Update on systemic treatment of upper tract urothelial carcinoma: a narrative review of the literature

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Abstract: Urothelial cancer (UC) is most commonly found in the urinary bladder, but can also appear in the upper urinary tract, where it is associated with several disease-specific challenges affecting its diagnosis, clinical staging, surgical management, and systemic therapy. A significant number of patients experience extra-vesical disease recurrence despite radical nephroureterectomy (RNU), leading to inevitable demise. Over the last years, the therapeutic armamentarium of UC has expanded with several systemic treatment options entering clinical care and deliver the potential to support a more individualized treatment in the near future. Currently, novel targeted therapies are emerging, accompanied with extensive biomarker research, which leads to a better understanding of the disease and therefore, reshaping the treatment landscape continuously and decisively. Though, systemic treatment of UTUC comes along with certain challenges that are specific to the disease, e.g., loss of renal function after RNU, which might result in ineligibility for a cisplatin-based chemotherapy. In this narrative review, the current standard of systemic treatment of UC in the perioperative and metastatic treatment setting are reported, with focus on UTUC. In addition, molecular aspects of UTUC, as well as future directions and specific implications for treatment of patients diagnosed with UTUC are discussed.

Keywords: Systemic therapy; chemotherapy; immune-checkpoint inhibitor; urothelial cancer; upper tract urothelial carcinoma (UTUC)

Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare disease, and accounts for approximately 5–10% of all urothelial cancers (UC). In western countries the incidence is low, with approximately 1–2 cases per 100,000 and mainly diagnosed in older male patients (1,2). In some Asian countries, the proportion of UTUC is reported in up to 25% of all UC patients and the majority diagnosed at an invasive stage (3).

Preoperative staging of UTUC is difficult, due to challenges in obtaining adequate tissue and suboptimal imaging (4,5), which can lead to difficulties in selecting patients who might benefit from neoadjuvant chemotherapy (NAC). Pathologic evaluation of small ureterorenoscopic biopsies can be demanding. Tumor grade can be determined correctly in the majority of patients with high grade UTUC, with a concordance between endoscopic biopsy

and nephroureterectomy specimen of up to >90% (6,7); upgrading of low grade biopsies occurs in a significant number of patients (7-9). Determination of tumor stage is accepted to be unreliable based on biopsy only (6,8). Therefore, UTUC is stratified based on risk factors, which are known to worsen prognosis. Surgical treatment recommendation, especially in terms of radicality of surgery and need for lymphadenectomy, is based on these risk categories (10-13).

The EAU guidelines refer to low risk tumors in case of unifocal disease, tumor size <2 cm, low grade cytology and biopsy, and no invasive aspects on computerized urography. All other tumors are considered as high-risk disease, especially if hydronephrosis or variant histology are present, as well as in patients who previously underwent radical cystectomy (RC) for high-grade cancer (10,14). Radical nephroureterectomy (RNU) is the standard for patients with high-risk disease. Though, one out of five patients treated with RNU for UTUC will experience disease recurrence, of which the majority of patients (82%) will die of the disease (15,16).

In UC, cisplatin-based NAC is standard for muscle-invasive urothelial bladder cancer (UBC) (17,18), but no evidence from randomized phase 3 trials is available for UTUC. In contrast, level 1 evidence for adjuvant chemotherapy (AC) is still lacking in high-risk UBC (18,19). Just recently, the POUT trial reported a significantly improved event-free survival (EFS) for patients undergoing platinum-based AC after RNU for UTUC (20).

In metastatic urothelial cancer (mUC), the standard first line treatment for eligible patients, who did not undergo NAC or AC is a cisplatin-based combination chemotherapy; recommendations for ineligible patients include either a carboplatin-based chemotherapeutic regimen or treatment with the immune-checkpoint inhibitors (CPI) atezolizumab or pembrolizumab, depending on the PD-L1 status of the tumor (21).

