

Optimal Time Point for Evaluation of Response to Pembrolizumab Treatment in Japanese Patients With Metastatic Urothelial Carcinoma

TERUO INAMOTO¹, RYO SATO², YUTO MATSUSHITA², TAIZO UCHIMOTO¹, KO NAKAMURA¹, KAZUMASA KOMURA¹, KAZUKI NISHIMURA¹, YUSUKE YANO¹, KYOSUKE NISHIO¹, SHOKO KINOSHITA¹, TATSUO FUKUSHIMA¹, TOMOHISA MATSUNAGA¹, KEITA NAKAMORI¹, TAKESHI TSUTSUMI¹, TAKUYA TSUJINO¹, HIROFUMI UEHARA¹, KIYOSHI TAKAHARA³, HIDEAKI MIYAKE² and HARUHITO AZUMA¹

¹Department of Urology, Osaka Medical and Pharmaceutical University, Takatsuki, Japan;

²Department of Urology, Hamamatsu University School of Medicine, Hamamatsu, Japan;

³Department of Urology, Fujita-Health University School of Medicine, Toyoake, Japan

Abstract. *Background/Aim:* The duration of pembrolizumab use in actual daily practice might be shorter than that in clinical trials because termination of pembrolizumab therapy is at the discretion of the physician. We retrospectively reviewed the response to pembrolizumab in Japanese patients with metastatic urothelial carcinoma (mUC) in relation to the time to response (TTR). *Patients and Methods:* The records of 165 patients treated with pembrolizumab for mUC were retrospectively analyzed. Response was evaluated at 2, 4, 6 and 8 months. TTR along with time to best response were analyzed. Phase II-III clinical trials were also reviewed to compare the TTR and time to best overall response. *Results:* The median patient age was 70 years. The objective response rate in the total cohort was 27.1% (42 out of 155 patients). Median TTR was 2.4 months and the time to best response was 3.1 months. Radiological evaluation at each time point significantly predicted overall survival (OS). Considering the evaluation

of response at 2, 4, 6 and 8 months, the response at later time points tended to predict OS better. Multivariate analysis showed that the evaluation of response at 8 months (hazard ratio=1.91, 95% confidence interval=1.16-3.16 months; $p<0.01$) and best response during the treatment (hazard ratio=1.69, 95% confidence interval=1.17-2.44; $p<0.01$) independently predicted improved OS. *Conclusion:* Given that response when evaluated at a later point during pembrolizumab treatment more favorably reflected improved survival than when assessed earlier, physicians may be encouraged to wait until at least the termination of pembrolizumab treatment to determine the best response.

Pembrolizumab was initially the only immunotherapeutic agent to have been granted regular approval by the U.S. Food and Drug Administration for treatment patients with locally advanced or metastatic urothelial carcinoma (mUC) who are not eligible to receive platinum-based therapies or whose disease becomes worse within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy. The approval was made based on the results of the phase III KEYNOTE-045 clinical trial published in the New England Journal of Medicine (1). Pembrolizumab led to improved median overall survival (OS) compared with chemotherapy of the investigator's choice. Median OS was 10.3 months among those who received pembrolizumab compared with 7.4 months among those in the control arm (1). Moreover, a larger proportion (21%) of patients who received pembrolizumab exhibited partial (PR) or complete response (CR) compared with those who received chemotherapy (11%). The approval of pembrolizumab for UC brings to five the number of immunotherapeutics targeting the immunological checkpoint system that are approved for

Correspondence to: Teruo Inamoto, MD, Ph.D., Department of Urology, Osaka Medical and Pharmaceutical University, 2-7 Daigaku-machi, Takatsuki City, Osaka 569-8686, Japan. Tel: +81 726831221, Fax: +81 726846546, e-mail: teruo.inamoto@ompu.ac.jp

Key Words: Response, pembrolizumab, prognosis, therapy switch.

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Table I. Patient background characteristics and pre-existing sites of metastasis associated with urothelial carcinoma (UC).

