Changing Paradigms in the Treatment of Advanced Urothelial Carcinoma: A 2020 Update

Abstract

Advanced urothelial cancer (aUC) is invariably lethal and standard of care, platinum-based chemotherapy has changed little over the past 25 years. However, the past 5 years have been transformational with the advent of immunotherapies and targeted therapies. In this review, the authors focus on the therapies that are showing the greatest promise and have changed, or will imminently impact, the treatment landscape of aUC. Checkpoint inhibition is showing deep and durable responses in some patients and trial activity is concentrated on identifying the most suitable position within the treatment paradigm along with the most appropriate patients and therapeutic combinations. Novel targeted therapies in aUC are gaining renewed interest with nectin-4 antibody drug conjugates and fibroblast growth factor receptor inhibitors, both receiving recent regulatory approvals. Bispecific antibodies, capable of binding to two targets at the same time, are also showing promise. This review discusses the preclinical data, the relevant past, and present clinical trials along with regulatory status to provide a concise overview of the current and impending treatment options for aUC.

INTRODUCTION

Urothelial cancer is the 9th most common cancer in the world and the 10th most common cancer in the UK. More than 10,000 new urothelial cancer cases occur in the UK every year, with a quarter of the patients presenting with locally advanced or metastatic urothelial carcinoma. Incidence rates are highest in older people (aged 85–89 years) and despite current treatment options the 5-year survival remains at only around 10%.

The treatment landscape of advanced urothelial cancer ([aUC]: locally advanced or metastatic urothelial carcinoma) is now rapidly evolving with a recent increase in the number of approvals by the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) (Figure 1).
This review summarises current treatment options for aUC, including cytotoxic chemotherapy and immune checkpoint blockade, with a focus on recent advances in targeted therapies and bispecific antibodies that are most likely to impact the management of aUC in the future.

**CYTOTOXIC CHEMOTHERAPY**

Platinum-based combination chemotherapy is currently the global first-line treatment for metastatic urothelial carcinoma. Combinations in use include MVAC (methotrexate, vinblastine, doxorubicin, cisplatin), gemcitabine and cisplatin, and gemcitabine and carboplatin. Response rates have been reported at around 30-40%. Second-line chemotherapy agents such as taxanes, vinflunine, ifosfamide, and oxaliplatin have only demonstrated modest benefits. For example, vinflunine, a microtubule inhibitor, led to only a 1.5 month improvement in progression-free survival (PFS) (median PFS: 3.0 versus 1.5; hazard ratio [HR]: 0.68; 95% confidence interval [CI]: 0.54–0.86; p=0.001) and 2.3 months improvement in overall survival (OS) (median OS: 6.9 versus 4.3 months; HR: 0.78; 95% CI: 0.61–0.99; p=0.04). Immune checkpoint inhibitors (CPI) are now routinely used instead of cytotoxic chemotherapy in the second-line setting.

**IMMUNOTHERAPY**

The past 4 years has seen regulatory approval of five separate CPI (Figure 1) for the treatment of aUC. The authors have presented some of the stronger trial data to support second-line, first-line, and maintenance CPI; emerging data of combination checkpoint inhibition; and then focus on an interesting future advance, bispecific antibodies.

**Immune Checkpoint Inhibitors**

The strongest current evidence for the use of CPI in aUC comes from the KEYNOTE-045 study, which compared pembrolizumab (PD-1 inhibitor) with standard of care chemotherapy in patients who had previously progressed on platinum-based chemotherapy. The co-primary endpoints were OS and PFS. With a median follow of 27.7 months, there was a 2.8 month improvement in survival with pembrolizumab compared to chemotherapy (median OS: 10.1 versus 7.3 months; HR: 0.7; 95% CI: 0.57–0.85; p<0.001) and in responders (response rate: 21.1% versus 11.0%) the median duration of response was substantially longer with the CPI (not reached versus 4.4 months). IMvigor211 was a Phase III study comparing atezolizumab (anti-PD-L1) to standard of care chemotherapy.
in patients who had previously progressed on platinum-based chemotherapy. Atezolizumab was also active in the second-line setting but failed to reach the primary endpoint of improved OS in PD-L1 positive patients, partly because of the statistical design and better-than-expected performance of the chemotherapy control arm. Both agents are approved by the EMA for use in second-line treatment.

First-line CPI was initially tested in patients with aUC who were cisplatin-ineligible (renal impairment, neuropathy, or poor Eastern Cooperative Oncology Group [ECOG] performance status). This was following objective response rates (ORR) of 29% in the KEYNOTE-052 trial and 23% in the IMvigor 210 trials, two Phase II trials testing pembrolizumab and atezolizumab, respectively, in this setting,9 which have led to the approval of these agents. The subsequent Phase III studies (KEYNOTE-361 and IMvigor130) compared chemotherapy with chemoimmunotherapy or immunotherapy alone in first-line metastatic disease. An interim analysis of these two studies suggested that CPI monotherapy may be less effective than chemotherapy in patients with low PD-L1 expression in the first-line setting,10 leading to an EMA restriction of CPI monotherapy to patients with high PD-L1 expression. The initial results of IMvigor130, after a median of 11.8 months, have been reported in abstract form showing that atezolizumab plus chemotherapy leads to a 1.9-month improvement in predicted median PFS (8.2 versus 6.3 months; p=0.023) compared to placebo.12 Although not yet presented, Pfizer had announced following the planned interim analysis that the JAVELIN Bladder 100 study of avelumab maintenance versus standard of care met its co-primary endpoint prolonging OS in patients with PD-L1-positive tumours.13 Given that there are now two positive studies in this setting, maintenance CPI may become a new standard of care.

