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Immune-related adverse events in urothelial cancer patients: Adjustment for immortal time bias

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Abstract

To investigate the association between the onset, severity, and type of immune-related adverse events (irAEs) and the efficacy of pembrolizumab in patients with platinum-pretreated advanced urothelial carcinoma (UC), we retrospectively collected clinical datasets of 755 patients and conducted landmark analysis. Patients who survived for fewer than 3 months were excluded from the evaluation to reduce the immortal time bias. In total, 620 patients were evaluated, of whom 220 patients (35.5%) experienced grade ≥2 irAEs, including 134 patients with grade 2 irAEs and 86 with grade ≥3 irAEs. Propensity score matching extracted 198 patients with and without grade ≥2 irAEs. The onset of grade ≥2 irAEs was associated with longer median progression-free survival (PFS) (8.3 months vs. 4.5 months, $p = 0.003$) and overall survival (OS) (20.4 months vs. 14.3 months, $p = 0.031$) and a higher objective response rate (ORR) (44.8% vs. 30.2%, $p = 0.004$). Patients with grade 2 irAEs had significantly

better oncological outcomes (PFS, OS, and ORR) than grade ≤1 and ≥3 irAEs. Patients with grade ≥3 irAEs had worse outcomes than grade 2 irAEs. Endocrine and skin irAEs were related with better survival outcomes, and the rate of severities was lower in these categories. In conclusion, the occurrence of irAEs, particularly low-grade irAEs, was predictive of pembrolizumab efficacy in patients with platinum-pretreated advanced UC.

KEYWORDS
immortal time bias, immune-related adverse events, pembrolizumab, therapeutic efficacy, urothelial carcinoma

1 | INTRODUCTION

Urothelial carcinoma (UC) is the fourth leading type of cancer, and more than 10% of cases are diagnosed in advanced stages.[1] Although platinum-based chemotherapy remains the mainstay of first-line treatment for metastatic UCs, the prognosis of platinum-pretreated advanced UC is poor because of the lack of proven later-line treatments.[2] The establishment of immune checkpoint inhibitors (ICIs) revolutionized the treatment of advanced UC in patients who failed prior platinum chemotherapy, and currently, four different ICIs have been approved by the Food and Drug Administration.[3–6]

Pembrolizumab, a humanized monoclonal anti–programmed death 1 (PD-1) antibody, exerts antitumor efficacy by inhibiting the negative regulation of immune response, which promotes cytotoxic T cell activity against cancer cells. According to the Keynote-045 trial, pembrolizumab significantly prolonged overall survival (OS) versus conventional chemotherapy in patients with platinum-pretreated advanced UCs (10.3 months vs. 7.4 months, $p = 0.002$).[6] Hyperactivation of the immune system by ICIs could damage normal tissues in various organs, and such events are termed immune-related adverse events (irAEs). The rate of irAEs with ICIs was reported to be 26.8% for any-grade events and 6.1% for grade ≥3 events,[7] and 5.6% of patients discontinued treatment because of adverse events (AEs).[6]

However, the number of responders to ICIs is limited, and biomarkers for predicting ICI efficacy are lacking. In addition to oncological features such as a microsatellite instability–high status and programmed death ligand 1 (PD-L1) expression, clinical features including the performance status (PS) and neutrophil-to-lymphocyte ratio (NLR) were previously studied as biomarkers.[8–10] Recently, an association between the onset of irAEs and the therapeutic efficacy of ICIs was suggested in melanoma and non–small cell lung cancer (NSCLC).[11–13] Rapid disease progression during ICI treatment would make irAEs clinically undetectable, which is one of the immortal time biases that underlie the evaluation of irAEs.[8,14] While there have been reports mentioning the relationship of irAEs with outcome in advanced UC,[15–18] due to the small sample size, study design, and frequency of irAEs, these previous studies have not accounted for this bias and the results remain controversial. Therefore, we attempted to minimize this immortal time bias by using large-scale real-world data, which enabled us to exclude cases who died early and to analyze the real association between irAEs and the efficacy of pembrolizumab in patients with platinum-pretreated advanced UCs.

