

Significant Improvement of Prognosis After the Advent of Immune Checkpoint Inhibitors in Patients with Advanced, Unresectable, or Metastatic Urothelial Carcinoma: A Propensity Score Matching and Inverse Probability of Treatment Weighting Analysis on Real-World Data

Makito Miyake¹, Nobutaka Nishimura^{1,2}, Takuto Shimizu^{1,3}, Mikiko Ohnishi⁴, Masaomi Kuwada⁴, Yoshitaka Itami⁵, Takeshi Inoue⁵, Kenta Ohnishi⁶, Yoshihiro Matsumoto⁶, Takanori Yoshida⁷, Yoshihiro Tatsumi⁸, Masatake Shinohara⁹, Shunta Hori¹, Yosuke Morizawa¹, Daisuke Gotoh¹, Yasushi Nakai¹, Satoshi Anai¹, Kazumasa Torimoto¹, Katsuya Aoki¹, Tomomi Fujii¹⁰, Nobumichi Tanaka^{1,11}, Kiyohide Fujimoto¹

¹Department of Urology, Nara Medical University, Kashihara, Nara, 634-8522, Japan; ²Department of Urology, Okanami General Hospital, Iga, Mie, Japan; ³Department of Urology, Saiseikai Chuwa Hospital, Nara, Japan; ⁴Department of Urology, Matsusaka Chuoh General Hospital, Matsusaka, Mie, Japan; ⁵Department of Urology, Nara Prefecture General Medical Center, Nara, Japan; ⁶Department of Urology, Hoshigaoka Medical Center, Hirakata, Osaka, Japan; ⁷Department of Urology, Tane General Hospital, Osaka, Japan; ⁸Department of Urology, JCHO Yamato Koriyama Hospital, Koriyama, Nara, Japan; ⁹Department of Urology, Osaka Gyoumeikan Hospital, Osaka, Japan; ¹⁰Department of Diagnostic Pathology, Nara Medical University, Kashihara, Nara, 634-8522, Japan; ¹¹Department of Prostate Brachytherapy, Nara Medical University, Kashihara, Nara, 634-8522, Japan

Correspondence: Makito Miyake, Department of Urology, Nara Medical University, 840 Shijo-cho, Nara, 634-8522, Japan, Tel +81-744-22-3051 (ext 2338), Fax +81-744-22-9282, Email makitomiyake@yahoo.co.jp

Purpose: The treatment landscape for advanced, unresectable, or metastatic urothelial carcinoma (aUC) has shifted substantially since the advent of immune checkpoint inhibitors (ICIs). We investigated the extent to which pembrolizumab therapy is superior to conventional chemotherapy as a second-line treatment.

Patients and Methods: A multicenter-derived database registered 454 patients diagnosed with aUC between 2008 and 2020. Of these, 94 patients (21%) who received second-line pembrolizumab and 75 (17%) who received second-line chemotherapy but never received third-line or later ICI therapy were included. We compared overall survival (OS) from the initial date of first-line chemotherapy between two groups by adjusting for prognostic factors through propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). The IPTW-adjusted hazard ratio and 95% confidence interval were estimated using a multivariate Cox regression analysis. To identify patients who were more likely to benefit from second-line pembrolizumab than from chemotherapy, we performed a subgroup analysis for OS with an IPTW-adjusted model.

Results: The PSM-adjusted comparison showed a significant improvement in the prognosis with second-line pembrolizumab use ($P = 0.01$). The OS benefit with the advent of pembrolizumab was 8 months (18 months vs 26 months). Multivariable analyses using IPTW adjustment demonstrated that lymph node metastasis ($P = 0.001$), lung metastasis ($P = 0.013$), and bone metastasis ($P = 0.003$) were poor independent prognostic factors, and pembrolizumab use ($P = 0.021$) was a favorable independent prognostic factor. Subgroup analyses revealed that pembrolizumab was associated with survival benefits over chemotherapy in all subgroups, including young patients (age <70 years), those who received radical surgery, and those without visceral metastasis.

Conclusion: We demonstrated a significant improvement in prognosis after the advent of pembrolizumab for patients with aUC. ICIs should not be restricted based on patient characteristics.

Keywords: urinary bladder neoplasms, immunotherapy, chemotherapy, survival, propensity score

Introduction

The prognosis of advanced, unresectable, or metastatic urothelial carcinoma (aUC) is poor with a reported median overall survival (OS) of 12–15 months.¹ The second-line treatment for this disease subset has not yet been established. In 2017, pembrolizumab, an immune checkpoint inhibitor (ICI) against programmed cell death 1, was approved by the US Food and Drug Administration, European Medicines Agency, and Japanese Pharmaceuticals and Medical Devices Agency, based on clear evidence from the KEYNOTE-045 study.² Recently, real-world data have presented oncological benefits and acceptable toxicity profiles of second-line or later pembrolizumab.^{3–6} However, management of aUC is still challenging due to the heterogeneity of patient population; the optimization of the treatment sequence is needed to achieve a durable response and prolonged survival.

Platinum-based cytotoxic chemotherapy has been the gold standard as a first-line treatment for several decades.⁷ The treatment landscape for aUC has shifted substantially since the advent of ICIs. The extent to which pembrolizumab is superior to conventional chemotherapy as a second-line treatment setting remains unclear in real-world practice. A retrospective study using an electronic health record system suggests that patients with aUC who received the chemotherapy-ICI sequence had improvement in OS compared to those who received the chemotherapy–chemotherapy sequence with a median OS 19.2 months vs 11.9 months, which was not statistically significant ($P = 0.13$).⁸

Herein, we compared the prognosis between patients treated with second-line pembrolizumab and those treated with second-line chemotherapy after initial first-line chemotherapy by adjusting for prognostic factors, including propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). Particular focus was given to the extent to which the treatment sequence influenced OS. Moreover, we performed a subgroup analysis to determine the population of patients who were more likely to benefit from second-line pembrolizumab than from second-line chemotherapy and those not likely to benefit.

