Heliyon 9 (2023) e15813

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Systematic review and meta-analysis

Immunotherapy with or without targeted therapy for metastatic upper tract urothelial carcinoma: case report and literature review

Kangxin Ni [a,1], Chenhao Yu [a,1], Huailan Wang [a], Shibin Zhu [a], Shicheng Yu [a], Gonghui Li [a,*]

[a] Department of Urology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, 310016, People's Republic of China

ARTICLE INFO

Keywords:
Upper tract urothelial carcinoma
Metastatic
Immune checkpoint inhibitor
Targeted therapy
Camrelizumab

ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) have been proved having a better safety profile compared to platinum-based chemotherapy and have demonstrated encouraging anti-tumor therapeutic effects for patients with metastatic urothelial carcinoma (mUC). However, few studies have evaluated the efficacy of ICIs in patients with metastatic upper tract urothelial carcinoma (mUTUC).

Case reports: Case 1 was a 71-year-old male patient diagnosed with left renal pelvic carcinoma, accompanied by a metastasis to the second lumbar spine. As the patient became refractory to chemotherapy, four cycles of camrelizumab, one of the ICIs, were administered, which helped to control the metastases and extend the patient's progression-free survival to five months. Case 2 was an 88-year-old female with middle and lower right ureter carcinoma with right iliac arteriovenous invasion. The patient received five cycles of camrelizumab plus vascular endothelial growth factor receptor 2 (VEGFR2) inhibitors and achieved stable disease.

Conclusion: For patients who are ineligible for chemotherapy, immunotherapy might be a feasible treatment, regardless of whether or not they are given VEGFR2 inhibitors

1. Introduction

Urothelial carcinoma (UC) is one of the most common malignancies worldwide, with approximately 90–95% of UCs located in the lower urinary tract, such as the bladder and urethra, and only 5–10% located in the upper urinary tract, such as the pelvis and ureters [1,2]. Microscopic hematuria, gross hematuria and/or low back pain due to ureteral obstruction are some of the early signs of upper tract urothelial carcinoma (UTUC), and systemic symptoms will develop in the advanced stages of the tumor. Radical nephroureterectomy (RNU) with partial bladder resection, whether minimally invasive or open, is the gold standard for the treatment of the majority of UTUC [3]. Endoscopic management (EM) is also beneficial in low-risk patients with normal renal function or those with isolated and/or impaired renal function. In low-grade UTUC, the overall survival (OS) is comparable between patients receiving EM and RUN. However, EM has higher local recurrence rates, which requires long-term strict surveillance and repeated interventions [4].

Unfortunately, approximately one-third of UTUC patients will eventually develop recurrence and metastases, and about 5% patients will have distant metastases at their initial appointment [5,6]. Currently, platinum-based chemotherapy, such as regimens

* Corresponding author.)
E-mail address: 3193119@zju.edu.cn (G. Li).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e15813
Received 15 September 2022; Received in revised form 16 April 2023; Accepted 21 April 2023
Available online 30 April 2023

containing cisplatin or carboplatin, is considered the first-line therapy for metastatic upper tract urothelial carcinoma (mUTUC) [7]. However, the response rate is only 40–60% with a median OS of approximately 2 years [7–9], accompanied by a high incidence of renal dysfunction [10,11]. Researchers have sought to explore novel therapeutic strategies. The advent of immunotherapy has greatly enhanced the therapeutic potential of UC, while overcoming the existing treatment limitation of the chemotherapy era. Since 2016, a total of five immune checkpoint inhibitors (ICIs) have been approved for metastatic UC (mUC) as first and second-line treatments [11]. As a PD-1 inhibitor, camrelizumab has received approval in China for treating relapsed or refractory classical Hodgkin lymphoma [12], and our research team reported a case of camrelizumab in the treatment for relapsed UTUC after RNU [13]. However, data extracted from subgroup analysis of UC have been controversial [14].

Herein, we reported two cases of mUTUC receiving immunotherapy with or without targeted therapy, and both of them benefited from ICIs.

2. Case reports

2.1. Case 1

A 71-year old male patient was referred to our hospital after suffering from low back pain and numbness in his left lower extremity. The computed tomography (CT) scan revealed that the left renal pelvic carcinoma had spread to the second lumbar spine. The patient underwent the RNU and the postoperative pathology demonstrated high-grade invasive UTUC invading renal parenchyma, fat tissue and nerves. The immunohistochemistry (IHC) using Rabbit SP263 (Ventana) antibody showed that the PD-L1 expression was 6% (shown in Fig. 1A and B). The patient initially received 6 cycles of chemotherapy, consisting of gemcitabine plus cisplatin. Six months later, the CT scan showed locally advanced tumor with multiple metastases in the liver and lumbar spine (shown in Fig. 2A and B). Given the possibility of chemotherapy resistance, the patient agreed to take camrelizumab (200 mg, once, every 3 weeks). After the following four cycles, the metastasis was gradually reduced (shown in Fig. 2C and D), and he was considered to have achieved a partial response (PR). The lumbar spine metastases had not progressed after eight cycles of therapy (shown in Fig. 2E and F). The patient experienced only mild rash during the 9-month follow-up period, and the progression-free survival (PFS) reached 5 months.

2.2. Case 2

An 88-year old female was admitted to the hospital for right abdominal pain. Flexible cystoscopy examination and CT scan revealed a mass in the middle and lower right ureter with invasion to the right iliac arteriovenous (shown in Fig. 3A and B). A subsequent needle biopsy suggested mUTUC and the IHC using Rabbit SP263 (Ventana) antibody showed the PD-L1 expression was 5% (shown in Fig. 1C and D). The combination of apatinib (250 mg qd), camrelizumab (200 mg, once, every 3 weeks) and radiotherapy (GTV, 10 MV-X SAD 100DT 5000 cGy/25F/37d; CTV, 10 MV-X SAD 100DT 4500 cGy/25F/37d) was administered for five cycles, and apatinib was

