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Outcomes of Avelumab Treatment in Advanced Urothelial Carcinoma According to Age, Performance Status, and Timing

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Abstract

Background/Aim: The efficacy and safety of avelumab according to age, performance status (PS), and infusion timing in patients with advanced urothelial carcinoma (UC) are unclear.

Patients and Methods: We retrospectively analyzed data from patients with advanced UC who received avelumab, without progression to first-line platinum-based chemotherapy. Efficacy and safety were evaluated according to age (<70, ≥70 to <80, and ≥80 years), PS (0 and ≥1), and infusion time of the first dose (early and late).

Results: Twenty-three patients were analyzed [age (<70 years, n=10; ≥70 to <80, n=8; ≥80, n=5; PS (PS0, n=20; PS≥1, n=3); timing (early, n=13; late, n=10)]. Rates of any-grade adverse events (AEs) and grade ≥2 AEs were not significantly influenced by age (p=0.748 and p=0.615, respectively), PS (p>0.999 and p=0.539), or timing (p=0.685 and p=0.618). The disease control rate was not significantly influenced by age (p=0.663), PS (p>0.178), or timing (p=0.417). Median progression-free survival (PFS) was not significantly influenced by age (p=0.979), PS (p=0.620), or timing (p=0.208). Median overall survival (OS) was not significantly influenced by age (p=0.354), PS (p=0.590), or timing (p=0.552). When patients were divided into two groups according to PFS ≥6 months, OS was significantly different between the PFS <6 months group and the ≥6 months group (p=0.016).

Conclusion: The efficacy and safety of avelumab maintenance therapy was not significantly influenced by age, PS, or infusion timing, and PFS ≥6 months could be a surrogate marker for OS.

Keywords: Urothelial carcinoma, avelumab, age, performance status, timing.

Introduction

Platinum-based chemotherapy has long been the standard of care for first-line treatment of unresectable locally advanced or metastatic urothelial carcinoma (UC), collectively termed advanced UC, in platinum-eligible patients (1). In addition, immune checkpoint inhibitors (ICIs) are administered as the next treatment, depending

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on the therapeutic effect of the primary platinum-based chemotherapy. Avelumab [an anti-programmed cell death ligand 1 (PD-L1) antibody] was administered as a switch maintenance treatment to patients without progression on platinum-based chemotherapy (2), and pembrolizumab (anti PD-1 antibody) was administered as a second-line treatment for patients who progressed during first-line platinum-based chemotherapy (3). After progression with these ICIs, enfortumab vedotin (EV), an antibody-drug conjugate directed toward Nectin-4, was administered as third-line treatment (4).

Recently, EV in combination with pembrolizumab was reported to result in significantly better outcomes than platinum-based chemotherapy as first-line treatment in patients with advanced UC (5). Less than four months after full approval for all patients by the U.S. Food and Drug Administration, EV plus pembrolizumab accounted for 50% of initiated frontline treatment regimens, replacing platinum-based chemotherapy (6). This combination treatment has been approved in Japan since September, 2024. However, clinicians are concerned about treatment interruptions due to treatment-related adverse events (TRAEs), particularly EV-related adverse events (AEs), that may occur early during treatment. TRAEs resulting in dose reduction, interruption of treatment, or withdrawal of treatment occurred in 32.4%, 51.0%, and 13.5% of patients in an EV monotherapy group in the third-line setting after platinum-containing chemotherapy and PD-1 or PD-L1 inhibitor treatment (4). We have also previously reported that TRAEs resulting in a dose reduction and withdrawal of EV after avelumab or pembrolizumab treatment occurred in 38.8% and 10.0% of patients, respectively (7).

However, it has also been reported that the rate of discontinuation due to TRAEs in the long-term follow-up analysis of patients who received avelumab maintenance was 11.6% (8, 9). In addition, platinum-based chemotherapy (gemcitabine and cisplatin or carboplatin) followed by avelumab maintenance therapy is still listed as another recommended first-line systemic therapy for advanced UC (10). Therefore, from the viewpoint of AEs, avelumab maintenance therapy after platinum-based chemotherapy may be a treatment option for elderly and poor performance status (PS) patients with advanced UC. Recently, it was reported that the time of day in which ICIs are administered could affect the outcomes of patients with cancer (11); however, there have been no reports on the relationship between the time of day in which avelumab maintenance therapy is administered and the clinical outcomes of patients with advanced UC.

The present study retrospectively evaluated the clinical outcomes of patients with advanced UC who were treated with avelumab maintenance therapy according to age, PS, and the timing of infusion.

Patients and Methods

Patient population. We identified 23 consecutive patients who received avelumab as a maintenance treatment for advanced UC (metastatic or locally advanced) that had not progressed radiologically after first-line platinum-containing chemotherapy. The patients were enrolled between March 2021 and September 2024. The regimen, duration, and number of cycles of first-line platinum-based chemotherapy, and the length of the interval between the end of chemotherapy and the start of avelumab maintenance varied according to the physician.

Avelumab was administered intravenously at a dose of 10 mg/kg on day 1, and the cycle was administered every 14 days until disease progression or the manifestation of intolerable side effects. Follow-up assessments included physical examination, laboratory tests, and a chest-abdominal-pelvic computed tomography scan. Imaging assessments were performed at baseline and after every 4-6 cycles of avelumab treatment, as well as when clinical symptoms worsened (12).

