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Original Article

Immune checkpoint inhibitors in advanced upper and lower tract urothelial carcinoma: a comparison of outcomes

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Objectives

To compare clinical outcomes between patients with locally advanced (unresectable) or metastatic urothelial carcinoma (aUC) in the upper and lower urinary tract receiving immune checkpoint inhibitors (ICIs).

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Patients and Methods

We performed a retrospective cohort study collecting clinicopathological, treatment, and outcome data for patients with aUC receiving ICIs from 2013 to 2020 across 24 institutions. We compared the objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) between patients with upper and lower tract UC (UTUC, LTUC). Uni- and multivariable logistic and Cox regression were used to assess the effect of UTUC on ORR, OS, and PFS. Subgroup analyses were performed stratified based on histology (pure, mixed) and line of treatment (first line, subsequent line).

Results

Out of a total of 746 eligible patients, 707, 717, and 738 were included in the ORR, OS, and PFS analyses, respectively. Our results did not contradict the hypothesis that patients with UTUC and LTUC had similar ORRs (24% vs 28%; adjusted odds ratio [aOR] 0.73, 95% confidence interval [CI] 0.43–1.24), OS (median 9.8 vs 9.6 months; adjusted hazard ratio [aHR] 0.93, 95% CI 0.73–1.19), and PFS (median 4.3 vs 4.1 months; aHR 1.01, 95% CI 0.81–1.27). Patients with mixed-histology UTUC had a significantly lower ORR and shorter PFS vs mixed-histology LTUC (aOR 0.20, 95% CI 0.05–0.91 and aHR 1.66, 95% CI 1.06–2.59), respectively).

Conclusion

Overall, patients with UTUC and LTUC receiving ICIs have comparable treatment response and outcomes. Subgroup analyses based on histology showed that those with mixed-histology UTUC had a lower ORR and shorter PFS compared to mixed-histology LTUC. Further studies and evaluation of molecular biomarkers can help refine patient selection for immunotherapy.

Keywords

bladder cancer, checkpoint inhibitor, immunotherapy, upper tract urothelial cancer, variant histology, #utuc, #uroonc

Introduction

Urothelial carcinoma (UC) is the sixth most common malignancy in the USA and fifth most common malignancy in Europe. In 2020, bladder cancer is estimated to result in 17 980 deaths in the USA and 49 185 deaths in Europe [1,2]. About 90–95% of UCs arise in the lower urinary tract (bladder and urethra), while the remaining 5–10% arise from the upper urinary tract (renal pelvis and ureter). Despite morphological similarities, lower and upper tract UC (LTUC, UTUC) have differences in epidemiology, tumour behaviour, molecular characteristics, and prognosis [3–5]. These differences may stem from distinct embryological origins, anatomical location, genetic features, discordant staging, and practical considerations in diagnosis and management [6,7]. Data regarding the management of UTUC are limited due to its lower prevalence. As a result, UTUC and LTUC are often treated as one entity with treatment decisions for UTUCs often informed based on data from LTUC-predominant populations, especially in the advanced disease setting. This approach may be suboptimal given the poorer outcomes for UTUC relative to LTUC with conventional LTUC-based therapies, when adjusted for stage [3].

The introduction of immune checkpoint inhibitors (ICIs) led to a paradigm shift in the treatment of locally advanced/unresectable or metastatic (a)UC for cisplatin-ineligible patients or after platinum-based chemotherapy [8]. Five ICIs have been approved by the United States Food and Drug Administration (FDA) for treatment of aUC in the USA, with pembrolizumab showing longer overall survival (OS) when compared to salvage chemotherapy (platinum-refractory setting) and avelumab plus best supportive care showing longer OS relative to best supportive care alone (post-platinum switch maintenance setting) [9,10]. UTUC representation in ICI trials has been variable, ranging from 14% to 30% [9–18]. Data from subgroup analyses between UTUC and LTUC have been limited and conflicting, with a number of trials showing a higher objective response rate (ORR) in UTUC with atezolizumab [12], while others favoured higher ORR in LTUC with pembrolizumab and avelumab [15,17]. To address this knowledge gap, we compared the ORR, progression-free survival (PFS), and overall survival (OS) between patients with advanced UTUC and LTUC receiving ICIs, using a multi-institution retrospective cohort. We hypothesised that given similarities in the pathogenesis, treatment response and outcomes would be similar in advanced UTUC and LTUC.