Rationale for this review is to give a summary of the current systemic treatment options for urothelial cancer and specific considerations for UTUC. Data for patients with metastatic UTUC is sparse and treatment recommendations are mostly based on extrapolation from mUC or on subgroups of patients with UTUC from clinical trials or retrospective cohort analysis (10). We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/tau-21-47).

Methods

To identify relevant published data, we used the PubMed/Medline search engine to conduct an online literature search using the terms (systemic therapy OR chemotherapy OR check-point inhibition OR targeted therapy OR trial) AND (urothelial cancer OR upper tract urothelial carcinoma) AND (management OR therapy OR treatment).

Only articles in English language were retrieved. The authors reviewed the extant articles with the intention to include the relevant data in this review. A manual search from authors' bibliographies was also used, when felt to be expedient. In order to identify ongoing neoadjuvant and adjuvant clinical trials of interest that have not been published yet, we accessed the clinicaltrials.gov online databank and provide the NCT number when appropriate. The search term 'upper tract urothelial carcinoma OR urothelial cancer' was used. Studies retrieved were screened and included if the study patients were diagnosed UTUC.

Discussion

Perioperative systemic therapy

NAC

In muscle-invasive bladder cancer (MIBC), the use of cisplatin-based NAC is supported by level 1 evidence, showing a statistically significant and clinically meaningful survival benefit (18). In contrast, there is only limited data available for high-risk UTUC from smaller retrospective and prospective series. Randomized phase 3 trials are ongoing, though patient recruitment can be challenging, in part, because of the rarity of the disease (22-24).

Retrospective analysis of a large cohort of patients who underwent RNU (n=1,363) revealed that use of NAC for high-risk UTUC is low, with only 3.4% of patients undergoing chemotherapy before radical surgery (3).

Though, the rational to use NAC for treatment of non-metastatic high-risk UTUC might be even greater than that in MIBC, as only half of patients undergoing RNU are eligible for a cisplatin-based chemotherapy before surgery and only one out of five patients remains eligible after RNU (25), mostly due to deterioration of renal function (26). In addition, NAC allows evaluation of pathological downstaging as prognostic marker (27). While several clinical trials are on the way (28), level 1 evidence for NAC in UTUC is still lacking (*Table 1*).

However, there are also multiple concerns regarding the

Table 1 Neoadjuvant trials for UTUC

Treatment	Identifier	Cohort	Clinical phase	Sample size	Primary endpoint
Chemotherapy					
Gem/Cis	NCT02876861	High grade	II	50	OS
Gem/Cis	NCT04574960	High grade	II	14	Safety
Gem/Cis	NCT01261728	High grade	II	54	pCR
Gem/Cis or MVAC	NCT02969083	High risk	II	200	DFS
Gem/Carbo or ddMVAC	NCT02412670	High grade	II	60	pCR
Combination therapy					
Durvalumab + Tremelimumab	NCT02812420	High risk, cisplatin-ineligible	II	15	Safety
Durvalumab + Gem/Platin	NCT04617756	High risk	II	99	pCR
Toripalimab + Gem/Cis	NCT04099589	High grade	II	34	pCR
Tislelizumab + Gem/Cis	NCT04672317	High grade	II	20	pCR
Other					
Tislelizumab	NCT04672330	High grade	II	20	pCR
Infigratinib	NCT04228042	Low and high grade, platin-ineligible	Ib	20	Safety

UTUC, upper tract urothelial carcinoma; Gem/Cis, Gemcitabine/Cisplatin; Carbo, Carboplatin; MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; ddMVAC, dose dense MVAC; OS, overall survival; pCR, pathologic complete response; DFS, disease free survival.

use of NAC in patients diagnosed with UTUC. Beside a potential increased peri-operative morbidity, there is a risk of a delay to definitive surgery, especially in patients not responding to NAC. One of the major clinical challenges is the quality of the primary biopsy and imaging methods used, which might result in difficulties to reliably identify invasive disease, leading to potential over-treatment.

Matin *et al.* evaluated the incidence of pathologic downstaging and pathological complete response (pCR) in patients with high-grade UTUC. Significant downstaging to the level of pCR was described in 14% of patients after NAC (29).