The best response to avelumab treatment was based on tumor response according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (13), and the disease control rate (DCR) was defined as the proportion of patients without progressive disease. The safety of avelumab was assessed using the Common Terminology

Table I. *Patient characteristics at the start of avelumab maintenance therapy according to age and performance status (PS).*

Characteristics	Total n=23	Age <70 n=10	Age ≥70, <80 n=8	Age ≥80 n=5	*p*-Value	PS PS 0 n=20	PS PS ≥1 n=3	*p*-Value
Age (years), median (IQR)	72 (64-77)	63 (61-67)	73 (72-75)	81 (80-81)	<0.001	70 (63-75)	78 (75-79)	0.166
Male sex, n (%)	15 (65.2)	8 (80.0)	6 (75.0)	1 (20.0)	0.076	13 (65.0)	2 (66.7)	>0.999
ECOG PS score, n (%)					0.286			<0.001
0	20 (87.0)	10 (100)	6 (75.0)	4 (80.0)		20 (100)	0	
≥1	3 (13.0)	0	2 (25.0)	1 (20.0)		0	3 (100)	
Primary tumor site, n (%)					0.719			0.339
Lower urinary tract	13 (56.5)	4 (40.0)	5 (62.5)	4 (80.0)		10 (50.0)	3 (100)	
Upper urinary tract	9 (39.1)	5 (50.0)	3 (37.5)	1 (20.0)		9 (45.0)	0	
Both	1 (4.4)	1 (10.0)	0	0		1 (5.0)	0	
Pure UC in histologic testing, n (%)	16 (69.6)	6 (60.0)	6 (75.0)	4 (80.0)	0.726	14 (70.0)	2 (66.7)	>0.999
Visceral metastasis at start of avelumab, n (%)	9 (39.1)	3 (30.0)	2 (25.0)	4 (80.0)	0.144	8 (40.0)	1 (33.3)	>0.999
Regimen of first-line platinum-based chemotherapy					0.568			0.560
GC	13 (56.5)	7 (70.0)	4 (50.0)	2 (40.0)		12 (60.0)	1 (33.3)	
GCarbo	10 (43.5)	3 (30.0)	4 (50.0)	3 (60.0)		8 (40.0)	2 (66.7)	
Best response to first-line platinum-based chemotherapy					0.060			0.560
CR or PR	13 (56.5)	8 (80.0)	2 (25.0)	3 (60.0)		12 (60.0)	1 (33.3)	
SD	10 (43.5)	2 (20.0)	6 (75.0)	2 (40.0)		8 (40.0)	2 (66.7)	

Criteria for Adverse Events version 5.0. (14). At our institution, outpatient chemotherapy infusion started between 9:00 and 17:00, and the cutoff was set at the midpoint (13:00). An avelumab infusion start time between 10:00 and 12:59 was defined as "early in the day", while a time between 13:00 and 16:00 was defined as "late in the day". Results were obtained from the medical records of each patient.

This retrospective study was approved by the Institutional Review Board of the National Hospital Organization Kyushu Cancer Center (2014-99) and was conducted in accordance with the Declaration of Helsinki and its amendments. Informed consent was obtained through an opt-out process owing to the retrospective nature of the study.

Statistical analysis. EZR ver.1.40 (Easy R, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used for all statistical analyses (15). The Mann-Whitney *U*-test was used to compare continuous variables, and Fisher's exact probability test was used to compare categorical variables. Overall survival (OS) with avelumab was calculated from the start of avelumab maintenance until the date of death, and progression-free survival (PFS) with avelumab was calculated from the start of avelumab until the date of investigator-assessed clinical and/or radiographic disease using the Kaplan-Meier method. For both OS and PFS, patients without an event were censored on the last follow-up date. Statistical significance was set at $p<0.05$.

Results

Table I summarizes the baseline characteristics of the 23 enrolled patients and the characteristics of the patients stratified by age (<70, ≥70 to <80, and ≥80 years) and PS (PS 0 and PS≥1). All patients with advanced UC who had not progressed on platinum-based chemotherapy as the first-line treatment received maintenance treatment with

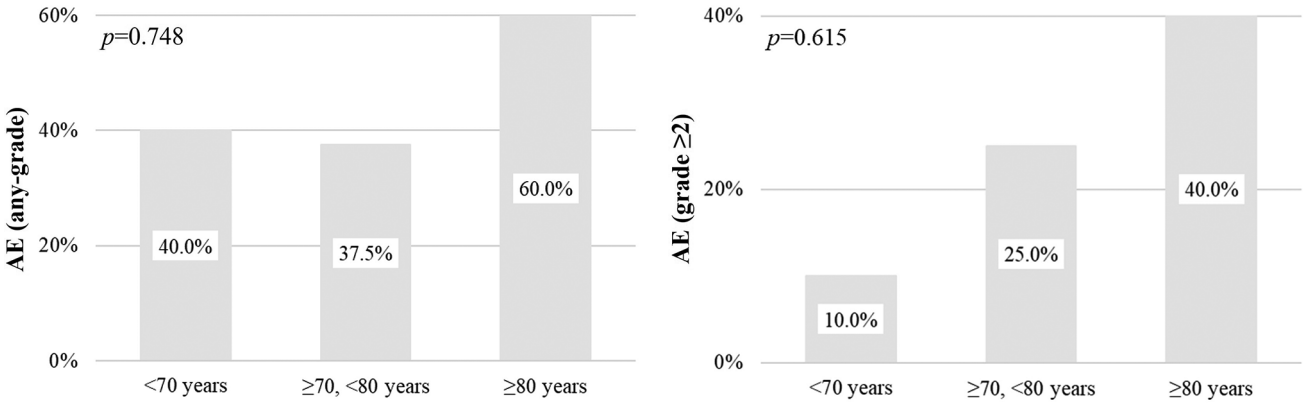

Figure 1. *Incidence of avelumab-related adverse events (any-grade and grade ≥2) according to age (<70, ≥70, <80, and ≥80 years).*