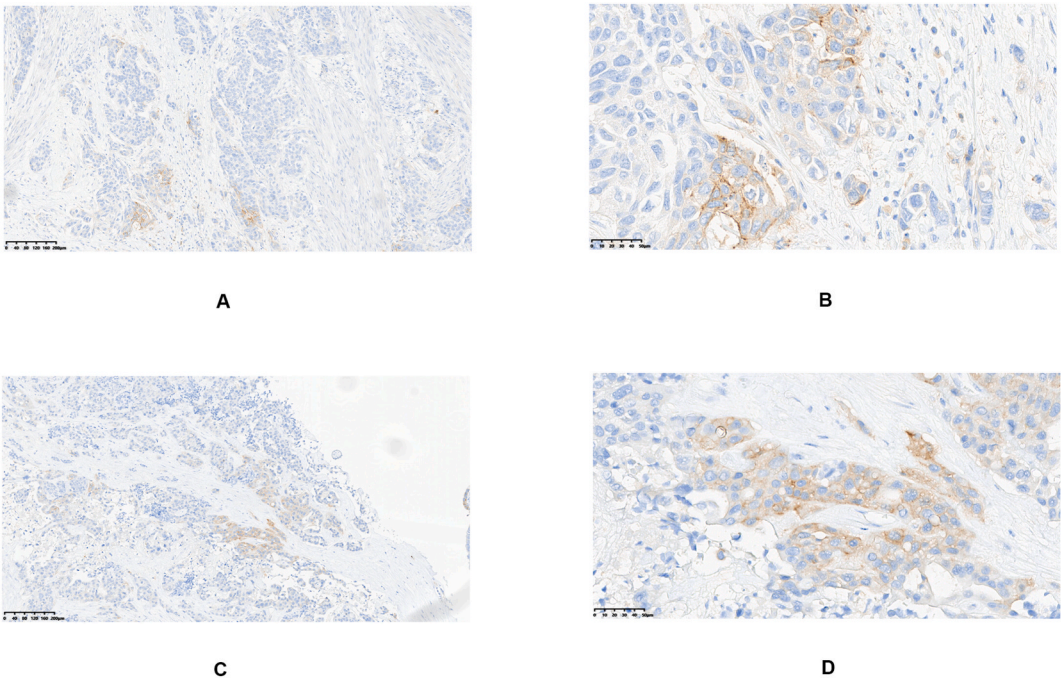

Fig. 1. Representative images of PD-L1 expression in mUTUC. A&B. The PD-L1 expression of case 1. C&D. The PD-L1 expression of case 2.

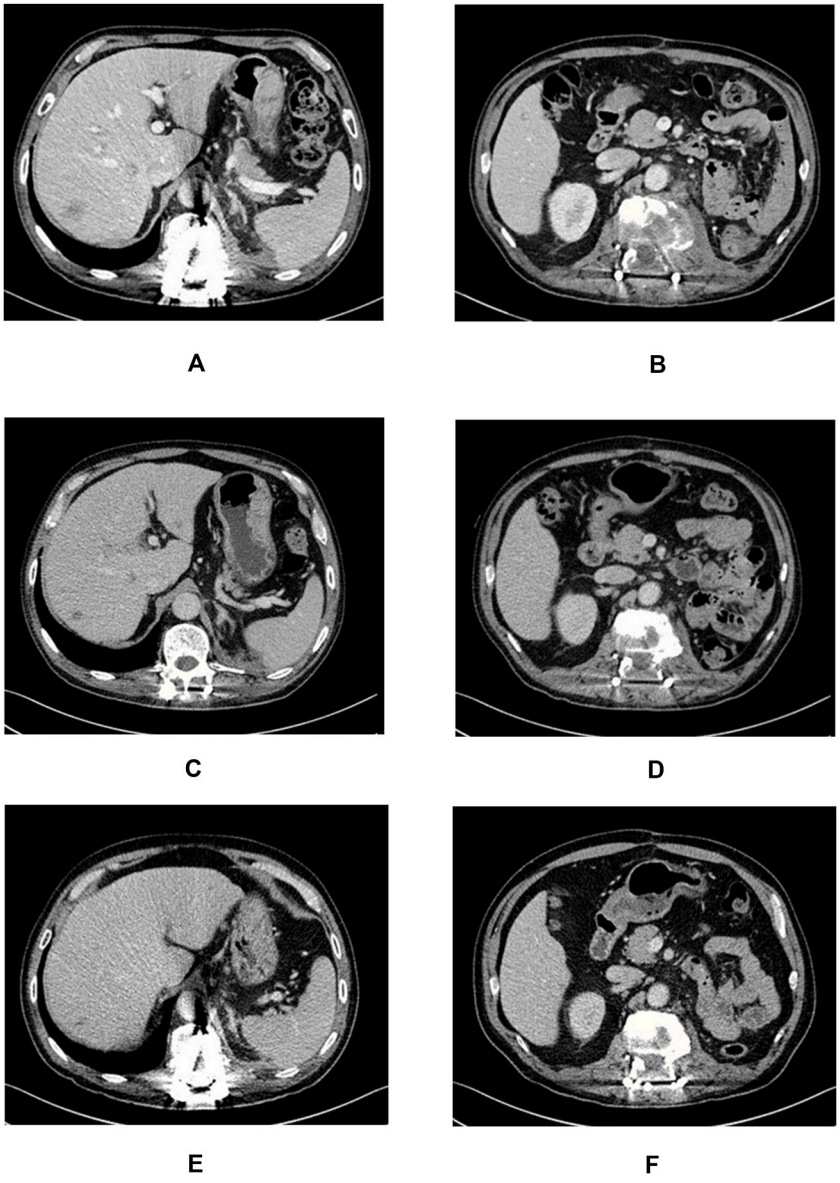

Fig. 2. The CT scan of case 1. A&B. The left renal pelvic carcinoma with multiple metastases in liver and lumbar spine. C&D. Partial response after the patient received RNU with subsequent 4 cycles of camrelizumab. E&F. The stable lesion after 8 cycles of camrelizumab.

discontinued due to lower extremity edema. The enhanced CT showed a faded mass at the original site 15 weeks later (shown in Fig. 3C and D), and the palliative radiotherapy was switched to gross target volume (GTV) (10 MV-X SAD 100DT 1200 cGy/4F/4d). The patient was considered to have achieved a stable disease (SD) and experienced weakness only during the 5-month follow-up period.