Patients and Methods

Patient Selection and Data Collection

After Institutional Review Board approval, we performed a retrospective cohort study comparing oncological outcomes

between patients with UTUC and LTUC. Patients with pure- or mixed-histology aUC receiving ICI monotherapy for this indication were included. Those receiving ICIs as part of a clinical trial, in combination with another agent, for an indication other than aUC, or those who received multiple lines of ICIs were excluded. Patients with pure non-urothelial histology were also excluded. Each participating institution identified patients using provider driven and electronic health record search algorithms to allow for consecutive evaluation. The collected data included baseline characteristics (demographics, clinicopathological, and laboratory variables), treatment response, and long-term clinical outcomes. Data were collected by chart abstraction using secure, web-based, standardised REDCap electronic data capture tools hosted at the Institute of Translational Health Sciences [19]. Data collected via alternative methods were uploaded into REDCap for secure storage and standardisation of variables.

All patients underwent standard of care imaging as per treating provider. The evaluation of both best response and progression were determined according to the chart abstractor's assessment based on best available information from clinical notes and radiographic studies and did not include a blinded central radiology review. Similarly, pathology assessment was based on chart abstraction and did not include central pathology review. The ORR was calculated as the sum of patients with investigator-designated (complete or partial) response divided by the total number of patients with available data. The OS was measured from the date of ICI initiation until the date of death; patients that were still alive were censored at the date of last follow-up visit. The PFS was measured from the date of ICI initiation until the date of radiographic and/or clinical progression, or death; patients without progression or death were censored at the date of last follow-up visit.

Statistical Analysis

Baseline characteristics were summarised with descriptive statistics and compared with chi-square test and Student's *t*-test for categorical and continuous variables, respectively. Univariable and multivariable logistic regression was used to estimate the odds ratio (OR) and 95% CI for ORR between UTUC and LTUC. In the multivariable analysis, we used two different a priori specified models based on the Bellmunt risk factors [20] – one adjusting for liver metastases, haemoglobin <100 g/L, and Eastern Cooperative Oncology Group (ECOG) performance status >0, individually; and the second model adjusting for the calculated Bellmunt score (i.e. liver metastases, haemoglobin <100 g/L, and ECOG performance status >0).

We used the Kaplan–Meier method for survival curves and to estimate median (m)OS and median (m)PFS. Cox regression was used to determine the effect of tumour location on OS and PFS; differences between groups were expressed as hazard ratios (HRs) and 95% CIs. Similar to above, for the multivariable analysis, we used two different a priori specified models adjusting for individual Bellmunt risk factors [20] or for the calculated Bellmunt score.

Additional subgroup analyses were performed to compare outcomes between patients with LTUC and UTUC stratified by treatment line (first line and subsequent/salvage), histology (pure- and mixed-histology UC), and specific tumour location (renal pelvis, ureter, bladder, urethra) for all outcomes of interest. Statistical significance was set at $P < 0.05$; all P values were two-tailed. All statistical analyses were performed using Stata IC 16.0 (StataCorp LLC, College Station, TX, USA).

Results

Patient Selection and Characteristics

A total of 984 patients with aUC received ICIs monotherapy between 2013 and 2020 across 24 different institutions. After excluding ineligible patients, 746 patients were included in our population (Fig. 1). A breakdown of patients according to institution is provided in Table S1. Baseline patient characteristics are presented in Table 1. Men comprised 76% of patients with LTUC and 62% with UTUC; 71% had smoking history within LTUC and 59% within UTUC. Liver metastases were found in 18% of patients with LTUC and 29% of patients with UTUC. A breakdown of the mixed-histology UC variants for each group is provided in Table S2.