Materials and Methods

Data Collection

This retrospective multi-institutional study was approved by the Nara Medical University Ethics Committee (reference protocol ID: 2891) and followed the principles of the Declaration of Helsinki. The study was also approved by the ethics committee of each participating institute. Informed consent was obtained from participants through posters and/or websites using the opt-out method.⁹ We reviewed 454 patients who were diagnosed with aUC between January 2008 and December 2020 in 17 collaborative hospitals. We recorded the following baseline characteristics of patients: age, sex, Eastern Cooperative Oncology

Group (ECOG)-performance status (PS), primary tumor site (bladder, renal pelvis, or ureter), radical surgery implementation, metastatic sites, serum creatinine levels, and eligibility for cisplatin according to the Galsky criteria.¹⁰ Creatinine clearance was estimated by the Cockcroft–Gault Equation as follows: $\text{creatinine clearance} = [(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})] / (72 \times \text{creatinine})$.¹¹ Follow-up data including clinical outcomes and survival were extracted from the initiation of systemic therapy to the last documented follow-up or data lock (July 2021).

Statistical Analysis

Clinicopathological characteristics were compared using Mann–Whitney U, chi-square, and Kruskal–Wallis tests. PSM and IPTW analyses were used to reduce the risk of bias through R version 4.0.0 (R Development Core Team, Vienna, Austria), and survival curves were generated using GraphPad Prism version 7.00 (GraphPad Software, San Diego, CA, USA). Statistical significance was set at $p < 0.05$ (two-tailed).

The baseline characteristics were matched by calculating the propensity score for each patient using a multivariable logistic regression model based on covariates, such as age, sex, ECOG-PS, primary site, surgical removal of primary organ, metastatic sites or target lesions, cisplatin eligibility, and first-line chemotherapy regimen use. A one-to-one matching with a caliper width of 0.2 was applied to maintain a large sample size and balance between two

groups: second-line chemotherapy group versus second-line pembrolizumab group. The standardized mean difference (SMD) was used to examine the balance of covariate distributions between the groups after PSM.¹² After PSM was applied, an SMD greater than 0.1 indicated that the covariate was imbalanced.¹³ OS was calculated using the Kaplan–Meier method from the date of first-line chemotherapy initiation to death due to any cause. The survival rates of the two groups were compared using the Log rank test.

IPTW, which is a form of the propensity score analysis, uses weighting by the inverse of the propensity score to reduce imbalance in possible confounders between the two groups.¹⁴ A multivariable Cox regression analysis was used to estimate the IPTW-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) as outcomes for the two groups. As a secondary endpoint of this study, we sought to identify a population more likely to benefit from second-line pembrolizumab than from second-line chemotherapy and those not likely to benefit at all; we performed a subgroup analysis for OS with an IPTW-adjusted model.

Results

Study Cohorts Based on Second-Line Therapy

Figure 1 shows the flowchart of the patient selection process. Of the 454 patients, the cohort was first restricted to 383 patients (84%), only including patients who received first-line chemotherapy for aUC. We excluded 29 patients who received pembrolizumab for recurrence within 12 months of neoadjuvant or adjuvant chemotherapy in the setting of radical surgery for localized muscle-invasive UC. Subsequently, 186 patients (49%) did not meet the study criteria on the first-line regimen and following therapy. Of the remaining 197 patients, 103 received second-line cytotoxic chemotherapy, while 94 received second-line pembrolizumab. Twenty-eight patients treated with pembrolizumab as a third-line therapy or later were then excluded from the study (n = 103), leaving 75 patients who received second-line cytotoxic chemotherapy and did not receive pembrolizumab later on.

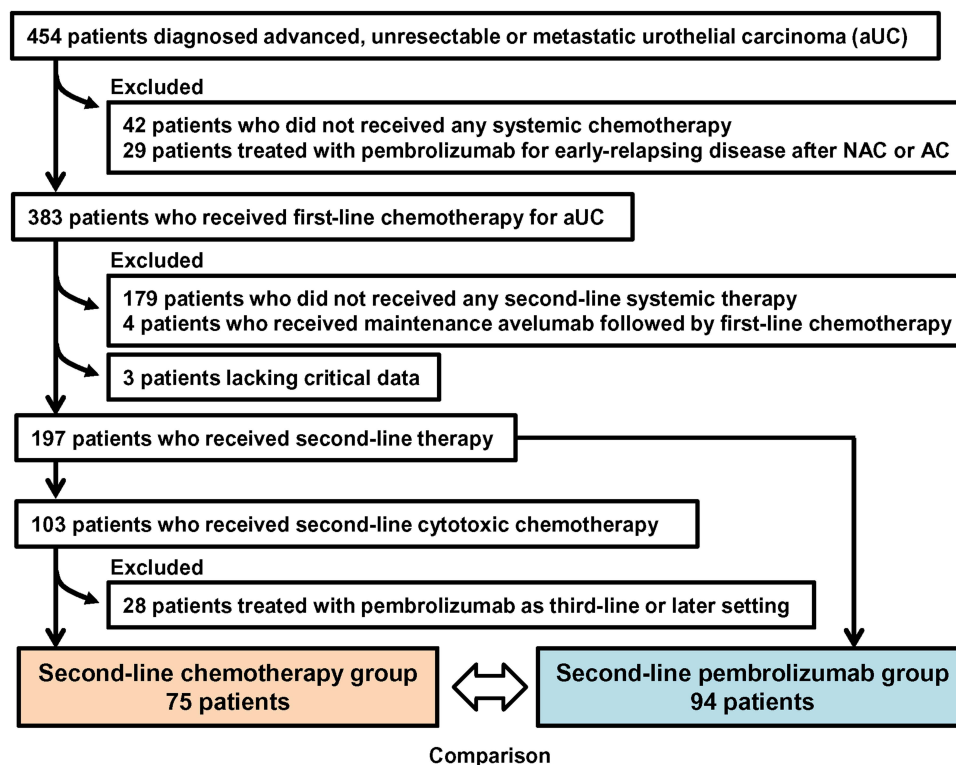


Figure 1 Flow chart for creation of patient cohort dataset. Among the 454 registered patients with aUC, 169 (37%) were eligible for this study. **Abbreviations:** NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; aUC, advanced, unresectable, or metastatic urothelial carcinoma.

