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Original Article
Clinical Investigation

Physical, but not laboratory, treatment-related adverse events are associated with favorable outcomes of enfortumab vedotin for advanced urothelial carcinoma: A landmark analysis

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Abbreviations & Acronyms
DCR = disease control rate
EV = enfortumab vedotin
ICIs = immune checkpoint inhibitors
ORR = objective response rate
OS = overall survival
PFS = progression-free survival
trAEs = treatment-related adverse events
UC = urothelial carcinoma

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Abstract:

Background: While the occurrence of immune-related adverse events has been recognized as a prognostic marker in patients receiving immune checkpoint inhibitors, the prognostic significance of treatment-related adverse events (trAEs) in patients undergoing antibody–drug conjugates such as enfortumab vedotin (EV) is controversial.

Methods: We reviewed 106 patients with advanced urothelial carcinoma who were treated with EV therapy at 10 institutions between 2021 and 2023. Associations of clinical parameters with overall survival and progression-free survival were assessed using the Cox proportional hazards model. For the assessment of trAEs, landmark analysis was conducted to minimize immortal time bias.

Results: Of 106 patients, 55 (51.9%) experienced disease progression and 44 (41.5%) died during the follow-up period. Any grade and grade ≥3 trAEs occurred in 94 (88.7%) and 44 (41.5%) patients, respectively. Common trAEs included skin disorders (74.5%), gastrointestinal disorders (62.3%), fatigue (50.0%), peripheral neuropathy (36.8%), and hematological disorders (37.7%). One patient died of interstitial pneumonia (grade 5). According to landmark analysis using 88 patients who survived for 2 months or more, trAEs were significantly associated with longer survival. Furthermore, when trAEs were classified into "physical trAEs" such as skin disorders and "laboratory trAEs" such as hematological disorders, the former were associated with longer survival while the latter were associated with shorter survival.

Conclusions: Physical, but not laboratory, trAEs are associated with favorable outcomes of EV therapy for advanced urothelial carcinoma. Both managing trAEs and utilizing them as prognostic markers are key points in the use of antibody–drug conjugates such as EV.

Key words: adverse event, enfortumab vedotin, immortal time bias, landmark analysis, urothelial carcinoma.

INTRODUCTION

Enfortumab vedotin (EV) is a novel antibody–drug conjugate which delivers monomethyl auristatin E to nectin-4-expressing cells.[1–3] Urothelial carcinoma (UC) has been considered as a good target for EV because it highly expresses nectin-4.[2,3] In 2021, EV was approved for advanced UC given that the EV-301 trial showed its superiority to non-platinum-based chemotherapy after platinum-based chemotherapy and immune checkpoint inhibitors (ICIs) such as pembrolizumab.[1] While the survival time of advanced UC has been significantly prolonged since the advent of pembrolizumab in 2017, EV and other new agents are expected to further prolong survival.[4,5] Recently, clinical outcomes of EV in real-world patients with advanced UC have increasingly been reported.[6–19] However, albeit its promising antitumor activity, EV has the unique complication profile due to its mechanism of action, including skin disorders, peripheral neuropathy, interstitial pneumonia, and so on.[20–23] Therefore, the management of treatment-related adverse events (trAEs) is a key point in treating patients with EV.[24]

The occurrence of immune-related adverse events has been recognized as a prognostic marker in patients treated with ICIs,[25,26] whereas the prognostic significance of trAEs in patients treated with antibody–drug conjugates such as EV is controversial. Despite many reports on EV in real-world patients,[6–23] few studies have investigated the prognostic impact of trAEs on outcomes of EV.[20] This might be partly because trAEs are likely to be underreported in the real-world setting compared to the clinical trial setting.[27] This study aimed to assess the prognostic significance of trAEs in advanced UC treated with EV by conducting a detailed evaluation of trAEs and using landmark analysis.

MATERIALS AND METHODS

Patients and treatments

This retrospective multi-institutional study was approved by the Institutional Review Board of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (approval number: 10565), as well as that of each participating institution. An opt-out approach was used to obtain informed consent from patients.