avelumab. The median age of the patients was 72 years (IQR=64-77), 10 patients (43.5%) were <70 years of age, 8 patients (34.8%) were ≥70 to <80 years of age, and 5 patients (21.7%) were ≥80 years of age. A total of 20 patients (87.0%) had a PS of 0, and 3 patients (13.0%) had a PS of ≥1. The majority of the patients were male (65.2%), the histologic type was pure UC in most patients (69.6%), and the primary tumor site was the upper urinary tract in more than half of the patients (56.5%). Visceral metastases were present in 39.1% of patients. The proportions of first-line platinum-based chemotherapy regimens were similar, with 56.5% receiving gemcitabine and cisplatin (GC) and 43.5% receiving gemcitabine and carboplatin (GCar). In addition, the proportion of best responses to first-line platinum-based chemotherapy was similar to that of the SD group (56.5% *vs*. 43.5%, respectively). There were no differences between age groups without age-related factors or between PS groups without PS-related factors.

Safety of avelumab by age, PS and timing. Overall, TRAEs of any grade were observed in 10 patients (43.5%), including 5 patients (21.7%) with grade ≥2 AEs. In the <70, ≥70 to <80, and ≥80 years groups, the rates of any-grade AEs were 40.0%, 37.5%, and 60.0% (p=0.748), respectively, whereas the rates of grade ≥2 AEs were 10.0%, 25.0%, and 40.0% (p=0.615), respectively (Figure 1). In the PS 0 and PS≥1 groups, the rates of any-grade AEs were 45.0% and 33.3% (p>0.999), respectively, whereas the rates of grade ≥2 AEs were 20.0% and 33.3% (p=0.539), respectively (Figure 2). In the early and late groups, the rates of any-grade AEs were 38.5% and 50.0% (p=0.685), respectively, whereas the rates of grade ≥2 AEs were 15.4% and 30.0% (p=0.618), respectively (Figure 3).

Efficacy of avelumab by age, PS, and timing. Overall, the median duration of follow-up after treatment with avelumab was 8.7 months (IQR=2.8-17.8 months); 11 patients died during follow-up, and DCR was confirmed in 14 patients (60.9%). There were no significant differences in the DCR between the <70, ≥70 to <80, and ≥80 years groups (50.0%, 62.5%, and 80.0%, p=0.663). Similarly, there were no significant differences in the DCR between the PS 0 and PS≥1 groups (60.0%, 66.7%, p>0.178) or between the early and late timing groups (69.2%, 50.0%, p=0.417) (Figure 4).

Overall, the median PFS and OS was 5.5 months [95% confidence interval (CI)=2.1-15.6] and 18.3 months (95%CI=10.3-35.1), respectively (Figure 5). The median PFS by age was 4.4 months [95%CI=1.2- not estimable (NE)] in the <70 years group, 5.6 months (95%CI=1.4-NE) in the ≥70 to <80 years group, and 5.5 months (95%CI=2.1-NE) in the ≥80 years group (p=0979). The median PFS by PS was 5.5 months (95%CI=2.0-6.4) in the

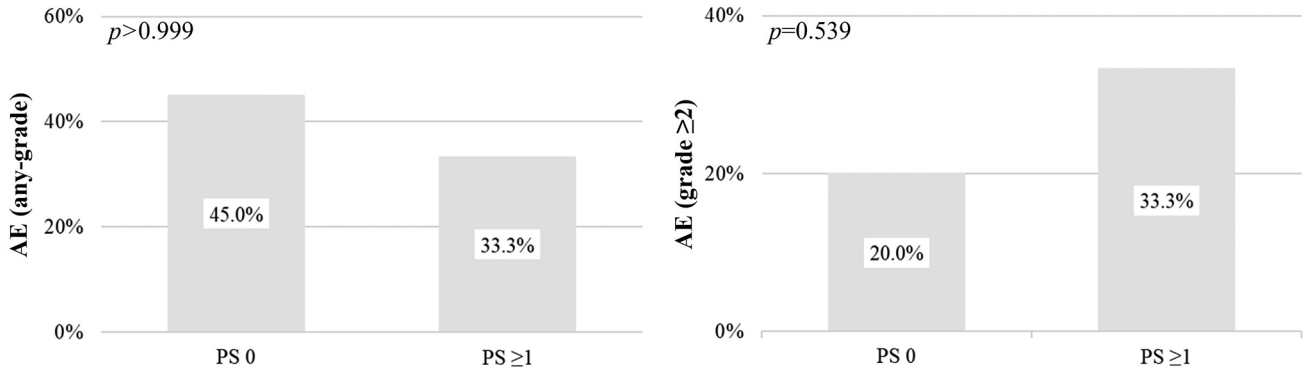

Figure 2. *Incidence of avelumab-related adverse events (AE) (any-grade and grade ≥2) according to performance status (PS) (PS 0 and PS≥1).*

