The Role of Antibody-Drug Conjugates in Urothelial Cancer: A Review of Recent Advances in the Treatment of Locally Advanced and Metastatic Urothelial Cancer

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ABSTRACT: Locally advanced and metastatic urothelial cancer (la/mUC) is an aggressive disease with poor prognosis. Platinum-based chemotherapy has remained the first-line treatment for decades and until recently no other treatment options existed. Today, novel agents called antibody drug conjugates (ADCs), including enfortumab vedotin (EV) and sacituzumab govitecan (SG), have been approved for la/mUC offering patients treatment options following or instead of traditional chemotherapy. The EV consists of the chemotherapy monomethyl auristatin E linked to anti-nectin-4 antibody. Single-agent response rates for EV are 40% to 52% including activity in patients with liver metastases, a phenotype associated with worse outcomes. In 2023, EV in combination with pembrolizumab almost doubled progression-free and overall survival versus platinum-based chemotherapy, which led to accelerated FDA approval as first-line treatment for all patients with la/mUC. Safety profile of EV monotherapy and combination with pembrolizumab is generally manageable with peripheral neuropathy and cutaneous toxicity among the most common treatment-related adverse events (TRAEs). The SG is another ADC targeting TROP-2 with SN-38 as payload. It is approved as late-line treatment for la/mUC with ORR 27% and most common TRAEs include gastrointestinal symptoms and neutropenia. Finally, a recent cancer agnostic accelerated approval for trastuzumab deruxtecan (T-DXd) in HER2-positive (IHC3+) solid tumors provides another active ADC option for biomarker-selected patients with treatment refractory la/mUC. Several new ADCs are being investigated in urothelial cancer (UC) clinical trials. This review summarizes the clinical studies and real-world data regarding the use of ADCs in UC.

KEYWORDS: Advanced/metastatic bladder cancer, antibody drug conjugates (ADCs), bladder cancer, checkpoint inhibitors, enfortumab vedotin (EV), Her2-positive bladder cancer, metastatic urothelial carcinoma, pembrolizumab, sacituzumab govitecan (SG)

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Introduction

Urothelial cancer occurs most commonly in the bladder but also in the ureters, and renal pelvis. Urothelial cancer of the bladder is the fourth most common cancer in men with about 62 420 estimated new cases and 12 160 new deaths in the United States for 2023 according to the American Cancer Society.[1,2] It is less common in women with about 19 870 estimated new cases and 4550 estimated deaths in the United States for 2023.[1,2] Bladder cancer tends to occur in older individuals, often smokers, with 90% of patients being above the age of 55.[2,3] Approximately 10% to 15% of patients present with metastatic disease (stage IV) at the time of diagnosis.[4] In addition, up to 50% of patients will experience distant recurrences including lymph nodes and visceral metastases within 3 years of treatments.[3]

Locally advanced (T3b, T4, and N1–N3) and metastatic urothelial cancer (la/mUC) has a historically poor approximate 13-month median overall survival (OS) with cis- or carboplatin-based chemotherapy which has been the first-line treatment for decades.[5,6] The approximate 50% of patients who are ineligible for cisplatin due to comorbidities have worse outcomes.[7] Monotherapy with programmed cell death protein 1 (PD-1) and ligand 1 (PD-L1) inhibitors added a survival benefit of 3 months compared with second-line chemotherapy but with poor disease control in patients with liver and bone metastasis, sites associated with the worst prognosis.[8] The addition of maintenance avelumab for those achieving clinical benefit on frontline platinum chemotherapy further improves survival from 14.3 months with chemotherapy alone to 21.4 months.[9] Finally, the upfront addition of nivolumab to cisplatin and gemcitabine improved OS from 18.9 months with chemotherapy alone to 21.7 months, as well as led to improved progression-free survival (PFS).[10]

In recent years, new antibody drug conjugates (ADCs) have been developed for the treatment of la/mUC, with improved treatment outcomes including cisplatin-ineligible patients and patients with visceral metastases. The purpose of this review is to summarize the landscape of current FDA-approved ADCs for la/mUC and to highlight ongoing ADC trials and new promising ADC targets.

FDA-Approved ADCs in Urothelial Cancer

There are currently 3 ADCs FDA-approved for use in urothelial cancer. Enfortumab vedotin (EV) and sacituzumab govitecan (SG) and are both approved for la/mUC and do not require biomarker selection for patient treatment. The cancer agnostic approval of trastuzumab deruxtecan (T-DXd) in HER-2-positive (IHC3+) solid tumors provides another ADC option for biomarker-selected patients. Table 1 summarizes UC clinical trials for FDA-approved ADCs and combination regimens.

Table 1. Summary of studies supporting FDA-approved ADC regimens.