**Combination Immunotherapy**

Given that response rates to CPI monotherapy are only in the order of 20–25%, other approaches are required to progress these agents. CPI is being tested in combination with chemotherapy as discussed above, but also with other CPI or with targeted therapies. However, these combination approaches have so far been disappointing, as exemplified by the DANUBE14 and BISCAY15 studies. A recent press release announced that the DANUBE study, a randomised Phase III trial of durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA4) versus chemotherapy in first-line metastatic urothelial cancer failed to meet either of its co-primary endpoints, OS or OS in patients with high PD-L1 expression.14 Two similar Phase III studies for first-line aUC are ongoing with the NILE study16 testing triplet therapy (durvalumab and tremilimumab and chemotherapy), and the Checkmate901 testing an alternative doublet CPI (ipilimumab and nivolumab)17 are still to report and help clarify whether CPI-CPI combinations or CPI-chemotherapy combinations are of benefit in aUC. In BISCAY,15 a biomarker-driven Phase II study that explored either durvalumab monotherapy or durvalumab in combination with poly (adenosine diphosphate ribose) polymerase inhibitors, fibroblast growth factor receptor (FGFR)3 inhibitors, or mTOR inhibitors as second-line therapy in aUC, no combination treatment met the prespecified efficacy target.

**Bispecific Antibodies**

Bispecific antibodies are capable of binding to two targets at the same time.18 These are early-stage molecules with most of the data derived from basic science and cell-line research, with some Phase I studies recruiting. One strategy of using a bispecific antibody is by targeting CD3 and a tumour antigen simultaneously. This can
recruit and activate T cells for effective tumour clearance by bringing the T cells closer to the cancer and activating them via the CD3 receptor pathway. Another strategy is to simultaneously target immune coinhibitory and costimulatory receptors. These receptors can be upregulated on activated T cells, including regulatory T cells, in the tumour microenvironment, and therefore using bispecific antibodies may increase the localisation of the antibodies to the tumour and improve tumour-specific clearance and reduce immune-related adverse events.

Preclinical data has suggested that bispecific antibodies may be a viable therapeutic option in urothelial cancer. B7-H3 is highly expressed on urothelial cancer cells. A CD3 and B7-H3 bispecific antibody armed on T cells demonstrated increased cytotoxicity towards bladder cancer cells. Secretion of IFN-γ and TNF-α was increased compared to unarmed activated T cells.\(^{19,20}\) The same group demonstrated similar results with a bispecific antibody against CD3 and CD155 armed on activated T cells, again demonstrating their results on bladder cancer cell lines. MGD009 is a humanised anti-B7-H3 and anti-CD3 bispecific antibody that is being evaluated for safety in a multicentre, open-label, Phase I dose escalation and cohort expansion study\(^{21}\) including patients with urothelial cancer. A Phase I study of MGD009 with an anti-PD1 antibody, MGA012\(^{22}\) is currently recruiting.

A CTLA-4 and OX40 bispecific antibody resulted in T-cell activation and regulatory T-cell depletion in vitro.\(^{23}\) Using syngeneic mouse models of bladder cancer, injections of this antibody resulted in durable tumour clearance.

LY3415244 is a TIM-3 and PD-L1 bispecific antibody. It is hoped that intrinsic and acquired resistance to immune checkpoint inhibition can be overcome by targeting and inhibiting both these co-inhibitory receptors. JIC-MC-JZDA is a multicentre, nonrandomised, open-label, Phase Ia/ Ib study assessing LY3415244. The Phase Ia study will recruit patients with any tumour type and the Phase Ib expansion cohorts will recruit patients who have previously received a PD-1 or PD-L1 inhibitor, in non-small cell lung cancer, urothelial cancer, and melanoma.\(^{24}\) Similarly, RO7121661 is an anti-PD-1/TIM-3 bispecific antibody that entered Phase I studies for treatment of patients with metastatic solid tumours.\(^{25}\) Bispecific antibodies targeting other immune co-inhibitory checkpoints are running in Phase I studies. MGD013 targets PD-1 and LAG-3 and is recruiting to Phase I.\(^ {26}\)

### Targeted Therapies

Multiple targeted agents, including small molecule inhibitors or antibodies, have been tested against vascular endothelial growth factors, epidermal growth factor receptors, mTOR, and the cell cycle. Unfortunately, none of these agents demonstrated sufficient activity or efficacy in trials to gain regulatory approval (Table 1).\(^ {6,27-43}\) Recently, two targets, nectin-4 and FGFR, have demonstrated great promise and are discussed in more detail here.

#### Nectin-4

Antibody–drug conjugates (ADC) enable the delivery of high concentrations of cytotoxic chemotherapy to tumour cells by enabling targeted delivery through conjugation with a monoclonal activity. This strategy has become a standard of care in some malignancies, for example TDM-1 in breast cancer.

Enfortumab vedotin (EV) is an ADC that binds to nectin-4, a transmembrane protein that regulates a number of cellular functions including angiogenesis, and is highly expressed in multiple tumours including urothelial, ovarian, lung, breast, and gastric.\(^ {44-46}\) Upon binding to nectin-4, EV is internalised into the cell where cytoplasmic proteases cleave the linker between the nectin-4 antibody and the drug payload monomethyl auristatin E (MMAE) (vedotin is an MMAE and a protease-cleavable linker to an antibody),\(^ {47}\) releasing its cytotoxic activity. More specifically, MMAE inhibits tubulin polymerisation, leading to mitotic arrest and downstream apoptotic cell death.