In the second-line chemotherapy group ($n = 75$), 49 patients (65%) received platinum-based chemotherapy, 15 patients (20%) received taxane-based chemotherapy, and 11 patients (15%) received gemcitabine monotherapy as the second-line setting. In the second-line pembrolizumab group, 64 patients were available for the cause of pembrolizumab discontinuation in our dataset. The second-line pembrolizumab was discontinued in 54 patients (84%) due to progressive disease, in four patients (6.3%) due to severe adverse events consisting of two interstitial lung disease, one interstitial kidney injury, and one Type 1 diabetes plus adrenal insufficiency, and in six patients (9.3%) due to patient offer.

Propensity Score-Matched Analysis for Second-Line Therapy

Table 1 summarizes patient characteristics of 169 study patients and compares the two groups based on second-line therapy before and after PSM. Several covariates, including age, the rate of surgical removal of primary organ, cisplatin eligibility, and first-line chemotherapy regimen had significant differences between the two groups prior to PSM. Adjustment using PSM resulted in a closely balanced distribution of baseline covariates between the two groups.

During the follow-up period, mortality occurred in 62 (83%) out of 75 second-line chemotherapy patients and 44 (47%) out of 94 second-line pembrolizumab patients. Median follow-up time for censored patients was 15 months. Although the survival curve comparison showed marginal differences ($P = 0.06$), the PSM-adjusted comparison showed significant improvement in the prognosis with second-line pembrolizumab use ($P = 0.01$; Figure 2). The OS benefit with the advent of pembrolizumab was 8 months (18 months vs 26 months).

IPTW-Adjusted Comparison of Survival for Second-Line Therapy

Given that only a relatively small number of patients in our cohort could influence the results of the analysis, IPTW was applied to adjust for patient characteristics between the two groups and to decrease the influence of possible confounding factors (Table 1, right rows). All weighted baseline characteristics included in the IPTW model were closely balanced between the two groups. Univariate and multivariate Cox regression analyses for OS with the unadjusted cohort and the IPTW-adjusted model are shown in Table 2. The multivariable analysis using IPTW adjustment demonstrated that lymph node metastasis ($P = 0.001$), lung metastasis ($P = 0.013$), and bone metastasis ($P = 0.003$) were poor independent prognostic factors, whereas pembrolizumab use ($P = 0.021$) was a favorable independent prognostic factor. We compare the OS of patients with the prognostic factors which are identified in Cox regression analyses (Table 2) between second-line chemotherapy group and second-line pembrolizumab group. Survival analysis of unadjusted cohorts suggested that patients receiving surgical removal of primary origin, those with lymph node metastasis, and those with bone metastasis could obtain significant benefit from the use of pembrolizumab (Figure 3).

Lastly, to identify subgroups that responded differently to the treatment modalities, we performed a subgroup analysis using the IPTW-adjusted population (Figure 4) and the unweighted population (Supplementary Figure S1). Figure 4 demonstrates that pembrolizumab use is associated with survival benefits over chemotherapy use in all subgroups examined, including young patients (age <70 years), those who received radical surgery, and those without visceral metastasis. In an analysis that considered the first-line chemotherapy regimens, the benefit of pembrolizumab over chemotherapy in patients treated with gemcitabine plus cisplatin combination chemotherapy (HR 0.67, 95% CI 0.41–1.09) appeared to have better outcomes than those treated with gemcitabine plus carboplatin combination chemotherapy (HR 0.95, 95% CI 0.47–2.02). Our finding suggested that the first-line gemcitabine plus cisplatin group were likely to benefit from second-line pembrolizumab as compared to the first-line gemcitabine plus carboplatin group.

Discussion

Our analysis clearly demonstrated a significant improvement in prognosis after the advent of ICIs for patients with aUC. Notably, some patients have a long survival benefit through a durable response to ICI therapy. Five-year follow-up data of the KEYNOTE-045 trial (data cutoff: 62.9 months) were updated and presented at the 2021 American Society of Clinical Oncology Annual Meeting.¹⁵ The median duration of response for responders was significantly longer for pembrolizumab (29.7 months) use than for chemotherapy (4.4 months) use. The strong association between tumor response and prolonged survival is one of the biggest advantages of ICI therapy, which is rarely observed in

Table 1 Characteristics of 169 Study Patients and a Comparison of the Second-Line Treatment: Unadjusted Population, PSM Population, and IPTW Population

Variables	Total	Unadjusted Population				PSM Population				IPTW Population		
		Second-Line Chemotherapy	Second-Line Pembrolizumab	P value	SMD	Second-Line Chemotherapy	Second-Line Pembrolizumab	P value	SMD	Second-Line Chemotherapy	Second-Line Pembrolizumab	SMD
N	169	75	94	–	–	59	59	–	–	75	94	–
Age (years old), median (IQR)	67.0 (63.0–74.0)	68.0 (63.0–75.0)	66.0 (62.0–72.0)	0.075	0.33	66.0 (62.5–73.5)	66.0 (63.0–72.5)	0.95	0.02	68.4	68.1	0.037
Sex				0.12	0.25			1.00	0.04			0.014
Male	125 (74%)	60 (80%)	65 (69%)			44 (74.6%)	43 (72.9%)			73%	73%	
Female	44 (26%)	15 (20%)	29 (31%)			15 (25.4%)	16 (27.1%)			27%	27%	
ECOG-PS				0.23	0.22			1.00	< 0.001			0.053
0–1	163 (96%)	74 (99%)	89 (95%)			58 (98.3%)	58 (98.3%)			97%	97%	
≥ 2	6 (3.6%)	1 (1.3%)	5 (5.3%)			1 (1.7%)	1 (1.7%)			2.70%	3.60%	
Primary site				0.88	0.03			1.00	0.03			0.056
Bladder	78 (46%)	34 (45%)	44 (47%)			27 (45.8%)	26 (44.1%)			42%	45%	
Upper urinary tract	91 (54%)	41 (55%)	50 (53%)			32 (54.2%)	33 (55.9%)			58%	55%	
Surgical removal of primary organ [†]				0.75	0.074			0.70	0.11			0.011
Yes	107 (63%)	46 (61%)	61 (65%)			37 (62.7%)	40 (67.8%)			61%	63%	
No	62 (37%)	29 (39%)	33 (35%)			22 (37.3%)	19 (32.2%)			39%	37%	
Cisplatin eligibility[#]				0.002	0.5			0.54	0.15			0.04
Cisplatin–fit	49 (29%)	31 (41%)	18 (19%)			18 (30.5%)	14 (23.7%)			29%	27%	
Cisplatin–unfit	120 (71%)	44 (59%)	76 (81%)			41 (69.5%)	45 (76.3%)			71%	73%	
Metastatic sites or target lesions^{##}												
Local lesion associated with primary tumor	78 (46%)	32 (43%)	46 (49%)	0.44	0.13	27 (45.8%)	26 (44.1%)	1.00	0.03	44%	46%	0.04
Lymph nodes	44 (26%)	18 (24%)	26 (28%)	0.60	0.084	16 (27.1%)	16 (27.1%)	1.00	<0.001	26%	27%	0.022