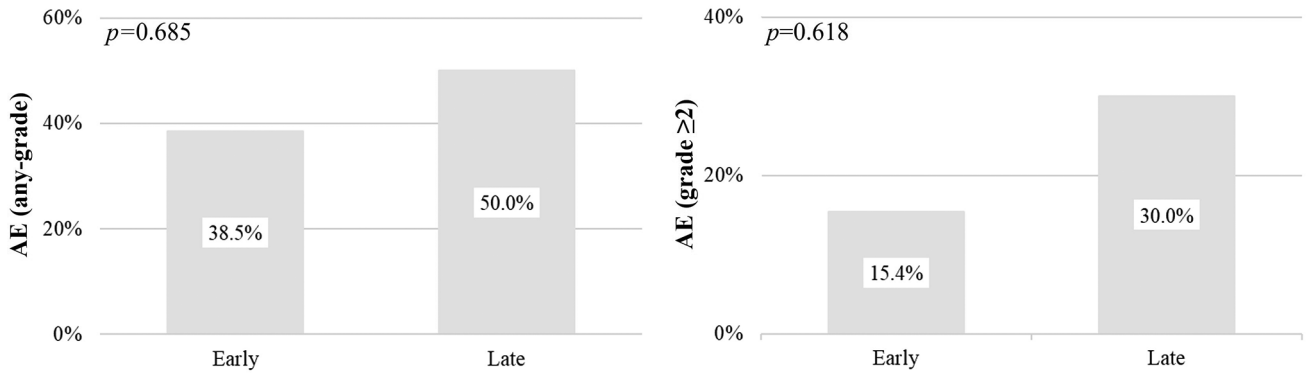

Figure 3. *Incidence of avelumab-related adverse events (AEs) (any-grade and grade ≥2) according to the infusion timing (early and late).*

PS 0 group, and 15.8 months (95%CI=1.4-NE) in the PS ≥1 group (p=0.620). The median PFS by the timing was 6.2 months (95%CI=2.1-1NE) in the early-timing group and 4.1 months (95%CI=1.2-15.6) in the late-timing group (p=0.208) (Figure 6).

The median OS by age was 23.4 months (95%CI=3.8-NE) in the <70 years group, 13.3 months (95%CI=9.1-NE) in the ≥70 to <80 years group, and 18.6 months (95%CI=9.3-NE) in the ≥80 years group (p=0.354). The median OS by PS was 13.3 months (95%CI=8.3-23.4) in the PS 0 group, and 13.7 months (95%CI=10.3-NE) in the PS ≥1 group (p=0.590) (Figure 6). The median OS by timing was 23.4 months (95%CI=8.3-NE) in the early-timing group and 18.1 months (95%CI=9.1-35.1) in the late-timing group (p=0.552) (Figure 7). When divided into two groups according to PFS ≥6 months, OS was significantly different between the PFS <6 months group (13.3 months, 95%CI=8.3-18.6) and the ≥6 months group (NE, 95%CI=17.0-NE) (p=0.016) (Figure 8).

Discussion

This retrospective study analyzed the safety and efficacy of avelumab maintenance therapy for advanced UC in relation to age, PS, and timing. The present study confirmed that the safety of avelumab-related AEs was not significantly influenced by age (<70, ≥70, <80, and ≥80 years), PS (PS 0 and PS≥1), or timing (early and late). Similarly, efficacy, as measured by the ORR, PFS, and OS, was not significantly influenced by age, PS, or timing.