Given that nectin-4 is expressed by 97% of aUC,\(^ {48,49}\) a global, Phase II, single-arm study of EV in patients with aUC who had previously been treated with platinum-based chemotherapy and anti-PD-1 or PD-L1 immune CPI was performed.\(^ {48}\) Here, 125 patients were treated with EV that was administered intravenously on Days 1, 8, and 15 of a 4-week cycle.
Table 1: Summary of clinical trials of targeted agents in advanced urothelial cancer that have not gained regulatory approval.6,27-43

| Author                      | Study name | Phase | Targeted agent                          | Primary endpoint | Patient selection                                      | Treatment                                                                 | Patients (n) | Response and survival                                                                 |
|-----------------------------|------------|-------|-----------------------------------------|------------------|--------------------------------------------------------|---------------------------------------------------------------------------|--------------|----------------------------------------------------------------------------------------|
| Petrylak et al., 2020       | RANGE"     | III   | Ramucirumab (anti-VEGFR2 antibody)      | PFS              | mUC, refractory to platinum-based chemotherapy         | Docetaxel and ramucirumab versus docetaxel and placebo                    | 530          | Ramucirumab/docetaxel versus placebo/docetaxel: RR: 24.5% versus 14.0% PFS: 4.07 months versus 2.76 months Median OS: 9.4 months versus 7.85 months |
| Rosenberg et al., 2020      | CALGB 90601 (Alliance) | III   | Bevacizumab (anti-VEGF antibody)        | OS               | mUC, first line                                        | Gemcitabine and cisplatin with bevacizumab or placebo                    | 506          | PFS HR: 0.77 (95% CI: 0.63–0.93) OS: 14.5 (GCB) versus 14                                |
| Grivas et al., 2014         | II         | Sunitinib (multiple kinase inhibitor including PDGF-R and VEGFR) | % with progression at 6 months | Advanced UC post primary chemotherapy | Maintenance sunitinib versus placebo | 54 | Sunitinib versus placebo: 6 months progression rate: 71.7% versus 64.3%. Median PFS: 2.9 months versus 2.7 months Median OS: 10.5 months versus 10.3 months |
| Bellmunt J et al., 2011     | II         | Sunitinib | TTP safety            | First-line in UC, ineligible to cisplatin | Sunitinib | 41 | PR: 8%; SD: 50% (45% of them ≥ 3 months) Median TTP: 4.8 months Median OS: 8.1 months |
| Gallagher et al., 2010      | II         | Sunitinib | ORR                   | mUC, post chemotherapy | Sunitinib 37.5 mg continuously (Cohort B) versus 50 mg for 4 weeks with 2 weeks off (Cohort A) | 78 | PR in 3/45 patients in cohort A and 1/32 patients in Cohort B. Clinical regression or stable disease: 43%. PFS: 2.4 months versus 2.3 months OS: 71 months versus 6.0 months |
| Author & Study name | Phase | Targeted agent | Primary endpoint | Patient selection | Treatment | Patients (n) | Response and survival |
|--------------------|-------|----------------|-----------------|-------------------|-----------|--------------|----------------------|
| Bellmunt et al., 2017; Wong et al., 2012 | II | Cetuximab (anti-EGFR antibody) | PFS | mUC, pretreated with one line of chemotherapy | Cetuximab with or without paclitaxel | 41 | PFS monotherapy versus combination: 7.6 versus 16.4  
| | | | | | | | OS: 17 versus 42  
| | | | | | | ORR: 25 in combination |
| Hussain et al., 2014 | II | Cetuximab | ORR | Advanced UC | Gemcitabine/cisplatin with or without cetuximab | 88 | Gemcitabine/cisplatin versus combination with cetuximab:  
| | | | | | | ORR: 57.1 versus 61.4  
| | | | | | | Grade 3-5 AE: 75 versus 83  
| | | | | | | Median PFS: 8.5 versus 7.6  
| | | | | | | Median OS: 17.4 versus 14.3  
| | | | | | | Monotherapy arm was closed |
| Miller et al., 2016 | II | Gefitinib (TKI against EGFR) | TTP | Advanced UC, in combination with first-line chemotherapy | Gefitinib and cisplatin chemotherapy with concomitant gefitinib (Arm A), sequential gefitinib (Arm B), or alone (Arm C) | 105 | Median TTP for arms A, B, and C were 6.1, 6.3, and 7.8 months, respectively |
| Choudhury et al., 2016 | II | Afatinib (TKI against HER2/EGFR) | PFS | mUC, platinum-refractory | Afatinib 40 mg/day continuously until progression or intolerance | 437 | Publication of initial results of 23 patients:  
| | | | | | | 21.7% met PFS3 (2/23 PR; 3/23 SD)  
| | | | | | | 83.3% with HER2 and/or ERBB3 alterations achieved PFS3 versus 0/15 patients without alterations (p<0.001)  
| | | | | | | Median TTP/discontinuation was 6.6 months in patients with HER2/ERBB3 alterations versus 1.4 months in patients without |
| Author          | Study name                       | Phase | Targeted agent                                           | Primary endpoint | Patient selection                                                                 | Treatment                                                                 | Patients (n) | Response and survival                                                                 |
|-----------------|----------------------------------|-------|----------------------------------------------------------|------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------|---------------------------------------------------------------------------------------|
| Bellmunt et al., 2015 | II/III Lapatinib (TKI against HER2/EGFR) | PFS   | mUC after first line chemotherapy, HER 1/2-positive | Maintenance lapatinib versus placebo | 232 | Median PFS for lapatinib and placebo was 4.5 versus 5.1 months. OS for lapatinib and placebo was 12.6 months and 12.0 months |
| Hussain et al., 2007 | II Trastuzumab (anti-HER2 antibody) | Toxicity | Advanced HER2/neu-positive UC | Trastuzumab in combination with paclitaxel, carboplatin, gemcitabine | 40 | Provisional results from publication: Most common Grade 3 or 4 was myelosuppression. Grade 3 sensory neuropathy occurred in 14.0%. Grade 1–3 cardiac toxicity was 22.7%. Therapy-related deaths (n=3). ORR: 70% (CR [n=5], PR [n=26], confirmed responses [n=25]). Median TTP and survival were 9.3 months and 14.1 months |
| Hainsworth et al., 2018 | IIa Trastuzumab/pertuzumab (anti-HER2/HER3 dimerisation antibody) | OS % of Atezolizumab-treated patients with tTMB ≥16 mutations/Mb with OR | HER2-positive mUC | Trastuzumab/pertuzumab, erlotinib, vemurafenib/cobimetinib, vismodegib, alectinib, and atezolizumab | 765 | Recruitment ongoing. Preliminary results: At median FU 5.4: 1 patient had CR, ongoing at 12.5 months; 2 PR; DOR 3.7 and 5.5 months, 2 SD for >4 months |
| Rose et al., 2018 | II Palbociclib (CDK4/6 inhibitor) | PFS   | mUC after failure of first-line chemotherapy | Palbociclib | 12 | Two patients (17%) achieved PFS4 with insufficient activity to advance to Stage 2. No responses were seen. Median PFS: 1.9 months. Median OS: 6.3 months |
Table 1 continued.