2 | MATERIALS AND METHODS

2.1 | Patients

This multicenter retrospective study was approved by the institutional review boards of 59 medical institutions in Japan (approval number at Kyoto University Graduate School of Medicine was R1783). This study conformed to the provisions of the Declaration of Helsinki. In total, 755 patients with platinum-pretreated advanced UC who started treatment with pembrolizumab from August 2015 to December 2019 were enrolled. Clinical datasets, including age, gender, smoking history, primary tumor site, variant histology, surgical removal of primary tumor, metastatic sites, number of prior chemotherapy, hemoglobin, albumin, NLR, Eastern Cooperative Oncology Group PS, number of pembrolizumab cycles, and irAEs, were collected until September 2021. In this study, treatment-related AEs excluding infection and events evidently due to disease progression were regarded as irAEs. Pembrolizumab administered after perioperative chemotherapy was categorized as the first-line treatment.

2.2 | Objectives

The primary objective of this study was to investigate the relationship between the occurrence of irAEs and the therapeutic efficacy of pembrolizumab in advanced UC. The efficacy of pembrolizumab was assessed using the objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 and by progression-free survival (PFS) and OS. PFS was defined as the time from the initiation of pembrolizumab to objective disease progression based on radiological assessments, and OS was defined as the time from the initiation of pembrolizumab therapy to death from any cause or the last day of follow-up. The secondary objective was to assess the impact of the severity and spectrum of irAEs on the efficacy of pembrolizumab. The severity of irAEs was assessed according to

Common Terminology Criteria for Adverse Events version 4.0, and grade ≥2 irAEs were regarded as clinically significant irAEs in this study. irAEs were categorized as hematologic, gastrointestinal, general fatigue, hepatic, renal, neurological, pulmonary, skin, endocrine, musculoskeletal, infusion reaction, and other.

2.3 | Statistical analysis

Landmark analysis was conducted, and to minimize the immortal time bias, patients who survived more than 3 months were included in the evaluation. Continuous parameters were assessed using the Mann-Whitney *U* test or Kruskal-Wallis test, and categorical data were examined using Pearson's chi-square test or Fisher's exact test. We used a propensity score matching (PSM) method to achieve the between-group comparability of the patients with and without clinically significant irAE (Figure 1). PSM was performed using the logistic regression model. Covariates including age, sex, smoking history, primary tumor site (upper urinary tract, bladder and urethra, or both), variant histology, surgical removal of the primary tumor, metastatic sites (lymph nodes, viscera, and liver), number of prior chemotherapies (pembrolizumab in the first, second, third, or fourth line or later), hemoglobin, albumin, NLR, and PS (0, 1, or ≥2) were converted into propensity scores. For the sensitivity analysis, two independent attempts were made to transfer 20% of randomly selected patients with grade ≥2 irAEs to a group of patients with grade 1 or no irAE before PSM was performed. The caliper width was 20% of the standard deviation of the logit of the score. The Kaplan-Meier method with the log-rank test was used to estimate OS and PFS. Cox proportional hazard models were used to model the hazard ratios (HRs) and 95% confidence intervals (CIs). All tests were two tailed, and $p < 0.05$ was defined as statistically significant. All statistical analyses were performed using JMP Pro (version 16.1.0, SAS Institute Inc.).

3 | RESULTS

3.1 | Patients

We identified 220 patients with grade ≥2 irAEs and 400 with grade 1 or no irAEs who survived longer than 3 months. In total, the median patient age was 71 years, 466 patients (75.2%) were male, and 545 patients (87.9%) had a PS of 0 or 1. The primary tumor was located in the upper urinary tract in 272 patients (43.9%) and in the bladder or urethra in 306 patients (49.4%), and 356 patients (57.4%) underwent primary tumor resection. Variant histology appeared in 59 patients (9.5%). Metastasis to the lymph nodes, viscera, and the liver was detected in 415 (66.9%), 363 (58.5%), and 91 patients (14.7%), respectively. Pembrolizumab was mainly initiated as second-line therapy (60.6%). Baseline patient characteristics are presented in Table 1.

3.2 | irAEs

Among the 620 enrolled patients, 220 patients (35.5%) experienced grade ≥2 irAEs, including 134 patients (60.9%) with grade 2 irAEs and 86 (39.1%) with grade ≥3 irAEs. There were no grade 5 irAEs. The numbers and characteristics of irAEs are presented in Table 2. Among grade ≥2 irAEs, endocrine ($n = 60$, 9.7%), skin ($n = 53$, 8.5%), gastrointestinal ($n = 43$, 6.9%), pulmonary ($n = 29$, 4.7%), and hepatic events ($n = 26$, 4.2%) occurred most frequently. The proportion of

