



# Emerging agents for the treatment of metastatic urothelial cancer

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Over the past few decades, platinum-based combination chemotherapy (PBCC) has been the preferred initial therapy for metastatic urothelial cancer (mUC). However, despite a response rate of approximately 50%, a small proportion of patients with distant metastases may be cured by cisplatin-based combination chemotherapy (CBCC). In addition, up to 50% of patients are not eligible for CBCC due to age or comorbidities. Furthermore, adverse effects from PBCC are a major concern. The emergence of check-point inhibitors (CPIs), particularly those with antibodies directed against programmed cell death 1 protein (PD-1) or its ligand (PD-L1), advanced the treatment of mUC. Avelumab switch-maintenance therapy is recommended in patients with locally advanced or mUC who did not progress on initial PBCC. With the recent advances in tumor molecular biology and the discovery of actionable therapeutic targets, the clinical application of targeted therapy is now being explored for mUC. Erdafitinib, a tyrosine kinase inhibitor of FGFR1–4, has shown positive outcomes in patients with advanced UC with FGFR alterations. Another recent technological development is antibody-drug conjugates (ADCs), which are complex molecules composed of an antibody linked to a biologically active cytotoxic drug (payload) that targets and kills tumor cells while sparing healthy cells. Enfortumab vedotin, a monoclonal antibody targeting nectin-4 conjugated to monomethyl auristatin E, has demonstrated clinically significant efficacy in patients who do not respond to both cytotoxic chemotherapy and CPIs. In this review, we describe switch-maintenance therapies using CPI, various targeted agents, and ADCs that have been investigated for mUC treatment.

**Keywords:** Antibody drug conjugate; Avelumab; Bladder cancer; Fibroblast growth factor receptor

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## INTRODUCTION

Metastatic urothelial cancer (mUC) is a fatal disease with a 5-year survival rate of 5% [1]. Platinum-based combination chemotherapy (PBCC) has been the standard first-line therapy for mUC, and is associated with a high response rate; however, the median survival of patients that receive cisplatin-based combination chemotherapy (CBCC)

is approximately 15 months and the 5-year survival rate is approximately 15% [2]. In addition, approximately 40% to 50% of patients are generally not eligible to use cisplatin due to comorbidities (renal dysfunction, poor performance status, neuropathy, or cardiovascular disease) [3]. Prior to the introduction of check-point inhibitors (CPIs), these patients were treated with carboplatin-based chemotherapy, despite achieving less response and shorter survival rates than

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those with CBCC.

Immunotherapy research related to CPIs has led to important advances in the treatment of mUC and other malignancies, particularly with antibodies directed against programmed cell death 1 protein (PD-1) or its ligand (PD-L1). CPIs block the suppressive signals produced by these immune checkpoint proteins and enhance antitumor T cell immunity [4]. From May 2016 to May 2017, the U.S. Food and Drug Administration (FDA) approved atezolizumab, durvalumab, avelumab, pembrolizumab, and nivolumab for patients with locally advanced UC or mUC whose disease recurred after PBCC [5]. Furthermore, atezolizumab and pembrolizumab were recently granted accelerated approval by the FDA as a first-line treatment for cisplatin-ineligible patients based on PD-L1 expression [6,7]. However, approximately 70% to 80% of patients may remain unresponsive to CPIs [8]. Furthermore, there are no predictive biomarkers, and it remains unclear when or whether treatment can be terminated. CPIs are not only used alone but have also been developed in combination with or sequentially to PBCC [9].

Chemotherapy with taxane, pemetrexed, or vinflunine could be considered as a subsequent therapy. However, single-agent chemotherapy is associated with a shorter duration of response, inconsistent improvement in survival, and adverse events (AEs) [10]. Thus, there remains an unmet need to develop additional therapies for patients who relapse following treatment with a PBCC and immunotherapy. In this milieu, there has been increasing interest in the use of another family of drugs, targeted therapies, and antibody-drug conjugates (ADCs).

This review summarizes the information and available data regarding the first-line systemic therapy containing switch maintenance using avelumab, various targeted agents, and ADCs that have recently shown promising results against mUC.

## SWITCH MAINTENANCE THERAPY USING CHECK-POINT INHIBITOR IN mUC

CBCC is the preferred initial therapy for patients with mUC who are cisplatin candidates. However, cisplatin-related toxicity remains a concern for many patients. In addition, cumulative toxicity of cisplatin-based chemotherapeutic agents limit treatment periods. There is a growing interest in maintenance therapy using fewer toxic drugs to prolong the benefits of first-line therapy. Maintenance therapy has already been established for several solid tumors, including ovarian, lung, breast, gastric, and colorectal cancers [11].

