

Clinical Outcomes of Enfortumab Vedotin in Advanced Urothelial Carcinoma With Prior Avelumab Versus Pembrolizumab Therapy

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Abstract. *Background/Aim:* This study retrospectively evaluated whether enfortumab vedotin (EV) monotherapy is effective as a late-line treatment according to prior treatment type in patients with advanced urothelial carcinoma (UC). *Patients and Methods:* We assessed consecutive patients from the Uro-Oncology Group in the Kyushu study population with lower and upper urinary tract cancer treated with EV monotherapy after platinum-based chemotherapy and immune checkpoint inhibitor therapy failure between December 2021 and March 2024. In particular, patients receiving avelumab maintenance or pembrolizumab therapy before EV for advanced UC were analyzed and compared according to the response rate, progression-free survival (PFS), and overall survival (OS). *Results:* Of the 80 enrolled patients, 31 and 49 received avelumab and pembrolizumab before EV therapy, respectively.

The avelumab and pembrolizumab groups had comparable objective response rates (48.4% vs. 44.9%, $p=0.820$) and disease control rates (77.4% vs. 67.3%, $p=0.448$). These two groups showed no significant difference in PFS from the initiation of EV (median: 6.4 months vs. 4.2 months, $p=0.184$); meanwhile, the avelumab group had better OS from the initiation of EV than the pembrolizumab group (median: 16.0 months vs. 10.2 months, $p=0.019$). Moreover, the median OS after first-line chemotherapy initiation was longer in the avelumab group than in the pembrolizumab group (40.3 months vs. 24.7 months, $p=0.054$). On multivariate analysis, avelumab maintenance therapy before EV reduced the mortality risk by 47% (95% confidence interval=0.27-1.03; $p=0.059$). *Conclusion:* EV monotherapy after avelumab maintenance therapy provides favorable survival outcomes in patients with advanced UC.

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In recent years, after platinum-based first-line chemotherapy, immune checkpoint inhibitor (ICI) therapy was introduced for advanced urothelial carcinoma (UC). In Japan, chemotherapy-sensitive and chemotherapy-resistant patients are generally treated with avelumab [anti-programmed cell death ligand 1 (PD-L1) antibody] and pembrolizumab [anti-programmed death 1 (PD-1) antibody], respectively (1, 2). In a large, randomized phase III trial (EV-301), enfortumab vedotin (EV), an antibody-drug conjugate (ADC) directed against nectin-4, reduced mortality risk by 30% compared with chemotherapy (3). In November 2021, Japan approved EV monotherapy after platinum-based chemotherapy and

subsequent ICI therapy failure on the basis of the EV-301 trial (3). Despite EV was used as a late-line treatment, we have previously reported the high therapeutic effect of EV monotherapy for metastatic UC in the real-world setting (4). The objective response rate (ORR) and disease control rate were 57.7% and 80.8%, respectively (4). The advent of EV as a novel drug remarkably transforms the landscape of pharmacotherapy for advanced UC.

It is possible that the sequential administration of platinum-based chemotherapy, ICI therapy, and ADC therapy is effective in managing advanced UC. However, the prognosis of avelumab maintenance therapy as a prior treatment of EV monotherapy is still poorly understood. Furthermore, the EV-301 trial did not indicate the proportion of avelumab used (3). Moreover, the JAVERIN bladder 100 trial included only few patients receiving EV after discontinuing avelumab maintenance therapy (5, 6). If effective, avelumab maintenance after platinum-based chemotherapy may offer relatively long overall survival (OS) duration (5). Therefore, comparing the survival outcomes of patients receiving EV according to the type of prior ICIs, such as avelumab and pembrolizumab, would be clinically interesting.

Hence, this research aimed to assess the efficacy, tolerability, and survival outcomes of EV monotherapy in patients with advanced UC according to prior treatment regimen. These patients were part of the multicenter retrospective Uro-Oncology Group in Kyushu (UROKYU) study.