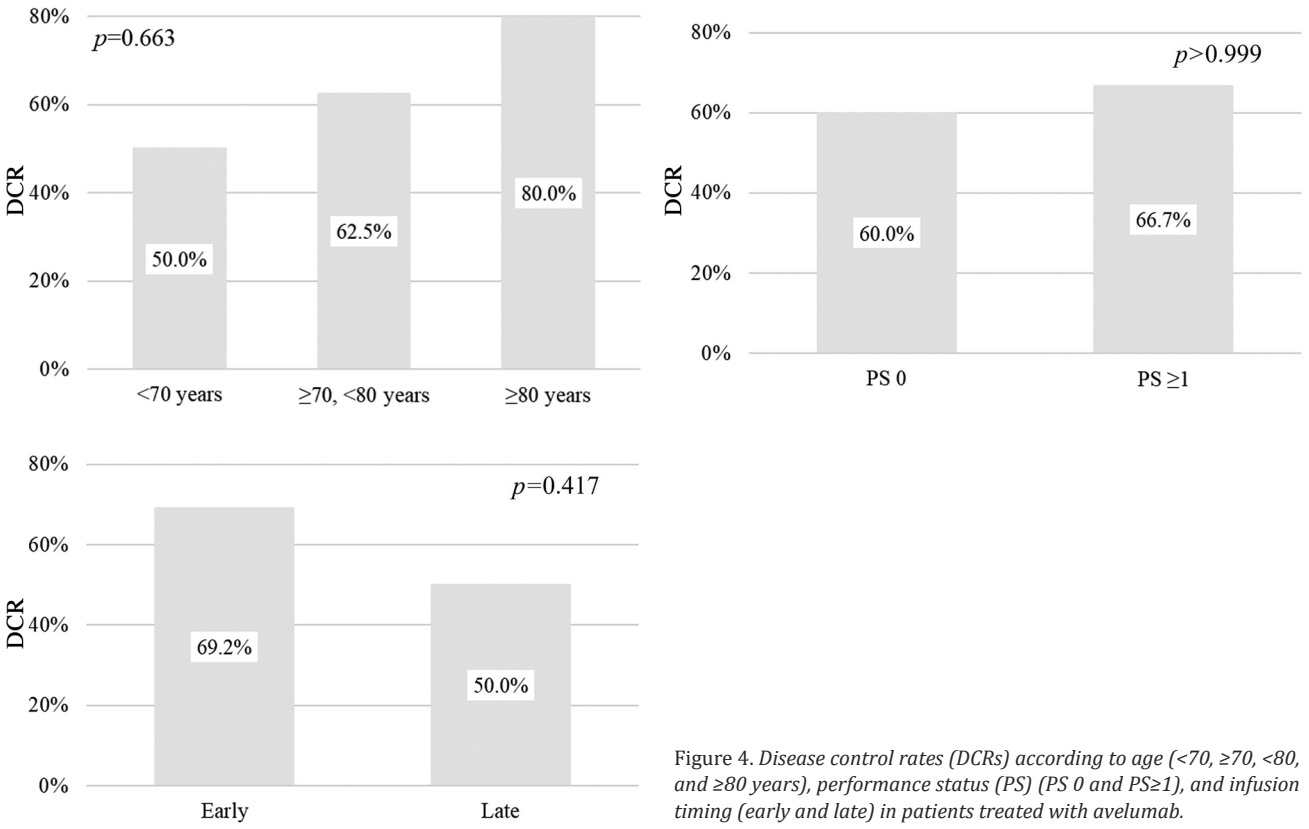

Figure 4. *Disease control rates (DCRs) according to age (<70, ≥70, <80, and ≥80 years), performance status (PS) (PS 0 and PS≥1), and infusion timing (early and late) in patients treated with avelumab.*

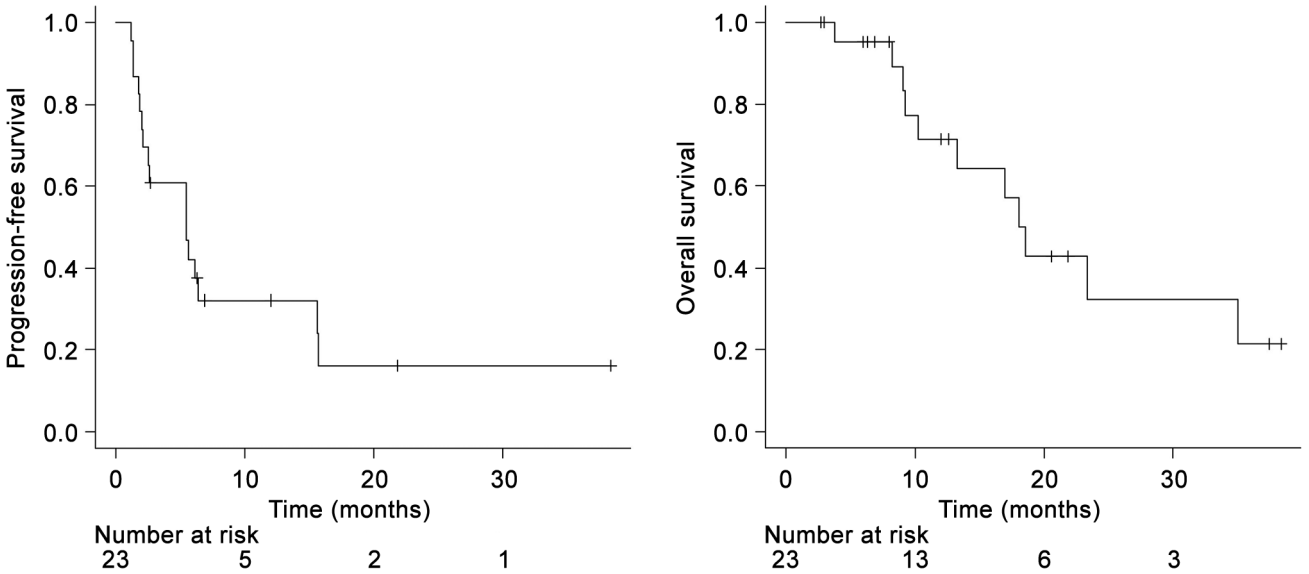

Figure 5. *Progression-free survival (PFS) and overall survival (OS) with avelumab in the overall population.*