However, maintenance therapy using targeted therapies or conventional chemotherapies have not shown an improvement in overall survival (OS) in patients with mUC [12-14]. Maintenance therapy can be categorized as continuation maintenance, in which an agent is continued as a part of the first-line regimen, or switch maintenance, in which an alternative less toxic agent is used [15]. Based on the effects of CPIs, pembrolizumab was investigated as a maintenance therapy (HCRN GU14-182) with a randomized phase II, double-blind placebo-control study of 108 patients with mUC who experienced complete response (CR) or partial response (PR) or stable disease (SD) after up to eight cycles of first-line PBCC [16]. The inclusion criteria were adequate organ function and Eastern Cooperative Oncology Group performance status (ECOG PS) of  $\leq 1$ . The criteria for exclusion were usage of chronic immunosuppressive drug, previous CPI therapy, and active brain metastases. Progression-free survival (PFS) was the primary end points. OS and treatment outcomes according to the PD-L1 combined positive score (CPS) were the secondary end points. Pembrolizumab (200 mg) was administered intravenously once every 3 weeks for up to 24 months in 55 patients as a switch-maintenance therapy. Alternatively, a placebo was administered in 53 patients during the same period of time. Pembrolizumab significantly prolonged the PFS than placebo (5.4 mo, 95% confidence interval [CI]=3.1–7.3 mo vs. 3.0 mo, 95% CI=2.7–5.5 mo; hazard ratio [HR]=0.65; log-rank  $p=0.04$ ). The OS was 22 months (95% CI, 12.9 months to not reached) with pembrolizumab and 18.7 months (95% CI, 11.4 months to not reached) with placebo. The OS in the study was not significantly different in patients with maintenance pembrolizumab versus placebo (log-rank  $p=0.7477$ ).

Another maintenance treatment using avelumab in a randomized phase III trial has been reported (JAVELIN Bladder 100) [17]. A total of 700 patients with locally advanced unresectable UC or mUC who experienced CR or PR or SD after 4 to 6 cycles of gemcitabine plus platinum-based chemotherapy were randomized to either maintenance avelumab or best supportive care (BSC) alone. Maintenance avelumab was administered at 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity after 4 to 10 weeks. The primary endpoint was OS, assessed among all patients who underwent randomization (overall population) and among those with PD-L1-positive tumors. The secondary endpoints were PFS and safety. The trial results suggested a significant improvement in the OS with avelumab versus placebo (21.4 mo vs. 14.3 mo; HR=0.79; one-sided  $p=0.0003$ ). In all patients, grade  $\geq 3$  toxicity rates were higher with maintenance avelumab than with BSC (47% vs. 25%),

with no new toxicity signals. Two patients died of toxicity associated with avelumab (sepsis and ischemic stroke). Treatment with maintenance avelumab was well tolerated. Based on these data, the US FDA approved avelumab for maintenance therapy in patients with locally advanced UC or mUC that did not progress with initial PBCC. The most recent NCCN guidelines for first-line systemic therapy for locally advanced UC or mUC recommend avelumab switch-maintenance therapy [18].

The clinical issue also arises from the pembrolizumab interchangeability of avelumab due to different dosing schedule (pembrolizumab can be given every six weeks whereas avelumab should be given every 2 weeks). However, the role of pembrolizumab is not established in the maintenance setting, as they have demonstrated PFS but not OS. Further follow-up data on pembrolizumab for OS are warranted, as these studies were underpowered for survival benefit and allowed a crossover trial design. Another challenge is duration of treatment; pembrolizumab administered for 24 months while the avelumab was administered until progression or intolerance and toxicity. Moreover, there are questions regarding which patient population will be more beneficial.

Several trials [12,19-21] have evaluated combinations of CPIs with chemotherapy as a first-line treatment for patients who are eligible for PBCC. However, combination regimens using CPI and chemotherapy have not shown significant improvement in OS compare to standard PBCC. Based on the available data, the combinations of chemotherapy with CPIs are not more promising than maintenance therapy with avelumab in first-line.

Switch-maintenance therapy using avelumab is recommended until progression or intolerance and toxicity in locally advanced unresectable UC or mUC that has not progressed after the initial PBCC treatment in both the total population and PD-L1 patients. Disease control achieved with chemotherapy may provide time for immunotherapy to exert its anti-tumor effect. Initiating immunotherapy before disease progression may result in more patients receiving treatment.