Patients and Methods

Patient population. We retrospectively evaluated 90 consecutive patients (the UROKYU study population) with metastatic UC in the lower and upper urinary tracts who received EV monotherapy after platinum-based chemotherapy and subsequent ICI therapy failure at six institutions between December 2021 and March 2024. These institutions were the University of Occupational and Environmental Health Hospital, National Hospital Organization Kyushu Cancer Center, Oita Prefectural Hospital, Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Miyazaki Prefectural Miyazaki Hospital, and Japanese Red Cross Fukuoka Hospital. All patients showed radiologically confirmed disease progression after ICI therapy. After excluding four patients because of no imaging evaluation and six patients who had previously received ICIs other than pembrolizumab or avelumab, we included 80 patients in the analysis. This study conformed to the principles of the Declaration of Helsinki, and the UROKYU study protocol was approved by the University of Occupational and Environmental Health Institutional Review Board (approval no.: CRG23-017).

Patient management. The regimen and number of cycles in first-line platinum-based chemotherapy were determined by each institution. After chemotherapy, patients with or without disease progression received pembrolizumab or avelumab, respectively. On days 1, 8, and 15, EV (1.25 mg/kg) was administered intravenously, and the treatment cycle was provided every 28 days until disease progression, intolerable adverse events (AEs), or consent

withdrawal. Follow-up examination included physical checkup, laboratory tests, and chest–abdominal–pelvic computed tomography. Imaging evaluation was conducted at baseline and after every one to three cycles of EV monotherapy or as clinically necessary.

Evaluation. The best response to EV was determined according to the Response Evaluation Criteria in Solid Tumors version 1.1 (7). The ORR was defined as the percentage of patients with complete response (CR) and partial response (PR), but not stable disease (SD) and progressive disease (PD). Furthermore, the disease control rate consisted of CR, PR, and SD. EV safety was also evaluated using the Common Terminology Criteria for Adverse Events version 5.0 to summarize the frequency of treatment-related AEs (8).

Statistical analysis. All statistical data were analyzed using the EZR version 1.40 (Easy R, Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (9). We evaluated between-group variances by using Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. We estimated the progression-free survival (PFS) from the date of EV monotherapy introduction to the date of progression or death, or to the date of the last follow-up in patients without disease progression. Moreover, we estimated each OS from the date of EV monotherapy or first-line platinum-based chemotherapy introduction to the date of death from any reason or to the date of the last follow-up in patients who survived. The PFS and OS were then compared between the two groups, using the Kaplan–Meier method. Cox regression univariate and multivariate analyses were also employed to estimate the hazard ratio (HR) and 95% confidence intervals (CI). Statistical significance was considered at $p < 0.05$.

Results

Patient characteristics. Of the 80 enrolled patients, 31 (38.8%) and 49 (61.2%) received avelumab and pembrolizumab before EV monotherapy, respectively. Table I shows the basic characteristics of the avelumab and pembrolizumab groups. Overall, the median age was 73 years, and 19 patients were female (23.8%). Age, sex, primary tumor site, Eastern Cooperative Oncology Group performance status (ECOG PS), anemia, liver metastasis, Bellmunt risk score (10), histologic type, first-line chemotherapy pattern, and EV cycles showed no significant difference between the avelumab and pembrolizumab groups. More than half of patients in each group received gemcitabine plus cisplatin as the first-line chemotherapy.

Oncological outcomes. Table II presents the best response from baseline in patients treated with EV stratified by prior ICIs. The ORR and disease control rates were similar between the avelumab and pembrolizumab groups.

The median follow-up period after receiving EV monotherapy was 8.0 months [interquartile range (IQR)=5.2–14.5 months], and that after receiving first-line platinum-based chemotherapy was 22.4 months (IQR=14.2–36.2 months), during which 12 (15.0%) patients continued EV and 46 (57.5%) died.

Table I. Patient characteristics.