Characteristic	Subgroup	Frequency (%)
Age	<70 Years	74 (44.8)
	≥70 Years	91 (55.2)
Original site	Bladder	106 (64.2)
	UTUC	59 (35.8)
Histological type	Pure UC	157 (95.2)
	Non-pure UC	8 (4.8)
ECOG PS	0-1	149 (90.3)
	≥2	16 (9.7)
Brain metastases	No	162 (98.2)
	Yes	3 (1.8)
Bone metastases	No	116 (70.3)
	Yes	49 (29.7)
Lung metastases	No	100 (60.6)
	Yes	65 (39.4)
Liver metastases	No	134 (81.2)
	Yes	31 (18.8)
Visceral metastases	No	74 (44.8)
	Yes	91 (55.2)
LNM outside the pelvic cavity	No	101 (61.2)
	Yes	64 (38.8)
Pelvic LNM	No	105 (63.6)
	Yes	60 (36.4)
irAE during the treatment	Grade 0-1	144 (87.3)
	Grade ≥2	21 (12.7)

ECOG PS: Eastern Cooperative Oncology Group performance status; irAE: immune-related adverse events; LNM: lymph node metastasis; UTUC: upper tract urothelial carcinoma.

treating patients with this type of cancer and 10 additional types (1). Another immunotherapeutic, atezolizumab, did not significantly improve OS for patients with mUC whose disease progressed after treatment with a platinum-based therapy compared with the chemotherapy arm in the phase III IMvigor211 trial (2). To date, four checkpoint inhibitors, atezolizumab (Tencentriq®), pembrolizumab (Keytruda®), nivolumab (Opdivo®) and avelumab (Bavencio®), have been approved for mUC, and increasing trial data have changed the treatment landscape for patients with mUC. Atezolizumab in second-line was voluntarily withdrawn in the U.S. market for the treatment of patients with mUC who had previously received platinum-based chemotherapy, given that it did not meet the primary endpoint of improving OS in the second-line treatment of patients with mUC who had high expression of programmed cell death ligand-1 (PD-L1) in the phase III IMvigor 211 trial (2), although it is still a treatment of choice for patients who are ineligible for cisplatin use due to frailty or comorbidities and whose tumors express PD-L1. The potential use of atezolizumab as initial treatment is still open to patients with treatment-naïve mUC until the further follow-up of OS in the phase III IMvigor130 trial that tests the addition of atezolizumab to

gemcitabine- and platinum-based chemotherapy (3). Durvalumab was also withdrawn from second-line use, given that the phase 3 DANUBE trial showed it lacked an OS benefit over platinum-based chemotherapy, whether as a single agent or in combination with the cytotoxic T-lymphocyte-associated antigen 4 inhibitor tremelimumab for patients with mUC who were either treatment-naïve or refractory to platinum-based therapy (4). Nivolumab in combination with ipilimumab is being investigated as first-line therapy *versus* standard of care in an ongoing phase III NCT03036098 trial (5).

Available agents for platinum-ineligible patients include pembrolizumab or atezolizumab in initial therapy. For the treatment approach after progression on platinum-based regimens, options include pembrolizumab, nivolumab, and avelumab. For patients whose disease does not progress on initial platinum-based chemotherapy, avelumab is an option as a maintenance immunotherapy.

Pembrolizumab treatment usually continues until unacceptable toxicity, confirmed disease progression, patient's or investigator's decision to withdraw, or completion of treatment. While the treatment landscape for mUC has drastically changed, an unmet need remains for appropriate timing of the switch to immunotherapy in patients with mUC whose disease progresses after platinum-based chemotherapy. This type of drug will continue to play a role for these patients who have few other treatment options because of ineligibility for chemotherapy and an effort to establish fine-tuning of the immunotherapy switch is an urgent need to help more patients living with mUC. With this in mind, in the present study, we tried to find the best time to assess response so as to predict survival accurately.

Patients and Methods

This was a retrospective study of data from two academic centers - Osaka Medical and Pharmaceutical University (Osaka, Japan) and the Hamamatsu University School of Medicine (Hamamatsu, Japan). The study was approved by the Institutional Review Board of the principal hospital of Osaka Medical and Pharmaceutical University (approval number: RIN-750-2571, 2022), and the present study followed the principles of the World Medical Association Declaration of Helsinki. The dataset includes patient survival data, clinicopathological background of patients with mUC (upper tract UC/UC of bladder) following cancer progression using platinum-based combined regimens between January 2018 and December 2020. Patients were required to have at least one radiologically measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1, in which a lesion is considered measurable when ≥10 mm in diameter as assessed using calipers (6). Patients who lacked measurable lesion information at the initiation of pembrolizumab treatment (n=3) were excluded from the analysis. Those without tumor response information from pembrolizumab initiation (n=7) were also excluded. Consequently, data on 165 patients with mUC treated with pembrolizumab as monotherapy after chemotherapy were collected for the present study (Table I).