## MOLECULARLY TARGETED AGENTS

Recently, genomic landscape and actionable driver mutations of UC have been reported by studies using next-generation sequencing and bioinformatics [22,23]. The Cancer Genome Atlas (TCGA) updated the results of most common mutations in MIBC: *TP53*, *PIK3CA*, *CDKN1A*, *ERCC2*, *FGFR3*, and *ERBB3* [22]. Recent studies have focused on

these actionable mutations.

### 1. Targeting fibroblast growth factor receptor

FGFRs are involved in several important physiological processes, including cell proliferation, differentiation, migration, and survival [24]. Studies have demonstrated that *FGFR* amplification and overexpression could result in cancer development through several mechanisms, including cell growth and angiogenesis, and may be associated with resistance to cancer treatment [25-27]. FGFR has four receptors (FGFR1–FGFR4), and certain *FGFR* aberrations have been observed in specific cancers such as FGFR1 amplification in squamous cell lung cancer [28].

In UC, *FGFR3* alterations are common, including point mutations and fusions [29]. Whereas, *FGFR3* alterations are more frequent in non-muscle invasive bladder cancer (up to 80% from Ta, from T1 to 30%) [30], and 12% to 15% patients with muscle invasive bladder cancer have *FGFR3* alterations [22,23,31,32]. The most common *FGFR3* alterations have activating point mutations in exons 7, 10, and 15 (S249C, R248C, Y375C, and G372C), and less commonly, gene fusions (*FGFR3-TACC3*, *FGFR3-BAIAP2L1*, *FGFR3-TACC3*, and *FGFR3-BAIAP2L1*) have been observed [29]. In addition to mutations, epigenetic regulation may lead to FGFR3 protein or mRNA overexpression in MIBC [33].

As *FGFR3* alterations play a significant role in the development in UC [29], FGFR3 signaling has been an attractive target, and several drugs have been evaluated in patients with UC [34-36].

The results of selected trials on FGFR inhibitors for mUC treatment are listed in Table 1 [35,37,38], and trials on ongoing molecularly targeted agent are listed in Table 2.

### 2. Erdafitinib

Erdafitinib is an orally administered, small molecule, pan-FGFR inhibitor developed for the treatment of cancers that express activating mutations, amplifications, and overexpression of FGFRs [39]. Erdafitinib binds to FGFR and suppresses FGFR phosphorylation, inhibits FGFR-related signaling pathways, and leads to the inhibition of proliferation and death of FGFR-overexpressing tumor cells [39].

BLC2001, an open label phase II clinical trial [35], enrolled 212 patients with measurable locally advanced UC or unresectable/mUC with pre-specified FGFR2/3 alterations from 14 countries in Asia, Europe, and North America.

The inclusion criteria were patients with ECOG PS of 0–2 and progression during/following  $\geq 1$  line of prior chemotherapy, patients on  $\leq 12$  months of (neo)adjuvant chemotherapy, or those who were cisplatin ineligible and chemo-

Table 1. Summary of the main FGFR inhibitors with clinical data in advanced urothelial carcinoma

Agent	Mechanism	Clinical trial/number of patients	Selection biomarker for inclusion	Setting/line	Outcome
Erdafitinib	Pan-FGFR	BLC2001, phase II [37]/99	FGFR3 mutation: R248C, S249C, G370C, Y373C FGFR2/3 fusions: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1	Progression on prior platinum-based CT/2nd line	ORR: 40% Median PFS: 5.5 months Median OS: 13.8 months
Rogaratinib	Pan-FGFR	FORT-1, random phase II-III [35]/87 (rogaratinib); 88 (chemotherapy)	FGFR mRNA overexpression: RNA scope score of 3 or 4	Progression on prior platinum-based CT/2nd line	ORR: 20%; 19% Median PFS: 2.7 months; 2.9 months Median OS: NR
Infgratinib	FGFR1-3	Phase I and expansion cohort [38]/67	FGFR3 mutation: R248C, S249C, G372C, A393E, Y375C, K652M/T, K652E/Q FGFR3 gene fusions were permitted, including but not limited to, FGFR3-TACC3 fusion	Patients who were unable to receive platinum CT/1st line	ORR: 20%; 25% Median PFS: 3.75 months Median OS: 7.75 months

CT, chemotherapy; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; NR, not reached.

naïve. During the initial analysis, the optimal treatment schedule when using erdafitinib was 8 mg/d during a 28-day cycle, which could be increased to 9 mg/d if the protocol-defined target serum phosphate levels were not attained, and if there were no significant treatment-related adverse events (TRAEs).