We retrospectively reviewed 106 patients with advanced UC who were treated with EV at 10 institutions between December 2021 and December 2023. The cohort included 39 patients who were analyzed in our previous study.[9] EV was administered at a dose of 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle.[1] Dose reduction was determined according to the institutional policy or the physicians' discretion considering the patient's condition.

Endpoints, follow-up, and statistical analysis

Endpoints of this study included overall survival (OS), progression-free survival (PFS), and treatment responses. PFS was defined as the time from the initiation of EV to disease progression or death, whichever occurred first. OS was defined as the time from the initiation of EV to death. Treatment responses, including disease progression, objective response rate (ORR), and disease control rate (DCR), were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1. The incidence and severity of trAEs were assessed using the Common Terminology Criteria for Adverse Events version 5.0. All patients underwent evaluations every 1–3 months that included routine blood tests, chest X-ray, and computed tomography. Follow-up information was obtained as of May 2024.

OS and PFS were estimated using the Kaplan–Meier method and compared using the log-rank test when needed. Associations of clinical parameters, including pretreatment factors and posttreatment trAEs, with OS and PFS were assessed using the Cox proportional hazards model. For the assessment of prognostic significance of trAEs, landmark analysis was used to minimize immortal time bias. All statistical analyses were performed using JMP Pro version 17.0.0 (SAS Institute). $p<0.05$ was considered significant.

RESULTS

Analyses of the whole population

Table 1 shows patients' characteristics in the whole population (n = 106). Similarly to the EV-301 trial,[1] about a third (32.1%) of the patients had liver metastasis. Two patients had not received platinum-based chemotherapy due to hemodialysis and allergy to platinum-containing agents. The median number of cycles of EV therapy was 4 (interquartile range [IQR]: 2–7). Dose reduction was carried out in 35 (33.0%) of the patients mainly due to the occurrence of trAEs.

Figure 1 illustrates Kaplan–Meier curves depicting PFS, OS, and treatment responses in the whole population. Of 106 patients, 55 (51.9%) experienced disease progression and 44 (41.5%) died during the median follow-up of 5 (IQR: 2–11) months. Median OS and PFS were 13 and 5 months, respectively. The ORR and DCR were 44.3% and 71.7%, respectively, which were comparable to those of the EV-301 trial (ORR: 40.6%; DCR: 71.9%).[1]

Table S1 shows univariable and multivariable Cox proportional hazard regression analyses of pretreatment factors for OS and PFS. Eastern Cooperative Oncology Group Performance Status ≥1 and bone metastasis were identified as independent predictors of shorter OS and PFS. However, liver metastasis was not associated with OS or PFS even in univariable analyses.

Profile of trAEs

Table 2 shows a summary of trAEs in the whole population (n = 106). Any grade and grade ≥ 3 trAEs occurred in 94 (88.7%) and 44 (41.5%) patients, respectively. Relatively common (>10%) trAEs included skin disorders (74.5%), gastrointestinal disorders (62.3%), fatigue (50.0%), peripheral neuropathy (36.8%), hematological disorders (37.7%), eye disorders (17.0%), and hyperglycemia (14.2%). Grade ≥ 4 trAEs occurred in five (4.7%) patients: water blister (grade 4); Stevens–Johnson syndrome (grade 4); neutropenia with anorexia (grade 4); neutropenia (grade 4); myelodysplastic syndrome accompanied with thrombocytopenia (grade 4); and

TABLE 1 Patients' characteristics in the whole population (n = 106).

