Review Article on Management of Advanced Genitourinary Malignancies

Treatment options for advanced urothelial cancer after progression on chemotherapy and immune checkpoint inhibitors: a literature review

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Objective: To describe the current treatment landscape in advanced urothelial cancer (aUC)/metastatic urothelial cancer and in particular to review the relevant literature highlighting recent advances in the treatment of patients with aUC after progression on chemotherapy and immune checkpoint inhibitor (ICI).

Background: aUC is a very aggressive disease with poor outcomes. Over the past several years, its treatment landscape has seen significant advances with the approval of ICI and targeted agents, which have led to improved outcomes. The current standard of care for most patients with aUC involves platinum-based chemotherapy followed by ICI after progression or as switch maintenance therapy (if no progression after chemotherapy). Treatment of patients following progression on ICI is more challenging, but novel therapies have been approved, such as erdafitinib for tumors with fibroblast growth factor receptor 2 (FGFR2) or FGFR3 activating mutation or fusion (can also be used following progression on platinum-based chemotherapy), enfortumab vedotin (EV) and sacituzumab govitecan (SG) in an unselected patient population. Many other trials in this space are currently ongoing and other promising agents may also potentially become available in the future.

Methods: Narrative overview of the recent literature relevant to the treatment of advanced/metastatic urothelial cancer following progression on chemotherapy and ICI was undertaken. Relevant literature was obtained from review of computerized databases including pubmed.gov and proceedings of major conferences including American Society of clinical Oncology (ASCO) Meetings, GU ASCO Symposia and European Society of Medical Oncology (ESMO) Meetings.

Conclusions: In this narrative review, we highlight the current dynamic treatment landscape in aUC, emphasizing the recent important developments and a few examples of ongoing clinical trials. In particular, we focus on therapy options available following progression on platinum-based chemotherapy and ICI, a treatment space where until recently there had been no FDA-approved treatment options. The recent pivotal trials of antibody drug conjugates (ADCs) that led to FDA approvals in this space are highlighted, as are other agents currently in development. We conclude by discussing future directions and ongoing challenges in this evolving disease space.

Keywords: Advanced urothelial cancer (aUC); bladder cancer; immune checkpoint inhibitor (ICI); chemotherapy; targeted therapy

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Introduction

Bladder cancer is a common malignancy and is among the top ten most common tumors worldwide with almost 600,000 cases and almost 200,000 deaths in 2018 (1). The majority of patients are men and the average patient is in their late 60s or early 70s at the time of diagnosis. Clinical and pathologic staging plays a very important role in prognostication and management. Most patients are diagnosed with non-muscle invasive bladder cancer (NMIBC), however up to 25% have muscle-invasive bladder cancer (MIBC) at the time of diagnosis, implying the invasion of the bladder muscularis propria, with about 5% having distant metastatic spread at time of diagnosis. Most patients with bladder cancer have tumors with urothelial carcinoma histology, but up to 15–25% may have pure or mixed histological variants, including but not limited to: squamous cell, adenocarcinoma/glandular features, neuroendocrine/small cell, micropapillary, plasmacytoid, nested, sarcomatoid, among others. These tumors can arise anywhere in the genitourinary tract, which includes urethra, bladder (most common site), ureters and renal pelvis. Both histology and location also influence the prognosis and treatment considerations, and generally speaking, upper tract tumors are considered more aggressive relative to lower tract, and histological variants more aggressive relative to tumors with urothelial histology. While patients with NMIBC and localized MIBC are candidates for curative intent treatment, patients with distant metastases are generally considered incurable. Even in this treatment setting however, several treatment options are available and the recent years have brought about important new treatment considerations specifically for advanced urothelial cancer (aUC) (2). Several agents and combinations are also currently in the clinical trial pipeline as part of this dynamic landscape. However, the treatment of patients progressing on initial lines of therapy remains very challenging. This review highlights the novel treatment options in aUC, focusing in particular on the treatment options available following progression on chemotherapy and immune checkpoint inhibitors (ICI). We present the following review in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/tau-21-123).

Methods

As part of this narrative literature review, we identified the relevant publications over the last 10 years in the English language related to the treatment of patients with advanced/metastatic urothelial cancer. Special focus was made on the literature related to the treatment of patients with aUC following progression on chemotherapy and ICI. Relevant literature was obtained from review of computerized databases including pubmed.gov, clinicaltrials.gov and proceedings of major conferences including American Society of clinical Oncology (ASCO) Meetings, Genitourinary ASCO Symposia and European Society of Medical Oncology (ESMO) Meetings.