The primary endpoint was confirmed objective response rate (ORR), and the secondary endpoints were duration of response (DoR), PFS, and OS. The median follow-up duration was 24.0 months, and the median duration of treatment was 5.4 months. The median age was 67 (36–87) years, and 88% had progressed or relapsed after chemotherapy; 43% had at least two courses of therapy and 77% had visceral metastases. Fifty-two percent of patients had a creatinine clearance of less than 60 mL/min. Most patients (69%) were FGFR mutation-positive/fusion-negative, 25% were FGFR mutation-negative/fusion positive, and 6% were FGFR mutation-positive/fusion-positive. The confirmed ORR was 40% (including 3% CR and 37% PR). The median DoR was 5.98 months. The median PFS was 5.52 months, and OS was 11.3 months, with 49% of patients alive at 12 months, and 31% at 24 months. The DoR, PFS, and OS were similar regardless of the primary tumor location or presence of visceral metastases [35,40]. Most TRAEs were grade 1/2, with a longer follow-up. In particular, 27% (27/101) of patients had a central serous retinopathy (CSR) event, which was established as a class effect of mitogen-activated protein kinase (MAPK) pathway inhibitors, and 3% (3/101) discontinued this therapy due to CSR. Most retinopathy events (63%, 17/27) had resolved at the time of data cutoff; 60% (6/10) of ongoing CSR events were grade 1. There was no treatment-related death [40].

Erdafitinib has recently been approved by the U.S. FDA based on the results of the BLC2001 study [41], which was the first time that a gene-targeted therapy was approved for treating UC. In patients with selected FGFR genetic aberrations, the NCCN guidelines recommend erdafitinib as an alternative preferred treatment option (Category-2A recommendation) as a subsequent-line systemic therapy for locally advanced UC or mUC [18].

The benefits of erdafitinib versus chemotherapy or immunotherapy are being explored in an ongoing randomized phase III trial (NCT03390504). Further studies comparing erdafitinib with the targeted agent EV are needed to determine the appropriate sequencing of these agents.

### 3. Vofatamab

Vofatamab is a fully human monoclonal antibody that blocks the activation of the wild-type and genetically acti-

Table 2. Key ongoing trials of molecularly targeted agents in advanced urothelial carcinoma

Agent	Trial	Design/number of patients	Setting/line	Arm(s)	Primary endpoint(s)
FGFR inhibitors Erdafitinib	THOR (NCT03390504)	Randomized phase 3/631	Platinum-treated with/without ICI-treated mUC with <i>FGFR</i> mutation or fusions/translocations/2nd or 3rd line	(1) Erdafitinib (2) Vinflunine (3) Docetaxel (4) Pembrolizumab Device: FGFR inhibitor Clinical Trial Assay (FGFRi CTA)	OS
	FIGHT-201 (NCT02872714)	Randomized phase 2/263	Platinum-treated or unfit mUC with <i>FGFR3</i> mutations/ fusions or other FGF/FGFR alterations/1st line	(1) (Intermittent Dose) Pemigatinib ( <i>FGFR3</i> mutations or fusions) (2) (Continuous Dose) Pemigatinib ( <i>FGFR3</i> mutations or fusions) (3) Pemigatinib (other FGF/FGFR alterations)	ORR
Debio 1347	FUZE (NCT03834220)	Single arm Phase 2/63	Treatment refractory solid tumors harboring <i>FGFR1-3</i> fusions/translocations/ 1st line	(1) Debio1347	ORR
FGFR inhibitor in combination with ICI Rogaratnib/atezolizumab	FORT-2 (NCT03473756)	Randomized Phase 1b:2/210	Treatment-naive cisplatin-unfit mUC with high <i>FGFR1</i> or 3 mRNA expression/1st line	(1) Rogaratnib+Atezolizumab (cisplatin-ineligible and have had no prior systemic treatment) (2) Placebo+Atezolizumab (3) Rogaratnib+Atezolizumab (until disease progression, unacceptable toxicity, death, consent withdrawal, or withdrawal from the study)	DLT, AEs, PFS
	FIGHT-205 (NCT04003610)	Randomized Phase 2/378	Treatment-naive cisplatin-unfit mUC with <i>FGFR3</i> mutation/fusion/1st line	(1) Pemigatinib+Pembrolizumab (2) Pemigatinib alone (3) Standard of Care (Chemotherapy or pembrolizumab)	PFS
Erdafitinib/cetrelimab	NORSE (NCT03473743)	Randomized Phase 1b:2/160	Treatment-naive cisplatin-unfit mUC with <i>FGFR3</i> mutation/fusion/1st line	(1) Two dosing cohorts (erdafitinib and cetrelimab; and erdafitinib, cetrelimab and cisplatin/carboplatin) (phase 1b/ dose escalation) (2) Erdafitinib/cetrelimab (phase 2/ dose expansion)	DLT, ORR, AEs