DRUG	STUDY	INTERVENTION	POPULATION	N	ORR	PFS[a]	OS[a](MEDIAN FOLLOW-UP)
EV	**EV-101 Phase 1**[11]	EV dose escalation up to 1.25 mg/kg on days 1, 8 and 15 of 28-day cycle	NECTIN-4-expressing solid tumors including mUC who progressed on ⩾1 prior chemotherapy and/or PD-1/PD-L1 inhibitors	112[a]	43%[b]	5.4[b]	12.3[b] (16.4)
EV	**Japanese phase 1 study**[12]	Arm A: 1.0 mg/kg on days 1, 8, and 15 of 28-day cycle Arm B: 1.25 mg/kg of EV on days 1, 8, and 15 of 28-day cycle	Japanese patients with la/mUC	**A**: 9 **B**: 8	**A**: 44.4% **B**: 25% **Overall**: 35.3%	-	-
EV	**EV 201 phase 2**[13,14]	EV dose 1.25 mg/kg on days 1, 8, and 15 of 28-day cycle	Cohort 1: Cisplati-eligible patients Cohort 2: Cisplatin-ineligible patients	**1**: 125 **2**: 89	**1**: 44% **2**: 52%	**1**: 5.8 **2**: 5.8	**1**: 11.7 (10.2) **2**: 14.7 (13.4)
EV	**EV-301 phase 3**[15]	EV 1.25 mg/kg on days 1, 8, and 15 of 28-day cycle versus investigator's choice of CT	la/mUC following disease progression with platinum and PD-1/L1 inhibitors	608	EV: 40.6% CT: 17.9%	EV: 5.55 CT: 3.71	EV: 12.88 CT: 8.97 (11.1)
EV + P	**Phase 1/2b**[16,17]	Cohort A: EV 1.25 mg/kg on days 1 and 8 of a 21-day cycle and P 200 mg Cohort K: EV 1.25 mg/kg on days 1 and 8 of a 21-day cycle and P 200 mg versus EV 1.25 mg/kg on days 1, 8, and 15 of 28-day cycle	Cisplatin-ineligible patients	**A**: 45 **K**: EV + P: 76 EV: 73	**A**: 73.3% **K**: EV + P: 64.5% EV: 45.2%	**A**: 12.3 **K**: EV + P: - EV: 8	**A**: 26.1 (20.0) **K**: EV + P: 22.3 (14.8) EV: 21.7 (15.0)
EV + P	**EV-302 phase 3**[18]	EV 1.25 mg/kg on days 1 and 8 of a 21-day cycle and P 200 mg on day 1 versus platinum-based chemotherapy	Previously untreated la/mUC	886	EV + P: 67.7% CT: 44.4%	EV + P: 12.5 CT: 6.3	EV + P: 31.5 CT: 16.1 (Overall: 17.2)
SG	**TROPHY-U-01 phase 2**[16,19]	SG 10 mg/kg on days 1 and 8 of a 21-day cycle	la/mUC after disease progression with platinum and PD-1/L1 inhibitors	113	27.4%	5.4	10.9 (9.1)
T-Dxd	**DESTINY-PanTumor02 Phase 2**[20]	5.4 mg/kg once in a 3-week cycle	HER2+ ([IHC] 3+/2+) solid tumors with disease progression post at least 1 prior therapy	UC: 41	35-56%	7.0 (4.2-9.7)	12.8 (11.2-15.1)

ADC: antibody-drug conjugate; CT: chemotherapy; EV: enfortumab; la/mUC: locally advanced / metastatic urothelial cancer; P: pembrolizumab; PD-1/PD-L1: programmed death-1 receptor/programmed death ligand-1; SG: sacituzumab govitecan; T-Dxd: trastuzumab deruxtecan .
[a]Presented in months.
[b]For patients with mUC who received 1.25 mg/kg dose of EV.

Enfortumab vedotin

The EV is an ADC consisting of a human monoclonal antibody targeting NECTIN-4, linked to the chemotherapy payload monomethyl auristatin E (MMAE) currently approved for the treatment of la/mUC as monotherapy and in combination with pembrolizumab (P).[21] The MMAE belongs to the family of auristatins, which are cytotoxic agents that induce apoptosis by binding and disintegrating microtubules.

NECTIN-4, also known as poliovirus receptor–related protein (PVRL4), is overexpressed in several solid tumors including breast, non–small-cell lung, pancreatic, ovarian, and bladder cancers.[21-23] In bladder cancer, although NECTIN-4 has been found to be overexpressed, its expression was found to be heterogeneous in non-urothelial histotypes including small-cell and squamous cell and sarcomatoid carcinomas in a retrospective study of 169 patient samples.[22,23] Moreover, in a retrospective study of 47 patients,

membranous NECTIN-4 expression was often decreased in metastatic sites compared with the primary tumor.[24] However, a different study showed NECTIN-4 amplification and protein expression to be stable in matched primary and metastatic tumors.[24] The same study demonstrated an association of NECTIN-4 amplification with improved response rate (96% vs 32%) and OS (hazard ratio [HR]: 0.08; 95% confidence interval [CI]: 0.02-0.34; $P < .001$) in a retrospective study of 108 patients.[24] NECTIN-4 expression when measured in prospective studies has been generally high, but responses have occurred in patients with low expression.[11] However, NECTIN-4 expression and amplification have not been shown to precisely correlate with response to treatment in prospective studies, despite the proposed targeted mechanism of EV.[11]

EV efficacy and toxicity in prospective clinical trials

Phase 1 studies. **EV-101** was a phase 1 dose escalation/expansion study that included patients with solid NECTIN-4-positive tumors including metastatic UC who had experienced disease progression with ⩾1 prior chemotherapy and/or immunotherapy agent.[11] The primary objectives of this study were safety and tolerability of EV as well as its pharmacokinetics.