3. Discussion

For locally advanced or metastatic UTUC, platinum-based chemotherapy is currently recommended as the standard first-line treatment; however, the prognosis is consistently unfavorable and renal function deterioration is a concern. Up to 50% of patients with late-stage disease are considered to be ineligible for cisplatin-based treatment because some individuals have impaired renal function, are in poor physical condition, or have other underlying comorbidities [15,16].

Immunotherapy shifts the balance from immune evasion to immunological eradication by reawakening the innate capacity to fight malignancies. The potential molecular pathways of drug targets for UTUC include cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed death 1 (PD1) and programmed death-ligand 1 (PD-L1) [2]. PD-L1 works with PD1 receptor and the PD1/PD-L1 pathway possesses an immune evasion effect to promote tumor progression [17]. Therefore, the PD1 or PD-L1 inhibitor could interfere with the binding of PD1 to its ligand and block inhibitory signals in T cells, thus suppressing the development of tumor cells.

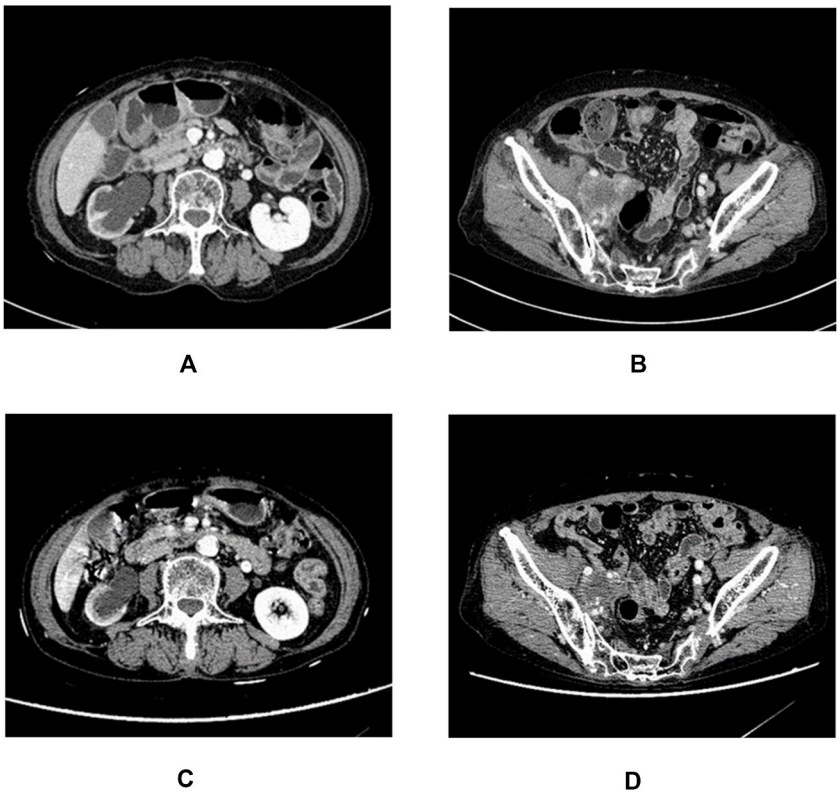

Fig. 3. The CT scan of case 2. A&B. The middle and lower right ureter carcinoma with invasion to right iliac arteriovenous. C&D. The stable disease lesion after 5 cycles of camrelizumab plus apatinib and radiotherapy.

The PD1 and its ligands also express in urothelial cancer [18]. To date, five ICIs have been approved by the Food and Drug Administration (FDA) for UTUC patients, including 2 PD1 inhibitors and 3 PD-L1 inhibitors [11].

The IHC staining for PD-L1 on tumor cells is one of the key biomarkers for predicting patient response to ICIs [19], but different antibodies and disparate cellular populations developed by each PD1/PD-L1 targeted medicine result in the different PD-L1 positivity thresholds–the combined positive score (CPS), the IHC status and the IC/TC percentage are used to evaluate the level of PD-L1 expression in tumor cells or immune cells, limiting the application of this promising biomarker [20]. Nevertheless, the role of PD-L1 expression in predicting treatment response cannot be ignored. Some studies have shown that the higher the PD-L1 expression level was, the longer the survival of patients achieved [19,21]. In addition, the PD-L1 status was associated with resistance. Patients with negative or low PD-L1 expression are more likely to develop primary drug resistance [22]. Some patients, perhaps due to variation in the IFN-γ response pathway, also developed acquired resistance to ICIs [22].

The PD-1 inhibitor camrelizumab has not been approved in China for the treatment of UC, and there are few reports of its use in the treatment of mUTUC. The two patients in this study had advanced cancer with a poor prognosis that had continued to progress during the time prior to treatment. Although both didn't reach the standard of PD-L1 IHC assay positive threshold, they were still given a trial of camrelizumab in view of the relatively advanced tumor stage and previous failed chemotherapy. On the other hand, camrelizumab therapy exhibited a considerable anti-tumor effect, resulting in PR and SD for the disease with a rather long PFS, and no serious adverse effects were observed in the medication. The detection of PD-L1 expression should be paid great attention to, so as to better develop the treatment strategy. In our future clinical practice, we will pay more attention to the PD-L1 expression level. For patients with PD-L1 positivity, we would recommend them to try ICIs, but for those with PD-L1 expression level close the positivity threshold, the ICIs could also be an alternative after obtaining full informed consent is obtained from the patients.

4. Literature review

4.1. Methods

4.1.1. Study selection

The Medline (PubMed), Embase, and Cochrane databases were searched for studies describing the effectiveness and safety of camrelizumab for UC between Jan 2000 and June 2022. MeSH search headings used were "immunotherapy", "immune checkpoint inhibitors", "vascular endothelial growth factor receptor 2", "targeted therapy", "advanced", "metastatic", "metastases", "upper tract

urothelial carcinoma" and "urothelial carcinoma". The combinations of these words were also used to diversify the search. The references of each included study were carefully checked All authors agreed on the final list of articles to be included.

4.1.2. Data collection process

Included manuscripts were independently reviewed by 2 authors (K.N. & H.W.) and any discrepancies were resolved by the senior author (G.L.).

4.1.3. Inclusion criteria

The studies that we included met the following criteria: focusing on advanced or metastatic UC; including data of patients with UTUC; including any of ICIs monotherapy group; human studies; English and Chinese language articles; perspective clinical trials.