Objective Response Rate

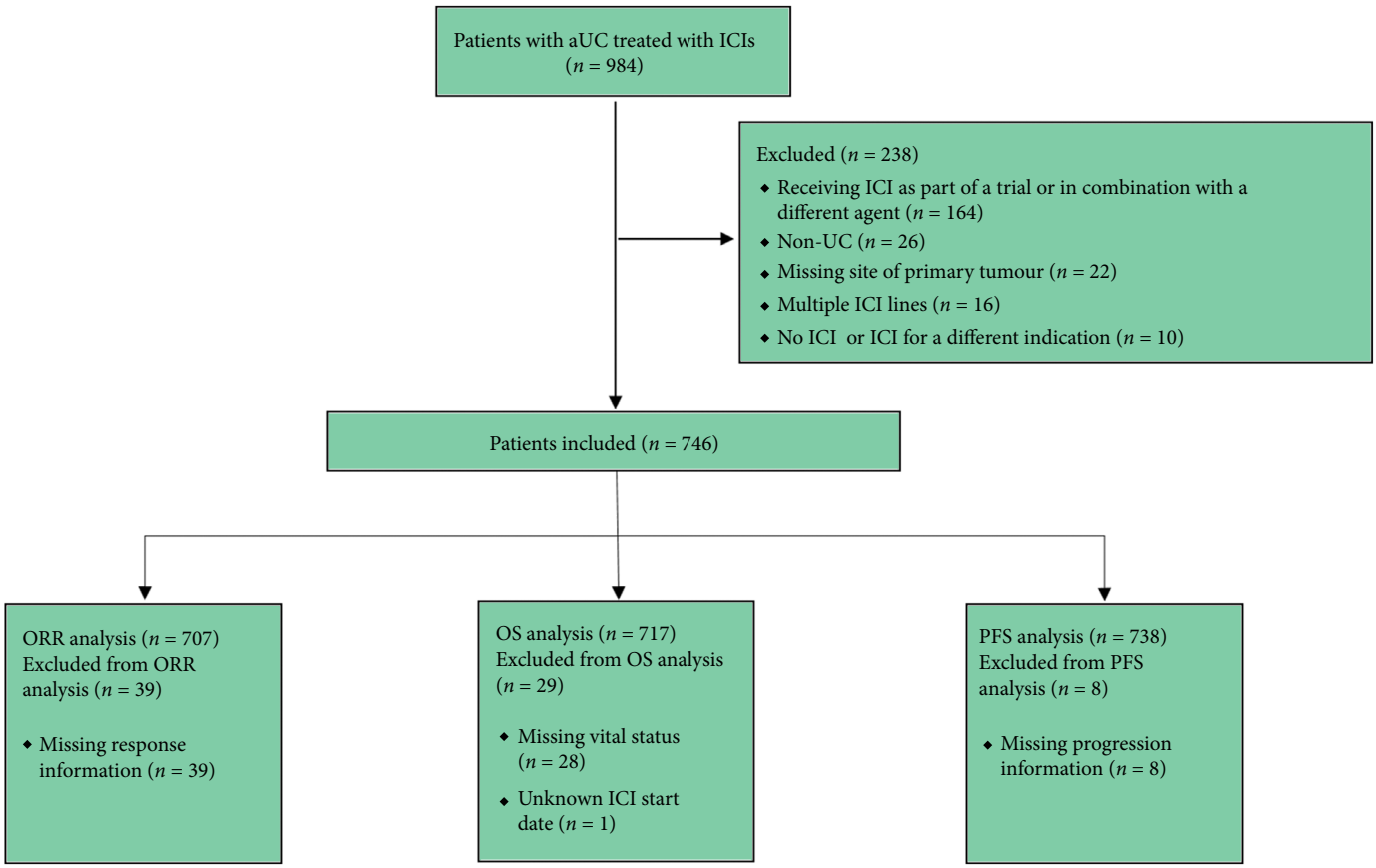
A total of 707 patients were included in the ORR evaluable population, with 83% having LTUC and 17% UTUC. Our results did not contradict the hypothesis that patients with UTUC and LTUC had similar ORRs (24% vs 28%; OR 0.81, 95% CI 0.52–1.27, $P = 0.36$; Table 2). Similarly, this hypothesis was not contradicted in either of the two multivariable logistic regression models or when further stratifying for either specific tumour location (not shown) or treatment line.

In the subgroup analysis according to histology, patients with mixed-histology UTUC ($n = 28$) had a significantly lower ORR compared to those with mixed-histology LTUC ($n = 170$) (11% vs 29%; model 1: adjusted (a)OR 0.20, 95% CI 0.05–0.91, $P = 0.03$/model 2: aOR 0.28, 95% CI 0.08–0.98, $P = 0.047$).