Characteristic	Avelumab (n=31)	Pembrolizumab (n=49)	p-Value
Median age, years (IQR)	73 (67-76)	73 (68-77)	0.809
Sex, n (%)			1.000
Male	24 (77.4)	37 (75.5)	
Female	7 (22.6)	12 (24.5)	
Primary tumor site, n (%)			0.162
Lower urinary tract	19 (61.3)	21 (42.9)	
Upper urinary tract	11 (35.5)	27 (55.1)	
Both	1 (3.2)	1 (2.0)	
ECOG PS score, n (%)			0.140
0	17 (54.8)	14 (28.6)	
1	9 (29.0)	24 (49.0)	
2	3 (9.7)	7 (14.3)	
3	2 (6.5)	4 (8.1)	
Anemia (Hb<10 g/dl), n (%)			0.448
Presence	7 (22.6)	16 (32.7)	
Absence	24 (77.4)	33 (67.3)	
Liver metastasis, n (%)			0.599
Presence	9 (29.0)	11 (22.4)	
Absence	22 (71.0)	38 (77.6)	
Bellmunt risk score, n (%)			0.168
0,1	22 (71.0)	27 (55.1)	
2,3	9 (29.0)	22 (44.9)	
Histology, n (%)			0.803
Pure UC	22 (71.0)	36 (73.5)	
Subtype of UC	9 (29.0)	13 (26.5)	
First-line chemotherapy, n (%)			0.494
Gemcitabine + cisplatin	17 (54.8)	30 (61.2)	
Gemcitabine + carboplatin	13 (41.9)	15 (30.6)	
Others	1 (3.2)	4 (8.2)	
EV cycles, median (IQR)	5 (4-8)	4 (2-7)	0.104

IQR: Interquartile range; ECOG PS: Eastern Cooperative Oncology Group performance status; Hb: hemoglobin; UC: urothelial carcinoma; EV: enfortumab vedotin.

The avelumab and pembrolizumab groups showed no significant difference in PFS [median=6.4 months (95%CI=4.4-9.1) and median=4.2 months (95%CI=2.9-5.8), respectively] (Figure 1A), whereas OS significantly differ between the two groups (Figure 1B). The median OS from the initiation of EV in the avelumab and pembrolizumab groups was 16.0 (95% CI=8.3-not estimable) and 10.2 (95%CI=5.7-13.9) months, respectively. Among the subgroups, a Bellmunt risk score of ≥ 2 was significantly associated with poor OS compared with the scores 0 and 1 [median=6.8 months (95%CI=4.6-13.9) and median=15.5 months (95%CI=11.9-19.9), respectively] (Figure 2). Furthermore, the avelumab group was associated with close to significant differences for median OS from the initiation of first-line platinum-based chemotherapy compared with the pembrolizumab group (40.3 months, 95%CI=24.9-not estimable and 24.7 months, 95%CI=17.8-43.8, respectively; $p=0.054$) (Figure 3).

Table II. Results of radiographic response to enfortumab vedotin monotherapy stratified by prior immune checkpoint inhibitor type.

	Avelumab (n=31)	Pembrolizumab (n=49)	p-Value
Response, n (%)			0.813
CR	1 (3.2)	2 (4.1)	
PR	14 (45.2)	20 (40.8)	
SD	9 (29.0)	11 (22.4)	
PD	7 (22.6)	16 (32.7)	
Objective response rate	15 (48.4)	22 (44.9)	0.820
Disease control rate	24 (77.4)	33 (67.3)	0.448

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table III shows the results of univariate and multivariate analyses predicting OS from the start of EV monotherapy for metastatic UC. After adjusting for clinicopathological variables, a Bellmunt risk score of ≥ 2 was found to be a significant independent predictor of OS. Notably, avelumab maintenance therapy before EV reduced the mortality risk by 47% (95%CI=0.27-1.03, $p=0.059$).

Safety profile. As shown in Figure 4, the incidence of AEs related to EV monotherapy was approximately 80% in both the avelumab and pembrolizumab group. The most common AE was skin toxicity. The rates of all AEs showed no significant differences between the two groups. The occurrence of treatment-related AEs of grade ≥ 3 was similar between such groups (avelumab group=29.0%, pembrolizumab group=26.5%). The major AEs with a grade of ≥ 3 included skin toxicity and neutropenia. Moreover, treatment-related AEs resulting in EV withdrawal and dose reduction occurred in three (9.7%) and 12 (38.7%) patients from the avelumab group and in five (10.2%) and 19 (38.8%) patients from the pembrolizumab group, respectively. Only one patient died because of an AE (toxic epidermal necrolysis).