A multi-institutional, prospective, two-armed phase 2 trial investigated pathological complete response (pCR) after NAC for high grade UTUC. While the gemcitabine/carboplatin arm closed early due too poor accrual, the majority of patients included in the accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) arm have completed all planned treatment cycles and achieved a pCR in 13.8% (90% CI: 4.9–28.8%) of patients (27).

Recent systematic reviews and meta-analyses found a pCR rate (ypT0N0M0) of 11% (95% CI: 8–15%), a pathologic partial response rate (pPR; ≤ ypT1N0M0) of 43% (95% CI: 34–52%) and a pathological downstaging (cT > pT) in 33% (95% CI: 14–52%) of cases (30). NAC was associated with higher rates of pathological downstaging (RR 6.48, 95% CI: 2.05–20.44, P=0.001) and pCR (RR 18.46, 95% CI: 3.34–99.24, P=0.001) (31) resulting in an improvement in OS of 56% (HR 0.44; 95% CI: 0.32–0.59) and CSS of 62% (HR 0.38; 95% CI: 0.24–0.61) (30). In addition, pathological downstaging was found to be the strongest prognostic factor for recurrence-free survival (RFS; HR 0.2, P<0.001), cancer specific survival (CSS; HR 0.19, P<0.001) and overall survival (OS; HR 0.40, P<0.001) in an international observational study in patients undergoing NAC and RNU for high risk UTUC (32).

Several ongoing clinical trials are currently evaluating NAC in UTUC (*Table 1*) including the multi-centric URANUS trial, which aims to explore the feasibility of perioperative chemotherapy in UTUC at various European centers (NCT02969083). Patients who are eligible for a cisplatin-based chemotherapy are randomized to receive either cisplatin-based NAC or AC. Patients ineligible for cisplatin-based perioperative chemotherapy undergo RNU only.

Despite the lack of level 1 evidence, the cumulative evidence suggests that NAC for locally advanced UTUC

can improve oncological outcome. Nevertheless, prospective studies are needed to clarify the clinical benefit of NAC for patients with locally advanced UTUC (33).

Neoadjuvant immunotherapy

In the neoadjuvant setting of UBC, two single-arm, phase 2 trials with pembrolizumab (PURE-01) (34) and atezolizumab (ABACUS) (35) in patients with non-metastatic or locally advanced UBC have been published recently. These trials included unselected patients and used a comparatively low number of treatment cycles in order to not delay potentially curative surgery (34-37). Though, no patients with UTUC were included into these trials.

At time of RC, neoadjuvant CPI treatment resulted in a pCR rate of 31% and 42% for atezolizumab and pembrolizumab, respectively. Response rates were dependent on tumor PD-L1 expression and increased in patients with PD-L1 positive tumors compared to those with PD-L1 negative tumors [37% *vs.* 25% for ABACUS (35) and 54% *vs.* 13% for PURE-01 (34)]. Whether these improved pCR rates to neoadjuvant CPI according to PD-L1 status translate into a survival benefit, has to be determined. The adverse events were similar to those observed in clinical trials evaluating CPI in metastatic UC and no delay, nor failure to undergo RC was noted in both trials (34,35).

With PURE-02, a multi-center prospective phase 2, single-arm trial is ongoing to evaluate pembrolizumab in the neoadjuvant setting in UTUC (38). This trial could have the potential to increase the generally low acceptance of neoadjuvant therapy in cancers of the upper and lower urothelial tract (39). In addition, several ongoing clinical trials evaluate the neoadjuvant treatment with novel targeting agents as monotherapy or in combination with chemotherapy (*Table 1*).

Adjuvant chemotherapy

Decision making about administration of AC after RNU is based on the information from the definitive pathological specimen with the aim to avoid over-treatment. However, RNU before systemic therapy may result in the exclusion of a significant number of patients. Analysis of the National Cancer Data Base (NCDB) between 2004 and 2012 revealed that only 23.54% of patients with pT3/4 and/or pN+ UTUC who underwent RNU received AC (40). Just recently, a randomized phase 3 clinical trial (POUT) has been published, demonstrating a significantly improved EFS in patients with locally advanced UTUC, when being treated with adjuvant gemcitabine/platin-based chemotherapy (20).