Overall Survival

A total of 717 patients were included in the OS analysis, with 82% having LTUC and 18% UTUC. Our results did not

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) diagram of patient selection.



contradict the hypothesis that patients with UTUC and LTUC had similar OS (mOS 9.8 months, 95% CI 7.9–14.3 months vs 9.6 months, 95% CI 8.2–11.4 months; HR 0.97, 95% CI 0.76–1.25, $P = 0.84$; Fig. 2A, Table 3). This remained true following adjustment in multivariable models (model 1: adjusted (a)HR 0.92, 95% CI 0.69–1.21, $P = 0.53$/ model 2: aHR 0.93, 95% CI 0.73–1.19, $P = 0.58$) or after stratifying by specific tumour location (not shown), line of therapy, or histology.

Progression-Free Survival

A total of 738 patients were included in the PFS analysis, with 83% and 17% with LTUC and UTUC, respectively. The mPFS was 4.1 months (95% CI 3.5–4.9 months) in the LTUC group and 4.3 months (95% CI 3.2–5.9 months) in the UTUC group (Fig. 2B, Table 4). Our results did not contradict the hypothesis that patients with UTUC and LTUC had similar PFS with univariable (HR 1.05, 95% CI 0.84–1.32; $P = 0.65$) and multivariable Cox regression, or after stratifying by specific tumour location (not shown) or line of therapy.

In the subgroup analysis according to histology, patients with mixed-histology LTUC ($n = 178$) had mPFS of 4.3 months (95% CI 3.0–7.4 months), compared to 2.2 months (95% CI 1.6–5.9 months) in patients with mixed-histology UTUC ($n = 30$); mixed-histology UTUC was associated with shorter PFS in the multivariable Cox regression adjusting for the calculated Bellmunt score (aHR 1.66, 95% CI 1.06–2.59; $P = 0.03$).

Discussion

In the present multicentre retrospective cohort study of patients with aUC receiving ICIs, our data did not contradict the null hypothesis that the ORR, OS, and PFS were similar between patients with UTUC and LTUC. However, patients with mixed-histology UTUC had a lower ORR and shorter PFS compared to patients with mixed-histology LTUC.

Previous clinical trials investigating the safety and efficacy of ICIs in aUC have provided conflicting data about the outcomes of ICI treatment for patients with advanced UTUC. In the cisplatin-ineligible cohort of the IMvigor210 Phase II trial on atezolizumab, the ORR was numerically higher in UTUC (39%, 13/33) compared to LTUC (16%, 14/85) [12]. In contrast, the ORR of UTUC was numerically lower compared to LTUC in the platinum-refractory cohort of the IMVigor210 trial (UTUC: 13%[seven of 52] vs LTUC: 23% [39/168]) [21], the IMvigor211 Phase III trial on atezolizumab (UTUC: 11% [10/94] vs LTUC: 18% [44/245]) [21], the KEYNOTE-052 Phase II trial of pembrolizumab (UTUC: 22% [13/59] vs LTUC: 28% [70/247]) [15], and the JAVELIN Phase I trial of avelumab (UTUC: 11% [four of 36] vs LTUC: 18% [23/125]) [17]. In regards to OS, UTUC and LTUC had comparable mOS according to an updated analysis of the platinum-refractory cohort of the IMvigor210 trial (UTUC vs LTUC: 7.9 vs 7.6 months) [25] and a *post hoc* analysis of the IMvigor211 trial (UTUC vs LTUC: 10.9 vs 9.7 months) [19]. The exploratory subset analysis of the KEYNOTE 045 Phase III trial suggested that pembrolizumab prolonged OS in both UTUC (HR 0.53, 95% CI 0.28–1.01) and LTUC (HR 0.77, 95% CI 0.60–0.97) compared to chemotherapy [9]. In our present study, the ORR, OS, and PFS were similar between the two groups. The exact tumour location in the urinary tract did not influence the results, although previous reports have shown differences in genomic features between renal pelvis and ureteric tumours [22].

In our present cohort, patients with mixed-histology UTUC histology had a significantly lower ORR (11%) compared to those with mixed-histology LTUC (29%). The breakdown of the mixed-histology UC variants among the two subgroups was largely similar. Prior prospective and retrospective studies have not suggested worse outcomes with ICI treatment for those with variant histology. In a recent Phase II trial of dual immune checkpoint blockade with nivolumab/ipilimumab in rare genitourinary malignancies, the ORR among the 19 patients with variant histology bladder cancer was 37% [23]. Furthermore, a previous retrospective analysis using a smaller size cohort in our multicentre database only noted neuroendocrine histology to be associated with worse outcomes with ICI therapy, while other variants showed no significant differences [24]. In our present study, patients with mixed-histology UTUC had a significantly lower ORR than mixed-histology LTUC after adjusting for Bellmunt score.