(Continued)

Table I (Continued).

Variables	Total	Unadjusted Population				PSM Population				IPTW Population		
		Second-Line Chemotherapy	Second-Line Pembrolizumab	P value	SMD	Second-Line Chemotherapy	Second-Line Pembrolizumab	P value	SMD	Second-Line Chemotherapy	Second-Line Pembrolizumab	SMD
Lung	53 (31%)	25 (33%)	28 (30%)	0.74	0.076	20 (33.9%)	17 (28.8%)	0.69	0.11	31%	32%	0.013
Liver	18 (11%)	10 (13%)	8 (8.5%)	0.33	0.16	3 (5.1%)	6 (10.2%)	0.49	0.19	10%	9.40%	0.004
Bone	24 (14%)	10 (13%)	14 (15%)	0.83	0.045	6 (10.2%)	8 (13.6%)	0.78	0.11	13%	14%	0.02
First-line chemotherapy regimen				0.09	0.35			0.96	0.08			0.08
GC	103 (61%)	52 (69%)	51 (54%)			38 (64.4%)	36 (61.0%)			63%	59%	
GCarbo	53 (31%)	17 (23%)	36 (38%)			16 (27.1%)	18 (30.5%)			29%	32%	
Others	13 (7.7%)	6 (8.0%) ^{¶¶}	7 (7.4%) ^{¶¶¶}			5 (8.5%)	5 (8.5%)			2.50%	3.10%	

Notes: [#]The Galsky criteria; ¹⁰ ^{###}Many patients had multiple metastatic sites; [¶]Other regimens consisted of 3 gemcitabine plus paclitaxel, 1 gemcitabine monotherapy, 1 gemcitabine plus nedaplatin, and 1 carboplatin plus paclitaxel; ^{¶¶}Other regimens consisted of 5 gemcitabine plus paclitaxel, 1 gemcitabine monotherapy, and 1 carboplatin plus paclitaxel; ^{¶¶¶}Radical cystectomy for bladder cancer or radical nephroureterectomy for upper urinary tract cancer.

Abbreviations: PSM, propensity score matching; IPTW, Inverse probability of treatment weighting; SMD, Standardized mean difference; IQR, interquartile range; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; GC, gemcitabine plus cisplatin combination chemotherapy; GCarbo, gemcitabine plus carboplatin combination chemotherapy.

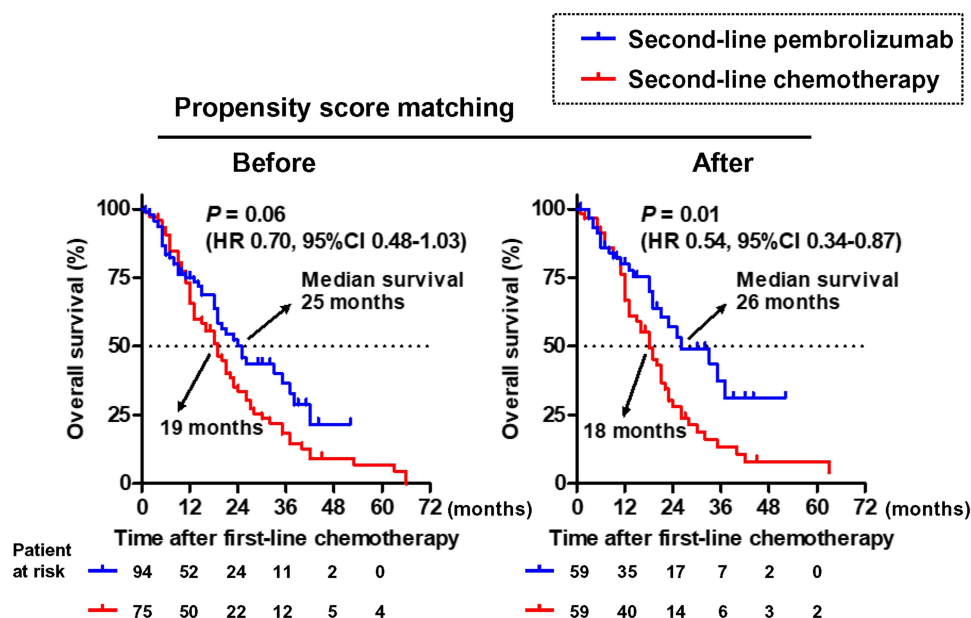


Figure 2 Overall survival curves for second-line therapy. Overall survival curves from the date of first-line chemotherapy initiation are plotted for patients with aUC who received first-line chemotherapy followed by second-line chemotherapy (red) or pembrolizumab (blue). Survival rates were compared between the second-line chemotherapy (n = 74) and pembrolizumab (n = 94) groups before propensity score matching (left) and between the adjusted second-line chemotherapy group (n = 59) and adjusted pembrolizumab (n = 75) groups after propensity score matching (right). The median survival duration is shown in the figures. The number of patients at risk over time is shown in the bottom.