| Author                                    | Study name   | Phase | Targeted agent             | Primary endpoint                                      | Patient selection | Treatment | Patients (n) | Response and survival |
|-------------------------------------------|--------------|-------|-----------------------------|-------------------------------------------------------|-------------------|-----------|--------------|----------------------|
| Milowsky et al., 201342                   |              | II    | Everolimus (mTOR inhibitor) | PFS-2 safety and toxicity                             | Metastatic TCC    | Everolimus | 46           | Most common Grade 3/4 toxicities were fatigue, infection, anaemia, lymphopenia, hyperglycaemia and hypophosphataemia. PR in nodal metastases (n=2), with 1 achieving a 94% decrease in target lesions and remaining on drug at 26 months. Minor tumour regression (n=12) |
| Niegisch et al., 201543                   | AUO Trial AB 35/09 | II    | Everolimus                  | RR                                                    | Second-Line treatment of advanced UC | Paclitaxel and everolimus | 28           | ORR: 13% PFS: 2.9 months Median OS: 5.6 months |

AE: adverse event; CR: complete response; CPS: combined positive score; DOR: duration of response; EGFR: epidermal growth factor receptor; FGFR: fibroblast growth factor receptor; FU: follow-up; GCB: germinal centre B-cell; HR: hazard ratio; HER2: human epidermal growth factor receptor; mTOR: mammalian target of rapamycin; mUC: metastatic UC; OR: overall response; ORR: overall response rate; OS: overall survival; PDGF-R: platelet-derived growth factor receptor; PD-L: programmed death ligand; PFS: progression-free survival; PR: partial response; RR: response rate; SD: stable disease; TEAE: treatment-emergent adverse events; TKI: tyrosine kinase inhibitor; tTMB: tissue tumour mutational burden; TTP: time to progression; UC: urothelial cancer; VEGFR: vascular endothelial growth factor receptor; 95% CI: 95% confidence interval.

The primary endpoint was ORR using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria. Secondary endpoints included duration of response, PFS, OS, safety, and tolerability.

Nectin-4 expression was assessed by immunohistochemistry (using a modified H-score, a continuous weighted scale). The ORR was 42% (95% CI: 35.1–53.2%), with 12% complete responses, which is markedly higher than any other third-line treatment that has been tested in aUC. The median duration of response was 7.6 months (range: 0.95–11.30 months). The estimated median PFS was 5.8 months (95% CI: 4.9–7.5 months) and the estimated median OS was 11.7 months (95% CI: 9.1 months to not reached). As well as this prolonged survival compared to historical controls, EV was also well tolerated with the most common grade ≥3 toxicities being neutropenia (8%), anaemia (7%), and fatigue (6%). Treatment-related adverse events led to dose reductions in 32% of patients and discontinuation of treatment in only 12% of patients, with no treatment-related deaths. The most common toxicities of any grade were fatigue (50%), alopecia (49%), decreased appetite (44%), dysgeusia (40%), peripheral sensory neuropathy (40%), nausea (40%), diarrhoea (40%), and maculopapular rash (27%). Based on results from the EV-201 trial, the FDA granted accelerated approval to EV in December 2019. The global registration Phase III study of third-line EV compared to standard of care chemotherapies (EV-301) has recently completed data accrual.
and initial results are expected towards the end of 2020.\textsuperscript{51}