Table 1 Baseline patients' characteristics.

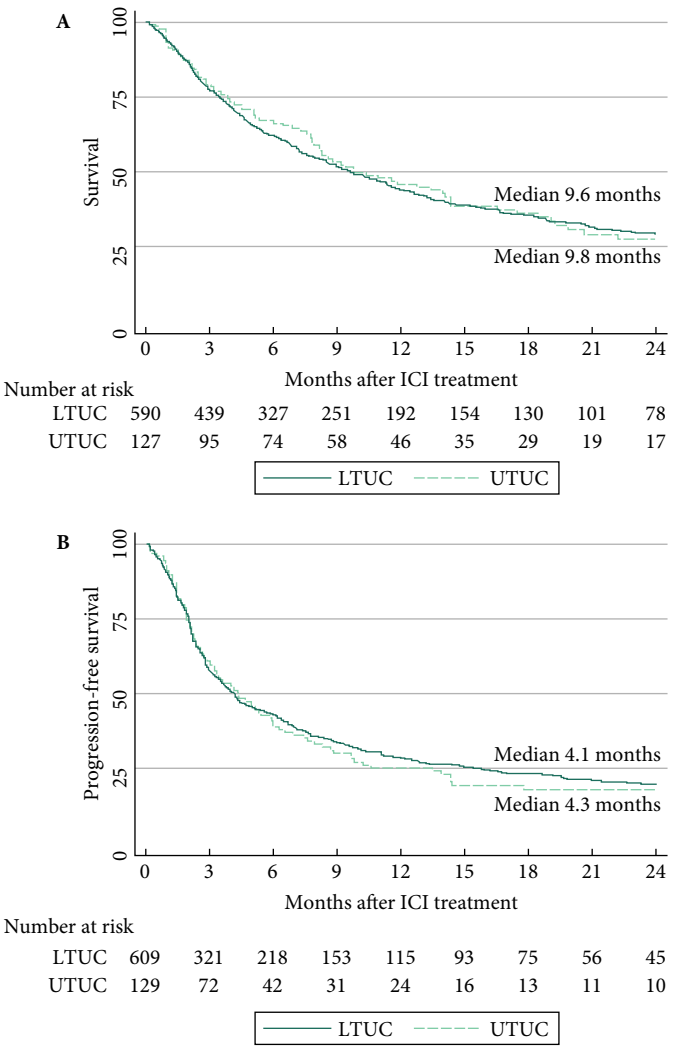
Characteristic	UTUC	LTUC	*P*
Number of patients	130	616	
Age, years, mean (SD)	70 (10)	69 (10)	0.39
Men, *n* (%)	80 (62)	469 (76)	**<0.001**
White Race, *n* (%)	99 (76)	456 (74)	0.61
Smoking history, *n* (%)	77 (59)	434 (71)	**0.01**
Previous cystectomy/(nephro)ureterectomy, *n* (%)			
Yes	80 (62)	300 (52)	**0.05**
Missing information	N/A	39/616	
Prior platinum-based (cisplatin or carboplatin) chemotherapy, *n* (%)	80 (62)	406 (66)	0.34
Site of primary tumour, *n* (%)			
Bladder	N/A	610 (99)	
Urethra	N/A	6 (1)	
Upper genitourinary system (unspecified)	45 (35)	N/A	
Renal pelvis	58 (45)	N/A	
Ureter	27 (21)	N/A	
Histology, *n* (%)			
Pure urothelial	100 (77)	438 (71)	0.20
Mixed urothelial	30 (23)	176 (29)	
Haemoglobin <100 g/L, *n* (%)	33 (27)	163 (27)	0.92
Liver metastasis, *n* (%)	37 (29)	112 (18)	**0.01**
ECOG performance status, *n* (%)			
0	26 (24)	120 (21)	0.86
1	58 (54)	304 (54)	
2	20 (19)	121 (22)	
3	4 (4)	16 (3)	
4	0 (0)	2 (1)	
Missing information, *n/N*	22/130	53/616	
Bellmunt risk factors, *n* (%)			
0	20 (15)	90 (15)	0.27
1	57 (44)	310 (50)	
2	42 (32)	187 (30)	
3	11 (9)	29 (5)	
Type of ICI, *n* (%)			
Atezolizumab	49 (38)	292 (48)	0.18
Pembrolizumab	67 (52)	252 (41)	
Nivolumab	9 (7)	44 (7)	
Durvalumab	3 (2)	17 (3)	
Avelumab	0 (0)	5 (1)	

Statistically significant values denoted in bold.