Current standard of care

Cisplatin-based chemotherapy has been the standard of care for aUC since the 1980s. One of the initial trials to show clinical efficacy of the classic cisplatin combination regimen MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) had an objective response rate (ORR) 69% with complete responses (CRs) in 37%, and PD as best response in only 23% (3). This combination regimen was shown to be superior to cisplatin monotherapy in a randomized prospective clinical trial with superior ORR (39% *vs.* 12%) and importantly superior mOS (12.5 *vs.* 8.5 months) (4). Subsequent clinical trials focused on the development of more tolerable regimens including dose-dense regimen (ddMVAC) administered in 2-week rather than 4-week cycles, along with G-CSF support (5). Additionally, a large randomized trial comparing the classic MVAC with gemcitabine/cisplatin (GC) in patients with aUC did show that GC was more tolerable with similar clinical outcomes including ORR, PFS and OS (6,7). The median OS in that trial was 15 months, with a 5-year OS of 13–15%, suggesting potential for long term responses in select patients treated with cisplatin-based chemotherapy (7). Consequently, the current NCCN guidelines recommend patients with aUC who are cisplatin-eligible to receive either GC or ddMVAC in the frontline setting.

Eligibility for cisplatin-based treatment is defined according to the established Galsky criteria (8), and most patients are considered ineligible for cisplatin-based chemotherapy due to inadequate renal function (GFR <60 mL/min) or poor PS ECOG (>1). Patients with aUC ineligible to receive cisplatin have treatment options that include carboplatin-based chemotherapy or ICI. Carboplatin-based regimens can be used in patients with a moderately impaired renal function (GFR 30–60 mL/min) and are usually better tolerated than cisplatin-based regimens, however have historically been considered to be associated with inferior outcomes (9). Additionally, both pembrolizumab (anti-PD-1 agent) and atezolizumab (anti-PD-L1 agent) have received accelerated FDA approval for the treatment of cisplatin-ineligible treatment-naïve patients with aUC with ORR reported at 23–29% in phase II single arm trials and CR rates approaching 10%. Importantly these agents were generally much better tolerated than frontline cytotoxic chemotherapy (10,11). A longer follow-up on the KEYNOTE-052 trial of frontline pembrolizumab alone showed median OS 11.3 months in all comers, but with higher ORR 47% and median OS 18.5 months in patients with higher PD-L1 expression (CPS ≥10) (12,13). Moreover the clinical benefit was consistent regardless of age or performance status (including ECOG 2) (14).

The FDA issued a label restriction suggesting that only cisplatin-ineligible patients with tumors expressing high PD-L1 be treated with frontline ICI monotherapy. However, patients with aUC judged to be ineligible for any platinum-based treatment can receive ICI monotherapy without additional PD-L1 testing (in the US only) based on FDA guidance. Consequently, the current standard of care for patients with aUC ineligible for cisplatin-based chemotherapy is either carboplatin-based chemotherapy (with avelumab switch maintenance if no progression) or consideration of atezolizumab or pembrolizumab for patients whose tumors have high PD-L1 expression based on the corresponding companion assay for each agent. The cisplatin-ineligible front-line space remains an area of clinical need and numerous clinical trial combinations, including antibody drug conjugates (ADCs) and novel immunotherapy agents are being explored in this space (15,16). Therefore, the treatment paradigm for treatment-naïve cisplatin-ineligible patients might potentially shift in the future.

Two large phase III clinical trials have investigated the combination of chemotherapy and ICI for treatment-naïve patients with aUC in comparison with platinum-based chemotherapy alone. IMvigor130 investigated the addition of atezolizumab to platinum-based chemotherapy *vs.* placebo/chemotherapy as frontline treatment in aUC, showing improvement in median PFS of 8.2 *vs.* 6.3 months (stratified HR 0.82, P=0.007) with no significant improvement in OS (16.0 *vs.* 13.4 months) at that time (17). The KEYNOTE-361 trial investigated the combination of frontline pembrolizumab with platinum-based chemotherapy *vs.* frontline chemotherapy alone, but did not meet its prespecified endpoints of PFS or OS improvement with the combination (18). The Danube trial assessed the combination of durvalumab and tremelimumab (in all comers), or durvalumab monotherapy (in the subset of PD-L1-high tumors) *vs.* standard platinum-based chemotherapy. Neither comparison met its primary endpoint of OS benefit in the intention to treat population (19). Two other large phase III clinical trials combining frontline platinum-based chemotherapy with ICI are yet to report: checkmate-901 is comparing the combinations of nivolumab and ipilimumab, or nivolumab and GC, *vs.* platinum-based chemotherapy, while NILE is comparing combinations of durvalumab with chemotherapy, or durvalumab with tremelimumab with chemotherapy, *vs.* platinum-based chemotherapy. Additionally, the enfortumab vedotin-302 (EV-302) trial, building on the impressive results of the EV/pembrolizumab in the EV-103 trial, is investigating the EV/pembrolizumab *vs.* platinum-based chemotherapy for treatment-naïve patients with aUC (16,20).