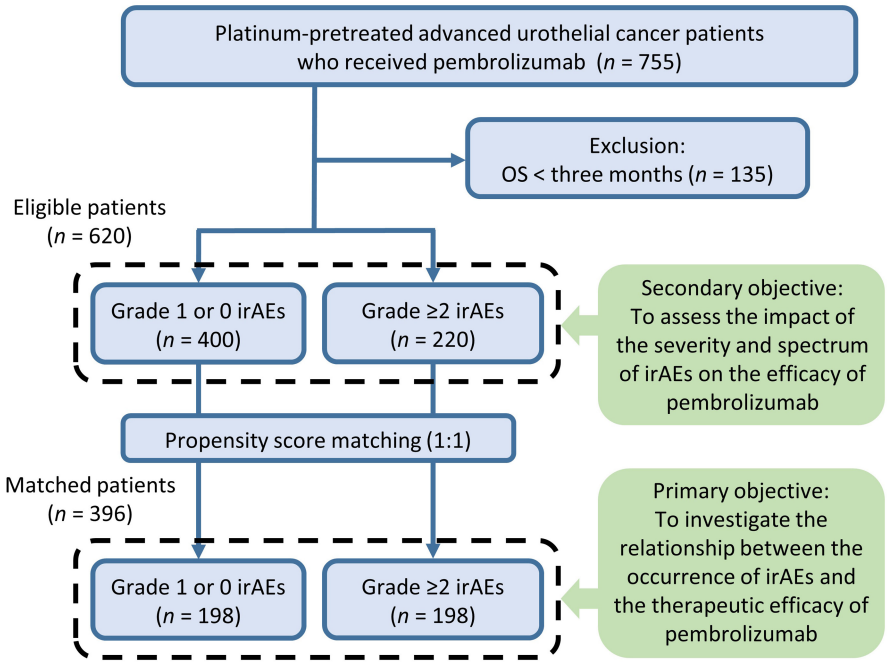


FIGURE 1 Flowchart of the study

TABLE 1 Baseline characteristics of patients classified by immune-related adverse events (irAEs) who survived longer than 3 months before and after propensity score matching

	Before propensity score matching					After propensity score matching			
	Grade 2 irAEs	Grade ≥3 irAEs	Grade ≥2 irAEs	Grade 1 or no irAEs		Grade ≥2 irAEs	Grade 1 or no irAEs		
Variable	*n* = 134	*n* = 86	*n* = 220	*n* = 400	*P*	*n* = 198	*n* = 198	*P*	*SD*
Age, years, median (range)	73 (66-77)	71 (66-75)	72 (66-77)	71 (65-77)	0.671	72 (66-77)	73 (67-77)	0.352	0.041
Gender, *n* (%)									
Male	96 (71.6)	66 (76.7)	162 (73.6)	304 (76.0)	0.560	146 (73.7)	147 (74.2)	0.909	0.011
Female	38 (28.4)	20 (23.3)	58 (26.4)	96 (24.0)		52 (26.3)	51 (25.8)		
Smoking history, *n* (%)	72 (53.7)	50 (58.1)	122 (55.5)	228 (57.0)	0.735	111 (56.1)	117 (59.1)	0.611	0.061
Primary tumor site, *n* (%)									
Upper urinary tract	64 (47.8)	44 (47.8)	108 (49.1)	164 (41.0)	0.124	92 (46.5)	91 (46.0)	0.954	0.010
Bladder/urethra	58 (43.3)	37 (43.0)	95 (43.2)	211 (52.8)		91 (46.0)	89 (45.0)		
Both	12 (9.0)	4 (4.7)	16 (7.3)	23 (5.8)		14 (7.1)	16 (8.1)		
Variant histology, *n* (%)	12 (9.0)	6 (7.0)	18 (8.2)	41 (10.3)	0.475	16 (8.1)	11 (5.6)	0.426	0.099
Surgical removal of primary site, *n* (%)	77 (57.5)	45 (52.3)	122 (55.5)	234 (58.5)	0.497	109 (55.1)	114 (57.6)	0.685	0.403
Metastatic site, *n* (%)									
Lymph nodes	90 (67.2)	56 (65.1)	146 (66.4)	269 (67.3)	0.859	133 (67.2)	133 (67.2)	1.000	0.000
Viscera	80 (59.7)	45 (52.3)	125 (56.8)	238 (59.5)	0.551	114 (57.6)	114 (57.6)	1.000	0.000
Liver	20 (14.9)	13 (15.1)	33 (15.0)	58 (14.5)	0.906	31 (15.7)	31 (15.7)	1.000	0.000
Line of pembrolizumab, *n* (%)									
First	17 (12.7)	14 (16.3)	31 (14.1)	69 (17.3)	0.232	31 (15.7)	30 (15.2)	0.888	0.072
Second	82 (61.2)	48 (55.8)	130 (59.1)	246 (61.5)		119 (60.1)	126 (63.6)		
Third	28 (20.9)	20 (23.3)	48 (21.8)	62 (15.5)		37 (18.7)	33 (16.7)		
Fourth or more	7 (5.2)	4 (4.7)	11 (5.0)	23 (5.8)		11 (5.6)	9 (4.6)		
Hb, g/dl, median (range)	11.1 (9.8-12.1)	10.9 (9.2-12.1)	11.0 (9.6-12.1)	10.7 (9.4-12.1)	0.270	10.9 (9.4-12.0)	10.7 (9.6-12.3)	0.823	0.046
Alb, g/dl, median (range)	3.8 (3.5-4.1)	3.7 (3.2-4.1)	3.8 (3.4-4.1)	3.8 (3.4-4.1)	0.843	3.8 (3.4-4.1)	3.7 (3.4-4.1)	0.610	0.002
NLR, median (range)	3.0 (2.0-4.3)	3.4 (2.1-4.6)	3.2 (2.0-4.3)	3.1 (2.1-4.7)	0.515	3.2 (2.0-4.6)	3.2 (2.2-4.6)	0.600	0.009
ECOG PS, *n* (%)									
0	73 (54.5)	36 (41.9)	109 (49.6)	226 (56.5)	0.168	103 (52.0)	108 (54.6)	0.878	0.052
1	48 (35.8)	37 (43.0)	85 (38.6)	125 (31.3)		72 (36.4)	67 (33.8)		
≥2	13 (9.7)	13 (15.1)	26 (11.8)	49 (12.3)		23 (11.6)	23 (11.6)		

