanTumor01	ORR = 27%	
BL-B01D1	EGFR & HER3 (Bispecific)	Ed-04	Phase II	BL-B01D1-201	ORR = 41%	

Table 1. Antibody-drug conjugates in advanced and metastatic urothelial carcinoma at or near-clinical use as of Sep. 2024; *courtesy of Pooya Dibajnia, BSc (Hons), MD, FRCPC and Aly-Khan Lalani, BSc (Hons), MD, FRCPC*

Abbreviations: BTC: bicyclic toxic conjugate; **CI:** confidence interval; **Dxd:** deruxtecan; **EGFR:** epidermal growth factor; **EMA:** European Medicines Agency; **EV:** enfortumab vedotin; **FDA:** Food and Drug Administration; **HER2:** human epidermal growth factor receptor 2; **HER3:** human epidermal growth factor receptor 3; **HR:** hazard ratio; **ICI:** immune checkpoint inhibitor; **IHC:** immunohistochemistry; **MMAE:** monomethyl auristatin E; **mOS:** median overall survival; **mPFS:** medial progression free survival; **mos:** months; **ORR:** objective response rate; **Pembro:** pembrolizumab; **Trop-2:** trophoblast cell surface antigen-2; **1L:** first-line; **2L:** second-line; **3L:** third-line

Disitimab vedotin is a novel HER2-targeting monoclonal antibody conjugated to the microtubule destabilizer MMAE via a protease-cleavable linker.[29] Two phase II trials have evaluated its efficacy in pre-treated aUC patients with HER2 IHC 2+ or 3+ expression **(Table 1)**.[29, 30] Notably, these trials were conducted in Asia, where the incidence of upper tract UC approached nearly 50% of the study population. In the combined analysis (n=107), the ORR was 50.5%, mPFS 5.9 months, and mOS 14.2 months. Subgroup analysis demonstrated a higher response rate for patients with IHC 2+ with fluorescence *in situ* hybridization (FISH) positivity, or IHC 3+ (ORR = 62.2%). Commonly observed toxicities included peripheral neuropathy (68.2%), neutropenia (50.5%), and liver enzyme elevation (42.1%). Similar to EV, the high incidence of peripheral neuropathy is attributable to its payload MMAE. DV currently holds Breakthrough Therapy designation from the FDA. The global phase III trial DV-001 is set to investigate the combination of DV and pembrolizumab in previously untreated patients with high HER2 expression compared to first-line chemotherapy.[31]

Emerging ADCs that employ bispecific antibodies to target two ErbB receptors is a novel approach that aims to improve efficacy of ADCs. BL-B01D1 is a first-in-class EGFR and HER3 targeting bispecific ADC. It contains an anti-EGFR monoclonal antibody fused to two anti-HER3 single chain variable fragments, which is linked to the topoisomerase inhibitor Ed-04 using a cleavable tetrapeptide-based cathepsin linker **(Figure 1)**.[32] This has been evaluated in a phase II trial involving previously treated patients. An ORR of 75.0% was observed in the cohort of patients with one prior line of therapy (n=12), and an ORR of 40.7% in patients with two or more previous lines of therapy (n=27).[33] Notably, biomarker analysis from this study has demonstrated good clinical activity regardless of level of EGFR/HER3 IHC expression. Common side effects included anemia (82%), thrombocytopenia (62%), neutropenia (56%), anorexia (47%) and nausea (44%). This first-in-class bispecific ADC holds promise across a spectrum of EGFR/HER3 expressions and requires further evaluation within a larger population.

Trop-2

Trop-2 is a cell surface glycoprotein implicated in signalling pathways of cell proliferation, migration, and invasion. It is highly expressed in many epithelial carcinomas, including UC.[34]

Sacituzumab govitecan (SG) incorporates the topoisomerase I inhibitor SN-38 as its payload and a hydrolysable pH-dependent linker.[35] In aUC, SG initially gained FDA Accelerated Approval after the results of a phase II trial in patients pre-treated with ICI and chemotherapy demonstrated an ORR of 28% and mOS of 10.9 months.[36-38] SG also demonstrated efficacy in cisplatin-ineligible patients previously treated with ICI, with an ORR of 32% and mOS of 13.5 months **(Table 1)**.[39] However, the confirmatory phase III TROPiCS-04 trial comparing SG to single-agent chemotherapy in a pre-treated population did not meet its primary endpoint for OS **(Table 1)**.[40] At the time of writing, SG does not have Health Canada approval in UC. Further research into the use of SG in combination with other agents are ongoing (NCT03547973).[41]