Discussion

In the EV-301 study, the percentage of patients receiving avelumab as pretreatment was not disclosed (3). Therefore, the impact of avelumab maintenance therapy on patients receiving EV monotherapy remains unknown. The ORR and disease control rates of the avelumab group were comparable to those of the pembrolizumab group. In addition, PFS did not significantly differ between the groups, but the avelumab group had favorable OS after EV initiation compared with the pembrolizumab group.

In 2023, the EV-301 trial presented that the median PFS and OS were 5.55 and 12.91 months, respectively, in patients with advanced UC treated with EV monotherapy (11).

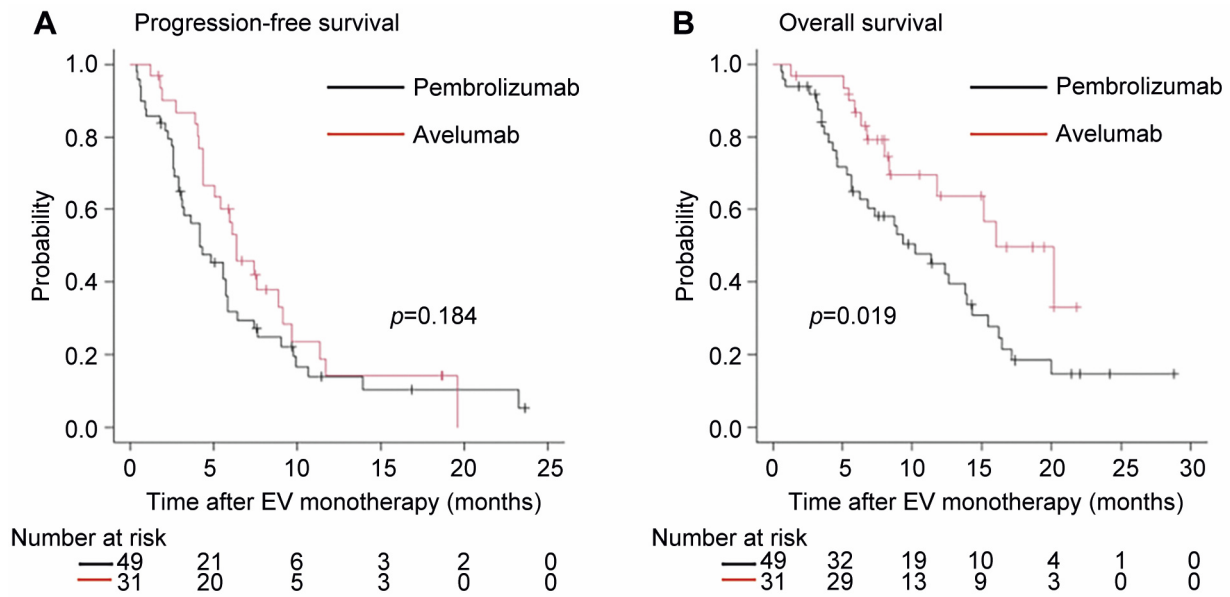


Figure 1. Kaplan–Meier curves for (A) progression-free survival and (B) overall survival after enfortumab vedotin monotherapy initiation in patients with advanced urothelial carcinoma stratified by the type of prior immune checkpoint inhibitors.