Abbreviations: HR, hazard ratio; CI, confidence interval.

conventional cytotoxic chemotherapy. Although over 4 years have passed since the approval of the use of ICIs, data regarding the superiority of second-line pembrolizumab over conventional chemotherapy in the real-world setting are still lacking.

In this study, we used the date of first-line chemotherapy initiation as the starting point for the survival analysis. Most previous studies have analyzed and reported survival rates from the date of ICI initiation.^{2-6,16} The pivotal trial, KEYNOTE-045, reported that median OS in the pembrolizumab group was 10.3 months as compared to 7.4 months in the chemotherapy group ($P = 0.002$), resulting in a 2.9-month survival benefit from the initiation of pembrolizumab or investigator's choice of chemotherapy. A recent report from the Japan Urological Oncology Group demonstrated a positive correlation between response to pembrolizumab and response to chemotherapy,¹⁶ implying that time-to-treatment failure of first-line chemotherapy is closely associated with that of second-line ICI therapy. Therefore, to discuss the real survival benefit from the advent of ICI, we need to evaluate survival from the initiation of first-line chemotherapy, not from the initiation of second-line therapy. Several reports have compared survival from first-line chemotherapy initiation between the chemotherapy-ICI sequence and chemotherapy-chemotherapy sequence. A retrospective study reported by Doshi et al using an electronic health record system suggested that patients who used second-line ICI had an improvement in OS compared to those who received the chemotherapy-ICI sequence with a median OS of 19.2 months versus 11.9 months; however, this was not statistically significant ($P = 0.13$), which may be attributed to the limited sample size.⁸ In addition, the authors did not perform background adjustments, such as PSM and IPTW. According to our background-adjusted analysis, the median OS of the chemotherapy-ICI sequence and the chemotherapy-chemotherapy sequence were 26 and 18 months, respectively. Thus, the prolonged survival by the advent of ICIs in the study reported by Doshi et al and our study are 7.3 months and 8 months (Figure 2, right), respectively. Given that the prognosis of aUC even with chemotherapy was extremely poor, with a median overall survival of 12–15 months,¹ an 8-month prolongation in the era of ICIs is considered a dramatic improvement.

Informing an appropriate patient population for treatment selection remains challenging. It is clinically important to identify patients who benefited from second-line pembrolizumab rather than from second-line chemotherapy and those who did not. Subgroup analysis is the assessment of treatment effects based on certain patient characteristics out

Table 2 Cox Proportional Hazard Regression Models for Overall Survival: IPTW Analysis

Variables	Unweighted						IPTW Models		
	Univariable			Multivariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age, years									
< 70	1								
≥ 70	1.07	0.73–1.58	0.72						
Sex									
Female	1								
Male	0.99	0.62–1.60	0.99						
ECOG-PS									
0–1	1								
≥ 2	1.11	0.35–3.51	0.86						
Primary site									
Bladder	1								
Upper urinary tract	0.97	0.66–1.43	0.88						
Surgical removal of primary organ [†]									
No	1			1			1		
Yes	0.65	0.44–0.95	0.026	0.68	0.46–1.02	0.06	0.68	0.45–1.01	0.053
Cisplatin eligibility [#]									
Cisplatin–fit	1								
Cisplatin–unfit	1.1	0.72–1.68	0.66						
Local lesion associated with primary tumor ^{##}									
No	1								
Yes	1.37	0.94–2.02	0.11						
Lymph nodes ^{##}									
No	1			1			1		
Yes	1.45	0.95–2.21	0.08	1.89	1.21–2.94	0.005	1.84	1.28–2.64	0.001
Lung ^{##}									
No	1			1			1		
Yes	1.78	1.19–2.65	0.005	1.83	1.21–2.77	0.004	1.69	1.12–2.56	0.013
Liver ^{##}									
No	1			1			1		
Yes	1.79	1.01–3.16	0.046	1.58	0.89–2.83	0.12	1.73	0.94–3.17	0.08
Bone ^{##}									
No	1			1			1		
Yes	2.19	1.29–3.73	0.004	2.24	1.29–3.88	0.004	2.42	1.50–3.92	0.003

(Continued)

Table 2 (Continued).

Variables	Unweighted						IPTW Models		
	Univariable			Multivariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
First-line chemotherapy									
GC	I								
Gcarbo	0.83	0.54–1.28	0.39						
Others	0.78	0.34–1.81	0.57						
Second-line therapy									
Cytotoxic chemotherapy	I			I			I		
Pembrolizumab	0.7	0.47–1.03	0.07	0.67	0.45–0.99	0.049	0.63	0.42–0.94	0.021

Notes: †Radical cystectomy for bladder cancer or radical nephroureterectomy for upper urinary tract cancer; #The Galsky criteria;¹⁰ ##Many patients had multiple metastatic sites.

Abbreviations: IPTW, Inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; GC, gemcitabine plus cisplatin combination chemotherapy; GCarbo, gemcitabine plus carboplatin combination chemotherapy.

of the total study population and is essential for the interpretation of oncology trials.¹⁷ Here, we performed a valid subgroup analysis with an IPTW-adjusted model to identify subgroups that benefited from the treatment. As expected, second-line pembrolizumab was associated with a greater survival benefit than that with second-line chemotherapy in all subgroups. Notably, patients who underwent surgical removal of the primary organ with malignancy obtained a significant survival benefit from pembrolizumab use rather than with conventional chemotherapy (Figure 4). A previous report has demonstrated that lung metastatic lesions are most likely to respond to pembrolizumab, whereas primary organ lesions are least likely to respond.¹⁸ Based on this evidence, a cytoreductive removal of primary organs in patients with aUC with well-controlled metastatic lesions may have a good overall response to pembrolizumab. The analysis of OS in key subgroups in the KEYNOTE-045 trial revealed that the benefit of pembrolizumab over chemotherapy was noted in patients without liver metastasis and in those who had tumor programmed cell death ligand 1 combined positive score of more than 1%. Similarly, our analysis showed that patients without liver metastasis were more likely to benefit from pembrolizumab compared to chemotherapy ($P = 0.06$, HR 0.66). We examined additional subgroups regarding metastatic lesions, demonstrating that patients without lung metastasis ($P = 0.02$, HR 0.55) and those without bone metastasis ($P = 0.08$, HR 0.67). The subgroup analysis suggested that ICIs should not be restricted based on patient characteristics. However, an appropriate interpretation of subgroup analyses, for example, statistical power, is vital to determine the population who would benefit most from these drugs.¹⁷