Table 2. Continued

Agent	Trial	Design/number of patients	Setting/line	Arm(s)	Primary endpoint(s)
ErbB family inhibitors	LUX-Bladder1 (NCT02780687)	Single arm phase 2/42	Platinum-treated or unfit mUC with HER2 or HER3 mutation or HER2 amplification (cohort A); EGFR amplification (cohort B)/2nd line	(1) Afatinib	PFS (at 6 months)
				(1) Trastuzumab+Pertuzumab (2) Erlotinib (3) Vemurafenib+Cobimetinib (4) Vismodegib (5) Alectinib (6) Alectinib	ORR
Pertuzumab/trastuzumab	My Pathway (NCT02091141)	Non-Randomized phase 2a/765	Treatment refractory solid tumors with HER2 amplification (by NGS, FISH, or CISH) and/or IHC3+ and/or HER2 actionable mutation/1st line	(1) Trastuzumab+Pertuzumab (2) Erlotinib (3) Vemurafenib+Cobimetinib (4) Vismodegib (5) Alectinib (6) Alectinib	ORR
VEGF inhibitor in combination with ICIs	LEAP-011 (NCT03898180)	Randomized phase 3/694	Treatment-naïve cisplatin-unfit PD-L1(+) or platinum-unfit mUC/1st line	(1) Pembrolizumab+Lenvatinib (2) Pembrolizumab+Placebo	PFS, OS
				(1) Atezolizumab+Bevacizumab	OS
Bevacizumab/atezolizumab	HCRN GU15-215 (NCT03272217)	Single arm phase 2/70	Treatment-naïve cisplatin-unfit mUC/1st line	(1) Atezolizumab+Bevacizumab	OS
Cabozantinib/pembrolizumab	PemCab (NCT03534804)	Single arm phase 2/39	Treatment-naïve cisplatin-unfit mUC/1st line	(1) Cabozantinib and Pembrolizumab	ORR

ICI, immune checkpoint inhibitor; mUC, metastatic urothelial cancer; OS, overall survival; ORR, objective response rate; DLT, dose-limiting toxicity; AE, adverse event; PFS, progression-free survival; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; NGS, next generation sequencing; FISH, fluorescence *in situ* hybridization; CISH, chromogenic *in situ* hybridization; PD-L1, ligand of programmed cell death 1 protein.

vated FGFR3 receptor. To evaluate an effective dose and AEs, the FIERCE21 (NT02401542) trial, a phase Ib/II, assessed vofatamab alone (at 25 mg/kg) or in combination with docetaxel (75 mg/m<sup>2</sup> every 3 wk).

The findings of the phase Ib study revealed that the combination of vofatamab and standard-dose docetaxel was well tolerated. Moreover, in contrast to wild-type tumors, FGFR3 alterations were associated with increased activity [42]. FGFR3 mutations or fusions were identified in over 20% of patients in the phase II expansion trial, in which over 600 patients were screened. The ASCO-GU 2019 posters revealed that while vofatamab was well tolerated (combinations and as a single agent), its effectiveness as a single agent was limited in the case of highly pretreated patients (ORR, 11%) [43].

#### 4. Rogaratinib

Rogaratinib is a pan-FGFR inhibitor. It reduces the proliferation of FGFR-addicted cancer cell lines of the bladder, lung, breast, and colon. The efficacy of rogaratinib is also closely correlated with FGFR mRNA expression [44].

A phase I study (NCT01976741) [45] involved three dose expansion cohorts (bladder, head and neck squamous cell, and non-small cell lung cancer) that evaluated safety and efficacy of rogaratinib in patients with solid tumors overexpressing FGFR1-3. The ORR was 23% and the disease control rate (DCR) was 60% for bladder cancer cohort with a favorable toxicity profile.