For patients with aUC treated with 4–6 cycles of platinum-based chemotherapy, achieving response or stable disease, switch maintenance avelumab is now the new standard of care (level I evidence). This is based on the Javelin Bladder 100 trial which randomized patients who had no progression after frontline platinum-based chemotherapy to receive avelumab plus best supportive care or best supportive care alone, as maintenance therapy. With 350 patients randomized per arm, the median OS was significantly longer with avelumab (21.4 *vs.* 14.3 months; HR 0.69; P=0.001) (21). A smaller randomized phase II trial of switch maintenance pembrolizumab vs placebo (with cross-over built in) showed a significant improvement in PFS for patients on pembrolizumab (median PFS 5.4 *vs.* 3.0 months, P=0.04), but did not show significant OS benefit (22).

For patients who have progression on platinum-based chemotherapy, ICI or the fibroblast growth factor receptor (FGFR) inhibitor erdafitinib can be used as second line

therapy. Initially five ICI were FDA-approved in this space: pembrolizumab, atezolizumab, nivolumab, avelumab and durvalumab; the FDA approvals were based mostly on data from several phase II trials, except for pembrolizumab (23-27). Recently, the post-platinum therapy applications for atezolizumab and durvalumab were voluntarily withdrawn. Only pembrolizumab is supported in this setting by level I evidence based on a randomized phase III trial that showed a significant OS advantage with pembrolizumab *vs.* salvage chemotherapy (docetaxel, paclitaxel or vinflunine) (median OS 10.3 *vs.* 7.4 months; HR 0.73, P=0.002) (24). This benefit was maintained beyond two years of follow-up with superior 2-year OS rate for pembrolizumab relative to chemotherapy (27% *vs.* 14%) and a recently updated superior 3-year OS rate (21% *vs.* 11%) (28,29). The phase III IMvigor211 trial with atezolizumab *vs.* salvage chemotherapy did not meet its primary endpoint (30).

For a molecularly-selected subset of patients with aUC refractory to platinum-based chemotherapy, erdafitinib is a targeted agent with a novel mechanism of action that received accelerated FDA approval in April 2019. It is estimated that around 15–20% of patients with bladder cancer harbor FGFR3 alterations (31), which are further enriched in upper tract urothelial tumors (32). A single arm, open label phase II trial, BLC2001, assessed the efficacy and safety of erdafitinib in 99 patients with aUC who progressed on prior platinum-based chemotherapy or were cisplatin-ineligible if chemotherapy naïve (33). Patients had to have documented FGFR2 or FGFR3 mutation or fusion in the tumor. A significant minority of the patients in this trial (22%) had also previously progressed on ICI. The confirmed ORR was 40%, with 37% PRs and 3% CRs, while another 39% had SD as best response. Importantly, among patients who had previously progressed on ICI the response rate was 59% (13/22), making this an additional viable treatment option in patients who have previously progressed on both platinum-based chemotherapy and ICI. Based on the initial phase II trial data, erdafitinib was granted FDA accelerated approval for platinum-refractory aUC in April 2019, but a confirmatory phase III trial is pending. The THOR phase III trial is randomizing patients with FGFR3 activating mutation or fusion and progression on prior ICI to receive either erdafitinib or salvage chemotherapy (taxane or vinflunine) and patients with prior chemotherapy to receive either erdafitinib or pembrolizumab. Additionally the NORSE trial is investigating the combination of erdafitinib and cetrelimab (anti-PD-1) in patients who previously progressed on at least one systemic therapy, but not a prior FGFR or PD-L1 inhibitor (34).

Recently approved treatments after progression on chemotherapy and ICI

As discussed so far, the current standard of care for the majority of patients with aUC involves treatment with platinum-based chemotherapy followed by treatment with anti-PD-L1, either as switch-maintenance for patients who achieve response or stable disease, or as second-line treatment for patients with progression (*Figure 1*). However, nearly all patients with aUC will unfortunately progress on chemotherapy and on ICI. In the post-ICI space, there was no established standard of care until very recently. Salvage chemotherapy agents used in this space, such as paclitaxel, docetaxel or vinflunine could be expected to have limited responses with ORR ~10–15% in this setting (35). Therefore, ADCs, such as EV and sacituzumab govitecan (SG), were developed to address that unmet need, while erdafitinib is also an option in that setting if not previously used, also based on the biomarker presence.