Given this encouraging level of activity in the third-line setting, EV has also been tested in combination with pembrolizumab (anti-PD-1) as a first-line therapy in patients who were ineligible to receive platinum chemotherapy. Initial results were presented at ESMO 2019,\textsuperscript{52} and updated at GU ASCO 2020.\textsuperscript{53} The overall response rate was 73.3\% with a complete response rate of 15.6\%. At a median follow up of 10.4 months, 55\% of the responders had an ongoing durable response. Treatment-related toxicities included fatigue (58\%; 11\% $\geq$ G3), alopecia (53\%), and peripheral sensory neuropathy (53\%; 4\% $\geq$ G3). However, one patient in the study died as a result of multiple organ failure. The FDA granted breakthrough designation to the EV and pembrolizumab combination in February 2020. This combination demonstrates encouraging efficacy compared to previous drugs used in the first-line setting and, if replicated in Phase III studies, could lead to a paradigm shift in the treatment of aUC.\textsuperscript{52,53} The EV-302 Phase III study will evaluate the EV and pembrolizumab combination therapy versus standard of care gemcitabine and platinum in the first-line treatment setting for aUC, with primary outcome measures of PFS and OS.

**Fibroblast Growth Factor Receptor**

FGFR activation results in signal transduction via the downstream MAPK and PI3K pathways, which regulate tumour survival and growth.\textsuperscript{52} FGFR3 alterations are present in approximately one-fifth of patients with urothelial bladder cancer and in one-third of patients with upper tract urothelial carcinomas.\textsuperscript{54}

Erdafitinib is a potent inhibitor of FGFR1-4 and a weaker inhibitor of VEGFR2. It has been the first targeted anticancer therapy to gain accelerated approval by the FDA\textsuperscript{55} for patients with aUC carcinoma with susceptible FGFR2 or FGFR3 mutations, based on the results of the BLC2001 study.\textsuperscript{56} Simultaneously, approval for the Therascreen\textsuperscript{®} (Qiagen, Hilden, Germany) FGFR RGQ RT-PCR Kit was given as the companion diagnostic. This is a reverse-transcriptase-PCR assay that tests for specific FGFR3 mutations or FGFR2/3 fusions using RNA extracted from formalin-fixed paraffin-embedded samples.

The BLC2001 study was an open-label Phase II study enrolling patients with aUC with prespecified FGFR alterations\textsuperscript{56} to treatment with oral erdafitinib. In total, 99 patients with specified FGFR3 gene mutations or FGFR2/3 gene fusions were recruited. Patients had to have progressed following treatment with one course of chemotherapy or within 12 months after neoadjuvant or adjuvant chemotherapy. The primary endpoint was ORR and secondary endpoints included duration of response, PFS, and OS.

Patients were initially randomised in a 1:1 ratio to either receive an intermittent regimen (10 mg per day, with daily administration for 7 days and off for 7 days) or a continuous regimen (6 mg per day). Subsequently, a planned interim analysis of safety and efficacy was performed in June and July 2016 and further enrolment to the intermittent-regimen group was halted. In August 2016, the study was converted to a single-group analysis following a protocol amendment to increase the starting dose to 8 mg per day in a continuous regimen.

The ORR was 40\% (95\% CI: 31–50), the median duration of response was 5.6 months (95\% CI: 4.2–7.2). The median PFS was 5.5 months (95\% CI: 4.2–6.0) and median OS was 13.8 months (95\% CI: 9.8–not reached). Patients with FGFR3 mutations were noted to have a better ORR (49\%) compared to those with FGFR2/3 fusions (16\%).

In terms of safety, 46\% of patients experienced a treatment-related adverse event at Grade 3 or higher. The most commonly reported toxicities that were Grade 3 or higher were hyponatraemia (11\%), stomatitis (10\%), and fatigue (7\%) and 13 patients had treatment discontinuation. This was because of detachment of the retinal pigment epithelium, hand-foot syndrome, dry mouth, and skin or nail events. Furthermore, 55 patients required a dose reduction, which was commonly a result of stomatitis (16 patients) and hyperphosphataemia (9 patients). Common adverse events included hyperphosphataemia (77\% all grade), stomatitis (58\% all grade), diarrhoea (51\% all grade), and dry mouth (56\% all grade). Hand-foot syndrome was at 23\% any grade. Hyperphosphataemia, a class effect of FGFR inhibition,\textsuperscript{57} which is thought to be secondary to inhibition of FGF23 signalling,\textsuperscript{58}
could be a useful pharmacodynamic biomarker. A randomised Phase III study (THOR)\(^5^9\) is now investigating the benefit of erdafitinib compared with chemotherapy or pembrolizumab, with a primary outcome of OS. Patients who have progressed on or after one or two prior treatments, at least one of which includes an anti-PD-1/PD-L1 agent (Cohort 1) or one prior treatment not containing an anti-PD-1/PD-L1 agent (Cohort 2).

Other FGFR inhibitors include infigratinib, rogaratinib, pemigatinib, and Debio 1347 (Debiopharm, Lausanne, Switzerland). Infigratinib (BGJ398) is a potent and selective FGFR1–3 inhibitor.\(^6^0\) An exploratory analysis of Phase II data\(^6^1\) demonstrated a difference in ORR in upper urinary tract urothelial carcinoma (50%) compared to lower urinary tract urothelial carcinoma (22%). The difference in ORR could be because of differences in genomic alterations between the two patient groups. A higher frequency of \(FGFR3\)-TACC3 fusions (12.5% versus 5.8%) and \(FGFR3\ R248C\) mutations (50% versus 11.5%), and a lower frequency of \(FGFR3\ S249C\) mutations (25% versus 59.6%) was found when comparing upper with lower urinary tract urothelial carcinoma.