The trial was closed early after recruitment of 261 patients, since the pre-planned interim analysis met the criterion for early closure. With a median follow-up of 30.3 months (IQR, 18.0–47.5 months), the 3-year EFS estimates were 71% (95% CI: 61–78%) and 46% (95% CI: 36–56%) for patients receiving AC or surveillance, respectively. AC resulted in a 55% reduction in relative risk of disease recurrence or death (HR 0.45, 95% CI: 0.30–0.68). Median disease-free survival among patients allocated to surveillance was 29.8 months (IQR, 6.3–not reached; 95% CI: 13.6–incalculable), and was not reached among patients undergoing AC. The trial design allowed dose-reductions or switch to a carboplatin-based regimen in patients, initially planned for cisplatin-based combination chemotherapy (20).

The majority of the 126 patients who started chemotherapy completed four cycles of AC (75%); there was no difference between the two pre-planned chemotherapy regimens. Thirty-one participants discontinued chemotherapy before receiving the planned four cycles and were delivered without any dose reduction in 91% (198/218) of the gemcitabine/cisplatin patients and 83% (186/223) of the gemcitabine/carboplatin patients. Sixteen patients (21%) intended to receive cisplatin-based AC had to be switched to carboplatin because of a drop in GFR after randomization (20).

The relative effect on survival of carboplatin- and cisplatin-based chemotherapies remains unclear in UC, since there is no sufficient data from randomized clinical trials comparing the two agents. The POUT trial underlines the benefit of adjuvant platinum-based chemotherapy for patients who underwent RNU for locally advanced or lymphogenic metastasized UTUC. While cisplatin should be the preferred agent for an AC; patients ineligible for cisplatin might still benefit from a carboplatin-based regimen (20).

In addition to this level 1 evidence, a recently published systematic review and meta-analysis (30) including 29 studies with two prospective randomized clinical trials (20,41), found that AC resulted in a 23% OS benefit (HR 0.77; 95% CI: 0.64–0.92), a 21% CSS benefit (HR 0.79; 95% CI: 0.69–0.91) and a 48% (HR 0.52; 95% CI: 0.38–0.70) improvement in disease-free survival (DFS) (30).

In a recent meta-analysis, AC was associated with improved metastasis-free survival (HR 0.65, 95% CI: 0.55–0.76, P<0.001) and CSS (HR 0.66, 95% CI: 0.57–0.77,

Table 2 Adjuvant trials for UTUC

Treatment	Identifier	Cohort	Clinical phase	Sample size	Primary endpoint
Chemotherapy					
Gem/Cis or MVAC	NCT02969083	High risk	II	200	DFS
Gem/Cis or Gem/Carbo	NCT01993979	pT2-4 pN0-3 M0; pTany N1-3 M0	III	261	DFS
Targeted therapies					
Infigratinib vs. placebo	NCT04197986	FGFR3 alteration	III	218	DFS

UTUC, upper tract urothelial carcinoma; Gem/Cis, Gemcitabine/Cisplatin; Carbo, Carboplatin; MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; DFS, disease free survival.

P<0.001), also in patients with locally advanced UTUC; indeed, the association of AC with OS was statistically significant only in patients with locally advanced UTUC (31).

Adjuvant immunotherapy

With IMvigor010, CheckMate274 and AMBASSADOR, there are three major randomized phase 3 clinical trials evaluating the CPIs atezolizumab, nivolumab or pembrolizumab in patients with high-risk UBC or UTUC. IMvigor010 has failed to show an improvement in RFS (42), while an exploratory biomarker analysis showed that post-surgical circulating tumor DNA (ctDNA) was found in 37% of the included patients. The interim OS analysis favored atezolizumab in ctDNA-positive patients (stratified HR 0.58; 95% CI: 0.39–0.85; P=0.005) with a median OS of 25.8 months for patients treated with atezolizumab compared to 15.8 months for patients on observation only (43).