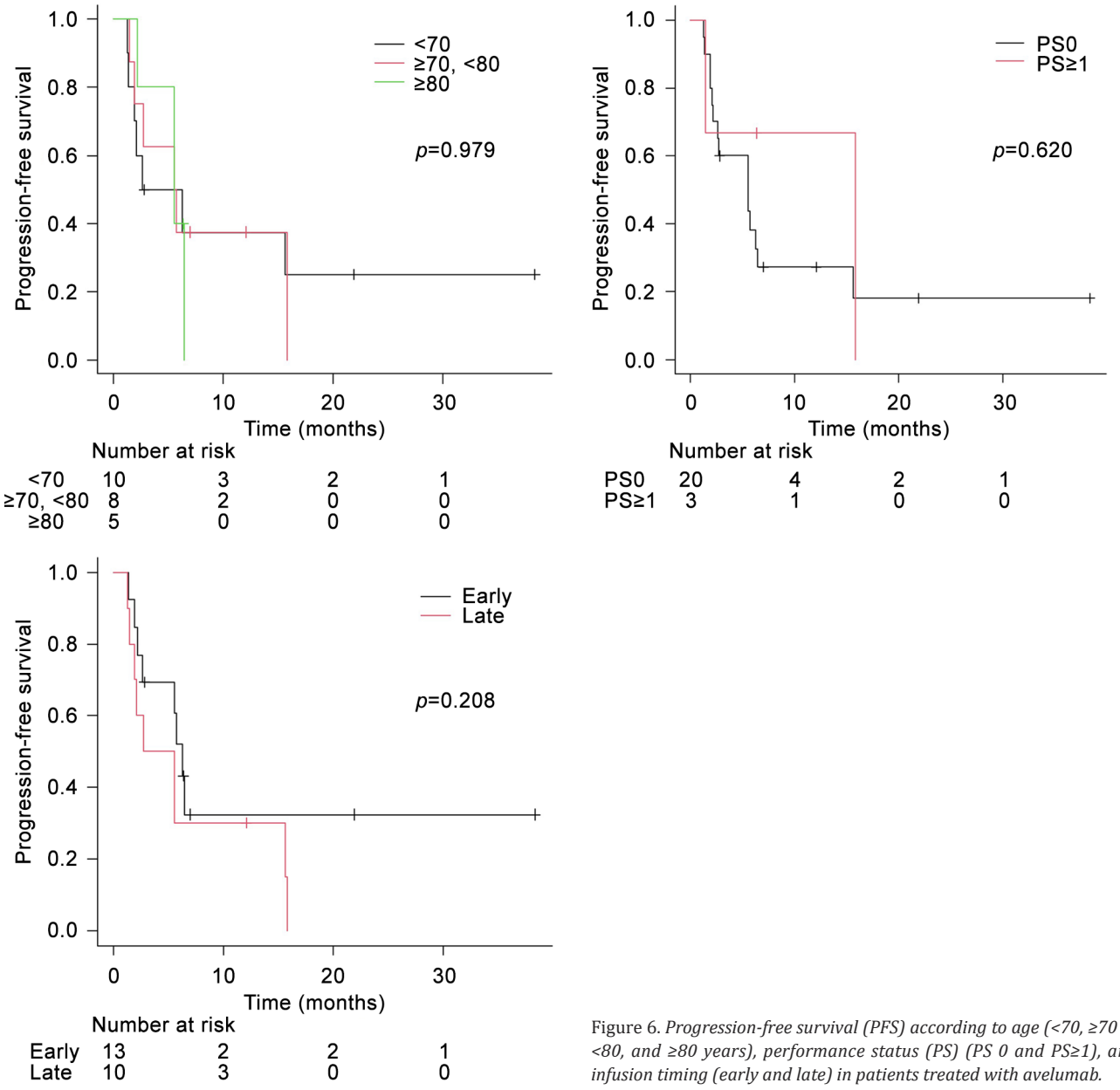

Figure 6. *Progression-free survival (PFS) according to age (<70, ≥70 to <80, and ≥80 years), performance status (PS) (PS 0 and PS≥1), and infusion timing (early and late) in patients treated with avelumab.*

Treatment options for advanced UC are rapidly expanding. However, despite the emergence of multiple treatment options in recent years, it is important for clinicians to recognize that most patients with advanced UC are not cured. In the most recent NCCN guidelines (10), new frontline options include the Category 1, "preferred" treatment of pembrolizumab plus EV based on the results of the EV-302 trial (5), and gemcitabine and cisplatin or carboplatin followed by avelumab maintenance therapy, which was the previous preferred regimen is still listed in Category 1 as "other recommended regimens" based on the results of the JAVELIN Bladder 100 trial (2).