Parameter	Value
Age, years, median (IQR)	72 (63–77)
Sex, no. (%)	
Male	75 (70.8)
Female	31 (29.2)
ECOG PS, no. (%)	
0	56 (52.8)
1	39 (36.8)
2	6 (5.7)
3	5 (4.7)
Primary tumor site, no. (%)	
Bladder	49 (46.2)
Upper urinary tract	42 (29.6)
Both	15 (14.2)
Resection of primary site, no. (%)	63 (59.4)
Lymph node metastasis, no. (%)	71 (67.0)
Visceral metastasis, no. (%)	81 (76.4)
Lung metastasis, no. (%)	49 (37.7)
Bone metastasis, no. (%)	34 (32.1)
Liver metastasis, no. (%)	34 (32.1)
Prior treatment lines, no. (%)	
1[a]	2 (1.9)
2	78 (73.6)
≥3	26 (24.5)
Prior platinum-based regimen, no. (%)	
GC	48 (45.3)
GCa	29 (27.4)
GC + GCa	12 (11.3)
ddMVAC	12 (11.3)
ddMVAC + GC	2 (1.9)
ddMVAC + GCa	1 (0.9)
None[a]	2 (1.9)
Prior ICI regimen, no. (%)	
Pembrolizumab	72 (67.9)
Avelumab	24 (22.6)
Avelumab + Pembrolizumab	6 (5.7)
Nivolumab	4 (3.8)
Cycles of EV therapy, median (IQR)	4 (2–7)

Abbreviations: ddMVAC, dose-dense methotrexate/vinblastine/doxorubicin/cisplatin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EV, enfortumab vedotin; GC, gemcitabine/cisplatin; GCa, gemcitabine/carboplatin; ICI, immune checkpoint inhibitor; IQR, interquartile range. [a]Platinum-based chemotherapy was not conducted due to hemodialysis (n = 1) and allergy to platinum-containing agents (n = 1).

interstitial pneumonia (grade 5). The last two trAEs occurred in the same patient, who developed thrombocytopenia and interstitial pneumonia simultaneously. The former required repeated platelet transfusion and turned out to be myelodysplastic syndrome by bone-marrow biopsy. The latter required steroid pulse therapy, and the patient eventually died of an exacerbation of interstitial pneumonia.

For reference, patients who underwent ≥4 (median) cycles of EV therapy were more likely to develop trAEs than those who underwent <4 cycles (55/57 [96.5%] versus 39/49 [79.6%], p = 0.006), which could be attributed to immortal time bias. Additionally, patients' characteristics according to the occurrence of skin disorders and peripheral neuropathy in the whole population (n = 106) are shown in Tables S2 and S3, respectively. For both kinds of trAEs, patients who developed trAEs received more cycles of EV therapy than those who did not.

Landmark analysis

To assess the prognostic significance of trAEs, landmark analysis was conducted to minimize immortal time bias: only patients who survived for 2 months or more (n = 88) were included in the analysis.[26] Of 88 patients, 46 (52.3%) experienced disease progression and 35 (39.8%) died, during the median follow-up of 7 (IQR: 4–13) months.

Overall, the occurrence of any trAEs was significantly associated with longer OS and PFS (Figure 2a,b). Figure S1 illustrates Kaplan–Meier curves according to respective types of trAEs. A significant correlation between the occurrence of trAEs and longer survival was observed in skin disorders for OS (Figure S1a) and peripheral neuropathy for OS and PFS (Figure S1e,f). A non-significant trend for longer survival was also observed in skin disorders for PFS (Figure S1b) and gastrointestinal disorders for OS (Figure S1c). To the contrary, the occurrence of hematological disorders was significantly associated with shorter OS and PFS (Figure S1m,n).

Based on the above observations, trAEs were classified into "physical trAEs," such as skin disorders, gastrointestinal disorders, peripheral neuropathy, eye disorders, fatigue, and interstitial pneumonia, and "laboratory trAEs," such as hematological disorders and hyperglycemia. Physical trAEs were significantly associated with longer OS and PFS (Figure 2c,