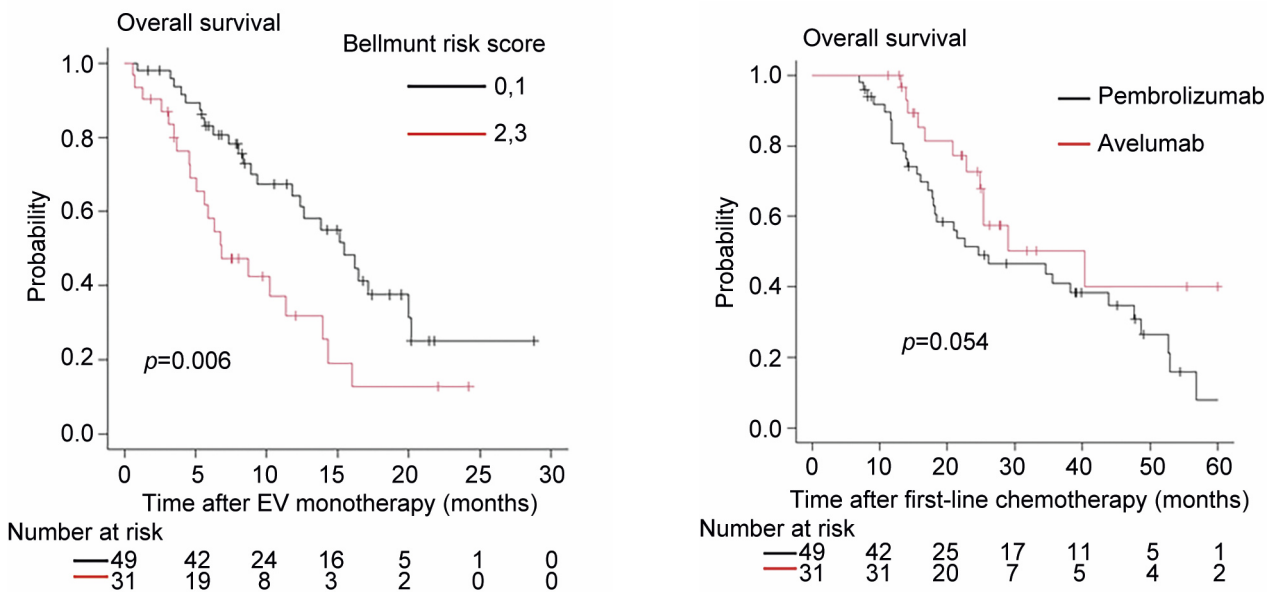


Figure 2. Kaplan–Meier curves for overall survival after enfortumab vedotin monotherapy initiation in patients with advanced urothelial carcinoma stratified by the Bellmunt risk score.

Figure 3. Kaplan–Meier curve for overall survival after first-line platinum-based chemotherapy initiation in patients treated with enfortumab vedotin as a late-line treatment stratified by the type of prior immune checkpoint inhibitors.

Regarding the use of avelumab maintenance before EV treatment, interesting results from two large multicenter studies in a real-world setting were reported at the 2024 American Society of Clinical Oncology Genitourinary (ASCO GU) Cancer Symposium. The Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) study conducted

in the United States (n=633) demonstrated the outcomes of patients with advanced UC treated with EV after avelumab switch maintenance (n=49) (12). The UNITE study showed that the ORR to EV was 54%, and the median PFS and OS from EV monotherapy initiation were 7.0 and 13.3 months, respectively. Interestingly, the OS (median=22.5 months) from

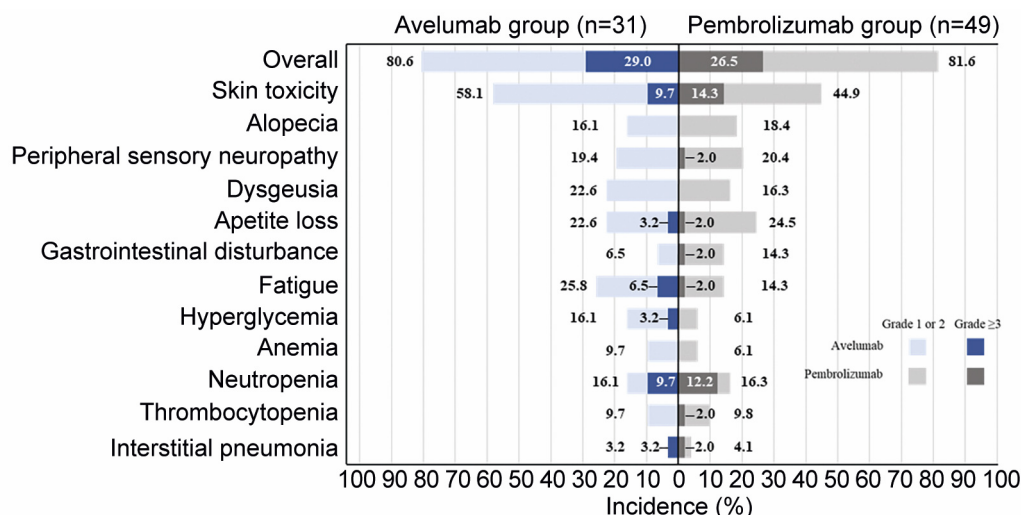


Figure 4. Treatment-related adverse events of enfortumab vedotin stratified by the type of prior immune checkpoint inhibitors.