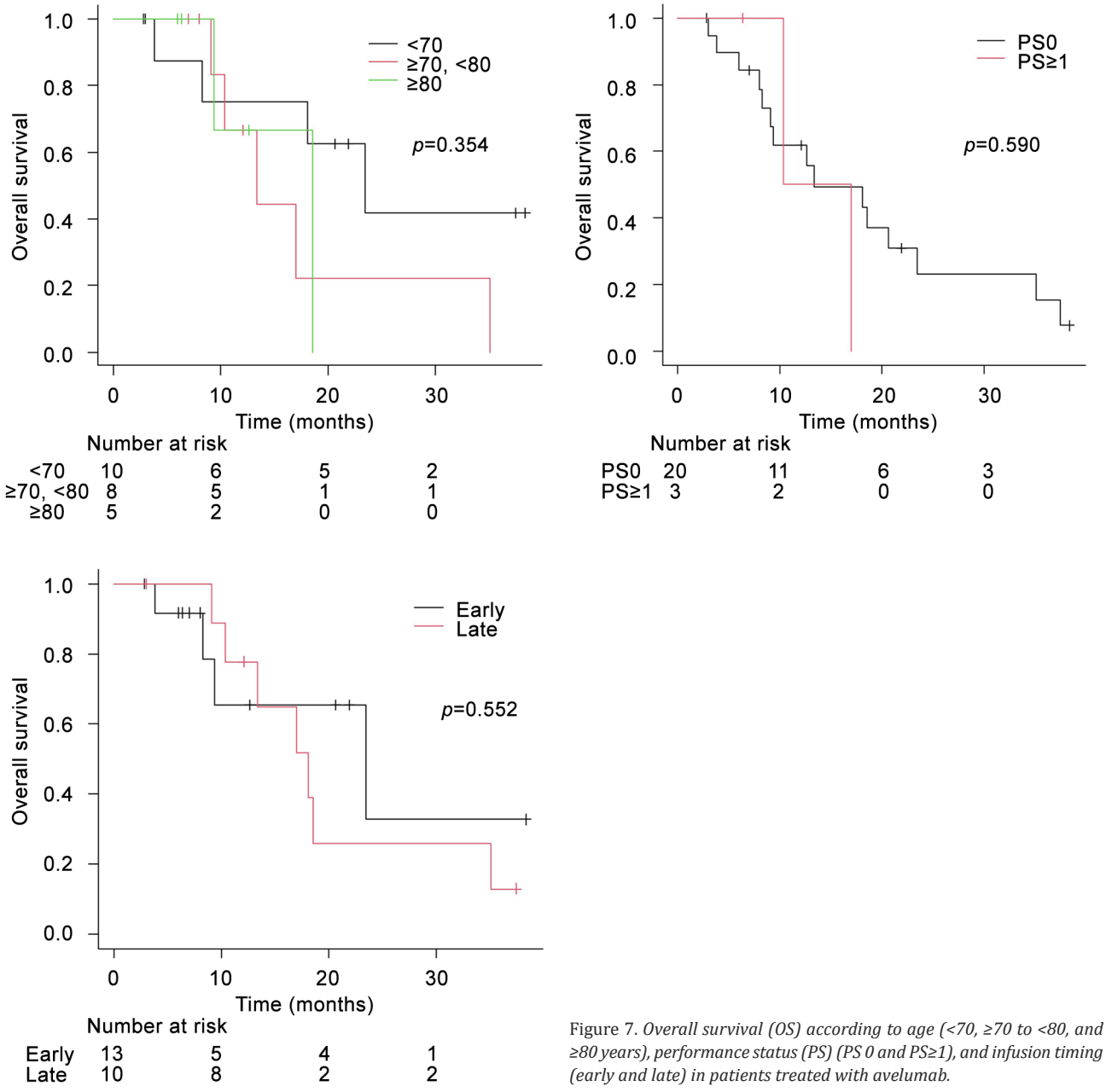

Figure 7. *Overall survival (OS) according to age (<70, ≥70 to <80, and ≥80 years), performance status (PS) (PS 0 and PS≥1), and infusion timing (early and late) in patients treated with avelumab.*

In the EV302 trial, after a median follow-up of 17.2 months, the median PFS with EV plus pembrolizumab was significantly longer in comparison to platinum-based chemotherapy (12.5 months *vs.* 6.3 months; HR=0.45; 95%CI=0.38-0.54; $p<0.001$), as was OS (31.5 months *vs.* 16.1 months; HR=0.47; 95%CI=0.38-0.58; $p<0.001$) and the confirmed ORR (67.7% *vs.* 44.4%, $p<0.001$). However, in the EV plus pembrolizumab arm, 55.9% of the patients experienced grade ≥3 TRAEs, 40.7% experienced TRAEs leading to a dose reduction of any treatment, and 35.0% experienced TRAEs leading to discontinuation of any treatment (discontinuation of

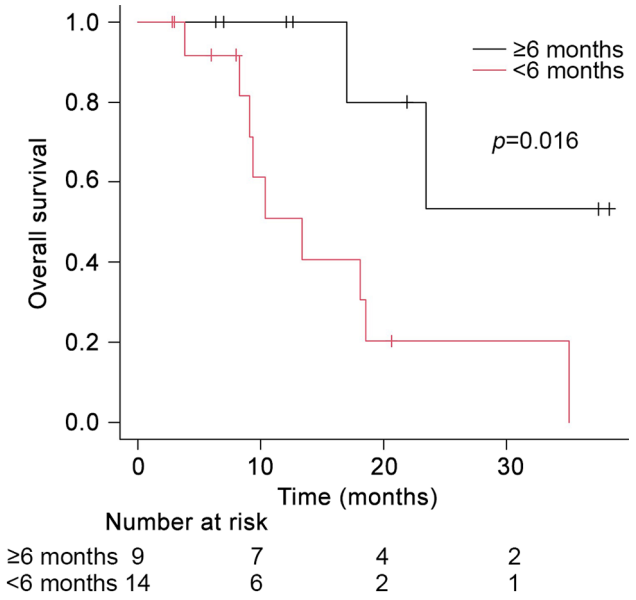

Figure 8. *Overall survival (OS) according to progression-free survival (PFS) (PFS ≥6 and <6 months) in patients treated with avelumab.*

EV in 29.5% of patients and discontinuation of pembrolizumab in 21.4% of patients).