Rogaratinib (BAY1163877) is a potent and selective inhibitor of FGFR 1–4.\(^6^2\) Results from the Phase I study were reported in 2016.\(^6^3\) A Phase III trial\(^6^4\) comparing rogaratinib against chemotherapy in metastatic urothelial carcinoma who have received prior platinum-based chemotherapy is currently active but not recruiting in January 2020.

The interim results of the FIGHT-201\(^6^5\) study, a Phase II, open-label, multicentre study of pemigatinib (INCB054828), was reported in 2018. Patients had to have previously progressed on one or more treatments and had \(FGFR3\) mutations or fusions (Cohort A) or other \(FGF/FGFR\) gene alterations (Cohort B). 64 patients were in Cohort A and with an ORR of 25% (95% CI: 14–40%). There were no responses determined by RECIST 1.1 in Cohort B. FIGHT-205,\(^6^6\) looking at pemigatinib plus pembrolizumab versus pemigatinib alone versus standard of care for participants with metastatic or unresectable urothelial carcinoma who are not eligible to receive cisplatin, are harbouring \(FGFR3\) mutation or rearrangement, and who have not received prior treatment, is currently recruiting.

Debio 1347 is a selective inhibitor of FGFR 1–3. The FUZE trial is an ongoing Phase II basket trial in \(FGFR\) fusion-positive advanced solid tumours irrespective of tumour histology, enrolling patients with aUC with at least one prior treatment line.\(^6^7\) The primary endpoint is ORR.

Targeting FGFR3 alone in pretreated patients has not demonstrated similar levels of ORR compared to the multitargeted FGFR inhibitors. A Phase II study of dovitinib, a multitargeted tyrosine kinase inhibitor with activity against FGFR3 looked at 44 aUC patients who progressed after at least one chemotherapy regimen. Patients were classified as \(FGFR3\) mutant or wild type. The study was not taken further because of a lack of ORR (0%; 95% CI: 0.0–26.5).

Small molecule tyrosine kinase inhibitors are not the only strategy to target the FGFR pathway in urothelial carcinoma. Vofatamab (B-701) is a fully human monoclonal antibody against FGFR3 that blocks activation of the wild type and genetically activated receptor. FIERCE-21 is a Phase Ib/2 study designed to evaluate vofatamab monotherapy or in combination with docetaxel in metastatic urothelial carcinoma with at least one treatment failure. The follow-up is immature at this time; however, data presented at ASCO GU 2019 showed that five out of 21 patients have had a partial response in the vofatamab combination arm compared to one out of 21 patients in the monotherapy arm.

**CONCLUSION**

This review discussed strategies that allow better targeting of aUC. ADC in the form of EV demonstrate good response rates in pretreated metastatic disease, and early results in the first-line setting are encouraging. There are now actionable genomic alterations in the form of FGFR inhibitors that can lead to better outcomes in selected groups of patients. Bispecific antibodies may allow urothelial cancer cells to be targeted specifically and overcome mechanisms of resistance to immune CPI.

There have been advances in developing targeted and personalised therapies in metastatic urothelial carcinoma. Further discussed here were
three different targeted agents demonstrating promise in both clinical trials and preclinical research (Figure 2).

The development of targeted agents in aUC has positive implications for patients' outcomes and treatment options. The challenge remains in optimising patient selection, sequencing of treatment, and whether combination strategies can lead to better outcomes. This represents a paradigm shift in the treatment of metastatic urothelial cancer, where previously treatment options were limited to cytotoxic chemotherapy.

Figure 2: Promising targeted treatment strategies in advanced urothelial cancer. FGFR: fibroblast growth factor receptor.

References
1. Antoni S et al. Bladder cancer incidence and mortality: a global overview and recent trends. Eur Urol. 2017;71(1):96-108.
2. Cancer Research UK. Bladder cancer statistics 2018. 2018. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer. Last accessed: 22 June 2020.
3. Alifrangis C et al. Molecular and histopathology directed therapy for advanced bladder cancer. Nat Rev Urol. 2019;16(8):465-83.
4. Gómez De Liaño A, Duran I. The continuing role of chemotherapy in the management of advanced urothelial cancer. Ther Adv Urol. 2018;10(12):455-80.
5. Bellmunt et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clinical Oncol. 2009;27(27):4454-61.
6. Bellmunt J et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med. 2017;376(11):1015-26.
7. Fradet Y et al. Randomized Phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of ≥2 years of follow-up. Ann Oncol. 2019;30(6):970-6.

8. Powles T et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, Phase 3 randomised controlled trial. Lancet. 2018;391(10122):748-57.

9. Stenehjem DD et al. PDI/PDL1 inhibitors for the treatment of advanced urothelial bladder cancer. Onco Targets Ther. 2018;11:5973-89.

10. Gourd E. EMA restricts use of anti-PD-1 drugs for bladder cancer. Lancet Oncol. 2018;19(7):e341.

11. Grande E et al. LBA34_PR - IMvigor211: Efficacy and safety from a Phase III study of atezolizumab (atezo) as monotherapy or combined with platinum-based chemotherapy (PBC) vs placebo + PBC in previously untreated locally advanced or metastatic urothelial carcinoma (mUC). Ann Oncol. 2019;30(5):v888-9.