A single-arm, non-randomized phase II trial of rogaratinib (NCT02459119) was performed in 17 patients with advanced UC who had progressed after 1–3 prior chemotherapy. Patients received a median of two previous treatments, including chemotherapy. Prior CPI had been administered to nine patients. The primary endpoint was PFS at 6 months, and the secondary endpoints were ORR, OS, and safety. In the absence of toxicity associated with rogaratinib, all patients started at 120 mg, QD, p.o. for one cycle (28 d) before escalating to 160 mg, QD, p.o. Three patients (17.6%) survived at 6 months without progression, who also showed mild regression, and one of them had received prior CPI. Thirteen patients (76.5%) had TRAEs and seven patients (41.2%) had grade 3 toxicity. No deaths were associated with the use of medication. There were no treatment-related deaths.

A phase II/III study (NCT03410693) in patients with locally advanced UC or mUC with high FGFR1/3 mRNA-expressing that have been treated with PBCC is currently ongoing to compare the effectiveness and safety of rogaratinib to chemotherapy. The primary endpoint was OS, and the secondary endpoints were PFS, ORR, DCR, DoR, safety, and tolerability. During the trial, 88 patients were assigned

to rogaratinib and 88 to chemotherapy treatment groups. The ORRs were 19.5% and 19.3% ( $p=0.56$ ) and DCRs were 49.4% and 55.7% ( $p=0.84$ ) for those treated with rogaratinib and CT, respectively. Grade 3/4 AEs occurred in 40 out of 86 (47%) patients that were treated with rogaratinib and in 46 out of 82 (56%) patients treated with CT [46].

## ANTIBODY-DRUG CONJUGATES

In 1900, Paul Ehrlich proposed the concept of “magic bullets” to treat human illnesses, including cancer [47]. ADCs appear to have been developed in the idealization of this concept and are now being increasingly used in various malignancies. ADCs contain an antibody (targeting specific tumor-associated antigens) attached to the cytotoxic drug (payload) to directly administer cytotoxic therapy to cancer cells, while conserving normal tissues. The target antigen is bound to the antibody structure, the conjugated molecule is internalized by tumor cells, and the linker undergoes intracellular cleavage, thus, the intracellular cytotoxic drug (generally a DNA damaging agent or microtubule inhibitor) is released [48]. The first ADC was approved by the U.S. FDA in 2000 [49]. In urologic oncology, enfortumab vedotin (EV) was approved by the U.S. FDA in 2019 to treat patients with locally advanced UC or mUC that have previously received a CPI and a platinum-based neoadjuvant/adjuvant chemotherapy [50].

### 1. Enfortumab vedotin

EV is a fully humanized monoclonal antibody against nectin-4. Nectin and nectin-like molecules are cell adhesion molecules of the Ca<sup>2+</sup>-independent immunoglobulin superfamily expressed in most types of cells. Nectin-4 is highly expressed in several tumors, including bladder, lung, breast, and gastric cancers [51–54]. The payload is a powerful antimetabolic agent, monomethyl auristatin E (MMAE), which blocks the polymerization of tubulin. MMAE has not been used as a therapeutic agent due to toxicity, but it is linked to an antibody resulting in the vedotin complex. The intent is to internalize EV into a specific cell via endocytosis where it undergoes lysosome degradation to subsequently release the cytotoxic payload.

The efficacy of EV has been demonstrated in an open-label phase II clinical trial (EV-201) conducted in 125 patients with advanced UC or mUC previously treated with PBCC and PD-1/PD-L1 inhibitors. In the trial, 70% were males, with a median age of 69 (range 40–84) years; 34% of the patients had primary UTUC and had previously received a median of two systemic therapies. Nectin-4 expression was detected

in all examined patients. At a median follow-up of approximately 10 months, the ORR was 44%, including a complete response rate of 12%. The findings revealed a median duration of tumor response of 7.6 months. The median OS was 11.7 months and the median PFS was 5.8 months. Responses were observed in all pre-specified patient subgroups. TRAE occurred in 40% or more of patients. These included fatigue (50%), alopecia (49%), rash (38%), decreased appetite (44%), taste distortion (40%), and peripheral neuropathy (50%). Treatment was discontinued in only 12% of the patients due to TRAEs, with peripheral sensory neuropathy (6%) being the most common cause. There was one treatment-related death (interstitial lung disease) [55]. On December 18, 2019, the FDA granted accelerated approval to EVs in patients with locally advanced UC or mUC who had previously received PD-1 or PD-L1 inhibitors and PBCC in the neoadjuvant/adjuvant, locally advanced, or metastatic setting [56].