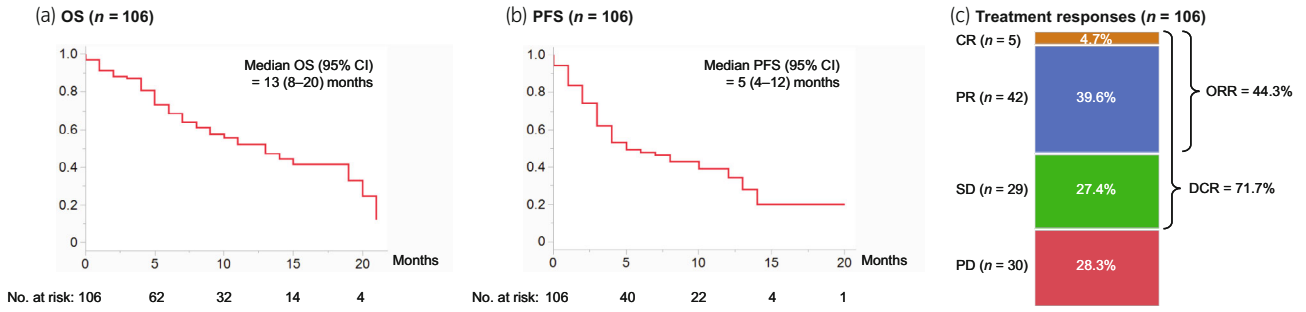

FIGURE 1 Kaplan–Meier curves depicting (a) PFS, (b) OS, and (c) treatment responses in the whole population (n = 106). CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PD; progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

TABLE 2 Summary of trAEs in the whole population (n = 106).

trAE	Any grade	Grade ≥ 3
Skin disorders, no. (%)	79 (74.5)	14 (13.2)
Rash	61 (57.5)	7 (6.6)
Pruritus	52 (49.1)	5 (4.7)
Alopecia	41 (38.7)	0 (0)
Dry skin	34 (32.1)	0 (0)
Water blister	13 (12.3)	1 (0.9)
Stevens–Johnson syndrome	2 (1.9)	2 (1.9)
Gastrointestinal disorders, no. (%)	66 (62.3)	8 (7.5)
Nausea	48 (45.3)	4 (3.8)
Dysgeusia	35 (33.0)	0 (0)
Vomiting	7 (6.6)	0 (0)
Constipation	26 (24.5)	1 (0.9)
Diarrhea	18 (17.0)	4 (3.8)
Peripheral neuropathy, no. (%)	39 (36.8)	5 (4.7)
Peripheral sensory neuropathy	35 (33.0)	5 (4.7)
Peripheral motor neuropathy	20 (18.9)	3 (2.8)
Eye disorders, no. (%)	18 (17.0)	0 (0)
Blurred vision	15 (14.2)	0 (0)
Dry eye	7 (6.6)	0 (0)
Keratitis	5 (4.7)	0 (0)
Fatigue, no. (%)	53 (50.0)	6 (5.7)
Interstitial pneumonia, no. (%)	6 (5.7)	3 (2.8)[a]
Other physical disorders, no. (%)[b]	10 (9.4)	1 (0.9)
Hematological disorders, no. (%)	40 (37.7)	17 (16.0)
Anemia	33 (31.1)	12 (11.3)
Neutropenia	11 (10.4)	6 (5.7)
Febrile neutropenia	2 (1.9)	2 (1.9)
Thrombocytopenia	5 (4.7)	1 (0.9)
Hyperglycemia, no. (%)	15 (14.2)	3 (2.8)
Other laboratory disorders, no. (%)[c]	7 (6.6)	4 (3.8)
Any trAEs, no. (%)	94 (88.7)	44 (41.5)
Physical trAEs	92 (86.8)	30 (28.3)
Laboratory trAEs	49 (46.2)	22 (20.8)

Abbreviation: trAE, treatment-related adverse event. [a]Including a grade 5 case. [b]Seizure (grade 3; n = 1), edema (grade 1 and 2; n = 2), nail change (grade 1; n = 2), arthralgia (grade 2; n = 1), vertigo (grade 2; n = 1), urinary tract pain (grade 2; n = 1), hematuria (grade 1; n = 1), headache (grade 1; n = 1), fever (grade 1; n = 1), and oral mucositis (grade 1; n = 1), including overlaps. [c]Myelodysplastic syndrome accompanied with thrombocytopenia (grade 4; n = 1), hypercalcemia (grade 3; n = 2), hyponatremia (grade 3; n = 1), hyperkalemia (grade 2; n = 1), hypoparathyroidism (grade 2; n = 1), and elevated liver enzymes (grade 2; n = 1).

d), whereas laboratory trAEs were significantly associated with shorter OS (Figure 2e) and showed a non-significant trend for shorter PFS (Figure 2f).