EV is an ADC that targets Nectin-4, which is a protein from the Nectin family that plays a role in cell adhesion and is highly expressed in aUC (36). EV is composed of an antibody targeting Nectin-4, which is conjugated to the potent microtubule disrupting chemotherapy agent MMAE. The interaction of the antibody portion of the ADC with Nectin-4 on the surface of the tumor cell leads to the internalization of the ADC complex into the tumor cell and the release of MMAE, which results in tumor cell death. EV was initially investigated in EV-101, a phase I dose escalation/expansion trial of Nectin-4-expressing solid tumors, including aUC that progressed on at least one prior chemotherapy regimen and/or prior ICI (37). Although initially Nectin-4 expression was a requirement for enrollment, the protocol was amended to remove it since the vast majority of patients exhibited high levels of Nectin-4 tumor staining by IHC. Patients were treated with escalating doses of EV up to 1.25 mg/kg on days 1, 8, 15 of a 28-day cycle, and although the maximum tolerated dose was not reached, the recommended phase II dose (RP2D) was 1.25 mg/kg. Overall, the treatment was relatively well tolerated with most common TRAEs including rash, peripheral neuropathy, fatigue, alopecia, and nausea. ORR among the 112 patients treated at the RP2D was 43% (5% CR).

EV-201 was a phase II single arm study of EV in

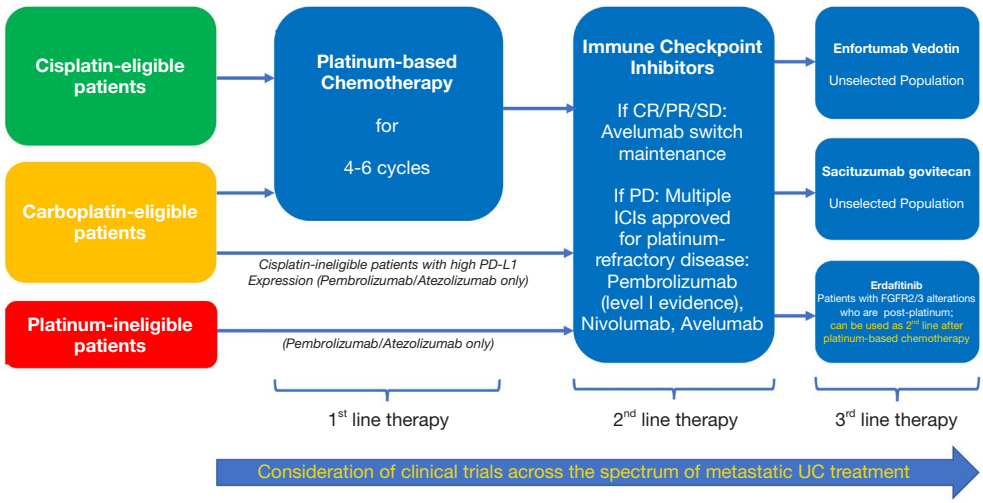

Figure 1 Current treatment landscape for patients with advanced urothelial cancer. CR, complete response; UC, urothelial carcinoma; ICI, immune checkpoint inhibitor; FGFR, fibroblast growth factor receptor.

patients with aUC divided in two cohorts (38). Cohort 1 enrolled patients who had received prior platinum-based chemotherapy and ICI, while cohort 2 enrolled patients whose disease had previously progressed on an ICI, but no prior chemotherapy given for aUC. The practice changing results from cohort 1 of EV-201 were published in the summer of 2019 (39). Among 125 patients, after a median follow-up of 10.2 months the confirmed ORR was 44% (12% CR, 32% PR) while another 28% of patients had SD as best response. The treatment was relatively well tolerated with most common TRAEs being fatigue, peripheral neuropathy, alopecia, and rash. Most TRAEs were G1 or G2 and no ≥G3 events occurred in more than 10% of patients. Importantly, responses were again observed in key patient subsets, including patients with liver metastases (ORR 38%), patients ≥75 years of age (ORR 35%) and patients with prior progression on ICI (ORR 41%). Updated data from cohort 1 was presented at the ESMO 2020 meeting, where after median follow-up of 22.3 months, the median OS was 12.4 months with 50.4% of patients being alive at 12 months and 34.2% alive at 18 months, respectively (40). These very encouraging results in the treatment-refractory setting led to FDA accelerated approval of EV in December 2019 for patients with aUC following progression on platinum-based chemotherapy and ICI.