Due to the extremely high median NECTIN-4 expression levels measured by immunohistochemistry (H score: 290/300) NECTIN-4 positivity was eventually removed as an inclusion criterion. Most patients enrolled (n = 155) had metastatic UC and were in late-line treatment setting with 120 (77%) patients having visceral metastases at time of enrollment. In total, 149 (96%) had received prior platinum-based chemotherapy, 112 (72%) had received programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors and 45 (29%) had received ⩾3 prior regimens. Median age was 67 years. Forty-four (28%) of patients were women and 38 (25%) had upper tract UC.

Patients received escalating weight-based doses up to 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle which was defined as the recommended phase 2 dose. The EV was well tolerated at the 1.25 mg/kg cohort with fatigue (53%) as the most common all-grade treatment-related adverse event (TRAE) followed by alopecia (46%) and decreased appetite (42%). Other TRAEs included decreased appetite, dysgeusia, nausea, peripheral sensory neuropathy, pruritus, and diarrhea. The most common ⩾ grade 3 event was maculopapular rash (3%). Reported objective response rate (ORR) for the 112 patients with mUC who received the recommended the recommended 1.25 mg/kg dose was 43% with 5% experiencing a complete radiographic response. Median OS was 12.3 months.

A smaller Japanese-based phase 1 study published prior to EV-101, included 17 patients with la/mUC who were randomized to 1 versus 1.25 mg/kg dose of EV.[12] This study also concluded that 1.25 mg/kg dose of EV was well tolerated with a similar toxicity reported in EV-101. The ORR was 35% including one complete response and median PFS was 8.1 months.

Phase 2 study. **EV-201** was a phase 2 international study of EV 1.25 mg/kg in patients with la/mUC with ORR as the primary endpoint.[13,14] The study included 2 separate cohorts: Cohort 1 included cisplatin-eligible patients with la/mUC following disease progression on platinum-based chemotherapy and PD1/PDL1 inhibitors and cohort 2 included cisplatin-ineligible patients who had been treated only with PD1/PDL1 inhibitors.

Cohort 1 included 125 cisplatin-eligible patients, including 88 (70%) men, 44 (35%) patients with upper tract UC, and 112 (90%) with visceral metastases.[13] Median age was 69 years. Reported median time to first response was 1.84 months. The EV had a clinically meaningful ORR of 44% (95% CI, 35.1% to 53.2%), including 12% complete responses. Median duration of EV treatment was 4.6 months and median duration of response was 7.6 months. The ORR was similar in subgroups historically associated with worse outcomes including patients with liver metastasis and tumors that did not to PD-1/L1 inhibitors. The drug was well tolerated with the most common TRAEs being fatigue (50%), any peripheral neuropathy (50%), alopecia (49%), and any rash (48%). The most common grade ⩾ 3 event was fatigue (6%).

Cohort 2 enrolled 89 patients with la/mUC previously treated with PD1/PDL1 inhibitors who were treated with the standard EV dose.[14] Median age was 75 years with 43% of patients having primary upper tract UC and 79% visceral metastasis at the time of enrollment. The ORR at cutoff was 52%, with 20% complete responses. Notably, this is the highest ORR reported in an la/mUC monotherapy trial, despite the comorbidities of cisplatin-ineligible participants: 12% had baseline ECOG performance status 2, 13% had hearing loss, and 69% had creatinine clearance < 60 mL/min at EV initiation. Overall EV was well tolerated with some of the most common TRAEs of hyperglycemia, decreased appetite, diarrhea, skin toxicities, and peripheral neuropathy. In all, 55% of patients experienced grade 3 or higher TRAEs, including neutropenia (9%), maculopapular rash (8%), and fatigue (7%). Four treatment-related deaths occurred due to acute kidney injury, metabolic acidosis, multiple organ dysfunction syndrome, and pneumonitis, although all 4 patients had other comorbidities.

Phase 3 study. **EV-301** was an international, open-label, randomized phase 3 trial of EV versus investigator's choice of docetaxel, paclitaxel, or vinflunine in patients with la/mUC following disease progression with platinum-based chemotherapy and PD-1/L1 inhibitors.[15] Overall survival was the primary endpoint. Of the 608 enrolled patients, 301 were randomized to the EV group. Both groups had largely similar baseline characteristics including 63 (20.9%) versus 75 (24.4%) females, 98 (32.65) versus 107 (34.9%) patients with upper tract tumor location and 52 (17.3%) versus 68 (22.1%) patients above 75 years in EV and chemotherapy groups, respectively. Among

EV-treated patients, 234 (77.7%) had visceral metastasis at treatment initiation compared with 250 (81.7%) in the chemotherapy group.