We are currently expecting frontier progress in multi-drug therapy to overcome tumor resistance and to improve the outcome of patients with aUC. For example, inhibiting WD Repeat Domain 5 (WDR5) by a small-molecule compound, OICR-9429, is potential therapeutic approach for bladder cancer cell. Expression of WDR5 was upregulated in bladder UC and was associated with high tumor grade, metastasis status, histologic subtype, and molecular subtype.¹⁹ Moreover, high expression level of WDR5 was linked with poor survival of bladder UC. OICR-9429 enhances chemosensitivity and PD-L1 expression in bladder UC cells, suggesting that the response to platinum-based chemotherapy or ICIs could be elevated by OICR-9429. Further basic and clinical studies are required to validate the real potential and benefit of combination therapies. Another issue to be discussed is future direction of application for tumor evaluation at UC. Evaluation using tumor tissue is limited because fixation time and condition vary among institutes and the gap between tissue collection and initiation of treatment. Thus, real-time liquid biopsy would be a more reliable application for patients with aUC. With the development of urine non-invasive diagnostic technology, the effective evaluation of chemotherapy combined with immunotherapy will be judged by the urine assays.^{20,21}

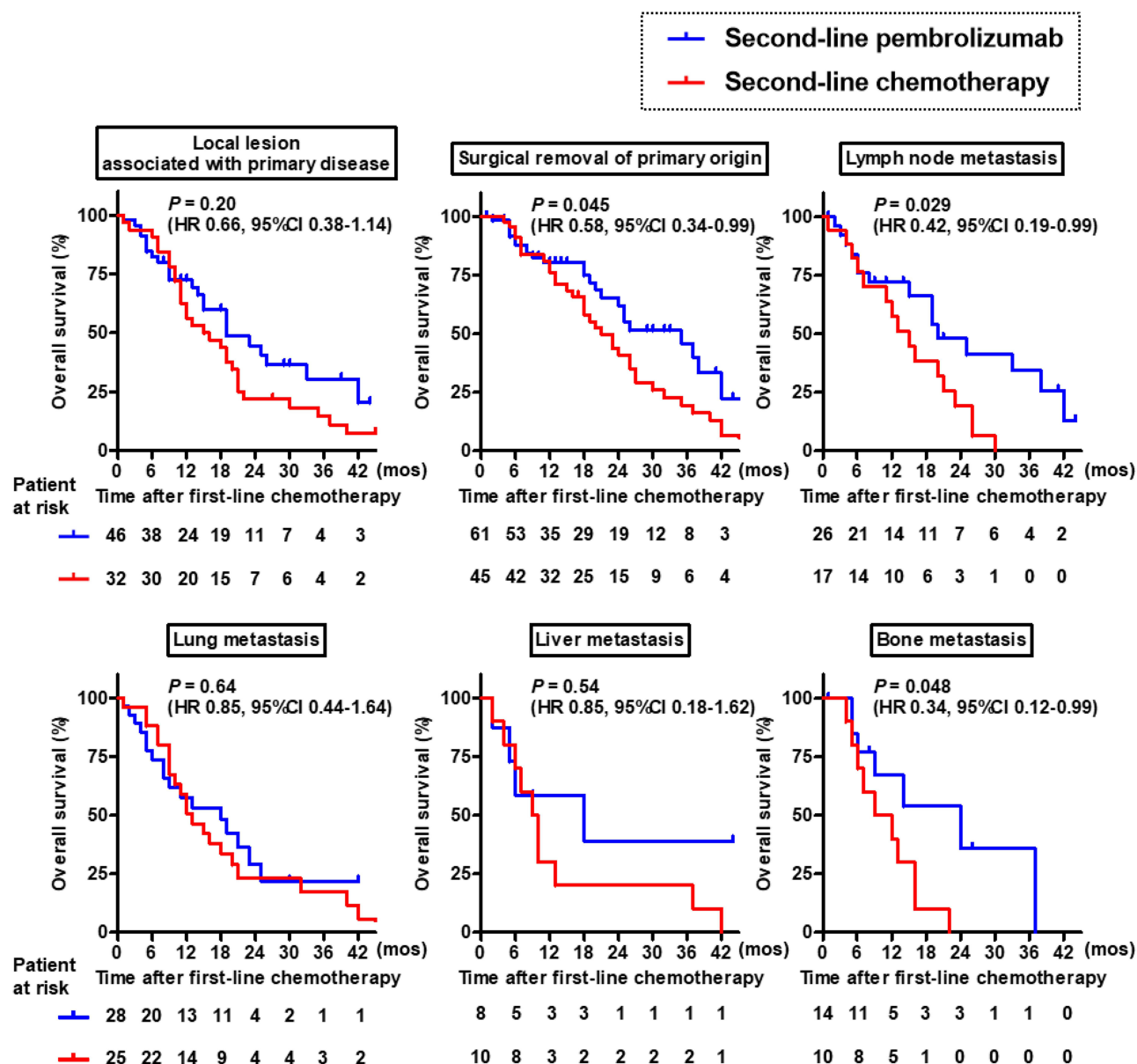


Figure 3 Overall survival curves for second-line therapy in patients with the prognostic factors. Overall survival curves from the date of first-line chemotherapy initiation are plotted for patients with the prognostic factors which are identified in the Cox regression analyses. Survival rates were compared between the second-line chemotherapy (red line) and pembrolizumab (blue line) groups by Log rank test. The number of patients at risk over time is shown in the bottom.

Abbreviations: HR, hazard ratio; CI, confidence interval.