Table S4 shows univariable and multivariable Cox proportional hazards regression analyses, including the occurrence of trAEs, for OS and PFS, using landmark analysis. For OS, bone metastasis, non-occurrence of any trAEs, non-occurrence of physical trAEs, and occurrence of laboratory trAEs were identified as independent predictors of shorter survival. For PFS, bone metastasis, non-occurrence of physical trAEs, and occurrence of laboratory trAEs were identified as independent predictors of shorter survival, whereas non-occurrence of any trAEs was not. Again, liver metastasis was not associated with OS or PFS even in univariable analyses.

For reference, Figure S2 illustrates Kaplan–Meier curves depicting OS and PFS according to trAEs and their grades. There were no significant differences in survival between grade ≥ 3 and grade ≤ 2 trAEs both for any trAEs and categorized (physical/laboratory) trAEs.

DISCUSSION

The present study assessed the prognostic significance of trAEs in advanced UC treated with EV using landmark analysis. In the whole population (n = 106), oncological outcomes and trAE profile of EV therapy in this study were in line with those in the EV-301 trial.[1] Subsequent landmark analysis (n = 88) showed that the occurrence of any trAEs was significantly associated with longer survival. Furthermore, when trAEs were classified into "physical trAEs" such as skin disorders and "laboratory trAEs" such as hematological disorders, the former were associated with longer survival while the latter were associated with shorter survival. This study is the first to propose the concept of categorized (physical/laboratory) trAEs for antibody–drug conjugates such as EV.

While the occurrence of immune-related adverse events has been recognized as a prognostic marker in patients receiving ICIs,[25,26] the prognostic significance of trAEs in patients undergoing antibody–drug conjugates has not been fully elucidated. Vlachou et al. reviewed 56 patients with advanced UC undergoing EV and reported that the response rate was higher in patients with cutaneous toxicity (or skin disorders) than in those without (57.7% vs. 24.0%, p = 0.0145).[20] Although the study did not conduct multivariable analysis or landmark analysis due to the small sample size, it was the first report demonstrating an association between EV-related cutaneous toxicity and response. Our study validated the concept of the study by a more comprehensive assessment of trAEs and by minimizing immortal time bias using landmark analysis.

Mechanisms underlying the association between physical trAEs (especially, skin disorders) and better prognosis remain unclear. As nectin-4 is normally expressed in epidermal keratinocytes and skin appendages, as well as in the urothelium, monomethyl auristatin E can be delivered into nectin-4-expressing normal tissues, such as the epidermis and epithelium of sweat glands and hair follicles, which eventually causes skin disorders.[24] Skin and tumor cells might show a similar reaction to EV according to the level of nectin-4 expression per each patient, skin reactions could be a surrogate marker of survival and treatment responses in patients treated with EV. While skin disorders have been reported as common trAEs of EV, severe skin disorders such as Stevens–Johnson syndrome have been highlighted.[20,21] Meanwhile, mild trAEs such as alopecia are likely to be underreported in the real-world setting. Alopecia is not life-threatening (highest grade = 2) but is cosmetically impactful, especially for female patients, which should thus be taken into account in clinical practice.[27] The present study also found that other physical trAEs such as peripheral neuropathy were associated with better prognosis. To the contrary, hematological disorders were associated with