Datopotomab deruxtecan (Dato-DXd) is another trop-2-targeting ADC currently under investigation. It contains the payload deruxtecan and a tetrapeptide-based cleavable linker that is plasma-stable. In a phase I basket trial that included 18 patients with heavily pre-treated aUC, the ORR was found to be 27.8%, with one patient achieving a complete response **(Table 1)**.[42] Currently, a phase II trial is underway to study Dato-DXd as a monotherapy and in combination with other agents (NCT05489211).[43]

These early phase studies have demonstrated SG and Dato-Dxd to have comparable toxicities largely attributed to their topoisomerase inhibitor payloads, including cytopenias, stomatitis, diarrhea, and febrile neutropenia.[36, 42] Similar to irinotecan, patients with *UGT1A1* polymorphisms appear to have a higher incidence of neutropenia.[44] Rare instances of pneumonitis have been reported for both ADCs.[38, 42] Further data is needed to better describe optimal dosing, the need for prophylactic medications (e.g. granulocyte colony-stimulating factor [G-CSF]), and the role of routine *UGT1A1* testing to mitigate toxicities.

Future Directions

Currently, EV is an established standard of care for the treatment of aUC in Canada; specifically, it is available in the post-chemotherapy and post-ICI setting and approval is anticipated with pembrolizumab as a first-line standard. There are opportunities to further

improve outcomes by exploring response to ADCs in different subgroups of UC, understanding resistance mechanisms, and examining the potential of combining ADCs with other therapies. Importantly, experience and education around combination use will help ensure safe delivery and utility in the academic and community settings – where much of mUC care can occur.

Histologic and molecular variations in UC warrant further study to identify differential responses to ADCs. Historically, variant histologies of UC, such as sarcomatoid and plasmacytoid differentiation, have been associated with worse outcomes. For EV, a retrospective analysis of patients with variant histologies (n=164) found an ORR of 35-56% in those with combined urothelial and variant components. This included squamous, micropapillary, plasmacytoid, sarcomatoid, adenocarcinoma, nested, and lipid cell variants. However, neuroendocrine/small cell differentiation was associated with an unfortunate 0% response rate to EV (n=9).[45] Moreover, patients with pure variant histologies (i.e., without a urothelial component) had markedly worse response rates. Prospective studies of variant histologies are currently ongoing for EV (NCT05756569), and it is likely that for certain histologies (i.e. neuroendocrine), chemotherapy may remain as the preferred upfront treatment.[46]

Understanding resistance mechanisms to ADCs is critically important in the context of the evolving horizon scan of systemic therapies. From a cellular perspective, resistance to ADCs can develop due to downregulation of the cell surface target (e.g. nectin-4),[47] or resistance to the payload.[48] Sequencing trials have demonstrated limited efficacy of serial ADCs despite different targets and payloads. In one trial involving 82 heavily pre-treated patients, sequencing SG after EV resulted in an ORR of 10%.[49] Given that SG and EV have different payloads and targets, this suggests other mechanisms of resistance are at play, and further research in this area is needed.

Several ongoing studies are examining combinations of two ADCs, as well as ADCs with other therapies. The ongoing phase I DAD trial is evaluating the combination of SG and EV in patients previously treated with platinum chemotherapy and ICIs, while the DAD-IO trial aims to evaluate the triplet combination of SG, EV, and pembrolizumab in the first-line setting (NCT04724018).[50] Other early phase trials are evaluating the combination of EV with erdafitinib (fibroblast growth factor receptor [FGFR] inhibitor),[51] cabozantinib (multi-target tyrosine kinase inhibitor),[52] and evorpacept (CD47 inhibitor).[53]

Conclusions

ADCs targeting nectin-4, trop-2, and the ErbB family are revolutionizing the treatment of aUC. EV has shown significant efficacy in the first- and subsequent-line settings and should be considered the standard of care globally. HER2-targeting ADCs T-DXd and DV show great promise in the subgroup of patients with high HER2 expression, with results from larger trials anticipated. Early evidence for trop-2 targeting ADCs is pending confirmatory phase III outcomes. Bispecific antibodies are an evolutionary step in the engineering of ADCs that may further improve efficacy of this class of therapeutics. Further research is needed to understand resistance mechanisms to ADCs and explore their potential in combination with other therapies, including other ADCs. Given the promising results and ongoing research, it is anticipated that ADCs will have a significant treatment role earlier along the UC disease trajectory in the future.

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Financial Disclosures:

PD: None declared.
AL: Grants/Research Support: BMS (Inst), BioCanRx (Inst), Novartis (Inst), Roche (Inst), Ipsen (Inst), EMD Serono (Inst);
Honoraria: AbbVie, Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, McKesson, Merck, Novartis, Pfizer, Roche, TerSera;
Administrative: Member of CDA/CADTH pCODR Expert Review Committee (pERC)

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