4.1.4. Exclusion criteria

Abstracts, editorials, case reports, reviews, meta-analysis, studies focusing on other diseases or study from same research group were excluded.

4.1.5. Outcomes of interest and definitions

Primary outcomes addressed were OS and PFS. Secondary outcome was ORR, hazard ratio (HR). Variables of interest included sample size (n), patient diagnosis, and the PD-L1 expression level. The PD-L1 expression level was defined according to the IHC staining on paraffin-embedded tumor specimens, and the positivity thresholds depended on the targeted drug and their specific antibodies using a PD-L1 assay (Ventana) approved by FDA [20].

4.2. Results

4.2.1. Eligible studies

After excluding the duplicate literature, 2135 reference were screened by title and abstract. Finally, overall 18 clinical trials were included based on our inclusion and exclusion criteria.

4.2.2. PD-1/PD-L1 inhibitor monotherapy

The efficacy of PD-1/PD-L1 inhibitor monotherapy in patients with advanced or metastatic UC has been evaluated in many clinical trials, including the KEYNOTE series, the CheckMate series, the MPDL3280A series, the Imvigor series, the JAVELIN series and the DANUBE series (shown in Table 1).

The KEYNOTE series focused on pembrolizumab. KEYNOTE 012(NCT01848834) enrolled the patients with PD-L1expression$\geq$1%, and the median OS and the median PFS were 13 months (95%CI 5–20) and 2 months (95%CI 2–4), respectively [23]. Results from the KEYNOTE 045 trail (NCT02256436) showed that the median OS was 10.3 months (95% CI 8.0–11.8) in the pembrolizumab group, significantly longer than that in the chemotherapy arm (7.4 months, 95% CI 6.1–8.3), with the median PFS being 2.1 months (95% CI 2.0–2.2) in the pembrolizumab cohort [24]. Influenced by the short follow-up time, the PFS was only 2 months (95% CI 2–3), with a 6-month PFS of 30% (95% CI 25–35) in the KEYNOTE 052 trial (NCT02335424) [19,25] In addition, the KEYNOTE-052 trail also reported the number of complications. The KEYNOTE-361 trial (NCT02853305) compared the efficacy between pembrolizumab combined with chemotherapy versus chemotherapy monotherapy, and the PFS didn't show significant difference [26].

The CheckMate series focused on nivolumab. In the CheckMate 032 (NCT01928394), the median OS was 9.7 months (95% CI 7.3–16.2), the median PFS was 2.8 months (95%CI 1.5–5.9), and the ORR was 25.7% (95%CI 16.2–37.2) [27]. The CheckMate 275 trail (NCT02387996) showed a median OS of 8.74 months (95% CI 6.05 to not reached) with a median PFS of 1.9 months (95% CI 1.9–2.3) and an ORR of 19.6% (95% CI 15.0–24.9) [28].

And the IMvigor series concentrated on atezolizumab. There were two cohorts in the IMvigor210 study (NCT02108652) [29,30]. The median OS was 15.9 months (95% CI 10.4 -not estimable) in cohort 1 and 2.7 months (95% CI 2.1–3.9) in cohort 2, while the median PFS was 2.7 months (95% CI 2.1–4.2) in cohort 1and 2.1 months (95% CI 2.1–2.1) in cohort 2, and the ORR was 23% (95% CI 16–31) in cohort 1 and 15% (95% CI 11–19) in cohort 2. Subsequently, two phase 3 randomized controlled trials IMvigor130 (NCT02807636) [31] and IMvigor211 (NCT02302807) [32] were conducted. In the IMvigor130 study, the OS was 15.7 months (95% CI, 13.1 to 17.8) in the atezolizumab monotherapy arm, which was shorter than in the atezolizumab plus chemotherapy arm and longer than in the chemotherapy arm [31]. In the IMvigor211 study, though the OS and PFS didn't show a significant difference between the atezolizumab cohort and the chemotherapy cohort, the safety profile was better in patients who received atezolizumab compared to chemotherapy. Disappointingly, the outcome data in UTUC patients were not analyzed for specificity [32].

The MPDL3280A also focused on atezolizumab [25]. The phase 1 single-arm trial presented that patients with mUC who were treated with ICIs monotherapy had a median OS of 10.1 months (95% CI 7.3–17.0) and a median PFS of 2.7 months (95% CI 1.4–4.3).

The JAVELIN series were focusing on avelumab. The JAVELIN Solid Tumor trial (NCT01772004) enrolled 249 patients with mUC who received avelumab, resulting in a median OS of 6.5 months (95% CI 4.8–9.5) and a median PFS of 6.3 weeks (95% CI 6.0–10.1) [33]. The JAVELIN Bladder 100 study (NCT02603432) enrolled patients whose disease was controlled with best supportive care such as first-line chemotherapy. The results revealed that sustained avelumab with best supportive care prolong OS [21].

As for durvalumab, Powels et al. conducted the phase 1/2(NCT01693562) [34] and phase 3 (NCT02516241) [35]clinical trials. The median OS was more than 1 year in both studies. The DANUBE trial also compared the efficacy and safety among the durvalumab

Table 1
Studies including PD-1/PD-L1 monotherapy in UC patients.