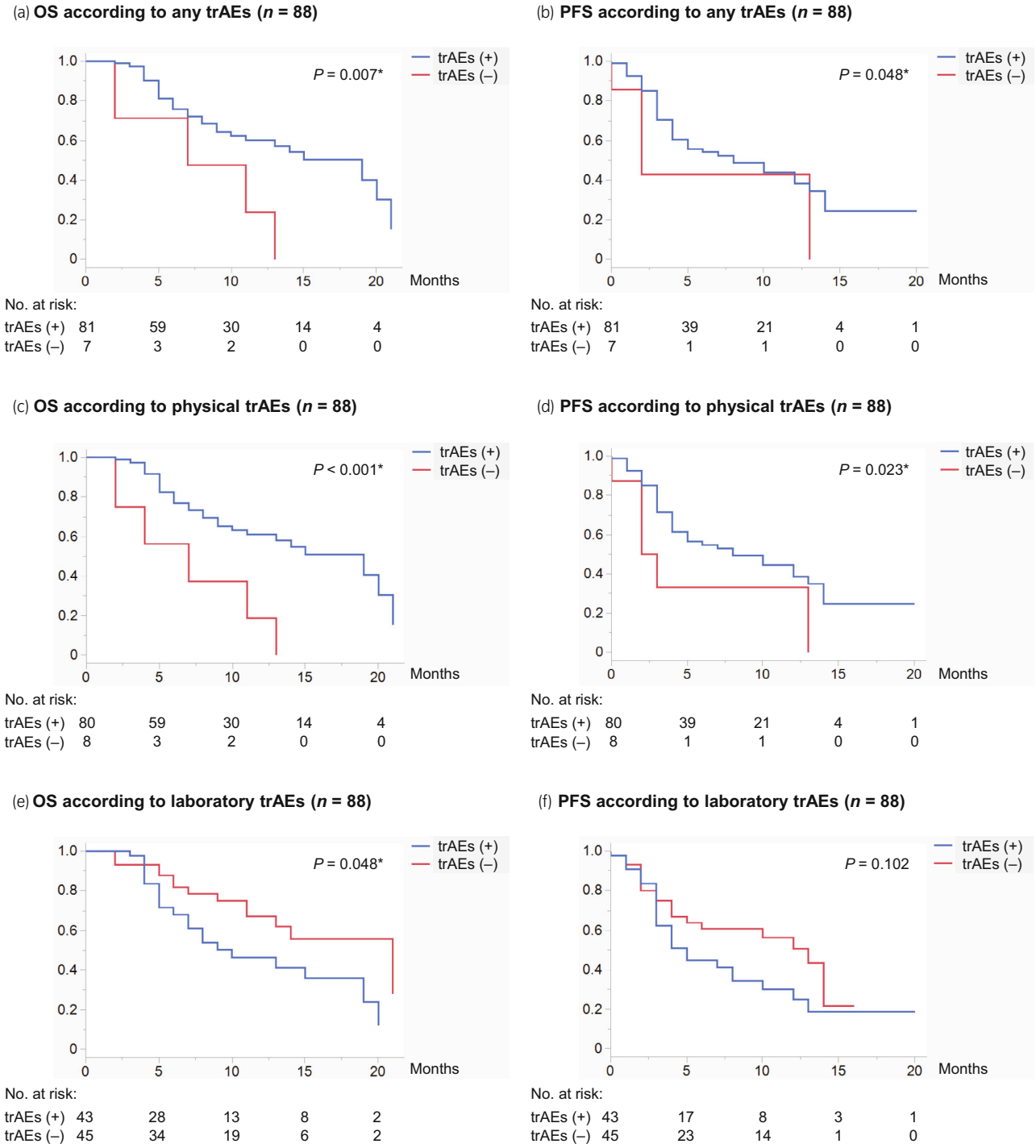

FIGURE 2 Kaplan–Meier curves depicting (a) OS and (b) PFS according to any trAEs, (c) OS and (d) PFS according to physical trAEs, and (e) OS and (f) PFS according to laboratory trAEs, using landmark analysis (n = 88). OS, overall survival; PFS, progression-free survival; trAE, treatment-related adverse event. *Statistically significant.

worse prognosis. This might reflect the host's vulnerability to monomethyl auristatin E rather than affinity to nectin-4 and might thus be negatively correlated with effectiveness of EV.