Table III. Results of univariate and multivariate analyses for overall survival in patients with advanced urothelial carcinoma (UC) treated with enfortumab vedotin monotherapy.

Variable	Comparison	Univariate		Multivariate	
		HR (95%CI)	<i>p</i> -Value	HR (95%CI)	<i>p</i> -Value
Age	≥73 vs. <73	1.04 (0.58-1.88)	0.894		
Sex	Female vs. male	1.00 (0.51-1.97)	0.994		
Primary tumor site	Upper vs. lower urinary tract	0.74 (0.41-1.32)	0.307		
Histologic type	UC subtype vs. pure UC	1.47 (0.78-2.76)	0.233		
Liver metastasis	Presence vs. absence	1.51 (0.77-2.97)	0.226		
Bellmont risk score	≥2 vs. 0,1	2.24 (1.24-4.05)	0.007	1.99 (1.10-3.63)	0.023
Platinum-based chemotherapy	Gemcitabine + cisplatin vs. gemcitabine + carboplatin	0.75 (0.40-1.41)	0.373		
Immune checkpoint inhibitor	Avelumab vs. pembrolizumab	0.47 (0.24-0.89)	0.022	0.53 (0.27-1.03)	0.059

HR: Hazard ratio; CI: confidence interval.

the start of platinum-based chemotherapy in this previous study was shorter than that in our UROKYU study (median=40.3 months). Probably, the durability of avelumab maintenance therapy affected the survival outcomes.

Another large multicenter study, the AVENANCE, conducted in France, analyzed the subsequent treatments received by patients with avelumab maintenance therapy (6). The AVENANCE study enrolled patients with advanced UC treated with chemotherapy (n=244), ADC therapy including EV (n=56) or sacituzumab govitecan (n=6), and other treatments (n=24) after avelumab therapy. Following avelumab maintenance, patients receiving ADC therapy and chemotherapy obtained a median OS (from the start of avelumab therapy) of 31.3 months and 14.4 months, respectively (platinum-based chemotherapy=16.7 months, other chemotherapy=13.6 months) (6). Interestingly, the median OS

from first-line platinum-based chemotherapy in patients with avelumab followed by ADC therapy was 41 months (6), which is consistent with our results. In our UROKYU study, the avelumab group was associated with close to significant differences with respect to the OS from the initiation of first-line platinum-based chemotherapy compared with the pembrolizumab group. This result supports that avelumab maintenance followed by EV had a clinically meaningful benefit in patients with advanced UC. Recently, EV-302 randomized phase III clinical trial revealed that the studied patients treated with EV combined with pembrolizumab had a longer OS than those treated with platinum-based chemotherapy in the first-line setting (median: 31.5 months vs. 16.1 months, $p<0.001$) (13). Currently, EV plus pembrolizumab therapy is not yet approved in Japan. However, in the near future, the difference in the survival outcomes

between platinum-based chemotherapy with avelumab maintenance followed by EV monotherapy and EV plus pembrolizumab followed by platinum-based chemotherapy should be evaluated. Additionally, the treatment sequence involving the combination therapy of nivolumab and gemcitabine plus cisplatin may be of interest (14).

Three years since the approval of EV, the use of EV monotherapy as a late-line therapy for metastatic UC has relatively increased in daily clinical practice. It is important to explore prognostic factors in patients with advanced UC in the ADC therapy era. We have previously reported that UC with a histologic subtype or divergent differentiation was significantly associated with shorter PFS from the initiation of EV therapy (HR=1.90, 95%CI=1.01-3.61) (15). However, individual factors, such as ECOG PS score=1, anemia, and liver metastasis were not found to be independent prognosticators of disease progression (15). Conversely, in the present UROKYU study, the combination of these Bellmunt risk factors was useful in predicting OS. Similarly, the UNITE study revealed that the median OS from EV initiation was 10.1 and 16.6 months in patients with Bellmunt risk scores of 0-1 and 2-3, respectively (HR=3.32, 95%CI=1.11-9.88) (16).