(Continues)

TABLE 1 (Continued)

Variable	Before propensity score matching					After propensity score matching			
	Grade 2 irAEs	Grade ≥3 irAEs	Grade ≥2 irAEs	Grade 1 or no irAEs	P	Grade ≥2 irAEs	Grade 1 or no irAEs	P	SD
	n = 134	n = 86	n = 220	n = 400		n = 198	n = 198		
irAE maximum grade, n (%)									
Grade 2	134 (60.9)	0	134 (60.9)	0		121 (61.1)	0		
Grade 3	0	69 (31.4)	69 (31.4)	0		62 (31.3)	0		
Grade 4	0	17 (7.7)	17 (7.7)	0		15 (7.6)	0		
Grade 5	0	0	0	0		0	0		
Cycles of pembrolizumab, n, median (range)	9 (5-20)	4.5 (3-10)	7 (3-17)	7 (4-16)	0.714	7 (4-17)	7 (4-16)	0.773	

Abbreviations: Alb, albumin; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio; SD, standardized difference.

severe events (grade ≥3/ grade ≥2) for each irAE was higher in the renal (76.9%), pulmonary (65.5%), and musculoskeletal categories (60.0%) and lower in the infusion reaction (0%), skin (13.2%), neurological (18.8%), and endocrine categories (25.0%). Multiple irAEs were observed in 64 patients (29.1%). Treatment discontinuation owing to irAEs occurred in 28 patients (20.9%) with grade 2 irAEs and 28 (32.6%) with grade ≥3 irAEs. There was no predictive factor for the presence of irAEs in our cohort (data not shown).