An ongoing multicenter open-label phase III study (EV-301) [57] randomized approximately 550 patients who progressed on platinum-containing chemotherapy and a CPI to EV (125 mg/kg d 1, 8, and 15, every 4 wk) vs. investigator choice of docetaxel, paclitaxel, or vinflunine (day 1, every 3 wk). The primary endpoint was the OS. In the trial, EV significantly improved the OS, with a reduced risk of death by 30% (HR=0.70; 95% CI=0.56–0.89;  $p=0.001$ ). Furthermore, EV significantly improved the PFS, a secondary endpoint, with a reduced risk of disease progression or death by 39% (HR=0.61; 95% CI=0.50–0.75;  $p<0.00001$ ). Among patients in the EV arm, the AEs were consistent with those listed in the U.S. Prescribing Information, with grade 3 or higher AEs, rash, hyperglycemia, decreased neutrophil count, fatigue, anemia, and decreased appetite, frequently occurring in 5% of patients.

Another ongoing study (EV-103) is a phase 1b/II trial evaluating EV combined with CPI and/or chemotherapy in patients with mUC in multiple cohorts. The preliminary results were recently announced [58]. EVs are used in combination with PD-1 inhibitors, pembrolizumab, and/or chemotherapy. The combination of pembrolizumab and EV regimen has shown encouraging and durable activity with an ORR of 73.3%, a median PFS of 12.3 months, and a reduction of 93% in target lesions. In terms of AEs, one patient had died of multi-organ failure. The most common AEs were fatigue (58%), alopecia (53%), and neuropathy (53%) [59]. Based on these results, in February 2020, the FDA granted breakthrough therapy designation for the combination of EV and pembrolizumab as a first-line setting for cisplatin-ineligible patients with locally advanced UC or mUC [60].

## 2. Other ADCs actively investigated for the treatment of mUC

Sacituzumab govitecan (SG) is an ADC that contains an antibody against the epithelial cell surface molecule Trop-2 that is attached to a cytotoxic drug (payload) of SN-38 (a potent derivative of irinotecan) [61]. The agent was recently granted FDA approval in patients with metastatic triple-negative breast cancer who had received at least two prior therapies [62].

Clinical data from the UC cohort of IMMU-132-01 [63] (i.e., a phase I/II basket study of solid tumors) in which patients received SG (10 mg/kg, days 1 and 8 out of the 21-d cycle) until progression or toxicity revealed an ORR of 31% (14/45) including 2 and 12 patients that experienced a CR and PR, respectively. The most common grade 3/4 AEs were neutropenia (38%), anemia (11%), hypophosphatemia (11%), diarrhea (9%), fatigue (9%), and febrile neutropenia (7%). Five out of 45 patients discontinued treatment due to AEs, and there were no treatment-related deaths.

TROPHY-U-01 (NCT03547973) [64] is a multi-cohort, global open-label, phase II study evaluating the clinical activity of SG (10 mg/kg, days 1 and 8 of the 21-d cycles) in patients with unresectable locally advanced UC or mUC. Cohort 1 included patients who progressed after PBCC and CPI. The primary endpoint was ORR; the secondary endpoints were PFS, OS, DoR, and toxicity. A total of 113 patients (78% men; median age 66 years; 72% ECOG PS 1; 62% with visceral metastases; receiving a median of three prior therapies) were included in the final analysis. The ORR was 27% (31/113) (6 CR, 25 PR). The ORR was 25.0% in patients with liver metastases. The median PFS, OS, and DoR were 5.4, 10.5, and 5.9 months, respectively. The most common grade 3/4 AEs were neutropenia (35%), anemia (14%), febrile neutropenia (10%), and diarrhea (10%). There was one treatment-related death (neutropenic sepsis).

Tisotumab vedotin is a first-class investigational ADC containing a tissue factor (TF)-specific, fully human monoclonal antibody conjugated to the microtubule-disrupting agent MMAE using a protease cleavable linker [65]. TF, a major component of the extrinsic coagulation cascade, is thought to play an important role in cancer growth, metastasis, and angiogenesis and is highly expressed in UC [66]. In a phase I/II study of solid tumors, 15 patients with mUC received a recommended phase II dose of 2 mg/kg every 3 weeks, with an ORR of 27%. Common TRAEs from 174 patients who participated in the study were fatigue, epistaxis, nausea, diarrhea, and peripheral neuropathy, and there was one treatment-related death [65]. Further studies of this drug in mUC treatment are warranted.