Aside from trAEs, several pretreatment factors were assessed in this study. Notably, liver metastasis was not associated with survival even in univariable analyses, which has been recognized as a strong poor prognosticator for advanced UC both in pre-ICI[28] and post-ICI[29] eras. Actually, this is in line with the result of the EV-301 trial that the benefit of EV was observed both in patients with and without liver metastasis.[1]

The limitations of this study included its retrospective design, relatively small sample size, and use of an ethnic-specific (i.e., Japanese) cohort, considering the different trAE profile in Japanese and other populations. In addition, this study did not analyze data on the timing of the trAE onset. Nevertheless, this is the first comprehensive assessment of prognostic significance of trAEs in patients treated with EV using landmark analysis. Given that EV has recently been approved as first-line treatment for advanced UC in combination with pembrolizumab,[30] the drug will be more widely used in the real-world setting. Results of this study will provide additional insight for both clinicians and patients who will use EV in clinical practice.

In conclusion, the occurrence of trAEs is a predictor of longer survival in advanced UC treated with EV. Furthermore, when trAEs are classified into two categories, physical, but not laboratory, trAEs are associated with favorable outcomes of EV more strongly. Not only managing trAEs but also utilizing them as prognostic markers will be key points in the use of antibody–drug conjugates such as EV in the near future.

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AUTHOR CONTRIBUTIONS

Satoru Taguchi: Conceptualization; methodology; formal analysis; writing – original draft. **Taketo Kawai:** Conceptualization; methodology; formal analysis; writing – original draft. **Yoshiki Ambe:** Data curation. **Kenjiro Kishitani:** Data curation. **Michio Noda:** Data curation. **Tomoyuki Kaneko:** Data curation. **Jimpei Miyakawa:** Data curation. **Yu Nakamura:** Data curation. **Hayato Hoshina:** Data curation. **Daisuke Obinata:** Data curation. **Kenya Yamaguchi:** Data curation. **Shigenori Kakutani:** Data curation. **Yoshitsune Furuya:** Data curation. **Yujiro Sato:** Data curation. **Yume Adachi:** Data curation. **Kazuma Sugimoto:** Data curation. **Keigo Sato:** Data curation. **Mariko Tabata:** Data curation. **Takehiro Tanaka:** Data curation. **Katsuhiko Nara:** Data curation. **Yukari Uemura:** Formal analysis. **Jun Kamei:** Data curation. **Yoshiyuki Akiyama:** Data curation. **Yusuke Sato:** Data curation. **Yuta Yamada:** Data curation. **Aya Niimi:** Data curation. **Daisuke Yamada:** Data curation. **Tappei Takada:** Writing – review and editing; supervision. **Sayuri Takahashi:** Writing – review and editing; supervision. **Yukio Yamada:** Writing – review and editing; supervision. **Hideyo Miyazaki:** Supervision; writing – review and editing. **Yutaka Enomoto:** Supervision; writing – review and editing. **Hiroaki Nishimatsu:** Supervision; writing – review and editing. **Tetsuya Fujimura:** Supervision; writing – review and editing. **Hiroshi Fukuhara:** Writing – review and editing; supervision. **Tohru Nakagawa:** Supervision; writing – review and editing. **Satoru Takahashi:** Writing – review and editing; supervision. **Haruki Kume:** Supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

Haruki Kume, Satoru Takahashi, Tohru Nakagawa, Tetsuya Fujimura, and Yusuke Sato are the editorial board members of International Journal of Urology.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

This study was approved by the Institutional Review Board of the Graduate School of Medicine and Faculty of Medicine, the University of Tokyo (approval number: 10565), as well as that of each participating institution.

INFORMED CONSENT

An opt-out approach was used to obtain informed consent from patients.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

Not applicable.

ANIMAL STUDIES

Not applicable.

FUNDING INFORMATION

We received no funding/grant support for this study.

DATA AVAILABILITY STATEMENT

The dataset analyzed in this study is available from the corresponding author upon reasonable request.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1.
Figure S2.
Table S1.
Table S2.
Table S3.
Table S4.