The EV was associated with approximately 4 months OS benefit compared with chemotherapy (HR = 0.70 [95% CI: 0.56-0.89]; $P = .00142$). Progression-free survival was 5.55 versus 3.71 months in the EV and chemotherapy groups, respectively (HR = 0.62 [95% CI: 0.51-0.75]; $P < .00001$). These results led to full FDA approval of EV. The ORR was 40.6% in EV and 17.9% in chemotherapy group (95% CI: 13.7-22.8, $P < .001$] with 4.9% and 2.7% complete responses, respectively. Frequency of any grade TRAEs and grade ⩾ 3 was comparable between groups. Alopecia (45.3%) and peripheral sensory neuropathy (33.8) were the most common any grade TRAEs associated with EV while maculopapular rash was the most common grade ⩾ 3 event (7.4%).

EV + pembrolizumab (P) trials. **EV-103** was a phase 1b/2, multicenter, open-label study, of first-line EV and pembrolizumab (P) in cisplatin-ineligible patients with la/mUC.[16,17] Patients received EV 1.25 mg/kg on days 1 and 8 of a 21-day cycle and pembrolizumab 200 mg intravenously on day 1. The primary end point was safety. The results from this study led to the approval of EV with pembrolizumab as first-line therapy for cisplatin-ineligible patients with la/mUC.

Cohort A was a dose expansion cohort of 51 patients.[16] Nine (20%) patients were women and 16 (35.6%) were older than 75 years. Most patients had visceral metastasis at time of enrollment (38 patients [88.4%]) and 15 (33.3%) had primary tumors located in the upper tract. Eight (17.8%) patients had ECOG PS of 2. Fourteen (31.1%) patients had high PD-L1 expression (combined positive score [CPS] ⩾ 10). Reported ORR was 73.3%, including 15.6% complete responses. Median PFS was 12.3 months. After nearly 4 years of follow-up, all patients had discontinued treatment with a median of 9 cycles.[25] The OS was 26.1 months (95% CI: 15.51—not reached) and PFS was 12.7 months (95% CI: 6.11—not reached)

Peripheral sensory neuropathy was the most common any grade TRAE (55.6%), and fatigue was the second most common (51.1%). Most common grade ⩾ 3 event was having asymptomatic increased lipase levels which occurred in 8 (17.8%) patients.

Cohort K enrolled 151 patients with la/mUC who were randomly assigned to EV monotherapy (N = 74) or EV plus pembrolizumab (N = 77).[17] The EV + P group included 54 (71.1%) men, whereas monotherapy included 56 (76.7). Mean age was 71 versus 74 years in the EV + P and monotherapy group, respectively. Among patients who received the combination regimen, 10 (13.2%) had ECOG PS > 2% and 64 (84.2%) had visceral disease versus 10 (13.7%) and 60 (82.2) patients in the other group. Thirty-one (40.8%) in the EV + P group and 28 (38.4%) in the monotherapy group had high PD-L1 score (CPS ⩾ 10).

The ORR among patients who received the combination was 64.5% (95% CI: 52.7-75.1) including 8 (10.5%) complete responses. Among patients treated with EV alone, ORR was 45.2% (95% CI: 33.5-57.3) and 3 (4.1%) experienced a complete response. However, there was no statistical comparison between groups. In terms of safety, both regimens were well tolerated with 48 (63.2%) grade ⩾ 3 TRAEs in the combination group and 35 (7.9%) in the monotherapy group. Common TRAEs in the EV + P group were fatigue (56.6%), peripheral sensory neuropathy (51.3%), alopecia (46.1%), and maculopapular rash (46.1). Maculopapular rash was also the most common grade ⩾ 3 event (17.1%). Similarly, in the monotherapy group, the most common TRAEs were peripheral sensory neuropathy (43.8%), fatigue (39.7%), decreased appetite (38.4), and alopecia (35.6%).

EV-302 was an open-label randomized phase 3 trial of EV in combination with pembrolizumab versus standard platinum-based chemotherapy in patients with previously untreated la/mUC.[26] Primary endpoints were PFS and OS. The study enrolled 442 patients in the EV + P group including 344 (77.8%) males, 135 (30.5%) patients with upper tract UC and 318 (71.9%) with visceral metastases. The chemotherapy group included 444 patients with largely similar baseline characteristics: 336 (75.7%) men, 104 (23.4%) primary tumors of the upper tract, and 318 (71.6%) patients with visceral disease. Median age was 69 years in both groups. Approximately half patients in each group were ineligible for cisplatin (54.3% vs 54.5%) and had high PD-L1 expression compared with (58% versus 57.9%).