In contrast, in the JAVELIN Bladder 100 trial, avelumab maintenance+best supportive care (BSC) significantly prolonged OS and PFS in comparison to BSC alone in patients with advanced UC without progression following platinum-based chemotherapy. After ≥2 years of follow-up for OS in all patients, the median OS measured from randomization (at the start of maintenance, *i.e.*, after chemotherapy) was 23.8 months *vs*. 15.0 months, respectively (HR=0.76; 95%CI=0.63-0.91; p=0.004); and median PFS was 5.5 *vs*. 2.1 months, respectively (HR=0.54; 95%CI=0.46-0.64; p<0.0001) (9). In a post-hoc exploratory analysis, the median OS measured from the start of first-line chemotherapy was 29.7 months in the avelumab arm *versus* 20.5 months in the control arm (HR=0.77; 95%CI=0.64-0.92) (16), and an OS benefit was observed across multiple patient subgroups (2, 9). This means that first-line maintenance therapy with avelumab may be suitable for patients with a wide range of characteristics. In a post-hoc exploratory analysis of patients who discontinued avelumab, antibody-drug conjugates and erdafitinib were used by a very small number of patients (17). In a real-world study, it was reported that the median OS was 41.5 (95%CI=34.5-NE) months in patients who received a treatment sequence of first-line PBC without disease progression followed by first-line avelumab maintenance and second-line EV (18). We also reported a similar result, in which the median OS from first-line platinum-based chemotherapy in patients receiving avelumab followed by EV therapy was 40.3 months (95%CI=24.9-NE) (7).

In terms of safety, 47.4% of patients in the avelumab group experienced a grade ≥3 adverse event, and 11.9% discontinued treatment because of an adverse event (2). In the long-term follow-up analysis of patients in the avelumab arm, grade ≥3 TRAEs occurred in 19.5% of patients, and the rate of discontinuation due to TRAEs was 11.6% (9). Because advanced UC is extremely difficult to cure, oncologists are likely to face the dilemma of determining which regimen is most appropriate and tolerable on an individual basis for patients seen in clinical practice. In each case, patients who prioritize efficacy to prolong survival or safety to maintain quality of life have different preferences, including treatment goals and expectations. Interestingly, according to patient preferences for first-line treatment of locally advanced or metastatic UC, patients were reported to be willing to accept a 7.8% reduction in the ORR to reduce the risk of peripheral neuropathy by 10%. For a 10% reduction in serious adverse events, mild to moderate nausea, or skin reactions, patients would accept reductions in the ORR of 5.5%, 3.7%, and 3.4%, respectively (19). In this retrospective study, there were no significant differences in treatment efficacy or safety according to age or PS. These results may provide useful information for patient preferences, especially when elderly patients and those with poor PS are choosing treatment, as these populations are typically underrepresented in clinical trials due to their relatively small populations, and it remains unclear whether these patients may benefit from a new treatment (20-22).

Although avelumab could only be administered to patients with no progression on platinum-based chemotherapy, it was reported that 34.3% of patients received ≥12 months of treatment and 19.5% of patients received ≥2 years of treatment in the JAVELIN Bladder 100 trial. In addition, in a post-hoc analysis of the subpopulation of patients who received ≥12 months of treatment, the median OS was not reached (95%CI=50.9 months-NE), grade ≥3 TRAEs occurring after ≥12 months were detected in 11.9% of patients, and no new safety signals were identified with longer durations of treatment (23). The present study showed that the median OS was not reached in the PFS ≥6 months group [PFS ≥6 months *vs*. <6 months: not reached (95%CI=17.0-NE) *vs*. 13.3 months (95%CI=8.3-18.6)]. Therefore, PFS ≥6 months could be a surrogate marker for an earlier treatment phase in avelumab maintenance treatment for OS in advanced UC.

Anti-tumor immunity has recently been shown to be dependent on the time of day. In immunodeficient mice and mice lacking lineage-specific circadian functions, dendritic cells (DCs) and CD8+ T cells exert circadian anti-tumor functions that control melanoma volume (24). Previous research has suggested that patients with advanced solid tumors who receive ICI infusions in the morning may have longer OS than those who receive infusions in the afternoon (25-27). Interestingly, the timing of the first dose has been reported to affect treatment efficacy (25, 28). Currently, there are no reports on the association between the timing of the first administration of avelumab and its clinical efficacy in patients with advanced UC. The present study showed that the treatment efficacy and safety tended to be superior in the early administration group relative to the late administration group, although the difference was not statistically significant.

Study limitations. This was a retrospective study with a small sample size and a short follow-up period. In addition, pre-avelumab factors, such as the regimen, cycle, and duration of platinum-based chemotherapy and the interval before avelumab administration, varied depending on the physician. This study included patients treated with avelumab prior to the approval of EV, which may have influenced the results.

Conclusion

In patients with advanced UC, the efficacy and safety of avelumab maintenance therapy was not significantly influenced by age, PS, or timing, and PFS ≥6 months could be a surrogate marker for OS.

Funding

No funding was received.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Study concept and design: N.F., M.N. and T.N.; acquisition of data: N.F., M.M., A.K., Y.F., M.N. and N.T..; statistical analysis: N.F., and T.N.; analysis and interpretation of data: all Authors; drafting of the original manuscript: N.F., M.N. and T.N.; critical revision of the manuscript for important intellectual content: all Authors; supervision: M.N. and T.N. All Authors have read and approved the final version of the manuscript.

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