Trial	Study design	Treatment	Mechanism	Line	Overall patients *vs.* UTUC patients, n	Number of Immunotherapy monotherapy group, n	Overall outcomes (Immunotherapy monotherapy group)	Number of patients with PD-L1 positivity, n	Outcomes in patients with PD-L1 positivity
KEYNOTE 012 (NCT01848834) (23)	Phase 1b	Pembrolizumab	PD-1 inhibitors	2 L	115	33; N/A	Median OS 13 months (95%CI 5–20)	33	Median OS 13 (95%Ci 5–20)
	Single-arm						Median PFS 2 months (95%CI 2–4)		Median PFS 2 (95%CI 2–4)
KEYNOTE 045 (NCT02256436) (24)	Phase 3	Pembrolizumab	PD-1 inhibitors	2 L	270; 48 (17.8%)	270	Median OS 10.3 months (95% CI 8.0–11.8)	164 (74 in pembrolizumab group)	HR: 0.57 (95%CI 0.37–0.88)
									Median OS 8.0 months (95% CI 5.2–12.3)
	RCT						Median PFS 2.1 months (95% CI 2.0–2.2)		Median PFD 2.1 months (95% CI 2.0–2.2)
KEYNOTE 052 (NCT02335424) (19)	Phase 2	Pembrolizumab	PD-1 inhibitors	1 L	370; 69 (18.6%)	370	Median PFS 2 months (95% CI 2–3)	110	OR: 38% (95% CI 29–48)
	Single-arm						ORR 24% (95% CI 20–29)		
KEYNOTE 361 (NCT02853305) (25)	Phase 3	Pembrolizumab	PD-1 inhibitors	1 L	1010; 211 (20.9%)	65	Median OS 15.6months (95%CI 12.1–17.9)	477 (160 in pembrolizumab group)	N/A
	RCT								
CheckMate 032 (NCT01928394) (26)	Phase 1/2	Nivolumab	PD-1 inhibitors	≥2 L	78; N/A	78	Median OS 9.7 months (95% CI 7.3–16.2)	14	N/A
	Single-arm						Median PFS 2.8 months (95%CI 1.5–5.9) ORR 25.7% (95%CI 16.2–37.2)		
CheckMate 275 (NCT02387996) (27)	Phase 2	Nivolumab	PD-1 inhibitors	≥1 L	265; N/A	265	Median OS 8.74 months (95% CI 6.05 to not reached)	81	OR 28.4% (95% CI 18.9–39.5)
	Single-arm						Median PFS 1.9 months (95% CI 1.9–2.3) ORR 19.6%, 95% CI 15.0–24.9)		
IMvigor210 cohort 1 (NCT02108652) (28)	Phase 2	Atezolizumab	PD-L1 inhibitors	1 L	123; 33 (26.8)	123	Median OS 15.9 months (95% CI 10.4 -not estimable)	32	Median OS 12.3 months (95% CI 6.0 -not estimable
	Single-arm						Median PFS 2.7 months (95% CI 2.1–4.2) ORR 23% (95% CI 16–31)		Median PFS 4.1 months (95% CI 2.3–11.8) ORR 22% (95% CI 9–40)
IMvigor210 cohort 2 (NCT02108652) (29)	Phase 2	Atezolizumab	PD-L1 inhibitors	2 L	310; 65 (21.0%)	310	Median OS 2.7 months (95% CI 2.1–3.9)	207	Median OS 11·4 months (95% CI 9.0–not estimable)
	Single-arm						Median PFS 2.1 months (95% CI 2.1–2.1) ORR: 15% (95% CI 11–19)		Median PFS 2.1 months (95% CI 2.1–4.1) ORR 6% (95% CI 18–36)

(*continued on next page*)

Table 1 (*continued*)

Trial	Study design	Treatment	Mechanism	Line	Overall patients *vs.* UTUC patients, n	Number of Immunotherapy monotherapy group, n	Overall outcomes (Immunotherapy monotherapy group)	Number of patients with PD-L1 positivity, n	Outcomes in patients with PD-L1 positivity
IMvigor130 (NCT02807636) (30)	Phase 3 RCT	Atezolizumab	PD-L1 inhibitors	1 L	1213; 312 (25.7%)	362 (89 were UTUC)	Median OS 15.7 months (95% CI 13.1–17.8)	287 (88 in atezolizumab monotherapy group)	Atezolizumab monotherapy group: Median OS NE (95% CI 17.7–NE)
IMvigor211 (NCT02302807) (31)	Phase 3 RCT	Atezolizumab	PD-L1 inhibitors	2 L	931; 126 (13.5%)	467	Median OS 11.1 months (95% CI 8.6–15.5)	234 (116 in atezolizumab monotherapy group)	Atezolizumab monotherapy group: Median OS 1111 months (95% CI 8·6–15.5)
MPDL3280A (NCT01375842) (32)	Phase 1	Atezolizumab	PD-L1 inhibitors	2 L	95; N/A	95	Median OS 10.1 months (95% CI 7.3–17.0)	50	Median OS 14.6 months (95% CI 9.0 months-not estimable)
	Single-arm						Median PFS 2.7 months (95% CI 1.4–4.3)		Median PFS 5.5 months (95% CI, 2.7–10.8)
JAVELIN Solid Tumor (NCT01772004) (33)	Phase 1	Avelumab	PD-L1 inhibitors	2 L	249; 58 (23%)	249	Median OS 6.5 months (95% CI 4.8–9.5)	82	Median OS 8.2 (5.7–13.7)
	Single-arm						Median PFS 6.3 weeks (95% CI 6.0–10.1)		Median PFS 11.9 (6.1–18.0)
JAVELIN Bladder 100 (NCT02603432) (21)	Phase 3	Avelumab	PD-L1 inhibitors	2 L	700; 106 (30.3%)	350	Median OS 21.4 months (95%CI 18.9–26.1)	358 (189 in avelumab group)	Avelumab group: Median PFS: 5.7months (95% CI, 3.7–7.4)
	RCT						Median PFS 3.7 months (95%CI 3.5–5.5)		OR: 13.8 (95%CI 9.2–19.5)
NCT01693562 (35)	Phase 1/2	Durvalumab	PD-L1 inhibitors	2 L	191; N/A	191	Median OS 18.2 months (95% CI, 8.1-not estimable Median PFS 1.5 months (95% CI 1.4–1.9 months)	98	Median OS 20.0 months (95% CI 11.6 -not estimable) Median PFS 2.1months (95% CI 1.4–2.8)
	Single-arm						ORR 7.8% (95% CI 12.7%–24.0%)		ORR 27.6% (95% CI 19.0%–37.5%)
DANUBE (NCT02516241) (34)	Phase 3	Durvalumab	PD-L1 inhibitors	2 L	1032;221 (21.4%)	346 (62 were UTUC)	Median OS 13.2months (95% CI 10.3–15.0)	621 (209 in durvalumab monotherapy group)	Median OS 14.4months (95% CI 10.4–17.3)
	RCT						Median PFS 2.3 months (95% CI 1.9–3.5)		Median PFS 2.4 months (1.9–3.7) **HR 0.89 (95% CI 0.71–1.11)**

monotherapy group, durvalumab plus tremelimumab group and chemotherapy monotherapy group. Although none of its coprimary endpoints were met, it highlighted out that the promising benefit of ICIs for treatment naïve mUC patients.