Nivolumab has been evaluated in the adjuvant setting of high-risk urothelial cancer in the randomized, placebo-controlled CheckMate274 trial. Patients were eligible with presence of muscle-invasive disease after NAC followed by radical surgery or locally advanced disease or local lymph node metastasis. In addition, patients unwilling to undergo or ineligible for adjuvant cisplatin-based chemotherapy were included (44). This trial also included 149 patients with UTUC (21%). Subgroup analysis reveals a clear benefit in RFS for patients with UBC [HR 0.62 (0.49–0.78)]. In patients with UTUC, the effect is not as distinct and independent of the tumor location. Both groups of patients, with either tumor in the renal pelvis (n=96) or the ureter (n=53), did not show a benefit in RFS when receiving nivolumab vs. placebo (44), which raises the question, if patients with UTUC unfit for cisplatin-based AC should undergo adjuvant treatment with nivolumab, or not.

In addition, several clinical trials in the adjuvant therapeutic setting are ongoing to evaluate different chemotherapeutic regimens or novel targeting agents (Table 2).

Systemic therapy of metastatic disease

Over the last years, significant progress in systemic therapy has been made with the introduction of CPI and targeted therapies into the treatment landscape. Though, cisplatin-based combination chemotherapy remains the standard first line therapy for patients with metastatic UC, who are eligible for cisplatin combined with either gemcitabine (GC) or MVAC.

Due to the rarity of the disease, only very limited data from clinical trials evaluating systemic therapies in metastatic UTUC are available. Recommendations are mostly based on extrapolation of data from UBC or small subgroups of patients with UTUC included in these clinical trials.

Importantly, the majority of patients with metastatic UTUC suffering renal impairment due to hydronephrosis, infiltration of the renal parenchyma depending on tumor location, or previous radical surgery.

Chemotherapy

Platinum-based combination chemotherapy regimens are the standard for eligible patients with mUC in the first line setting. Trials including patients with newly diagnosed mUC have shown a median OS of approximately 15 and 10 months for patients receiving cisplatin- and carboplatin-based chemotherapeutics, respectively (45,46). These results have been confirmed and even exceeded in terms of ORR for carboplatin-based regimens in chemotherapy-only arms from recent clinical trials [i.e., in IMvigor130 (47), KEYNOTE-361 (48), and DANUBE (49)]. These trials are comparing CPI single agents, CPI-chemo or CPI-CPI

combinations to first line platinum-based chemotherapy. Data on treatment of metastatic UTUC is sparse and recommendations are mainly based on experience, extrapolated from metastatic UBC (10).

Recently, an individual patient data meta-analysis supported this approach, as location of the primary tumor within the urothelial tract was not associated with differential response to platin-based chemotherapy (50).

In addition, patients with mUC, who have not progressed on first line platin-based chemotherapy, had a clinically meaningful improved OS, when chemotherapy was followed by treatment with avelumab. This switch to maintenance therapy led to a median OS of 21.4 *vs.* 14.3 months in those who did not receive maintenance therapy (HR 0.69; 95% CI: 0.56–0.86) (51). The trial included 187 patients with UTUC (27%), while no specific data on this subgroup has been published so far.

Second line chemotherapy for mUC with vinflunine shows a marginal survival benefit over best supportive care; it has been approved by the European Medical Agency (EMA) for the post-platinum setting, meanwhile being relegated to the third line, post-CPI setting (52).

Immunotherapy

CPI have broadened the therapeutic options of mUC and have been approved as first line treatment in cisplatin-ineligible patients with PD-L1 positive tumors (atezolizumab, pembrolizumab) by both FDA and EMA (53,54); and in patients ineligible for chemotherapy (FDA) independent of PD-L1 expression.