Each incidence of treatment-related AEs in the avelumab group was statistically comparable to that in the pembrolizumab group. The most frequently observed treatment-related AE in both groups was skin toxicity. Grade ≥ 3 skin toxicity, neutropenia, and fatigue were more common in both our UROKYU study and the EV-301 trial (11). Interestingly, the incidence rates of AEs of grade ≥ 3 were 29.0% and 26.5% in the avelumab and pembrolizumab group, respectively, and 52.4% overall in the EV-301 trial (11). Our study also had fewer treatment discontinuations resulting from AEs than the clinical trial, despite providing routine practice in patients with worse conditions. Although EV dose was reduced in approximately 28% of our avelumab and pembrolizumab groups, Clennon *et al.* reported that patients receiving EV with relative dose intensity $>80\%$ and $\leq 80\%$ had similar clinical outcomes (17).

Previously, using patient report outcome, our early experience with EV monotherapy demonstrated that the score of health-related quality of life (HRQoL) remained stable from baseline to post-EV introduction (4). Most recently, Rosenberg *et al.* reported that HRQoL outcomes with EV were maintained, significantly delaying the time to first confirmed clinically deterioration compared to chemotherapy from baseline to week 12 in the EV-301 trial (18). Given that EV monotherapy is used as a late-line treatment, both drug efficacy and the AE profile, as well as HRQoL maintenance, are important factors to consider.

Study limitations. It is retrospective and nonrandomized in design and has a relatively small sample size. In addition, it

included patients with UC in both the upper and lower urinary tracts. The regimen and number of cycles of first-line chemotherapy were not uniform. Moreover, avelumab maintenance therapy in Japan had not been available before 2021 regardless of the efficacy to first-line chemotherapy. The radiologic response to EV was left to the investigators' assessment at each institution without central review. Furthermore, molecular markers, such as PD-L1, tumor mutation burden, microsatellite instability status, and fibroblast growth factor receptor amplification were not investigated. In addition, the differences in skin toxicity and peripheral nerve neuropathy in response to EV should be compared, as suggested by some reports (19, 20).

Nevertheless, our data suggest that patients with prior avelumab maintenance therapy have relatively favorable OS from the start of EV regardless of the advanced-stage. Presently, the efficacy of EV against advanced UC stratified by prior pembrolizumab and avelumab therapies remains rarely reported. Although the mechanism by which these anti-PD-1 and PD-L1 antibody agents affect prognosis in the EV-treated cohort is still not understood, the avelumab group had only one determination of tumor progression before EV monotherapy from the start of first-line chemotherapy to EV monotherapy introduction. Conversely, in the pembrolizumab group, disease progression could be determined from each of the primary chemotherapy and subsequent ICI therapy. Recently, Shindo *et al.* reported that median OS from the initiation of avelumab and pembrolizumab treatments was not reached and 658 days, respectively (21). Owing to lower responsiveness of the ORR to the avelumab and pembrolizumab therapies (1, 22), the key is to promptly initiate EV monotherapy without delay in patients with advanced-stage UC. Especially, the EV-301 trial presented that the best response to prior ICIs was PD in 68.9% (11). Moreover, we have recently reported that four cycles of first-line platinum-based chemotherapy can be adequate in patients with metastatic UC (23). Thus, our current study supports the optimal therapeutic sequence (platinum-based chemotherapy, avelumab maintenance therapy, and EV monotherapy) for patients with advanced UC in Japan. To our knowledge, this study is the first to report the AE profile of EV monotherapy according to the type of prior ICIs.

Conclusion

The response and tolerability to EV monotherapy in patients with advanced lower and upper urinary tract UC were comparable between those who received prior avelumab and pembrolizumab. However, regarding OS, EV monotherapy after avelumab maintenance therapy resulted in a more favorable prognosis in advanced-stage UC compared to EV monotherapy following pembrolizumab therapy.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

AM: Conceptualization, methodology, investigation, data curation, statistical analysis, and writing of the original draft. NF: Conceptualization, methodology, investigation, data curation, reviewing, and editing. TT, HM, YS, YH, KK, and TN: Investigation, data curation, and reviewing. KK, NS, IT MN: Reviewing. KH and NF: Supervision. All Authors discussed, verified, and approved the final version of the article.

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