Table 2 ORR according to tumour location.

Analysis	Location	ORR, % (95% CI)	Univariable, OR (95% CI)	Multivariable 1, OR (95% CI)	Multivariable 2, OR (95% CI)
Primary	LTUC (*n* = 584)	28 (25–32)	Reference	Reference	Reference
	UTUC (*n* = 123)	24 (18–33)	0.81 (0.52–1.27)	0.73 (0.43–1.24)	0.83 (0.53–1.31)
Subgroup by histology	Pure LTUC (*n* = 414)	28 (24–33)	Reference	Reference	Reference
	Pure UTUC (*n* = 95)	28 (20–38)	1.02 (0.62–1.67)	1.00 (0.56–1.78)	1.06 (0.65–1.75)
	Mixed LTUC (*n* = 170)	29 (23–37)	Reference	Reference	Reference
	Mixed UTUC (*n* = 28)	11 (4–29)	0.29 (0.09–1.00)	0.20 (0.05–0.91)	0.28 (0.08–0.98)
Subgroup by line of therapy	First-line LTUC (*n* = 328)	31 (26–36)	Reference	Reference	Reference
	First-line UTUC (*n* = 57)	35 (24–48)	1.23 (0.68–2.23)	1.17 (0.58–2.37)	1.25 (0.69–2.28)
	Subsequent-line LTUC (*n* = 256)	26 (21–32)	Reference	Reference	Reference
	Subsequent-line UTUC (*n* = 66)	15 (8–26)	0.51 (0.25–1.06)	0.51 (0.22–1.20)	0.53 (0.25–1.09)

Fig. 2 Kaplan–Meier curve of (**A**) OS and (**B**) PFS according to tumour location.



Therefore, we hypothesise that this difference may be attributed to inherent biological differences rather than confounding prognostic factors; however, this hypothesis needs to be further tested. Notably, previous studies have reported significant differences in the genomic makeup, transcriptomic profile, and immunogenicity context between UTUC and LTUC [4,5,25], and among the different mixed-histology UC variants [26]. This may suggest that patients with variant histology in UTUC are a particularly high-risk population.

There are several potential underlying mechanisms behind the differences in the response to ICIs among individuals. As with many solid tumours, the degree of T-cell infiltration in the tumour microenvironment has prognostic value in aUC [27]. Specifically, the non-T-cell-inflamed tumour phenotype has been associated with poor response to ICI and worse prognosis [28]. Most patients with UTUC express the non-T-cell-inflamed phenotype, which may account for the lower ORR and inferior survival of patients with UTUC in several clinical trials [15,17,21,25]. Molecular pathways associated with the non-T-cell-inflamed phenotype include the β-catenin, peroxisome proliferator-activated receptor gamma (PPAR-γ), and fibroblast growth factor receptor 3 (FGFR3)-driven pathways [29]. Many UTUC tumours may have FGFR3 mutation or fusion (up to 40–60% in high-grade, up to 74% low-grade), significantly higher compared to LTUC, which may be associated with the non-T-cell-inflamed phenotype [22,25,30,31]. However, the prognostic and predictive (regarding benefit with ICI) value of FGFR3 activating mutation or fusion is still uncertain [32,33]. On the other hand, UTUC is associated with an only slightly higher rate of microsatellite instability (MSI) compared to LTUC [22,34]. Tumours with MSI seem to have better response to ICI [12,35]. Epigenetic factors may also account for differences in response to ICI [6].