Median PFS was 12.5 months among patients who received EV + P versus 6.3 months in the chemotherapy group (31.5 vs 16.1 months; HR: 0.45, 95% CI: 0.38-0.54). Median OS was almost double in the EV + P group compared with the chemotherapy group (31.5 vs 16.1 months; HR: 0.47, 95% CI: 0.38-0.58). Interestingly, subgroup analysis for OS showed benefit with EV + P in all subgroups examined. The ORR was also higher in the EV + P group (68% vs 44%) with an impressive 29.1% complete responses versus 12.5% in the chemotherapy group.

The combination therapy was generally well tolerated with skin reactions and peripheral neuropathy being the most common any grade TRAEs and the most common grade ⩾ 3 events. More specifically, any grade skin reactions were reported in 66.8% of patients and grade ⩾ 3 skin reactions in 15.5%. Any grade neuropathy was observed in 63.2% of patients and grade ⩾ 3 in 6.8. These were the most common TRAEs among chemotherapy-treated patients as well, with 13.9% and 0.2% any grade and grade ⩾ 3 skin events, respectively, and 12.2% and 0% any grade and grade ⩾ 3 peripheral neuropathy.

The study was presented at the 2023 European Society of Medical Oncology (ESMO) Annual Congress and led to full FDA approval of EV with pembrolizumab as first-line treatment for all patients with la/mUC in December 2023.[18]

Enfortumab and Pembrolizumab now is the preferred frontline regimen for cisplatin-eligible and cisplatin-ineligible patients in US and European Guidelines.[27,28]

Sacituzumab govitecan

Sacituzumab govitecan is another FDA-approved ADC targeting trophoblast cell surface antigen 2 (TROP-2) via the humanized monoclonal antibody hRS7 IgG1κ. The chemotherapy payload in SG is SN-38, the active metabolite of irinotecan which is a topoisomerase 1 inhibitor.[19,29]

TROP-2 is encoded by *TACSTD2* and is a member of tumor-associated calcium signal transducer (*TACSTD*) gene family, which also includes the gene encoding epithelial cell adhesion molecule (EpCAM) also known as TROP-1.[30] TROP2 is overexpressed in many carcinomas, including colorectal cancer, gastric cancer, and pancreatic cancer.[30]

TROP2 has been found to be highly expressed in the RNA and protein level, in all subtypes of bladder and upper tract UC except neuroendocrine tumors.[31,32]

The coupling of SN-38 to the anti-TROP-2 antibody has been shown to increase its efficacy in vivo and in vitro.[33] TROP-2 is a transmembrane glycoprotein found on the surface of trophoblasts.[29] It is highly expressed in a most epithelial cancers including UC,[34] drives cancer cell growth, and has been associated with poor patient outcomes.[29,35-37]

SG efficacy and toxicity in prospective clinical trials. First, FDA approved in triple-negative breast cancer, SG showed promising results in phase 1/2 basket studies.[38] Safety was assessed across different metastatic solid tumors, including 45 patients with previously treated la/mUC for whom reported ORR was 31% with 2 complete responses.[39-42]

Phase 2 study. **TROPHY-U-01** (NCT03547973) was multicohort, open-label, phase 2 study of SG in patients with la/mUC. Sacituzumab is administered intravenous 10 mg/kg dose on days 1 and 8 of a 21-day cycle. Primary outcome was ORR. It initially included 6 cohorts, but as of December 2023, cohort 5 was canceled.

Cohort 1 included 113 patients with la/mUC who had experienced disease progression with platinum-based chemotherapy and checkpoint inhibitors.[19] Median age was 66 years and 78% of patients were men. At the time of enrollment, 66.4% of patients had visceral disease. Patients were heavily pretreated with 59% having ⩾3 prior metastatic lines of therapy. All patients had platinum-based chemotherapy, and all expect one had prior checkpoint inhibitors. The ORR was 27% (95% CI: 19-37) with 6 (5%) patients having a complete response. Median PFS was of 5.4 months and OS was 10.9 months. These results led to the drug's accelerated FDA approval for la/m UC on April 2021.

The drug was well tolerated with most common TRAEs being diarrhea (65%), nausea (60%), fatigue (52%), alopecia (47%), and neutropenia (46%). Most common grade ⩾3 TRAEs were neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), and febrile neutropenia (10%). Interestingly, the study included 11.5% of patients homozygous for UGT1A1 and 41.6% who were heterozygous; these patients were found to have numerically higher frequency of neutropenia compared with the 39.8% of patients with wild-type mutations (54% vs 51% vs 38%, respectively).

Cohort 2 included platinum ineligible patients following disease progression with first-line checkpoint inhibitors.[43] Eighteen patients with 50% women and median age of 79 years were enrolled. In total, 67% of patients had visceral disease at enrollment. Patients had median of 2 (range:1-5) prior lines of therapy. Reported ORR was 28% with no complete responses. Most common grade ⩾3 TRAEs were neutropenia (39%), fatigue (33%), diarrhea (28%) leukopenia (22%), anemia (17%), and febrile neutropenia (11%).