12. Gaisky MD et al. Randomized double-blind Phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients (pts) with metastatic urothelial cancer (mUC): HCRN GU14-182. J Clin Oncol. 2019;37(15 Suppl):4505.

13. Pfizer. Bavencio significantly improved overall survival in patients with locally advanced or metastatic urothelial carcinoma. 2020. Available at: https://investors.pfizer.com/investor-news/press-release-details/2020/BAVENCIO-Significantly-Improved-Overall-Survival-in-Patients-With-Locally-Advanced-or-Metastatic-Urothelial-Carcinoma/default.aspx. Last accessed: 22 June 2020.

14. AstraZeneca. Update on Phase III DANUBE trial for imfinzi and tremelimumab in unselectable, Stage IV bladder cancer. 2020. Available at: https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-phase-iii-danube-trial-for-imfinzi-and-tremelimumab-in-unselectable-stage-iv-bladder-cancer-06302020.html. Last accessed: 22 June 2020.

15. Powles T et al. An adaptive, biomarker directed platform study in metastatic urothelial cancer (BISCAY) with durvalumab in combination with targeted therapies. Ann Oncol. 2019;30(Suppl 5):v356-7.

16. Guardant Health, Inc. Noninvasive vs invasive lung evaluation (NILE). NCT03516143. https://clinicaltrials.gov/ct2/show/NCT03516143. Last accessed: 22 June 2020.

17. Bristol-Myers Squibb. Study of nivolumab in combination with ipilimumab or standard of care chemotherapy compared to the standard of care chemotherapy alone in treatment of participants with untreated inoperable or metastatic urothelial cancer (CheckMate901). NCT03036098. https://clinicaltrials.gov/ct2/show/NCT03036098.

18. Lameris R et al. Bispecific antibody platforms for cancer immunotherapy. Crit Rev Oncol Hematol. 2014;92(3):153-65.

19. Ma W et al. Targeting immunotherapy for bladder cancer using anti-CD3 + B7-H3 bispecific antibody. Cancer Med. 2017;8(10):S167-77.

20. Ma W et al. Targeting immunotherapy for bladder cancer by using anti-CD3 x CD155 bispecific antibody. J Cancer. 2019;10(21):S153-61.

21. Tolcher AW et al. Phase 1, first-in-human, open label, dose escalation study of MGD009, a humanized B7-H3 x CD3 dual-affinity re-targeting (DART) protein in patients with B7-H3-expressing neoplasms or B7-H3 expressing tumor vasculature. J Clinical Oncol. 2016;34(15 Suppl):TPS3105.

22. Shankar S et al. A Phase 1, open label, dose escalation study of MGD009, a humanized B7-H3 x CD3 DART protein, in combination with MGA012, an anti-PD-1 antibody, in patients with relapsed or refractory B7-H3-expressing tumors. J Clin Oncol. 2018;36(15 Suppl):TPS2601.

23. Kvanhnammar AM et al. The CTLA-4 x OX40 bispecific antibody ATOR-1015 induces anti-tumor effects through tumor-directed immune activation. J Immunother Cancer. 2019;7(1):103.

24. Bellmunt J et al. HER2 as a target in metastatic urothelial carcinoma of the urothelium. Urol Int. 2014;93(1):692-701.

25. Hussain M et al. A randomized Phase 2 trial of gemcitabine/cisplatin with or without cetuximab in patients with advanced urothelial carcinoma. Cancer. 2014;120(5):692-701.

26. Miller K et al. A Phase II study of the Central European Society of Anticancer-Drug Research (CESAR) group: results of an open-label study of gemcitabine plus cisplatin with or without cetuximab in patients with advanced or metastatic transitional cell carcinoma of the urothelium. Urol Int. 2016;96(1):5-13.

27. Choudhury NJ et al. Aftinab activity in platinum-refractory metastatic urothelial carcinoma in patients with ERBB alterations. J Clin Oncol. 2016;34(18):2165-71.

28. Bellmunt J et al. HER2 as a target in invasive urothelial carcinoma. Cancer Med. 2015;4(6):844-52.

29. Powles T et al. Phase III, double-blind, randomized trial that compared maintenance laptinib versus placebo after first-line chemotherapy in patients with human epidermal growth factor receptor 1/2-positive metastatic bladder cancer. J Clin Oncol. 2017;35(1):48-55.

30. Hussain MH et al. Trastuzumab, paclitaxel, carboplatin, and gemcitabine in advanced human epidermal growth factor receptor-2/ neu-positive urothelial carcinoma: results of a multicenter Phase II National Cancer Institute trial. J Clin Oncol. 2007;25(16):2218-24.

31. Hainsworth JD et al. Targeted therapy for advanced solid tumors on the basis of molecular profiles: results from MyPathway, an open-label, Phase IIa multiple basket study. J Clin Oncol. 2018;36(6):536-42.
40. Bryce AH et al. Pertuzumab plus trastuzumab for HER2-positive metastatic urothelial carcinoma (mUC): pooled analysis of data from MyPathway. J Clin Oncol. 2017;35(6 Suppl):348.

41. Rose TL et al. Phase II trial of palbociclib in patients with metastatic urothelial cancer after failure of first-line chemotherapy. Br J Cancer. 2018;119(7):801-7.