3.3 | Occurrence of clinically significant irAEs and efficacy

After stratifying patients on the basis of the occurrence of clinically significant irAEs, 198 patients were extracted from each group by PSM and included in further analyses. Baseline characteristics were well balanced between the groups (Table 1). Median PFS was 8.3 months in patients with grade ≥2 irAEs, versus 4.5 months in patients with grade 1 or no irAEs ($p = 0.003$; Figure 2A), and median OS was 20.4 months in patients with grade ≥2 irAEs, versus 14.3 months in patients with grade 1 or no irAEs ($p = 0.031$; Figure 2B). ORR was significantly higher in patients with grade ≥2 irAEs (44.8% vs. 30.2%, $p = 0.004$). No difference was observed in the median (interquartile range [IQR]) number of cycles of pembrolizumab between patients with grade ≥2 and with grade 1 or no irAEs (7 [4-17] vs. 7 [4-16], $p = 0.773$). Multivariate analysis illustrated that the presence of grade ≥2 irAEs was associated with significantly longer PFS (HR = 0.48, 95% CI = 0.31-0.73, $p < 0.001$) and a trend toward favorable OS (HR = 0.71, 95% CI = 0.48-1.03, $p = 0.070$; Figure S1). The sensitivity analyses were conducted by transferring 20% of randomly selected patients with grade ≥2 irAEs to patients with grade 1 or no irAEs followed by PSM, and similar favorable prognosis was shown in patients with grade ≥2 irAEs (Figure S2). Additionally, PSM was conducted in patients with OS longer than 6 months, and the occurrence of clinically significant irAEs was also associated with significant improvements in PFS, OS, and ORR (Table S1). In patients with clinically significant irAEs, multivariate analysis illustrated that the nonsmoker was associated with good response (HR = 2.51, 95% CI = 1.25-5.03, $p = 0.010$) and PS ≥1 was related with no response (HR = 0.35, 95% CI = 0.17-0.71, $p = 0.004$) (Table S2).

3.4 | Severity and spectrum of irAEs and efficacy

Comparing patients with grade ≤1 irAEs with those with grade 2 or ≥3 irAEs, median PFS (4.5 months vs. 9.0 months vs. 4.5 months, $p < 0.001$; Figure 3A), median OS (14.4 months vs. 23.5 months vs. 13.1 months, $p < 0.001$; Figure 3B), and median ORR (29.6% vs. 45.8% vs. 37.3%, $p = 0.003$) were significantly better among patients with grade 2 irAEs. No statistical difference in response was observed between patients with grade 1 or no irAEs and those with grade ≥3 irAEs. Interestingly, 56 patients who discontinued pembrolizumab because of irAEs had significantly longer median PFS (19.5 months vs.

5.3 months, $p = 0.008$) and numerically better median OS (26.9 months vs. 17.8 months, $p = 0.112$) than patients who continued pembrolizumab despite completing fewer cycles of pembrolizumab (median [IQR]: 5 [3-8] vs. 8 [4-20], $p < 0.001$; Figure 4). This trend was seen not only in grade 2 irAEs but also in grade ≥3 irAEs, and 58 patients who continued treatment in grade ≥3 irAEs had worse outcomes than patients who discontinued treatment (data not shown) (Appendix A).

When investigating each type of irAEs and the efficacy of pembrolizumab, only endocrine and skin irAEs were related with significantly better survival outcomes. Median PFS was 10.5 months ($p = 0.005$; Figure 3C) in patients with endocrine irAEs and 12.8 months ($p < 0.001$; Figure 3E) in those with skin irAEs. Median OS was 33.2 months ($p = 0.001$; Figure 3D) in patients with endocrine irAEs and 32.1 months ($p = 0.012$; Figure 3F) in patients with skin irAEs. Patients with single and multiple irAEs had similar objective responses (median PFS: 8.3 months vs. 6.0 months, $p = 0.140$; median OS: 18.8 months vs. 22.0 months, $p = 0.641$; Figure S3).

TABLE 2 Details of immune-related adverse events (irAEs)

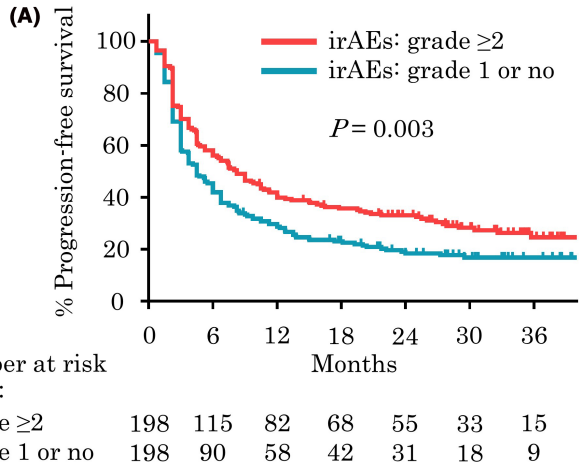
Category of irAEs	Grade ≥2 *n* (%)	Grade 2 *n* (%)	Grade ≥3 *n* (%)	ROS %
Endocrine	60 (9.7)	45 (7.3)	15 (2.4)	25.0
Skin	53 (8.5)	46 (7.4)	7 (1.1)	13.2
Gastrointestinal	43 (6.9)	32 (5.2)	11 (1.8)	25.6
Pulmonary	29 (4.7)	10 (1.6)	19 (3.1)	65.5
Hepatic	26 (4.2)	15 (2.4)	11 (1.8)	42.3
General fatigue	23 (3.7)	16 (2.6)	7 (1.1)	30.4
Neurological	16 (2.6)	13 (2.1)	3 (0.5)	18.8
Hematologic	14 (2.3)	10 (1.6)	4 (0.6)	28.6
Renal	13 (2.1)	3 (0.5)	10 (1.6)	76.9
Musculoskeletal	5 (0.8)	2 (0.3)	3 (0.5)	60.0
Infusion reaction	4 (0.6)	4 (0.6)	0 (0.0)	0.0
Other	16 (2.6)	8 (1.3)	8 (1.3)	50.0
Total	302	204	98	32.5