In *cohort 3*, SG was tested in combination with pembrolizumab as second-line treatment in patients who had tumor progression after platinum-based therapy who have not had prior immune checkpoint inhibitor therapy.[44] Forty-one patients were enrolled including 83% men, and 78% of patients having visceral metastases. Median age was 67 years. There was a promising 41% ORR with 8 complete responses; thus, the study met its primary endpoint. Median number of cycles was 8. Median PFS was 5.3 months and median OS was 12.7 months. All patients experienced at least 1 TRAE of any grade. The regimen was well tolerated with 61% of patients experiencing grade ⩾3 TRAEs, including neutropenia (37%), leukopenia (20%), and diarrhea (20%).

Cohorts 4 and 6 are ongoing, and no results have been published yet.[45] Cohort 4 evaluates SG in combination with cisplatin as first-line therapy for metastatic UC, followed by maintenance avelumab with SG or the checkpoint inhibitor zimberelimab with SG. Cohort 6 includes first-line SG monotherapy, SG plus checkpoint inhibitors (zimberelimab or zimberelimab + domvanalimab), or carboplatin + gemcitabine followed by avelumab maintenance in cisplatin-ineligible patients with metastatic UC. The results of the phase 3 trial evaluating SG versus physician's choice chemotherapy in patients with la/mUC urothelial cancer post platinum and anti (PD-1/PD-L1) therapy are soon awaited (NCT04527991).

Trastuzumab Deruxtecan

Recent interest has also developed in HER-2-directed ADCs, as HER-2 expression is high in approximately 6.7% to 37.5% of la/mUC.[46,47] Trastuzumab deruxtecan (T-Dxd) is a HER-2-binding ADC previously approved for breast carcinoma.[20,48] The payload of T-Dxd is a topoisomerase 1 inhibitor similarly to SG.

The DESTINY-PanTumor02 Phase II Trial included 7 solid tumor cohorts with disease progression post at least 1 prior standard agent and required tumors have HER-2-overexpression

by IHC (3+ or 2+). The ORR across all solid tumors was 37.1%, with a median duration of response of 11.3 months. In the 41 patient urothelial cancer cohort, the ORR of 5.4 mg/kg q 3 weeks T-Dxd was 35% for (HER-3 2+) and 56% for (HER-2 3+) by IHC score.[20] The total PFS in the combined bladder cancer cohort was 7 months, and a combined OS of 12.8 months in this heavily pretreated cohort. Serious adverse events grade 3 and high were seen in 41.5% of this group including previously reported GI toxicity and neutropenia. Drug-related pulmonary toxicity is a well-described side effect of T-DXd, and was reported in 10.5% of the entire 267 patient solid tumor cohort, and led to 3 deaths. In April 2024, the FDA granted accelerated approval to T-Dxd with unresectable or metastatic HER-2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. This is a powerful new therapy for fit, biomarker-selected patients with treatment refractory urothelial cancer.

Real-world data

Due to the explosion of agents with activity in mUC, and combinations in clinical studies, it is important to define the optimal sequencing of treatments as well as identify biomarkers of response to ADCs and ADC combinations. A lot of real-world studies have proposed such biomarkers; however, none of them are prospectively validated. *TP53* or *MDM2* alterations have been retrospectively correlated with improved survival after either EV or SG monotherapy in multicenter studies.[49,50] Other promising biomarkers of response to EV include alterations in *KDM6A, MDM2, ERBB2*.[50,51] However, all of these promising data require further validation in prospective studies.

Regarding the efficacy of EV in subgroups of patients traditionally excluded from clinical trials including patients with significant comorbidities and glomerular filtration rate <30 mL/min the Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) study reported similar outcomes to those observed in clinical trials.[52] However, a numerically lower ORR was reported for patients with variant histology tumors compared with pure UC.[49] Moreover, cutaneous toxicity correlated with improved ORR and disease control rate after EV treatment in a retrospective cohort of patients with la/mUC.[53] Severity of EV-related cutaneous events was also associated with prior checkpoint therapy in a small retrospective study.[54] Frequency of EV-related cutaneous toxicity also appeared to be numerically increased among black compared with White patients in a singe-center and a multicenter real-world cohort.[55] A multicenter Japanese study of EV-treated patients including 556 patients concluded that EV relative dose intensity did not correlate with survival.[56]

Despite the excellent response of EV in patients with liver metastases, a poor prognostic factor in patients with UC, little is known about its effects in brain metastases, a rare metastatic location in UC.[15,26] Brain metastases are also associated with poor prognosis and patients with central nervous system (CNS) disease were excluded from EV clinical trials.[15] A case series of 67 patients treated with EV monotherapy and combination regimens reported that 9 (13.4%) patients developed brain metastases during or after EV treatment.[57] This result is higher than what had been previously reported (1%-3%) and could indicate decreased CNS activity of EV.[57] An alternative and likely explanation could be that the prolonged survival of patients with advanced UC, resulting from the development of novel treatments like EV, allows more time for CNS metastases to develop.[57] A recent case series of 3 patients with brain metastases has been reported, all with radiographic benefit, indicates use of enfortumab may be a reasonable strategy in selected patients with brain metastases starting EV.[58]

Other approved ADCs such as SG and T-Dxd have shown promising results in the treatment of breast cancer CNS metastases.[59,60] However, the effects of these drugs in patients with UC metastasized to the brain has not been reported.