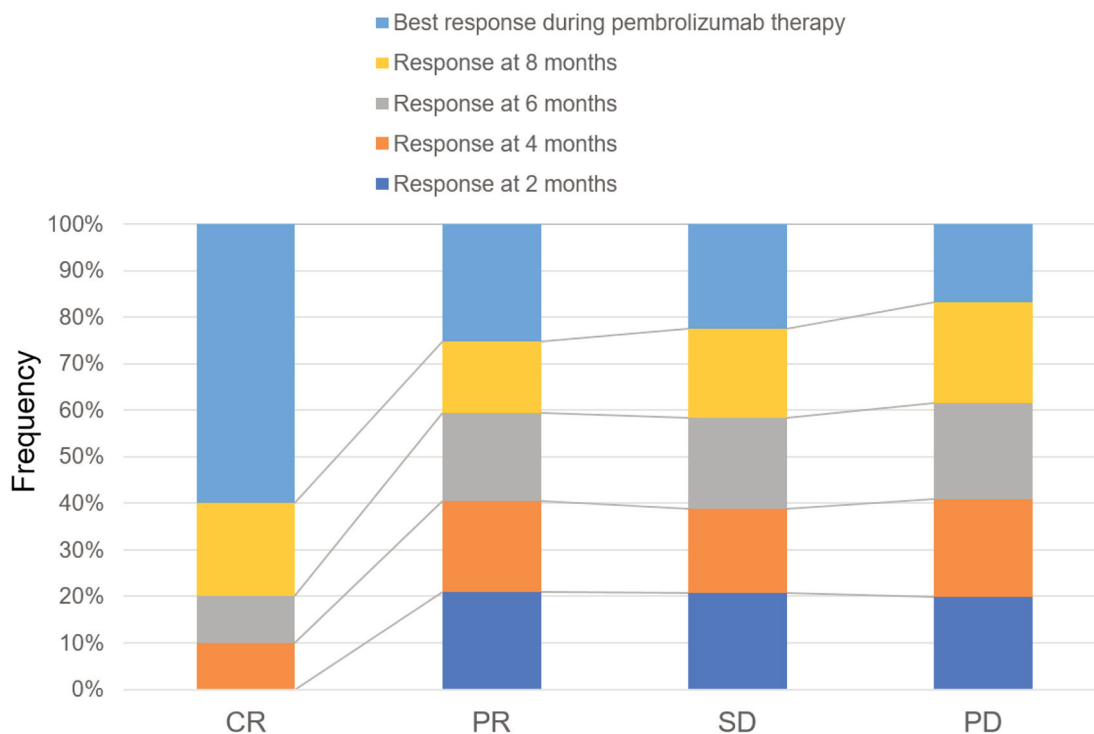


Figure 1. Tumor response to pembrolizumab according to Response Evaluation Criteria for Solid Tumors v1.1 (6) by imaging review. CR: Complete response; PR: partial response; PD: progressive disease; SD: stable disease.

Pembrolizumab was administered intravenously at 200 mg once every 3 weeks, or at 400 mg once every 6 weeks (7). Tumor response to pembrolizumab was evaluated according to RECIST version 1.1 (6) and iRECIST criteria (7) to allow the identification of atypical responses, which include pseudoprogression. Follow-up evaluation to identify tumor progression was carried out at 2, 4, 6 and 8 months. Additional evaluation using magnetic resonance imaging, or positron-emission tomography computed tomography (CT), and bone scintigraphy was further conducted when needed for the diagnosis of immune-confirmed disease progression (8). The disease response was defined as CR, progressive disease (PD), PR, or stable disease (SD). PD was defined as at least a 20% increase in the sum of diameters of target lesions. For the iRECIST evaluation, baseline CT served as a reference to determine the response to pembrolizumab treatment [iCR or iPR, and stable disease (iSD)]. The nadir (smallest sum of diameters to date) served as a reference to determine progression. Disease progression was defined as immune-unconfirmed progressive disease (iUPD) and immune-confirmed disease progression. Discontinuation of immunotherapy due to clinical progression or death was also considered as disease progression.

The primary endpoint of the study was the determination of OS, which included all deaths within the cohort under investigation, and did not separate those due to the disease of interest from those due to other causes. The secondary endpoint of the study was the comparison of response evaluated at 2, 4, 6 and 8 months to determine the best overall response after treatment. Objective overall response (ORR) was defined as the proportion of patients who achieved CR or PR according to RECIST version 1.1 (6) and iRECIST (7). Adverse events (AEs) were collected and reported

using the U.S. National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0 (9). Discontinuation of pembrolizumab treatment due to disease progression or a treatment-related AE was determined by the physician.