Despite the demonstrated activity of ICIs in the platinum-refractory space, patients receiving ICIs for aUC still have a poor prognosis. As with previous clinical trials, the ORR to ICI therapy in our present study was <30% regardless of tumour location. In addition, the mPFS and mOS did not exceed 5 and 10 months, respectively, implying that most patients have progression in a short amount of time and die from the disease a few months later. Therefore, more work is needed to identify biomarkers, new therapy targets, and other strategies to guide therapy selection and optimise outcomes. While clinical models to predict response or survival have been proposed [36,37], much work remains to identify and prospectively validate predictive tools. Newer techniques, such as 'liquid biopsy' may also provide a minimally invasive alternative to conventional tumour tissue analysis for next-generation sequencing [38–41]. In addition, there are strategies aiming to improve the efficacy of ICIs in aUC by combining them with (i) other ICIs, (ii) anti-FGFR3 targeted agents, (iii) platinum-based chemotherapy, (iv) localised treatments (e.g. radiotherapy), and (v) antibody-drug conjugates (e.g. enfortumab vedotin, sacituzumab govitecan), among others [42–44]. As with many combination regimens, we should carefully consider whether potential improvement of outcomes is the result of drug independence (which may address tumour heterogeneity among patients) rather than true additivity or synergism (which may address intra-tumour heterogeneity in an individual patient) [45].

The strengths of our present study include a large sample size and diverse patient population originating from multiple institutions across North America and Europe, approaching in a 'real world' setting. Nonetheless, limitations still apply and warrant careful interpretation of our present results. Our present study was retrospective in nature and lacked patient randomisation, matching, or other adjustments to fully address potential confounding or selection biases. ECOG

Table 3 OS according to tumour location.

Analysis	Location	Median OS, months (95% CI)	Univariable, HR (95% CI)	Multivariable 1, HR (95% CI)	Multivariable 2, HR (95% CI)
Primary	LTUC (n = 590)	9.6 (8.2–11.4)	Reference	Reference	Reference
	UTUC (n = 127)	9.8 (7.9–14.3)	0.97 (0.76–1.25)	0.92 (0.69–1.21)	0.93 (0.73–1.19)
Subgroup by histology	Pure LTUC (n = 417)	9.3 (7.8–11.4)	Reference	Reference	Reference
	Pure UTUC (n = 98)	10.9 (8.3–14.4)	0.89 (0.67–1.18)	0.78 (0.55–1.08)	0.83 (0.62–1.10)
	Mixed LTUC (n = 173)	10.6 (6.7–14.1)	Reference	Reference	Reference
	Mixed UTUC (n = 29)	7.6 (2.4–19.1)	1.30 (0.82–2.09)	1.46 (0.88–2.41)	1.36 (0.85–2.17)
Subgroup by line of therapy	First-line LTUC (n = 339)	10.9 (7.9–13.2)	Reference	Reference	Reference
	First-line UTUC (n = 62)	13.4 (8.3–19.9)	0.89 (0.62–1.29)	0.77 (0.50–1.19)	0.85 (0.58–1.24)
	Subsequent-line LTUC (n = 251)	8.6 (7.3–10.9)	Reference	Reference	Reference
	Subsequent-line UTUC (n = 65)	8.4 (5.3–14.0)	1.03 (0.74–1.43)	0.94 (0.65–1.36)	1.05 (0.75–1.46)

Table 4 PFS according to tumour location.

Analysis	Location	Median PFS, months (95% CI)	Univariable, HR (95% CI)	Multivariable 1, HR (95% CI)	Multivariable 2, HR (95% CI)
Primary	LTUC (n = 609)	4.1 (3.5–4.9)	Reference	Reference	Reference
	UTUC (n = 129)	4.3 (3.2–5.9)	1.05 (0.84–1.32)	0.98 (0.76–1.26)	1.01 (0.81–1.27)
Subgroup by histology	Pure LTUC (n = 431)	4.1 (3.4–4.9)	Reference	Reference	Reference
	Pure UTUC (n = 99)	4.6 (3.3–6.9)	0.93 (0.72–1.21)	0.83 (0.61–1.12)	0.87 (0.67–1.13)
	Mixed LTUC (n = 178)	4.3 (3.0–7.4)	Reference	Reference	Reference
	Mixed UTUC (n = 30)	2.2 (1.6–5.9)	1.52 (0.98–2.37)	1.55 (0.97–2.49)	1.66 (1.06–2.59)
Subgroup by line of therapy	First-line LTUC (n = 347)	4.6 (3.5–6.3)	Reference	Reference	Reference
	First-line UTUC (n = 62)	4.6 (2.5–8.3)	1.04 (0.75–1.44)	0.85 (0.58–1.25)	1.01 (0.73–1.41)
	Subsequent-line LTUC (n = 262)	3.7 (3.0–4.4)	Reference	Reference	Reference
	Subsequent-line UTUC (n = 67)	4.1 (2.8–5.9)	1.04 (0.77–1.42)	0.98 (0.70–1.39)	1.07 (0.79–1.47)