This accelerated approval was contingent on the results of EV-301, the confirmatory phase III randomized trial comparing EV monotherapy with salvage chemotherapy (investigator choice of docetaxel, paclitaxel or vinflunine) in this setting. Recently published results of this trial reported superior outcomes with EV compared to salvage chemotherapy with significantly longer OS (HR 0.70; P=0.001) and PFS (HF 0.62; P<0.001) (41). Increasingly, real world data are emerging that also support the safety and efficacy of EV across a broad spectrum of patients. A multi-institutional retrospective study presented at the ESMO 2020 assessed the use of EV in an initial cohort of 83 patients and found an ORR 47%, consistent with what was reported in trials. Importantly, responses were observed in patient subsets of interest who may have been excluded from clinical trials, such as patients with significant baseline neuropathy, diabetes mellitus regardless of its control, ECOG PS 2/3, or with significantly impaired renal function (42). Recently reported data from cohort 2 of the EV-201 trial also support the use of EV as second line therapy in patients previously treated with ICI, but not platinum-based chemotherapy. Among 89 patients, confirmed ORR was 52% (95% CI: 40.8–62.4), including 20% CR, median DOR about 11 months and mOS about 14.7 months (43). As of early 2021, EV has been established as a standard of care for patients with aUC who previously progressed on platinum-based regimen and ICI, and it appears that clinical benefit may extend also to patients who have not been previously treated with platinum-based chemotherapy. However, many questions remain, including optimal sequencing of this agent in the broader aUC treatment paradigm, toxicity mitigation/

control and potential predictive biomarkers. Other novel agents are also emerging in the post-ICI space.

SG

Among the most promising new investigational therapies for patients with aUC whose disease has progressed on prior ICI is another ADC, SG, previously known as IMMU-132. SG is composed of a humanized antibody directed against Trop-2, which is linked to SN-38, an active metabolite of irinotecan. Trophoblast cell-surface antigen 2 (Trop-2) is a trans-membrane protein involved in several signaling pathways associated with tumor growth, invasion and spread, which is overexpressed on many epithelial tumors including urothelial carcinoma. Higher expression of Trop-2 has been linked to poor prognosis. In UC, increased expression of Trop-2 has been indeed correlated with cancer severity (44).

SG was originally investigated in a first-in-human trial of 25 patients with a variety of epithelial tumors who had experienced progression on conventional treatments (45). Four different dose levels of 8, 10, 12 and 18 mg/kg were administered on days 1 and 8 of a 21-day cycle, and patients were not pre-selected based on Trop-2 expression levels. The agent was found to have acceptable toxicity overall with neutropenia being the dose limiting adverse event, while 8 and 10 mg/kg doses were selected for phase II trials. Subsequent results of the aUC cohort from the phase I/II basket trial included 41 patients treated at the RP2D of 10 mg/kg (46). These were pre-treated patients with a median of three prior therapies who received a median of 12 doses of SG as part of this trial. ORR was 34% (1 CR, 13 PRs) in the overall population and importantly 39% in patients with liver metastases. The median time to response was 1.9 months and median DOR was 12.9 months. Most common grade ≥3 adverse events included neutropenia (28%), fatigue (9%), anemia (9%) and diarrhea (6%). Updated data from this trial presented in 2019 reported the confirmed ORR at 31% and median PFS and OS to be 7.3 and 18.9 months, respectively among 45 patients (47). These promising results led to the development of a global multi-cohort phase II trial, TROPHY-U-01 (48).

TROPHY-U-01 (NCT03547973) was a single-arm, phase II trial evaluating the antitumor activity of SG (10 mg/kg on days 1 and 8 of a 21-day cycle) in 140 patients with aUC (49). Cohort 1 was the pivotal cohort including patients who progressed on both platinum-based chemotherapy and ICI and aimed to enroll 100 patients. Cohort 2 included platinum-ineligible patients who progressed on ICI and is aiming to enroll 40 patients. Most recently, an updated analysis of cohort 1, including 113 evaluable patients, was presented at the ESMO 2020 meeting. The ORR based on central review was 27% (31/113) with 6 CRs and 25 PRs, while the clinical benefit rate was 37% (42/113). Median duration of response was 5.9 months, whereas median PFS and OS were 5.4 months and 10.5 months, respectively. Toxicities were consistent with previously reported results with most common grade ≥3 adverse events included neutropenia (35%), anemia (14%), febrile neutropenia (10%) and diarrhea (10%). One treatment-related death from neutropenic sepsis was reported. Preliminary results from Cohort 2 of TROPHY-U-01 were also presented at the ASCO 2020 meeting (50). Among 18 evaluable patients, with a median follow-up of 6 months the ORR was 28% (5/18, all PRs) and most patients did have reduction in target lesions. Most common adverse events included cytopenias, particularly neutropenia, fatigue and diarrhea. Cohort 3 of TROPHY-U-01 which combines SG with pembrolizumab in aUC previously progressed on platinum-based chemotherapy is currently enrolling (51). Further cohorts from this trial will also investigate combinations of SG in the treatment-naïve setting. Based on the initial promising data from cohort 1, SG was granted accelerated FDA approval in April 2021 for patients with aUC following progression on platinum-based chemotherapy and ICI. TROPICS-04 (NCT04527991) is the ongoing confirmatory large phase III trial randomizing patients who progressed on platinum-based chemotherapy and ICI to receive SG or a chemotherapy agent of investigator's choice (docetaxel, paclitaxel or vinflunine) (52).