While it is without a doubt that EV-P combination has revolutionized the management of la/mUC, an interesting question that has risen is whether the unprecedented response and survival outcomes seen with EV-P is due to just the additive effect of the combination therapy, or synergy between the agents. No definitive answer exists to date. The ORR to EV-P combination is approximately 68% which at first seems to be the result of simply adding ORR to EV (approximately 40%) and P (approximately 25%).[15,26,61] However, the answer is not that simple since patients who respond to EV and patients who respond to P are not mutually exclusive and we would expect some overlap. In addition, NECTIN-4 has been associated with PI3K-AKT pathway activation and synergy of PI3K inhibition with anti–CTLA-4 agents has been previously reported.[62,63] Thus, NECTIN-4 ADCs may have synergy with other immune checkpoint inhibitors such as P, potentially via activation of the PI3K pathway.

Regarding the optimal sequencing of currently approved ADCs, very little is known, as these agents have been developed contemporaneously. In TROPHY-U-01 cohort 1, only 10 (8.8%) patients had prior EV with an ORR of 30% in that small group.[19] Reported ORR for SG varies from 17% to 23% in retrospective studies.[49] One small single-center study of 10 patients reported worse outcomes with stable disease as best response to SG in patients previously treated with EV.[64] In addition, PFS, OS, and ORR to SG were numerically higher in patients who had experience complete or partial response to prior EV compared with nonresponders.[65] Data of outcomes following EV-P combination are also scarce and mainly extrapolated from retrospective studies.[66] Reported ORR of patients treated with prior EV and prior P are 32% with platinum chemotherapy, 31% with erdafitinib, and 21% to 30% with SG.[65-68]

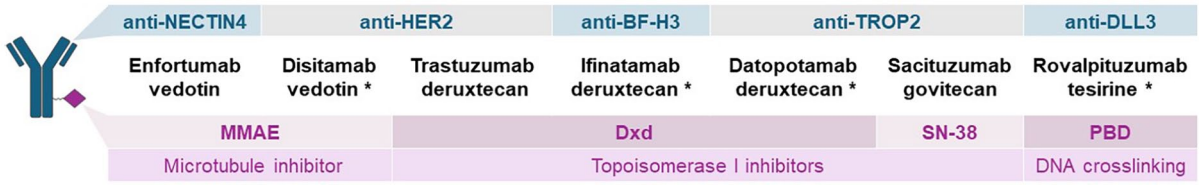

Figure 1. Mechanism of antibody drug conjugates (ADCs) used in urothelial cancer.
ADC targets are presented in blue, and payload is presented in purple. * represents ADCs in ongoing clinical trials that have not been approved.

Finally, a small retrospective study of 42 patients with non-muscle-invasive bladder cancer demonstrated increased NECTIN-4, TROP-2, and HER-2 following Bacillus Calmette-Guerin (BCG) treatment raising the question of whether these recently approved ADCs can also be effective in earlier disease stages.[69] A study of intravesical EV is underway in patients with non-muscle-invasive urothelial bladder cancer with BCG—unresponsive disease (NCT05014139).

Future Directions

New combinations with approved ADCs

Given the promising efficacy of single-agent EV and SG, and the recent approval of EV plus pembrolizumab as first-line treatment for patients with mUC, EV, and SG have been tested in combination with other agents. One question as a result of EV-302 is what is now the optimal second-line therapy for patients with mUC. In cohort 3 of phase 2, TROPHY-U-01 SG in combination with pembrolizumab demonstrated a meaningful 41% ORR.[70] As a result of the above study, one would ask whether switch to SG plus continuation of programmed death-1 blockade (with pembrolizumab) results in survival superior to second-line platinum-based chemotherapy. In the DAD phase 1 trial, patients with mUC who had tumor progression on platinum-based chemotherapy and immune checkpoint inhibitor were treated with combination EV plus SG, achieving a 70% response rate.[71] However, in this small cohort, toxicity of this combination was higher compared with monotherapy studies with 70% of patients experiencing grade ≥ 3 events.[27,29,49]

In a phase 1b study, Galsky and colleagues determined that the combination of T-Dxd and nivolumab in patients whose tumors were HER-2 positive (2+ or 3+), and who received platinum-based chemotherapy (NCT03523572), led to a 37% ORR.[72]