Clinical variables measured at the initiation of pembrolizumab included age, sex, smoking status, performance status, pathological type, stage, primary tumor location (upper tract vs. bladder), Eastern Cooperative Oncology Group performance status (0 vs. ≥ 1), pathological information at diagnosis (pure UC/non-pure UC), achievement of objective response at 2 months of pembrolizumab treatment, location of metastatic sites, and immune-related AEs (grades 0-1 vs. ≥ 2).

All statistical analyses were conducted using SPSS ver. 24 (IBM, Armonk, NY, USA). To assess the assumption of normality of continuous variables, the Kolmogorov-Smirnov test was performed. Student's *t*-test was performed to assess differences between two variables. The Kaplan-Meier method was used to estimate the survival rate and log-rank test was used to compare it among survival curves. The level of statistical significance was set at $p < 0.05$. Cox proportional hazards models were used to model survival time using covariate-adjusted hazard ratios (HRs).

Results

A total of 165 patients were enrolled in this study. The median age of the whole cohort was 70 years [95% confidence interval (CI)=69-72 years]. Baseline characteristics of the entire study population are summarized in Table I. The median

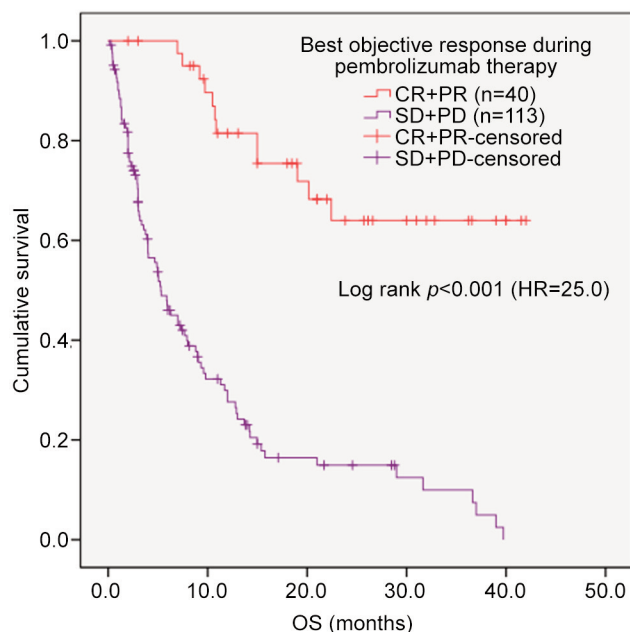


Figure 2. Kaplan-Meier estimate of the duration of overall survival (OS) in patients achieving partial (PR) or complete (CR) responses versus those with stable disease (SD) or disease progression (PD).

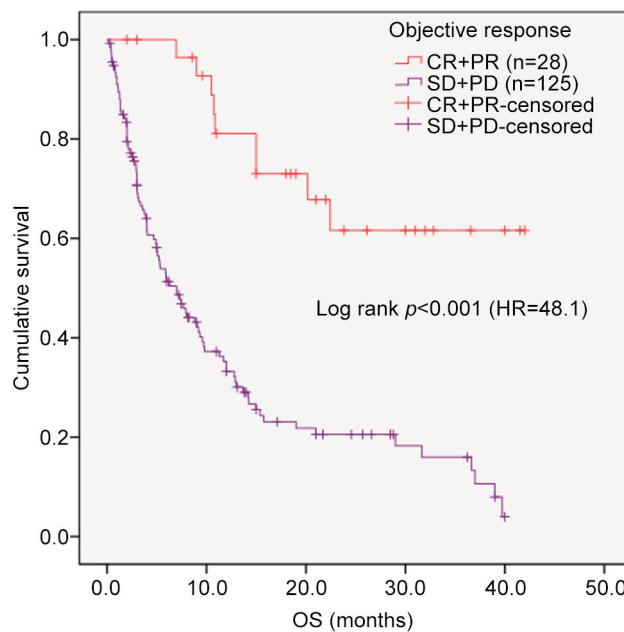


Figure 3. Kaplan-Meier estimate of the duration of overall survival (OS) according to response at 8 months of pembrolizumab therapy.

OS was 7.0 months (95% CI=5.1-9.0 months). Among these patients, the most common pathological type was pure UC (157 cases), followed by non-pure UC (8 cases).