With both EV and SG now available as treatment options in the post-platinum and post-ICI third-line space, potential future questions will revolve around the optimal sequencing of these agents as well as potential biomarkers predicting response to either agent. Due to the largely non-overlapping toxicities and mechanism of action of these two ADCs, potential treatment decision between the two drugs could be based on efficacy, presence of existing medical comorbidities (e.g., severe peripheral neuropathy that can be important in the context of prior treatment), toxicity profiles, level of evidence, provider comfort, patient preference and insurance coverage.

Other agents and molecularly selected therapies

A number of other novel agents are also being investigated

in aUC refractory to ICI. ASG-15ME is another ADC that targets SLITRK6 with a payload of MMAE chemotherapy agent, similar to EV (53). SLITRK6 is a type I transmembrane protein that can be highly expressed in bladder cancer. Initial activity and safety of ASG-15ME was investigated in a phase I dose escalation trial of 51 patients with aUC progressing on at least one prior chemotherapy regimen, with six different dose levels studied (54). The ORR was 33%, including robust ORR 42% (5/12 patients) who had previously progressed on ICI. The agent was considered well tolerated with the most common TRAE being fatigue in 44% of patients, however no follow-up data with this drug have been presented to date in aUC.

Many clinical trials in aUC—and thus potential future treatment options—are molecularly driven, selecting patients with alterations commonly found in aUC for specific targeted treatments. The approval of erdafitinib for FGFR2/3-altered aUC was discussed above and has validated this approach. Overexpression of HER2, a transmembrane receptor involved in cell proliferation, and commonly also found in breast and gastric cancers, is another alteration commonly found in aUC for which multiple treatments have been considered. Trastuzumab deruxtecan (DS-8201a) is an ADC consisting of an antibody targeting HER2 linked to a topoisomerase inhibitor. This drug recently received FDA accelerated approval for patients with metastatic HER2-positive breast cancer and is being investigated in a phase Ib trial in aUC in combination with nivolumab in patients previously progressing on chemotherapy (55). Another ADC targeting HER2 is RC48-ADC, which is comprised of another HER2 targeting antibody, hertuzumab, which is conjugated with MMAE. This agent was initially assessed in a phase I basket trial of multiple solid malignancies and administered every 2 weeks. The drug was well tolerated with most common side effects including cytopenias and liver function test elevation. The ORR was 33% in evaluable patients and one of the partial responses was recorded in a patient with aUC (56). Based on the initial results, a phase II dose expansion trial was pursued at a dose of 2 mg/kg every 2 weeks in aUC previously treated with at least one systemic therapy. All eligible patients had HER2-positive tumors (IHC 2/3+). Among 43 patients, 18.6% had prior ICI; the ORR was 60.5% in the overall population and 75% in those previously treated with ICI, while TRAEs were consistent with previously reported data (57,58). Another trial of RC48-ADC in patients with aUC following progression on platinum, gemcitabine and taxane was presented at the 2021 ASCO annual meeting (NCT03809013). This trial completed enrollment in September 2020 and included a total of 64 patients with HER2-overexpressing urothelial tumors (IHC 2+ or 3+). The independently assessed ORR was 46.9% and median OS was 14.8 months (59). Importantly, among 19 patients who had prior ICI, ORR was 42%; ORR in patients with visceral metastases was 45%. TRAEs were consistent with previously reported data.

PRS-343 is another novel bispecific antibody targeting HER2 and CD137 (4-1BB), a costimulatory molecule playing an important role in immune regulation (60). CD137 protein is part of the TNF receptor family that is expressed on several important immune cell subtypes, such as $CD4^+$ and $CD8^+$ T-cells, B cells and NK cells (61). An update of the phase I dose escalation trial of PRS-343 in patients with advanced HER2+ solid tumors was recently presented at the ESMO 2020 meeting (62). Among 70 patients enrolled, 33 were treated at active dose levels and evaluable for response, although there were only two patients with aUC. The ORR and DCR were 12% and 52%, respectively, but were associated with higher dose levels, while post-treatment expansion of $CD8^+$ T-cells was also observed. The treatment was well tolerated with most common TRAEs (>5%) related to mild infusion reaction, nausea, and arthralgia. The combination of PRS-343 and atezolizumab is also being pursued in a phase I clinical trial of patients with HER2-positive solid tumors including aUC (NCT03650348).