Promising new ADCs

Novel approaches used to develop ADCs typically involve modifying the target bound by the ADC, the linker, or the payload (Figure 1). Datopotamab deruxtecan (DS-1062, Dato-DXd) is an anti-TROP2 antibody that uses the topoisomerase I inhibitor Dxd payload instead of the SN-38 (also a topoisomerase I inhibitor) used in SG.[73] Dato-DXd was tested in the first in human, phase 1 TROPION-PanTumor01 study which included a cohort of patients with mUC, with a response rate of 19.2% in the mUC cohort.[74] Another ADC using Dxd as the payload is ifinatamab deruxtecan, which is currently in a first in human clinical trial (NCT04145622). Ifinatamab deruxtecan uses the novel B7H3 target, which is highly expressed in bladder cancer in at least one study.[75]

In addition, pooled data from 2 phase 2 studies (NCT03507166 and NCT03809013) of disitamab vedotin (DV), a HER-2 antibody with a MMAE payload, revealed a 51% response rate in patients with HER-2 positive tumors, and had tumor progression on platinum and taxane therapy.[76] In addition, another ongoing phase 2 trial is evaluating the efficacy and safety of DV in patients with HER-2-positive urothelial cancer.[77] Galsky and colleagues are testing DV plus pembrolizumab versus chemotherapy in patients with untreated Her2 positive mUC in an ongoing phase 3 study (NCT05911295).

Mechanisms of resistance to ADCs are underexplored, and at current it is not clear whether a switch from one ADC to another with identical payload is a reasonable strategy. For example, DV has the same MMAE payload as EV and it is unknown whether the response rate for DV is similarly high after treatment with first-line EV + pembrolizumab. Similarly, is efficacy impaired when ADCs with similar protein targets are given in sequence, for example, does datopotamab deruxtecan have a high response rate if given after SG? The answer is not obvious; however, downregulation of surface proteins may impact downstream efficacy of subsequently given agents. In HER-2-positive breast cancer, the HER-2 targeting ADC T-Dxd has efficacy when given after T-DM1, despite both having similar protein targets.[78] One potential solution is the incorporation of bicycle agents, which differ from ADCs due to their short half-life pharmacokinetics (similar to small molecules), and their ability to be cleaved to release payload, while in the tumor microenvironment, instead of requiring internalization.[79] A phase 1/2 study of BT8009 (NCT04561362) demonstrated 4 of 8 (50%) patients with mUC with no other treatment options had an objective response.[80] Based on these findings, the Duravelo-2 trial will open in 2024 with plan to compare BT8009 plus pembrolizumab versus chemotherapy in the first-line setting, with this combination also tested in a cohort of patients with previously treated mUC.

Rovalpituzumab tesirine (Rova-T) is another ADC targeting DLL3 with a DNA-damaging pyrrolobenzodiazepine

dimer toxin payload.[81] Rova-T has shown promising results in preclinical models of DLL3-positive small-cell bladder cancer tumors.[81] However, a phase 3 study of Rova-T versus standard of care topotecan as second-line treatment for patients with small-cell lung cancer demonstrated lower OS and higher incidence of serosal effusions, photosensitivity reaction, and peripheral edema among Rova-T-treated patients.[82]

Finally, CUB domain–containing protein 1 (CDCP1) is a interesting target for UC and other solid tumors. Recently, an ADC targeting CDCP1 with MMAE payload induced breast cancer cell death in vitro and high CDCP1 expression was found in 53% of tumors examined in a retrospective study of 1047 bladder cancer biopsies.[83,84]

Study limitations

The main limitation of this study is that we did not perform a systemic review of the literature in this rapidly changing field.

Conclusions

In conclusion, ADCs are a powerful class of agents that have become increasingly important components of la/mUC therapy. Enfortumab and pembrolizumab for la/mUC in biomarker unselected patients are now the frontline standard. This is important as delays in treatment for biomarker assessment can impact therapy eligibility, timing to start, and ultimately outcomes in this aggressive disease. With more agents approved and, on the horizon, a toolkit for clinicians to rationally sequence therapy based on use of biomarkers at baseline and in tissue at progression, and with the understanding of response and resistance mechanisms to these agents, particularly with similar or same payload, will be vital to clinical care. How best to combine ADCs to potentially intensify effect in the frontline, sequence them with other agents, and find effective biomarkers predictive of outcomes and toxicity, as well as to describe and overcome resistance mechanisms will be important questions to answer in the future.

The differences in toxicity and efficacy of treating patients with sequential ADC with the same payload and different targets also remain to be fully investigated. For example, HER-2 targeting DV does not seem to cause hyperglycemia where EV can. Future trials will determine whether switching to a different agent with the same payload for patients with response, but poor tolerance is a viable option. Exploration of the roles of multi- agent synergy and drug resistance mechanisms will further inform future treatment strategies and areas of trial development.

Author contributions

Evangelia Vlachou: concept/design, data gathering and interpretation, manuscript writing, approved the version to be published.

Burles Avner Johnson 3rd: concept/design, data gathering and interpretation, manuscript writing, approved the version to be published.

Jean Hoffman-Censits: concept/design, data interpretation, critical manuscript revision/editing, approved the version to be published.

All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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