Prospective trials showed the median TTR to pembrolizumab to be 2.1 months for mUC or high tumor-mutation burden solid cancer, and 2.8 months for clear-cell renal carcinoma (Table I). The present cohort exhibited a median TTR and time to best response of 2.4 (95% CI=0.7-10) and 3.1 (95% CI=1.8-10) months, respectively. At the time of the 2-month analysis, the results of response evaluation were as follows: 30 Patients had achieved PR, 37 had SD, and 98 had PD. The total ORR (defined as the proportion of patients with CR and PR) was 18.2% (Figure 1). At the 4-month analysis, one patient had achieved CR, 28 had PR, 32 had SD, and 104 had PD. The ORR was 17.6% at 4 months, 17.0% at 6 months, and 14.5% at 8 months. Median time to best response during pembrolizumab therapy was 3.1 (95% CI=1.8-10.0) months. Six patients achieved CR, 36 had PR, 40 had SD, 83 PD. One patient with PR at 2 months experienced CR 2 months later. One patient with SD at 2 months achieved CR in an additional 2 months, and CR at 8 months. A further four CR cases were detected after 8 months of pembrolizumab treatment (Figure 1).

The median OS for all treated patients was 10.1 (95% CI=5.1-9.0) months. Patients who achieved CR or PR at the median TTR of 2.4 months ultimately survived longer than those who exhibited SD or PD response at that time (mean estimated survival=31.9 vs. 10.4 months; log-rank $p < 0.001$,

HR=25.0; Figure 2). Moreover, patients who achieved CR or PR at 8 months of pembrolizumab treatment ultimately survived longer than those who exhibited SD or PD response at that time (mean estimated survival=31.4 vs. 12.5 months; log-rank $p < 0.001$, HR=58.1; Figure 3). The ORR at 4, 6 and 8 months of pembrolizumab treatment significantly predicted OS by Cox univariate analysis (Table II). By Cox multivariate analysis, best response and response at 8 months remained independent prognostic factors for prediction of OS (Table II).

Discussion

A clinical dilemma in the management of mUC managed by immuno-oncological drugs is when to stop the active drug. Pembrolizumab is PD1 receptor inhibitor whose efficacy has been demonstrated in several clinical trials. It has been approved for the treatment of mUC by the Food and Drug Administration.

The TTR to immunotherapeutics for UC range from 1.9 to 2.1 months, which seems a bit shorter compared to the 1.9-3.5 months for renal-cell carcinoma (Table III) (1-3, 10-20). In the KEYNOTE-045 trial, the mean TTR to pembrolizumab was 2.7 months versus 2.4 months in the control group. When focused on the KEYNOTE trial populations with a PD-L1 combined positive score (CPS) $\geq 10\%$ and CPS $\geq 1\%$, the TTR of the PD-L1-positive population tended to be little longer than that of the intention-to-treat (ITT) populations. The median TTR to

Table II. Univariate and multivariate Cox regression analyses for overall survival in the whole patient cohort.

Response	Univariate			Multivariate		
	HR	95% CI	p-Value	HR	95% CI	p-Value
At median TTR	2.366	1.755-3.19	<0.01			
At 4 months	2.994	2.12-4.23	<0.01			
At 6 months	3.139	2.205-4.468	<0.01			
At 8 months	3.154	2.146-4.636	<0.01	1.91	1.16-3.16	0.01
Best during pembrolizumab therapy	2.538	1.955-3.295	<0.01	1.69	1.17-2.44	0.01

CI: Confidence interval; HR: hazard ratio; TTR: time to response.

Table III. Phase III/III prospective trials with description of time to response (TTR) and overall response rate (ORR) for patients with urogenital malignancies.