This study has several limitations. First, its retrospective nature has an inherent potential for selection bias; furthermore, the decision criteria for first-line chemotherapy, timing of changing the treatment and interval of radiographic evaluation were dependent on the institutional protocol and physician's discretion. The cohort was derived from multiple institutions, which may have introduced inconsistencies in surgical skills, clinical interpretations, and pathological diagnoses. Moreover, we had enrolled patients diagnosed between 2008 and 2019. The treatment strategy, modality, and surgical skill change over time, which may influence outcomes. Second, the site and number of unresectable or metastatic lesions were consistent between the first-line chemotherapy groups. Third, we did not consider a history of radiotherapy, irrespective of the intention to undergo radical treatment or receive palliative treatment; a possible abscopal effect or a positive impact on immunogenic cell death from radiotherapy has also been reported.^{22–24} Fourth, this study did not include the analysis of molecular biomarkers, such as PD-1 or PD-L1 immunostaining and other possible

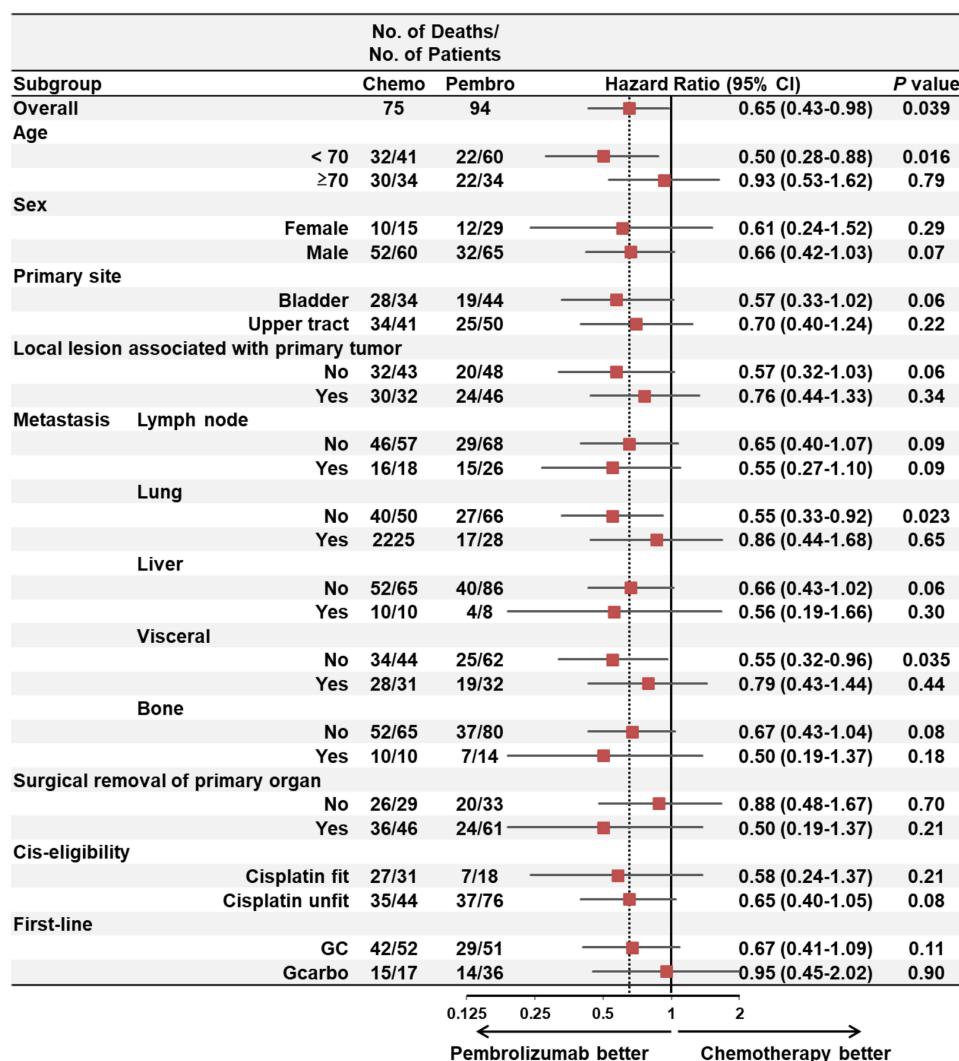


Figure 4 An analysis of overall survival in key subgroups in inverse probability of treatment weighting (IPTW) population. The dashed line indicates the rate of overall survival in the entire population.

Abbreviations: HR, hazard ratio; CI, confidence interval; GC, gemcitabine plus cisplatin combination chemotherapy; GCarbo, gemcitabine plus carboplatin combination chemotherapy.

molecular biology-based factors. Further research is required to strengthen our findings and confirm the benefits of second-line pembrolizumab in the real-world setting. Fifth, the statistical power may be limited because of the number of patients. Finally, the analysis did not include any patients treated with maintenance avelumab followed by first-line chemotherapy, which has been one of the standard treatments as of 2021.

Conclusion

Recently, we have experienced dramatic changes in the clinical management of UC and significantly improved the prognosis of patients with aUC, in the era of ICI. While further evidence and advancements from ongoing clinical trials of ICI therapy emerge, clinicians need to update contemporary unmet medical needs and consider how the upcoming evidence manifests in the real-world setting. We believe that our findings can serve as a benchmark for future studies.

Abbreviations

aUC, advanced, unresectable and metastatic urothelial carcinoma; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; IPTW, inverse probability of treatment weighting; OS, overall survival; PSM, propensity score matching; SMD, standardized mean difference.