In addition, five CPIs (avelumab, durvalumab, pembrolizumab, atezolizumab, and nivolumab) have been approved for the treatment of mUC after platinum-based chemotherapy by the FDA, of which three (pembrolizumab, atezolizumab, and nivolumab) have also been approved by the EMA. Pembrolizumab is the only CPI with level 1 evidence in the second line, post-platinum setting, derived from a prospective randomized phase 3 clinical trial (KEYNOTE-045) (55). Atezolizumab failed to reach the primary endpoint in IMvigor211 (56) and all other CPIs have been granted initial accelerated approval based on single-arm, phase 2 trials (57-59).

All of these trials included both, patients with UBC and UTUC, and improved objective response rates (ORR) for patients with UTUC have been reported in some of the trials.

In first line setting, IMvigor210 (cohort 1) included 33 patients with UTUC (27.7% of the cohort). In this subgroup, a favorable ORR of 39% (95% CI: 17–51%) compared to patients with lower urinary tract tumors (LTUC), for who the ORR was 17% (95% CI: 9–26%) (53). Though, data is not consistent with KEYNOTE-052, the second single-arm, phase 2 trial, that lead to accelerated approval of pembrolizumab. In this trial, 19% of the entire cohort (69/370) had an UTUC. The ORR was 22% (95% CI: 12–35%) for those patients compared to 28% (95% CI: 23–34%) in patients with LTUC (54).

The phase 3 clinical trial KEYNOTE-361, evaluated the pembrolizumab in the first line setting either as monotherapy or in combination with platin-based combination chemotherapy and compared it to combination chemotherapy alone. The trial did not reach its prespecified level of significance for the primary endpoint. The subgroup of patients with UTUC (21%; 146/703 patients) shows a significant improvement in PFS when treated with the combination over chemotherapy alone, though this does not translate into a benefit in OS (48).

IMvigor130, which evaluated atezolizumab in a similar setting in a phase 3 clinical trial, included patients with mUC, of who 26% (312/1,213 patients) harbored an UTUC (26%). The trial showed a statistically significant improvement in PFS, though it failed to show a significant improvement in OS for both the combination of atezolizumab with platin-based chemotherapy or atezolizumab alone compared tox first line platin-based combination. Data in the subgroup of patients with UTUC have not been published so far (47).

The DANUBE phase 3 trial evaluated durvalumab alone or in combination with tremelimumab versus platinum-based chemotherapy in the first line setting of mUC including 221 patients (21% of patients) with UTUC. The trial did not reach either of the co-primary endpoints of overall survival and did not report separate results for the subgroup of patients with UTUC (49).

In the second line setting, subgroup analysis of KEYNOTE-045 revealed a trend towards an improved OS to pembrolizumab compared to second line chemotherapy in patients with UTUC (HR 0.53; 95% CI: 0.28–1.01), which was even more pronounced than that in LTUC patients (HR 0.77; 95% CI: 0.60–0.97) (55). Conversely, this effect was not observed in the IMvigor211 trial, which compared atezolizumab to second line chemotherapy (56).

Novel targeted therapies

Due to the commonly found renal impairment in patients with metastatic UTUC, novel targeted therapeutical approaches, which are not dependent on the renal function, are of special interest. Genetic characterization revealed that UTUC is often associated with luminal-papillary characteristics and harbors high FGFR3, which correlates with a T-cell depleted immune microenvironment (60) and therefore offers the potential as target for novel therapies.

Recently, an increasing number of clinical trials are evaluating targeting agents (61). The pan-FGFR targeting erdafitinib and the novel antibody-drug conjugate (ADC) enfortumab vedotin (EV) have both been granted accelerated approval for mUC by the FDA.

Results from BLC2001, a single-arm, phase 2 trial evaluating the tyrosine kinase inhibitor of FGFR1–4 erdafitinib has recently been published. Patients with locally advanced or metastatic UC who harbor a FGFR3 mutation or FGFR2/3 fusion were included; either treatment naïve patients, who were ineligible for cisplatin-based combination chemotherapy or those who experienced disease progression to at least one previous chemotherapeutic were included. Treatment with erdafitinib resulted in an ORR of 40% with a median PFS and OS of 5.5 and 13.8 months, respectively. The response rate in patients (n=22) previously treated with CPI was even higher (59%) (62).