Drug	Cancer type	Line	Trial name	Phase	Median TTR, months (95% CI)	ORR	Reference
Pembrolizumab	UC	2 nd	KEYNOTE-045	III	2.1 (1.4-6.3)	21.10%	Bellmunt <i>et al.</i> (1)
	UC	1 st	KEYNOTE-052	II	2.1 (1.3-9.0)	28.60%	Vukly <i>et al.</i> (8)
	(cisplatin-ineligible)						
	UC	1 st	KEYNOTE-057 (cohort A)	II	–	41.0%(CR)	Balar <i>et al.</i> (19)
	(high-risk NMIBC)						
	ccRCC	1 st	KEYNOTE-427 (cohort A)	II	2.8 (2.5-12.9)	36.40%	McDermott <i>et al.</i> (16)
Pembrolizumab	nccRCC	1 st	KEYNOTE-427 (cohort B)	II	2.8 (0.1-8.3)	26.70%	McDermott <i>et al.</i> (15)
	MSI-High solid tumors	≥2 nd	KEYNOTE-158	II	2.1 (1.3-10.6)	34.30%	Marabelle <i>et al.</i> (17)
	TMB-High solid tumors	≥2 nd	KEYNOTE-158	II	–	29.40%	Marabelle <i>et al.</i> (18)
Atezolizumab	UC	2 nd	NCT02108652	II	2.1 (2.0-2.2)	15.00%	Rosenberg <i>et al.</i> (11)
	UC	2 nd	IMvigor 211	III	–	13.40%	Powles <i>et al.</i> (2)
	UC	1 st	IMvigor 130	III	–	23.00%	Galsky <i>et al.</i> (3)
Nivolumab	RCC	≥2 nd	CheckMate 025	III	3.5 (1.4-24.8)	25.00%	Motzer <i>et al.</i> (14)
	UC	1 st	CheckMate 275	II	1.9 (1.8-2.0)	19.60%	Sharma <i>et al.</i> (10)
Avelumab+axitinib	RCC	1 st	JAVELIN Renal101	III	2.8 (1.1-15.0)	52.50%	Motzer <i>et al.</i> (13)
Avelumab	UC	2 nd	–	III	2.0 (1.7-16.4)	–	Powles <i>et al.</i> (12)

ccRCC: Clear-cell renal-cell carcinoma; MSI-High: high frequency of microsatellite instability; nccRCC: ccRCC: non-clear-cell renal-cell carcinoma; NMIBC: non-muscle-invasive bladder cancer; UC: urothelial carcinoma; TMB: tumor mutation burden.

pembrolizumab was 2.1 (1.4-5.3) months for the CPS≥10% population and 2.2 (95% CI=1.4-5.3) in the CPS ≥1% population. The ORR of the CPS≥10% population by RECIST v1.1 was 21.1% in the pembrolizumab arm *versus* 11.0% in the control arm (21, 22). In the pembrolizumab arm, the rate of complete response was higher at 9.3% compared with 2.9% in the chemotherapy arm. The median duration of response was not reached in the pembrolizumab arm compared with 4.4 months in the chemotherapy arm.

The trial findings translated into ORR differences between the pembrolizumab-treated cohort and controls, focusing on the CPS cohort. The ORR for the pembrolizumab-treated cohort was 10.0% higher in the ITT population, peaked at

17.2% in the CPS≥10% population, 15.6% in the CPS ≥1% population, 5.1% in the CPS<10% population, and 3.9% in the CPS <1% population (21, 22). The ORR to immunotherapeutics for UC range from 13.4% through 41.0%, except for avelumab (Table II). In the JAVELIN Bladder100 trial, the study did not focus on the ORR, because conceptually the trial was based on maintenance therapy.

Although TTR and ORR are described in most of the modern clinical trials, the time to reach the best response was not specified in most (Table III). In the present study, the TTR was 2.4 months, which corresponds to those for other immunotherapeutics for mUC and time to the best response were 3.1 months, which was not specified in other studies. In

our cohort, the ORR and median OS were 18.2% and 7.0 months, respectively, which were comparable to other initial studies assessing the potency of pembrolizumab treatment in Japan (21). Furubayashi *et al.* investigated the cycles of platinum-based chemotherapy before switching to pembrolizumab in mUC and found that around six cycles of chemotherapy are necessary for an optimal response for pembrolizumab (23). In the present study, we tried to find the best time to assess response so as to predict survival accurately and found that 8 months after pembrolizumab initiation may be the optimal time for the analysis of response. Further prospective studies focusing on the right time and indication for immunotherapy discontinuation are warranted.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in connection with this article.

Authors' Contributions

Research design: Teruo Inamoto and Haruhito Azuma; article writing: Teruo Inamoto and Ryo Sato; research: Yuto Matsushita, Taizo Uchimoto, Ko Nakamura, Kazumasa Komura, Yusuke Yano, Kazuki Nishimura, Shoko Kinoshita, Kyosuke Nishio, Tatsuo Fukushima, Keita Nakamori, Tomohisa Matsunaga, Takeshi Tsutsumi, Takuya Tsujino, Hirofumi Uehara, Hideaki Miyake and Haruhito Azuma; analytic tools: Kiyoshi Takahara; data analysis: Teruo Inamoto and Taizo Uchimoto.

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