4.2.3. Combination therapy of anti-PD-1/PD-L1 therapy plus VEGFR inhibitors

54 patients were recruited in a phase I clinical trial (NCT02496208) and received ICI with or without VEGFR inhibitor for genitourinary (GU) tumors. Among them, 15 (28%) were UC patients, with a median follow-up time of 44.6 months, patients with mUC showed a median PFS of 12.8 months and a median OS of 25.4 months, but the difference of efficacy and toxicity between mUC patients treated with ICIs only or with VEGFR inhibitors has not been analyzed [36].

Between 2015 and 2016, 24 patients with mUC were recruited in a trial (NCT02443324) and started to receive combination therapy of PD-1 inhibitor accompanied with VEGFR inhibitor, among which 13% UC patients achieved ORR, and 1.9 months PFS and 6.4 months OS were observed with a median follow-up time of 32.8 months [37].

5. Conclusion

ICIs like camrelizumab with/without VEGFR2 inhibitors could be a potential salvage treatment alternative for UTUC patients with poor performance status or ineligible for chemotherapy.

Consent for publication

Written and informed consent was taken from the patients for publication.

Author contribution statement

Kangxin Ni: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Chenhao Yu: Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Huailan Wang; Shibin Zhu; Shicheng Yu: Wang: Performed the experiments; Wrote the paper. Gonghui Li: Conceived and designed the experiments.

Data availability statement

Data will be made available on request.

References

[1] M. Roupret, M. Babjuk, M. Burger, O. Capoun, D. Cohen, E.M. Comperat, N.C. Cowan, J.L. Dominguez-Escrig, P. Gontero, A. Hugh Mostafid, J. Palou, B. Peyronnet, T. Seisen, V. Soukup, R.J. Sylvester, B. Rhijn, R. Zigeuner, S.F. Shariat, European association of urology guidelines on upper urinary tract urothelial carcinoma: 2020 update, Eur. Urol. 79 (1) (2021) 62–79.

[2] F. Soria, S.F. Shariat, S.P. Lerner, H.M. Fritsche, M. Rink, W. Kassouf, P.E. Spiess, Y. Lotan, D. Ye, M.I. Fernandez, E. Kikuchi, D.C. Chade, M. Babjuk, A. P. Grollman, G.N. Thalmann, Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC), World J. Urol. 35 (3) (2017) 379–387.

[3] G. Lughezzani, M. Sun, P. Perrotte, S.F. Shariat, C. Jeldres, L. Budaus, A. Alasker, A. Duclos, H. Widmer, M. Latour, G. Guazzoni, F. Montorsi, P.I. Karakiewicz, Should bladder cuff excision remain the standard of care at nephroureterectomy in patients with urothelial carcinoma of the renal pelvis? A population-based study, Eur. Urol. 57 (6) (2010) 956–962.

[4] T. Kawada, E. Laukhtina, F. Quhal, T. Yanagisawa, P. Rajwa, M. Pallauf, M. von Deimling, A. Bianchi, B. Pradere, H. Fajkovic, D. Enikeev, P. Gontero, M. Roupret, T. Seisen, M. Araki, S.F. Shariat, Oncologic and safety outcomes for endoscopic surgery versus radical nephroureterectomy for upper tract urothelial carcinoma: an updated systematic review and meta-analysis, Eur Urol Focus. 9 (2) (2023) 236–240.

[5] V. Margulis, S.F. Shariat, S.F. Matin, A.M. Kamat, R. Zigeuner, E. Kikuchi, Y. Lotan, A. Weizer, J.D. Raman, C.G. Wood, Outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration, Cancer 115 (6) (2009) 1224–1233.

[6] J.J. Leow, Z. Liu, T.W. Tan, Y.M. Lee, E.K. Yeo, Y.L. Chong, Optimal management of upper tract urothelial carcinoma: current perspectives, OncoTargets Ther. 13 (2020) 1–15.

[7] Y.Y. Qu, Z. Sun, W. Han, Q. Zou, N. Xing, H. Luo, X. Zhang, C. He, X.J. Bian, J. Cai, C. Chen, Q. Wang, D.W. Ye, Camrelizumab plus famitinib for advanced or metastatic urothelial carcinoma after platinum-based therapy: data from a multicohort phase 2 study, J. Immunother. Cancer 10 (5) (2022).

[8] A. Necchi, R.W. Joseph, Y. Loriot, J. Hoffman-Censits, J.L. Perez-Gracia, D.P. Petrylak, C.L. Derleth, D. Tayama, Q. Zhu, B. Ding, C. Kaiser, J.E. Rosenberg, Atezolizumab in platinum-treated locally advanced or metastatic urothelial carcinoma: post-progression outcomes from the phase II IMvigor210 study, Ann. Oncol. 28 (12) (2017) 3044–3050.

[9] A. Bianchi, M. von Deimling, M. Pallauf, T. Yanagisawa, T. Kawada, H. Mostafaei, F. Quhal, E. Laukhtina, P. Rajwa, M. Majdoub, R.S. Motlagh, B. Pradere, P. I. Karakiewicz, M.A. Cerruto, A. Antonelli, S.F. Shariat, Perspectives on the future of urothelial carcinoma therapy: chemotherapy and beyond, Expet Opin. Pharmacother. (2022) 1–19.

[10] S.J. Crabb, Treatment of upper urinary tract urothelial carcinoma, Lancet 395 (10232) (2020) 1232–1234.

[11] G. Califano, I. Ouzaid, P. Verze, J.-F. Hermieu, V. Mirone, E. Xylinas, Immune checkpoint inhibition in upper tract urothelial carcinoma, World J. Urol. 39 (5) (2020) 1357–1367.

[12] A. Markham, S.J. Keam, Camrelizumab: first global approval, Drugs 79 (12) (2019) 1355–1361.

[13] K. Ni, Z. Wang, S. Yu, J. Zheng, G. Li, Camrelizumab monotherapy leading to partial remission for relapsed upper tract urothelial carcinoma after radical nephroureterectomy: a case report, Transl. Androl. Urol. 10 (4) (2021) 1821–1826.