Epigenetic modifiers are another important group of agents currently being investigated in aUC, as chromatin-modifying gene alterations are commonly found in bladder cancer (63). In particular, combinations of epigenetic modifiers with ICI are of interest given the hypothesis that novel tumor antigens may be exposed with this treatment. A phase I/II trial combining the epigenetic modifier guadecitabine with atezolizumab (NCT03179943) in patients with ICI-refractory aUC completed enrollment with results pending soon. Similar phase I trials investigating other epigenetic modifiers, such as abexinostat/pembrolizumab combination (NCT03590054) are also ongoing. Multiple other classes of agents have also been investigated in aUC sometimes with disappointing results. In one such example, the poly (ADP-ribose) polymerase (PARP) inhibitor rucaparib was investigated as single agent in the ATLAS phase II trial, which included a molecularly unselected population with the majority of patients having received both platinum-based chemotherapy and ICI. No confirmed responses were seen in this setting (64).

Table 1 Selected clinical trials in advanced urothelial cancer following progression on PD-L1 treatment

Clinical trial	Phase	Treatment	Treatment setting	ORR (%)	NCT number
EV-101	I	Enfortumab vedotin	aUC s/p chemo/ICI	43	NCT02091999
EV-201 (cohort 1)	II	Enfortumab vedotin	aUC s/p chemo/ICI	44	NCT03219333
EV-201 (cohort 2)	II	Enfortumab vedotin	aUC s/p ICI (cisplatin-ineligible)	52	NCT03219333
EV-301	III	Enfortumab vedotin *vs.* chemotherapy (randomized)	aUC s/p chemo/ICI	41*	NCT03474107
SG phase I/II basket study (UC cohort)	I/II	Sacituzumab govitecan	aUC s/p ≥1 therapy; (95% chemo, 48% ICI)	31 (post-ICI 23)	NCT03547973
TROPHY-U-01 (cohort 1)	II	Sacituzumab govitecan	aUC s/p chemo/ICI	27	NCT03547973
TROPHY-U-01 (cohort 2)	II	Sacituzumab govitecan	aUC s/p ICI (cisplatin-ineligible)	28	NCT03547973
TROPICS-04	III	Sacituzumab govitecan *vs.* chemotherapy (randomized)	aUCs/p chemo/ICI	N/A	NCT04527991
RC48-ADC phase II urothelial study	II	RC48-ADC	HER2 + aUC patients s/p platinum and ICI (19%)	51; post-IO 75	NCT03507166
RC48-ADC phase II urothelial study	II	RC48-ADC	HER2 + aUC patients s/p platinum-based regimen and taxane; ICI (30%)	47; post-IO 42	NCT03809013

*, ORR in the enfortumab vedotin arm of EV-301. ORR, objective response rate; EV, enfortumab vedotin; aUC, advanced urothelial carcinoma; ICI, immune checkpoint inhibitor; chemo, chemotherapy; SG, sacituzumab govitecan; UC, urothelial carcinoma; ADC, antibody drug conjugate.

A summary of selected clinical trials in aUC following progression on ICI is presented in *Table 1*.

Other agents with potential activity in aUC include vascular endothelial growth factor receptor antagonists such as ramucirumab, or multikinase inhibitors including cabozantinib. Ramucirumab was investigated in the post-platinum space as part of the phase III RANGE trial which randomized 530 patients with aUC to receive docetaxel with ramucirumab or docetaxel with placebo and allowed prior treatment with ICI. Adding ramucirumab to docetaxel led to a statistically significant improvement in PFS [4.1 *vs.* 2.8 months; HR 0.696 (95% CI: 0.573–0.845), P<0.001], but no significant improvement in OS [9.4 *vs.* 7.9 months; HR 0.887 (95% CI: 0.724–1.086), P=0.25] (65). Activity of cabozantinib was assessed as part of a phase II study in patients with platinum-refractory aUC. Among 42 post-platinum patients with aUC evaluable for response, ORR was 19% indicating single-agent activity (66). With strong pre-clinical rationale of combining cabozantinib with ICI, a phase I trial investigated the combination of cabozantinib with nivolumab or with nivolumab and ipilimumab in patients with aUC either naïve or refractory to ICI (67). The combination of cabozantinib with ICIs demonstrated manageable toxicities and reported responses in 5 out of 13 patients with aUC, thus suggesting potential benefit of adding cabozantinib to ICI treatment to overcome resistance to immunotherapeutic agents in this space (68).