**Table 3.** Summary of the clinical data on the main antibody–drug conjugates against advanced urothelial carcinoma

Antibody-drug conjugates	Target antigen/chemical linker	Cytotoxic compound	Trial type/number of patients	Patients	Outcome
Enfortumab vedotin	Nectin-4/Protease-cleavable	MMAE	Phase 2/128	mUC, prior platinum and ICB 40% liver metastases	ORR: 44% (12% CR) Median DoR: 8 months Median PFS: 6 months Median OS: 12 months
Enfortumab vedotin+pembrolizumab	Nectin-4/Protease-cleavable	MMAE	Phase 1b/45	mUC, first-line cisplatin-ineligible 33% liver metastases	ORR: 73% (16% CR) Median DoR: NR Median PFS: 12 months Median OS: n/a
Sacituzumab govitecan	Trop-2/Acid-labile	SN-38	Phase 1,2/45	mUC, ≥1 systemic therapy (95% prior platinum and 38 T prior ICB) 75% liver metastases	ORR: 31% (4% CR) Median DoR: 13 months Median PFS: 7 months Median OS: 19 months
RC48-ADC	HER2/Cathepsin-cleavable	MMAE	Phase 2/43	HER2+ mUC (by IHC), ≥1 line of chemotherapy (19% prior ICB) 47% liver metastases	ORR: 61% (0% CR) Median DoR: n/a Median PFS: NR Median OS: n/a

MMAE, monomethyl auristatin E; mUC, metastatic urothelial cancer; ICB, immune checkpoint blockade; ORR, objective response rate; CR, complete response; DoR, duration of response; PFS, progression-free survival; OS, overall survival; NR, not reached; n/a, not available; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

**Table 4.** Key ongoing trials of novel antibody-drug conjugates in advanced urothelial carcinoma

Antibody-drug conjugates	Trial	Design/number of patients	Setting	Arm(s)	Primary endpoint(s)
Enfortumab vedotin	EV-302 (NCT04223856)	Randomized phase 3/760	Front-line, Cis-Eligible	(1) EV+Pembrolizumab (2) Gem/Cis or Gem/Carbo (3) EV+Pembrolizumab+Cis/Carbo	PFS, OS
	KEYNOTE-905/EV-303 (NCT03924895)	Randomized phase 3/836	Neoadjuvant	(1) Pembrolizumab+Surgery (2) Surgery alone (3) Enfortumab Vedotin+Pembrolizumab+Surgery	pCR rate, EFS
	EV-103 (NCT03288545)	Single-Arm Phase 1b, 2/407	Multicohort Phase 1b, 2	(1) EV monotherapy (2) EV+Pembro (3) EV+Pembro+(Cis or Carbo) (4) EV+Cis (5) EV+Carbo (6) EV+Gem	Safety, ORR
Sacituzumab govitecan	TROPHY-U-01, NCT03547973	Single-Arm Phase 2/201	Second- and third-line mUC (postplatinum and/or ICB)	Sacituzumab Govitecan	ORR
Trastuzumab deruxtecan	NCT03523572	Single Arm Phase 2/407	Secondline HER2+ mUC (post-platinum)	Trastuzumab Deruxtecan+Nivo	Safety, ORR

EV, enfortumab vedotin; Cis, cisplatin; Gem, gemcitabine; Carbo, carboplatin; PFS, progression-free survival; OS, overall survival; pCR, pathological complete response; EFS, event-free survival; ORR, objective response rate; mUC, metastatic urothelial cancer; ICB, immune checkpoint blockade; HER2+, human epidermal growth factor receptor 2-positive; Nivo, nivolumab.

The clinical data on the main ADC and key ongoing trials of novel ADC against advanced UC are summarized in Tables 3 and 4.

## CONCLUSIONS

Although systemic treatment options for mUC have stagnated for decades, they have significantly changed in recent years. Switch-maintenance therapy using avelumab in patients whose disease had not progressed on PBCC represents a new first-line standard of care for mUC. Erdafitinib (a pan-FGFR inhibitor) has shown significant benefits in patients with advanced UC with FGFR alterations. The efficacy of EV (a monoclonal antibody targeting nectin-4 conjugated to MMAE) demonstrated clinically significant benefits in patients who do not respond to cytotoxic chemotherapy. Clinicians should be aware of new therapies and agents to provide optimal patient care, select appropriate treatments, and properly sequence treatments when indicated.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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## AUTHORS' CONTRIBUTIONS

Research conception and design: Ho Kyung Seo. Drafting of the manuscript: Whi-An Kwon. Critical revision of the manuscript: Ho Kyung Seo. Obtaining funding: Ho Kyung Seo. Administrative, technical, or material support: Ho Kyung Seo and Whi-An Kwon. Supervision: Ho Kyung Seo. Approval of the final manuscript: Ho Kyung Seo and Whi-An Kwon.

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