EV is an ADC targeting the surface protein Nectin-4, which is highly expressed in UC. Recently, results from several early clinical trials have been published with promising results and phase 3 trials are ongoing in mUC. In the EV-101 trial, patients with solid tumors expressing Nectin-4, including 155 patients with heavily pretreated mUC, treatment with EV showed clinically meaningful and durable response to EV. An ORR of 43% resulted in a median duration of response of 7.4 months, a median OS of 12.3 months, and a 12-month OS rate of 51.8% (63).

EV has also been investigated in a phase 2 clinical trial (EV-201), including patients with locally advanced or metastatic UC, who have been pre-treated with CPI and platinum-based chemotherapy (cohort 1). With an ORR of 42%, including 9% of patients showing CR, the OS rates were 50.4% and 34.2% at 12 and 18 months, respectively (64). Based on these results, combined with a manageable safety profile, EV was granted accelerated FDA approval for this indication.

These results have been recently confirmed in the phase 3 trial of EV for the treatment of patients with locally advanced or metastatic urothelial carcinoma who had previously received platinum-containing chemotherapy and had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor (EV-301).

Progression-free [5.55 *vs.* 3.71 months; HR (95% CI), 0.62 (0.51 to 0.75); P<0.001] and overall survival [12.88 *vs.* 8.97 months; HR (95% CI) 0.70 (0.56 to 0.89); P=0.001] were longer in the EV group than in the chemotherapy group. The clinical trial included 205 patients with UTUC (34%). Subgroup analysis based on location of the primary tumor revealed a significant benefit in terms of OS in patients with UBC [HR 0.67 (0.51–0.88)], while in patients with UTUC it did not reach statistical significance [HR 0.85 (0.57–1.27)] (65).

In first line treatment of mUC, the combination of EV with pembrolizumab in cisplatin- ineligible patients is under evaluation, with preliminary results from this phase 1b trial (EV-103). Indeed, the combination showed an ORR of 73.3%, with 15.6% CR (66); a phase 3 trial with this combination therapy is ongoing (NCT04223856, EV-302).

Future directions and conclusions

Recent genomic and gene expression studies in localized and metastatic UTUC, revealed a number of altered molecular pathways, such as FGFR3, TP53, or germline mutations in mismatch repair (MMR) genes that might have implications for future targeted therapies in the perioperative (*Tables 1,2*) and the metastatic treatment setting (67,68). Further research is needed of this molecular and genomic profiling of UTUC can be implemented in the treatment algorithm thereby leading to improved survival outcomes in patients with this devastating disease.

Over the next years, results of several phase 2 and 3 clinical trials are expected to provide additional treatment options for metastatic UC including patients with UTUC. These trials evaluate front-line CPI compared to chemotherapy, alone or in combination, FGFR targeting agents and antibody-drug conjugates. Furthermore, extensive research of predictive biomarkers is ongoing to guide a more individualized treatment approach for each patient. Several biomarkers such as microsatellite instability (MSI), deficiencies in DNA damage repair genes (DDR), and tumor mutational burden (TMB) are under investigation to predict response to those therapies, and targetable genetic alterations, such as EGFR, ERBB2, ERBB3, PIK3CA, and RAS have been found as potential

oncogenic drivers in subsets of UC (69), with the potential as novel therapeutics.

Clinical trials evaluating the use of neoadjuvant immune checkpoint inhibitors in patients with high risk UTUC are also on their way with the potential to increase the generally low acceptance of neoadjuvant therapy in UTUC. New therapeutic options and the potential implementation of biomarkers to guide patient selection are likely to reshape the treatment landscape for UC in the near future. Special attention to the differential impact of these therapies on UTUC versus LTUC will be required to help build solid evidence for evidence-based systemic treatment of UTUC.

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Footnote

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Ethical Statement: the authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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