42. Milowsky MI et al. Phase II study of everolimus in metastatic urothelial cancer. BJU Int. 2015;116(4):462-70.

43. Niegisch G et al. Second-line treatment of advanced urothelial cancer with paclitaxel and everolimus in a German Phase II Trial (AUO Trial AB 35/09). Oncology. 2015;89(2):70-8.

44. Takano A et al. Identification of nectin-4 oncoprotein as a diagnostic and therapeutic target for lung cancer. Cancer Res. 2009;69(16):6694-703.

45. DeRycke MS et al. Nectin 4 overexpression in ovarian cancer tissues and serum: potential role as a serum biomarker. Am J Clin Pathol. 2010;134(5):835-45.

46. Zeindler J et al. Nectin-4 expression is an independent prognostic biomarker and associated with better survival in triple-negative breast cancer. Front Med (Lausanne). 2019;6:200.

47. Challita-Eid PM et al. Enfortumab vedotin antibody-drug conjugate targeting nectin-4 is a highly potent therapeutic agent in multiple preclinical cancer models. Cancer Res. 2016;76(10):3003-13.

48. Rosenberg JE et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death ligand 1 therapy. J Clin Oncol. 2019;37(29):2592-600.

49. American Association for Cancer Research (AACR). Targeting nectin-4 in bladder cancer. Cancer Discov. 2017;7(8):OF3.

50. Ishibashi H et al. Sex steroid hormone receptors in human thymoma. J Clin Endocrinol Metab. 2003;88(3):2309-17.

51. Petrylak DP et al. EV-301: A Phase III trial in progress evaluating enfortumab vedotin versus chemotherapy in patients with locally advanced or metastatic urothelial carcinoma. Ann Oncol. 2019;30(x):ix-6.

52. Holmes CJ et al. EV-103: Initial results of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma. Ann Oncol. 2019;30(Suppl 5):v356-v402.

53. Rosenberg JE et al. Study EV-103: Preliminary durability results of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma. J Clin Oncol. 2020;38(6 Suppl):441.

54. Szakánsos J et al. Genomic characterization of upper tract urothelial carcinoma. Eur Urol. 2015;68(6):970-7.

55. American Health & Drug Benefits. FDA oncology update. Am Health Drug Benefits. 2019;12(4):198-200.

56. Loriot Y et al. Erardatifinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med. 2019;381(4):338-48.

57. Chae YK et al. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. Oncotarget. 2017;8(9):16052-74.

58. Yanochko GM et al. Pan-FGFR inhibition leads to blockade of FGF23 signaling, soft tissue mineralization, and cardiovascular dysfunction. Toxicol Sci. 2013;135(2):451-64.

59. Janssen Research & Development, LLC. A study of erdafitinib compared with vinflunine or docetaxel or pembrolizumab in participants with advanced urothelial cancer and selected fibroblast growth factor receptor (FGFR) gene aberrations. NCT03390504. https://clinicaltrials.gov/ct2/show/NCT03390504.

60. Pal SK et al. Efficacy of BGJ398, a fibroblast growth factor receptor 1-3 inhibitor, in patients with previously treated advanced urothelial carcinoma with FGFR3 alterations. Cancer Discov. 2018;8(7):812-21.

61. Pal SK et al. Infigratinib in upper tract urothelial carcinoma versus urothelial carcinoma of the bladder and association with comprehensive genomic profiling/cell-free DNA results. Cancer. 2020;126(11):2597-606.

62. Grünewald S et al. Rogaratinib: a potent and selective pan-FGFR inhibitor with broad antitumor activity and a promising preclinical cancer models. Int J Cancer. 2019;145(5):1346-57.

63. Joeger M et al. Developmental therapeutics. Phase I study of the pan-fibroblast growth factor receptor (FGFR) inhibitor BAY 1163877 with expansion cohorts for subjects based on tumor FGFR mRNA expression levels. Ann Oncol. 2016;27(Suppl 6):vi552-vi587.

64. Bayer. Study of rogaratinib (BAY1163877) vs chemotherapy in patients with FGFR (fibroblast growth factor receptor)-positive locally advanced or metastatic urothelial carcinoma (FORT-1). NCT03410693. https://clinicaltrials.gov/ct2/show/NCT03410693.

65. Necchi A et al. Interim results of fight-201, a Phase II, open-label, multicenter study of INCBO54828 in patients (pts) with metastatic or surgically resectable urothelial carcinoma (UC) harboring fibroblast growth factor (FGF)/FGF receptor (FGFR) genetic alterations (GA). Ann Oncol. 2018;29(Suppl 8):vi319.

66. Incyte Corporation. Pemigatinib + pembrolizumab vs pemigatinib alone vs standard of care for urothelial carcinoma (FIGHT-205). NCT04003610. https://clinicaltrials.gov/ct2/show/NCT04003610.

67. Hyman DM et al. FUZE clinical trial: a Phase 2 study of Debio 1347 in FGFR fusion-positive advanced solid tumors irrespectively of tumor histology. J Clin Oncol. 2019;15 Suppl):TPS3157.

68. Milowsky MI et al. Phase 2 trial of dovitinib in patients with progressive FGFR3-mutated or FGFR3 wild-type advanced urothelial carcinoma. European J Cancer. 2014;50(18):3145-52.

69. Necchi A et al. Fierce-21: Phase II study of vofatamab (B-701), a selective inhibitor of FGFR3, as salvage therapy in metastatic urothelial carcinoma (mUC). J Clin Oncol. 2019;37(7 Suppl):409.