Future directions

ICIs have profoundly altered the treatment landscape in aUC over the past several years, and now form the backbone for the standard of care, as either frontline treatment in platinum-ineligible patients, post-platinum switch maintenance treatment, or treatment for platinum-refractory disease. Increasingly, ICIs are moving into earlier treatment setting trials as well. In the neoadjuvant space, very promising phase II trials have shown compelling pathologic CR rates supporting five ongoing phase III peri-operative trials in localized MIBC (69,70). Phase II trials of ICI and combinations of chemotherapy plus ICI have shown initial promising results (71-74). In the pure adjuvant space,

Table 2 Examples of treatments for advanced urothelial cancer tested in various clinical trials

Conventional cytotoxic agents	Immunotherapy	Targeted therapies
Chemotherapy	Checkpoint inhibitors	Anti-angiogenesis
Antibody-drug conjugates	Vaccines	FGFR inhibitors
Radiation	Cytokines	HER family inhibitors
	Adoptive cell-based therapy	PARP inhibitors
	Other immuno-modulating agents	Chromatin remodeling (i.e., HDAC inhibitors)
		Other (i.e., monoclonal antibodies, TKIs)

FGFR, fibroblast growth factor receptor; HER, human epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerase; HDAC, histone deacetylase; TKI, tyrosine kinase inhibitor.

large randomized clinical trials have investigated the role of ICIs for high-risk disease at the time of radical surgery. While the IMvigor010 trial did not show significant benefit of adjuvant atezolizumab *vs.* observation (75), recently reported Checkmate-274 trial did show a significant disease-free survival benefit of adjuvant nivolumab *vs.* placebo in a similar patient population (76). The results of the AMBASSADOR trial of adjuvant pembrolizumab *vs.* observation and PROOF-302 (infigratinib *vs.* placebo) are still pending. For patients with BCG-unresponsive NMIBC who cannot undergo or refuse radical cystectomy, pembrolizumab is FDA-approved based on the results of Keynote-057 single arm phase II trial, while atezolizumab has also shown results in this treatment space (S1605 trial) without having FDA approval (77,78).

Increasingly ICI-based combinations are being tested into the frontline space as well, particularly for the cisplatin-ineligible population, which is in especially high need of novel therapies. As part of the EV-103 clinical trial, the cohort of treatment-naïve patients treated with combination of pembrolizumab plus EV showed a robust response rate of 73%, leading to a randomized cohort of pembrolizumab/EV *vs.* EV to be enrolled in that same trial (16). Other trials of molecularly selected patients in the frontline space are also ongoing. This includes patients with low PD-L1 status being enrolled into the PIVOT-10 trial of combination nivolumab with NKTR-214 (pegylated IL-2) (15), while the LEAP-011 trial is testing the combination of pembrolizumab with either lenvatinib or placebo (79). For patients with FGFR3-altered tumors a number of trials are investigating the combination of ICIs with FGFR3 inhibitors (34,80,81).

Despite these very promising developments and novel directions, the unfortunate reality remains that many patients with aUC may not respond to ICI, and nearly all patients eventually develop resistance and have tumor progression. Many patients are too sick or frail to tolerate third or fourth-line therapy, therefore decisions regarding treatments earlier in their disease course become more critical (82). The arsenal of currently available and possible future treatment options in aUC has expanded substantially (*Table 2*), but much remains to be learned in this challenging disease space. Important questions remain about resistance mechanisms to ICI and the optimal selection of patients for ICI monotherapy or therapy intensification. Significant research looking at prognostic and predictive biomarkers is underway and over the next few years may shed additional light on these very important questions.

Conclusions

The treatment landscape of aUC has seen dramatic changes over the past several years and remains a rapidly changing and dynamic space. The current treatment paradigm for most patients involves treatment with platinum-based chemotherapy followed by anti-PD-L1 agents as either switch maintenance therapy or as treatment for platinum-refractory disease. At the time of progression on PD-L1 therapy, novel treatment options have also recently emerged. For molecularly-selected patients whose tumors harbor FGFR2 or FGFR3 activating mutation or fusion, erdafitinib is a treatment option in the platinum-refractory space and appears to also be effective for patients progressing on prior ICI. For an unselected population of patients with prior progression on platinum-based chemotherapy and ICI, EV (ADC targeting Nectin-4), and SG (ADC targeting Trop-2) are great treatment options. A number of other experimental therapies are also being

developed in the post-ICI treatment space with very promising data. Increasingly novel therapies are also being developed for other molecularly selected populations, such as HER2 overexpression, including ADCs and bispecific antibodies, while combinations of either anti-VEGF or anti-FGFR agents with ICI look promising. Although significant advances in the treatment of platinum-refractory aUC have been made with several agents approved in this setting since 2016, this remains an aggressive and generally incurable disease. Further research focusing on novel treatment combinations as well as mechanisms of resistance and biomarkers of response will continue advancements in the field that are so urgently needed to help more patients.

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