[14] S.M. Esagian, A.R. Khaki, L.N. Diamantopoulos, L. Carril-Ajuria, D. Castellano, I. De Kouchkovsky, J.J. Park, A. Alva, M.A. Bilen, T.F. Stewart, R.R. McKay, V. S. Santos, N. Agarwal, J. Jain, Y. Zakharia, R. Morales-Barrera, M.E. Devitt, A. Nelson, C.J. Hoimes, E. Shreck, B.A. Gartrell, A. Sankin, A. Tripathi, R. Zakopoulou, A. Bamias, A. Rodriguez-Vida, A. Drakaki, S. Liu, V. Kumar, M.P. Lythgoe, D.J. Pinato, J. Murgic, A. Frobe, M. Joshi, P. Isaacsson Velho, N. Hahn, L. Alonso Buznego, I. Duran, M. Moses, P. Barata, M.D. Galsky, G. Sonpavde, E.Y. Yu, P. Msaouel, V.S. Koshkin, P. Grivas, Immune checkpoint inhibitors in advanced upper and lower tract urothelial carcinoma: a comparison of outcomes, BJU Int. 128 (2) (2021) 196–205.

[15] A. Bamias, K. Tzannis, L.C. Harshman, S.J. Crabb, Y.N. Wong, S. Kumar Pal, U. De Giorgi, S. Ladoire, N. Agarwal, E.Y. Yu, G. Niegisch, A. Necchi, C.N. Sternberg, S. Srinivas, A. Alva, U. Vaishampayan, L. Cerbone, M. Liontos, J. Rosenberg, T. Powles, J. Bellmunt, M.D. Galsky, R. Investigators, Impact of contemporary patterns of chemotherapy utilization on survival in patients with advanced cancer of the urinary tract: a Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC), Ann. Oncol. 30 (11) (2019) 1841.

[16] M. De Santis, J. Bellmunt, G. Mead, J.M. Kerst, M. Leahy, P. Maroto, T. Gil, S. Marreaud, G. Daugaard, I. Skoneczna, S. Collette, J. Lorent, R. de Wit, R. Sylvester, Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986, J. Clin. Oncol. 30 (2) (2012) 191–199.

[17] J. Bellmunt, T. Powles, N.J. Vogelzang, A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: the future is now, Cancer Treat Rev. 54 (2017) 58–67.

[18] M.E. Keir, M.J. Butte, G.J. Freeman, A.H. Sharpe, PD-1 and its ligands in tolerance and immunity, Annu. Rev. Immunol. 26 (2008) 677–704.

[19] A.V. Balar, D. Castellano, P.H. O'Donnell, P. Grivas, J. Vuky, T. Powles, E.R. Plimack, N.M. Hahn, R. de Wit, L. Pang, M.J. Savage, R.F. Perini, S.M. Keefe, D. Bajorin, J. Bellmunt, First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study, Lancet Oncol. 18 (11) (2017) 1483–1492.

[20] J. Zhu, A.J. Armstrong, T.W. Friedlander, W. Kim, S.K. Pal, D.J. George, T. Zhang, Biomarkers of immunotherapy in urothelial and renal cell carcinoma: PD-L1, tumor mutational burden, and beyond, J. Immunother. Cancer 6 (1) (2018) 4.

[21] T. Powles, S.H. Park, E. Voog, C. Caserta, B.P. Valderrama, H. Gurney, H. Kalofonos, S. Radulovic, W. Demey, A. Ullen, Y. Loriot, S.S. Sridhar, N. Tsuchiya, E. Kopyltsov, C.N. Sternberg, J. Bellmunt, J.B. Aragon-Ching, D.P. Petrylak, R. Laliberte, J. Wang, B. Huang, C. Davis, C. Fowst, N. Costa, J.A. Blake-Haskins, A. di Pietro, P. Grivas, Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, N. Engl. J. Med. 383 (13) (2020) 1218–1230.

[22] S. Bagchi, R. Yuan, E.G. Engleman, Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance, Annu. Rev. Pathol. 16 (2021) 223–249.

[23] E.R. Plimack, J. Bellmunt, S. Gupta, R. Berger, L.Q. Chow, J. Juco, J. Lunceford, S. Saraf, R.F. Perini, P.H. O'Donnell, Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study, Lancet Oncol. 18 (2) (2017) 212–220.

[24] J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, D.F. Bajorin, K. Investigators, Pembrolizumab as second-line therapy for advanced urothelial carcinoma, N. Engl. J. Med. 376 (11) (2017) 1015–1026.

[25] D.P. Petrylak, T. Powles, J. Bellmunt, F. Braiteh, Y. Loriot, R. Morales-Barrera, H.A. Burris, J.W. Kim, B. Ding, C. Kaiser, M. Fasso, C. O'Hear, N.J. Vogelzang, Atezolizumab (MPDL3280A) monotherapy for patients with metastatic urothelial cancer: long-term outcomes from a phase 1 study, JAMA Oncol. 4 (4) (2018) 537–544.

[26] T. Powles, T. Csoszi, M. Ozguroglu, N. Matsubara, L. Geczi, S.Y. Cheng, Y. Fradet, S. Oudard, C. Vulsteke, R. Morales Barrera, A. Flechon, S. Gunduz, Y. Loriot, A. Rodriguez-Vida, R. Mamtani, E.Y. Yu, K. Nam, K. Imai, B. Homet Moreno, A. Alva, K. Investigators, Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial, Lancet Oncol. 22 (7) (2021) 931–945.

[27] P. Sharma, M.K. Callahan, P. Bono, J. Kim, P. Spiliopoulou, E. Calvo, R.N. Pillai, P.A. Ott, F. de Braud, M. Morse, D.T. Le, D. Jaeger, E. Chan, C. Harbison, C. S. Lin, M. Tschaika, A. Azrilevich, J.E. Rosenberg, Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial, Lancet Oncol. 17 (11) (2016) 1590–1598.

[28] P. Sharma, M. Retz, A. Siefker-Radtke, A. Baron, A. Necchi, J. Bedke, E.R. Plimack, D. Vaena, M.O. Grimm, S. Bracarda, J.A. Arranz, S. Pal, C. Ohyama, A. Saci, X. Qu, A. Lambert, S. Krishnan, A. Azrilevich, M.D. Galsky, Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial, Lancet Oncol. 18 (3) (2017) 312–322.