performance status, which may affect survival with ICI therapy in aUC [46], was missing in a proportion of patients. We were unable to examine differences in T-cell infiltration/density, biomarker expression (e.g. programmed death-ligand 1 [PD-L1], gene expression profiling, DNA damage response gene mutations, MSI status, tumour mutational burden), across different subgroups, which may be related to ICI response [25,47]. There could have been heterogeneity in data collection and treatment (and surveillance) practices across participating institutions. For example, imaging to assess progression was performed based on routine care rather than standardised time intervals. In addition, there was no central radiology review to provide standardisation. In particular, treatment response was assessed according to investigator evaluation instead of central review, which may account for the slightly higher ORR observed in our present study compared to clinical trials [15,17]. The lack of central pathology review precluded us from obtaining important histopathological information, such as the percentage of variant histology among different specimens. Histopathological assessment was performed according to the standard practices of each participating institution; however, all the institutions have focussed pathology expertise in UC as tertiary referral centres. These practices may have significantly varied among institutions, due to differences in the size, source, and quality of tumour specimens, the percentages of tumour content, urothelial and variant tumour tissue, as well as inter-observer variability. Finally, we were unable to obtain granular data on the breakdown of locally advanced (unresectable) vs metastatic disease in each group, response to previous therapy, and time interval from last dose of previous therapy to ICI initiation.

Conclusion

Clinical trial data on response and outcomes of ICIs in UTUC are conflicting. In our present study, patients with UTUC and LTUC receiving ICIs were noted to have a similar ORR, OS, and PFS. However, mixed-histology UTUC had a significantly lower ORR and shorter PFS compared to mixed-histology LTUC. Further studies and evaluation of molecular biomarkers can help optimise patient selection for ICI therapy.

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Conflict of Interest

Dr. Neeraj Agarwal has served in a consulting role for Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Janssen, Merck, Nektar, Novartis, Pfizer, Pharmacyclics, Seattle Genetics; and has received institutional research funding from AstraZeneca, Bavarian Nordic, Bayer, Bristol-Myers Squibb, Calithera, Celldex, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, GlaxoSmithKline, Immunomedics, Janssen, Medivation, Merck, Nektar, New Link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Takeda, and Tracon. Dr. Ajjai Alva reports personal fees from AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer, EMD Serono, Onc Live, and research grants from AstraZeneca, Bristol-Myers Squibb, Merck, Prometheus, and Progenics. Dr. Aristotelis Bamias reports personal fees from Roche, Bristol-Myers Squibb, and MSD. 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Dr. Daniel Castellano has served in a consulting/advisory role for Janssen Oncology, Roche/Genentech, Astellas Pharma, AstraZeneca, Pfizer, Novartis, Ipsen, Bristol-Myers Squibb, MSD Oncology, Bayer, Lilly, Sanofi, Pierre Fabre, and Boehringer Ingelheim; has received travel accommodations from Roche/Genentech, Pfizer, and Bristol-Myers Squibb; and has received institutional research funding from Janssen Oncology. Dr. Michael E. Devitt has served in an advisor/speaker role for Bayer. Dr. Alexandra Drakaki has served in an advisory board of Genentech/Roche and Merck and in a consultant role in AstraZeneca. Dr. Ignacio Duran reports personal fees from Roche/Genentech, MSD, AstraZeneca, Bristol-Myers Squibb, Astellas, Seattle Genetics; and research grants from Roche/Genentech, and AstraZeneca. Dr. Matthew D. Galsky reports personal fees from Merck, Pfizer, Bristol-Myers Squibb, AstraZeneca, Seattle Genetics and research grants from Merck, Bristol-Myers Squibb, AstraZeneca, and Genentech. 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Abbreviations: ECOG, Eastern Cooperative Oncology Group; FGFR3, fibroblast growth factor receptor 3; (a)HR, (adjusted) hazard ratio; ICI, immune checkpoint inhibitor; MSI, microsatellite instability; ORR, objective response rate; (a)OR, (adjusted) odds ratio; ORR, objective response rate; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; (a)(LT)(UT)UC, (advanced) (lower tract) (upper tract) urothelial carcinoma.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Number of patients included in the analysis according to institution.
Table S2. Breakdown of mixed urothelial carcinoma variants.