Acknowledgment

The clinicopathological statistics are based on the results of contributions from a number of institutions listed as follows: Nara Medical University Hospital, Kindai University Nara Hospital, Nara City Hospital, Nara Prefecture Seiwa Medical Center, Osaka Kaisei Hospital, Yamatotakada Municipal Hospital, Nara Prefecture General Medical Center, Koseikai Takai Hospital, Tane General Hospital, Matsusaka Chuo General Hospital, Okanami general Hospital, Saiseikai Chuwa Hospital, Hoshigaoka Medical Center, JCHO Yamato Koriyama Hospital, Osaka Gyoumeikan Hospital. We thank the contributions of many urologists who are not listed as co-authors.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

References

- Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108. doi:10.3322/caac.21262
- Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015–1026. doi:10.1056/NEJMoa1613683
- Tamura D, Jinnouchi N, Abe M, et al. Prognostic outcomes and safety in patients treated with pembrolizumab for advanced urothelial carcinoma: experience in real-world clinical practice. *Int J Clin Oncol*. 2020;25(5):899–905. doi:10.1007/s10147-019-01613-9
- Kobayashi K, Suzuki K, Hiraide M, et al. Association of immune-related adverse events with pembrolizumab efficacy in the treatment of advanced urothelial carcinoma. *Oncology*. 2020;98(4):237–242. doi:10.1159/000505340
- Patterson K, Prabhu V, Xu R, et al. Cost-effectiveness of pembrolizumab for patients with advanced, unresectable, or metastatic urothelial cancer ineligible for cisplatin-based therapy. *Eur Urol Oncol*. 2019;2(5):565–571. doi:10.1016/j.euo.2018.09.009
- Narita T, Hatakeyama S, Numakura K, et al. Comparison of pembrolizumab with conventional chemotherapy after first-line platinum-based chemotherapy for advanced urothelial carcinoma in real-world practice: a multicenter retrospective study. *Int J Urol*. 2021;28(9):899–905. doi:10.1111/iju.14601
- Narayanan S, Harshman LC, Srinivas S. Second-line therapies in metastatic urothelial carcinoma. *Hematol Oncol Clin North Am*. 2015;29(2):341–359. doi:10.1016/j.hoc.2014.10.007
- Doshi GK, Bhanegaonkar A, Kearney M, et al. Treatment sequencing patterns in patients with metastatic urothelial cancer treated in the community practice setting in the United States: SPEAR-bladder (study informing treatment pathway dEcision in bladder cAnceR). *Clinicoecon Outcomes Res*. 2020;12:645–656. doi:10.2147/CEOR.S264942
- Vellinga A, Cormican M, Hanahoe B, Bennett K, Murphy AW. Opt-out as an acceptable method of obtaining consent in medical research: a short report. *BMC Med Res Methodol*. 2011;11(1):40. doi:10.1186/1471-2288-11-40
- Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *Lancet Oncol*. 2011;12(3):211–214. doi:10.1016/S1470-2045(10)70275-8
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41. doi:10.1159/000180580
- Zhang Z, Kim HJ, Lonjon G, Zhu Y; written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching. *Ann Transl Med*. 2019;7(1):16. doi:10.21037/atm.2018.12.10
- Miyake M, Iida K, Nishimura N, et al. Non-maintenance intravesical Bacillus Calmette-Guérin induction therapy with eight doses in patients with high- or highest-risk non-muscle invasive bladder cancer: a retrospective non-randomized comparative study. *BMC Cancer*. 2021;21(1):266. doi:10.1186/s12885-021-07966-7
- Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661–3679. doi:10.1002/sim.6607
- Bellmunt J, Necchi A, de Wit R, et al. Pembrolizumab (pembro) versus investigator's choice of paclitaxel, docetaxel, or vinflunine in recurrent, advanced urothelial cancer (UC): 5-year follow-up from the Phase 3 KEYNOTE-045 trial. *J Clin Oncol*. 2021;39(15 suppl):4532. doi:10.1200/JCO.2021.39.15_suppl.4532
- Kato M, Kobayashi T, Matsui Y, et al. Impact of the objective response to and number of cycles of platinum-based first-line chemotherapy for metastatic urothelial carcinoma on overall survival of patients treated with pembrolizumab. *Int J Urol*. 2021;28(12):1261–1267. doi:10.1111/iju.14686
- Amatya AK, Fiero MH, Bloomquist EW, et al. Subgroup analyses in oncology trials: regulatory considerations and case examples. *Clin Cancer Res*. 2021;27(21):5753–5756. doi:10.1158/1078-0432.CCR-20-4912

18. Furubayashi N, Negishi T, Sakamoto N, et al. Organ-specific tumor response to pembrolizumab in advanced urothelial carcinoma after platinum-based chemotherapy. *Onco Targets Ther.* **2021**;14:1981–1988. doi:10.2147/OTT.S299724
19. Zhang J, Zhou Q, Xie K, et al. Targeting WD repeat domain 5 enhances chemosensitivity and inhibits proliferation and programmed death-ligand 1 expression in bladder cancer. *J Exp Clin Cancer Res.* **2021**;40(1):203. doi:10.1186/s13046-021-01989-5
20. Chen X, Zhang J, Ruan W, et al. Urine DNA methylation assay enables early detection and recurrence monitoring for bladder cancer. *J Clin Invest.* **2020**;130(12):6278–6289. doi:10.1172/JCI139597
21. Miyake M, Owari T, Hori S, Nakai Y, Fujimoto K. Emerging biomarkers for the diagnosis and monitoring of urothelial carcinoma. *Res Rep Urol.* **2018**;10:251–261. doi:10.2147/RRU.S173027
22. Bonfante G, Fantinel E, Masini C, Bergamaschi F, Micali S, Rocco B. Exceptional response to immunotherapy in association with radiotherapy in patient with breast metastasis from urothelial carcinoma: a case report. *Urol Case Rep.* **2020**;34:101444. doi:10.1016/j.eucr.2020.101444
23. Ishiyama Y, Takagi T, Yoshida K, et al. Possible abscopal effect in urothelial carcinoma of the upper urinary tract after treatment with immune checkpoint inhibitors. *IJU Case Rep.* **2019**;3(1):25–27. doi:10.1002/iju5.12133
24. Fukushima H, Kijima T, Fukuda S, et al. Impact of radiotherapy to the primary tumor on the efficacy of pembrolizumab for patients with advanced urothelial cancer: a preliminary study. *Cancer Med.* **2020**;9(22):8355–8363. doi:10.1002/cam4.3445

Cancer Management and Research

Dovepress

Publish your work in this journal

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/cancer-management-and-research-journal>