[29] A.V. Balar, M.D. Galsky, J.E. Rosenberg, T. Powles, D.P. Petrylak, J. Bellmunt, Y. Loriot, A. Necchi, J. Hoffman-Censits, J.L. Perez-Gracia, N.A. Dawson, M.S. van der Heijden, R. Dreicer, S. Srinivas, M.M. Retz, R.W. Joseph, A. Drakaki, U.N. Vaishampayan, S.S. Sridhar, D.I. Quinn, I. Duran, D.R. Shaffer, B.J. Eigl, P. D. Grivas, E.Y. Yu, S. Li, E.E. Kadel 3rd, Z. Boyd, R. Bourgon, P.S. Hegde, S. Mariathasan, A. Thastrom, O.O. Abidoye, G.D. Fine, D.F. Bajorin, I.M.S. Group, Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial, Lancet 389 (10064) (2017) 67–76.

[30] J.E. Rosenberg, J. Hoffman-Censits, T. Powles, M.S. van der Heijden, A.V. Balar, A. Necchi, N. Dawson, P.H. O'Donnell, A. Balmanoukian, Y. Loriot, S. Srinivas, M.M. Retz, P. Grivas, R.W. Joseph, M.D. Galsky, M.T. Fleming, D.P. Petrylak, J.L. Perez-Gracia, H.A. Burris, D. Castellano, C. Canil, J. Bellmunt, D. Bajorin, D. Nickles, R. Bourgon, G.M. Frampton, N. Cui, S. Mariathasan, O. Abidoye, G.D. Fine, R. Dreicer, Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial, Lancet 387 (10031) (2016) 1909–1920.

[31] M.D. Galsky, J.A.A. Arija, A. Bamias, I.D. Davis, M. De Santis, E. Kikuchi, X. Garcia-Del-Muro, U. De Giorgi, M. Mencinger, K. Izumi, S. Panni, M. Gumus, M. Ozguroglu, A.R. Kalebasty, S.H. Park, B. Alekseev, F.A. Schutz, J.R. Li, D. Ye, N.J. Vogelzang, S. Bernhard, D. Tayama, S. Mariathasan, A. Mecke, A. Thastrom, E. Grande, I.M.S. Group, Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial, Lancet 395 (10236) (2020) 1547–1557.

[32] T. Powles, I. Duran, M.S. van der Heijden, Y. Loriot, N.J. Vogelzang, U. De Giorgi, S. Oudard, M.M. Retz, D. Castellano, A. Bamias, A. Flechon, G. Gravis, S. Hussain, T. Takano, N. Leng, E.E. Kadel 3rd, R. Banchereau, P.S. Hegde, S. Mariathasan, N. Cui, X. Shen, C.L. Derleth, M.C. Green, A. Ravaud, 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 391 (10122) (2018) 748–757.

[33] M.R. Patel, J. Ellerton, J.R. Infante, M. Agrawal, M. Gordon, R. Aljumaily, C.D. Britten, L. Dirix, K.W. Lee, M. Taylor, P. Schoffski, D. Wang, A. Ravaud, A. B. Gelb, J. Xiong, G. Rosen, J.L. Gulley, A.B. Apolo, Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial, Lancet Oncol. 19 (1) (2018) 51–64.

[34] T. Powles, P.H. O'Donnell, C. Massard, H.T. Arkenau, T.W. Friedlander, C.J. Hoimes, J.L. Lee, M. Ong, S.S. Sridhar, N.J. Vogelzang, M.N. Fishman, J. Zhang, S. Srinivas, J. Parikh, J. Antal, X. Jin, A.K. Gupta, Y. Ben, N.M. Hahn, Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study, JAMA Oncol. 3 (9) (2017), e172411.

[35] T. Powles, M.S. van der Heijden, D. Castellano, M.D. Galsky, Y. Loriot, D.P. Petrylak, O. Ogawa, S.H. Park, J.L. Lee, U. De Giorgi, M. Bogemann, A. Bamias, B. J. Eigl, H. Gurney, S.D. Mukherjee, Y. Fradet, I. Skoneczna, M. Tsiatas, A. Novikov, C. Suarez, A.P. Fay, I. Duran, A. Necchi, S. Wildsmith, P. He, N. Angra, A. K. Gupta, W. Levin, J. Bellmunt, Ds investigators, Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial, Lancet Oncol. 21 (12) (2020) 1574–1588.

[36] A.B. Apolo, R. Nadal, D.M. Girardi, S.A. Niglio, L. Ley, L.M. Cordes, S.M. Steinberg, O. Sierra Ortiz, J. Cadena, C. Diaz, M. Mallek, N.N. Davarpanah, R. Costello, J.B. Trepel, M.J. Lee, M.J. Merino, M.H. Bagheri, P. Monk, W.D. Figg, J.L. Gulley, P.K. Agarwal, V. Valera, H.J. Chalfin, J. Jones, H. Streicher, J.J. Wright, Y. M. Ning, H.L. Parnes, W.L. Dahut, D.P. Bottaro, P.N. Lara Jr., B. Saraiya, S.K. Pal, M.N. Stein, A. Mortazavi, Phase I study of cabozantinib and nivolumab alone or with ipilimumab for advanced or metastatic urothelial carcinoma and other genitourinary tumors, J. Clin. Oncol. 38 (31) (2020) 3672–3684.

[37] R.S. Herbst, H.T. Arkenau, R. Santana-Davila, E. Calvo, L. Paz-Ares, P.A. Cassier, J. Bendell, N. Penel, M.G. Krebs, J. Martin-Liberal, N. Isambert, A. Soriano, M. Wermke, J. Cultrera, L. Gao, R.C. Widau, G. Mi, J. Jin, D. Ferry, C.S. Fuchs, D.P. Petrylak, I. Chau, Ramucirumab plus pembrolizumab in patients with previously treated advanced non-small-cell lung cancer, gastro-oesophageal cancer, or urothelial carcinomas (JVDF): a multicohort, non-randomised, open-label, phase 1a/b trial, Lancet Oncol. 20 (8) (2019) 1109–1123.