Abbreviations: ROS, rate of severity = grade ≥3 / grade ≥2.

4 | DISCUSSION

In this retrospective study, the occurrence of irAEs, especially low-grade irAEs, was strongly associated with higher ORR and longer PFS and OS in patients with platinum-pretreated advanced UC receiving pembrolizumab. The relationship between the onset of irAEs and ICI efficacy was recently described in some meta-analyses, and patients with anti-PD-1/L1 antibody–related AEs had better PFS, OS, and ORR.[12,13] However, most of these findings are from patients with melanoma or NSCLC, with limited reports based on data from patients with UC.[15–19] Maher et al. conducted a pooled analysis of 1747 patients with advanced UC from seven clinical trials, and better OS was observed in patients with anti-PD-1/L1 antibody–related AEs (HR = 0.45, 95% CI = 0.39-0.52).[15] Kijima et al. retrospectively evaluated 97 patients with UC receiving pembrolizumab and revealed significant improvements in ORR (52% vs. 16%, $p < 0.01$) and PFS (11.0 months vs. 3.6 months, $p = 0.02$) in patients with irAEs.[16]

One of the problems in analyzing patients with and without irAEs is the immortal time bias.[8,14] Because most irAEs occur within the first few weeks to months of treatment initiation,[20] irAEs in patients with short survival might be clinically undetected, resulting in patients being classified as irAE-free. In the setting of ICI usage in the second or later lines in particular, survival tends to be short, and this bias could be sufficient to change the results. Unfortunately, most previous reports focusing on patients with UC could not consider this bias because of their small sample sizes or study designs. Recently, Kawai et al. reported that the incidence of irAEs is a predictor of the efficacy of pembrolizumab in UC after minimizing this bias using time-dependent analysis, whereby the survival time of each patient who experienced irAEs from time of starting pembrolizumab treatment to time of final observation was divided into time from the start of pembrolizumab to the onset of initial irAE and time after



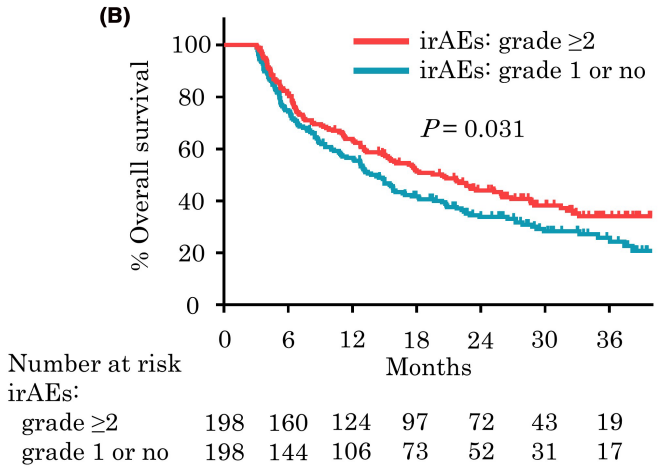


FIGURE 2 Kaplan-Meier plots analysis showing progression-free survival (A) and overall survival (B) for 396 patients with grade ≥2 immune-related adverse events (irAEs) and with grade 1 or no irAEs who survived longer than 3 months after propensity score matching

the onset of initial irAE.[21] By assigning the former period to the irAEs (–) cohort and the latter period to the irAEs (+) cohort, the survival time of the irAE (+) cohort was underestimated, allowing for a more conservative analysis than landmark analysis. While their method of minimizing the effect of immortal time bias by time-dependent analysis is commendable, even with that method, this problem has not been completely resolved because the modified irAE (–) cohort still includes many early deaths.

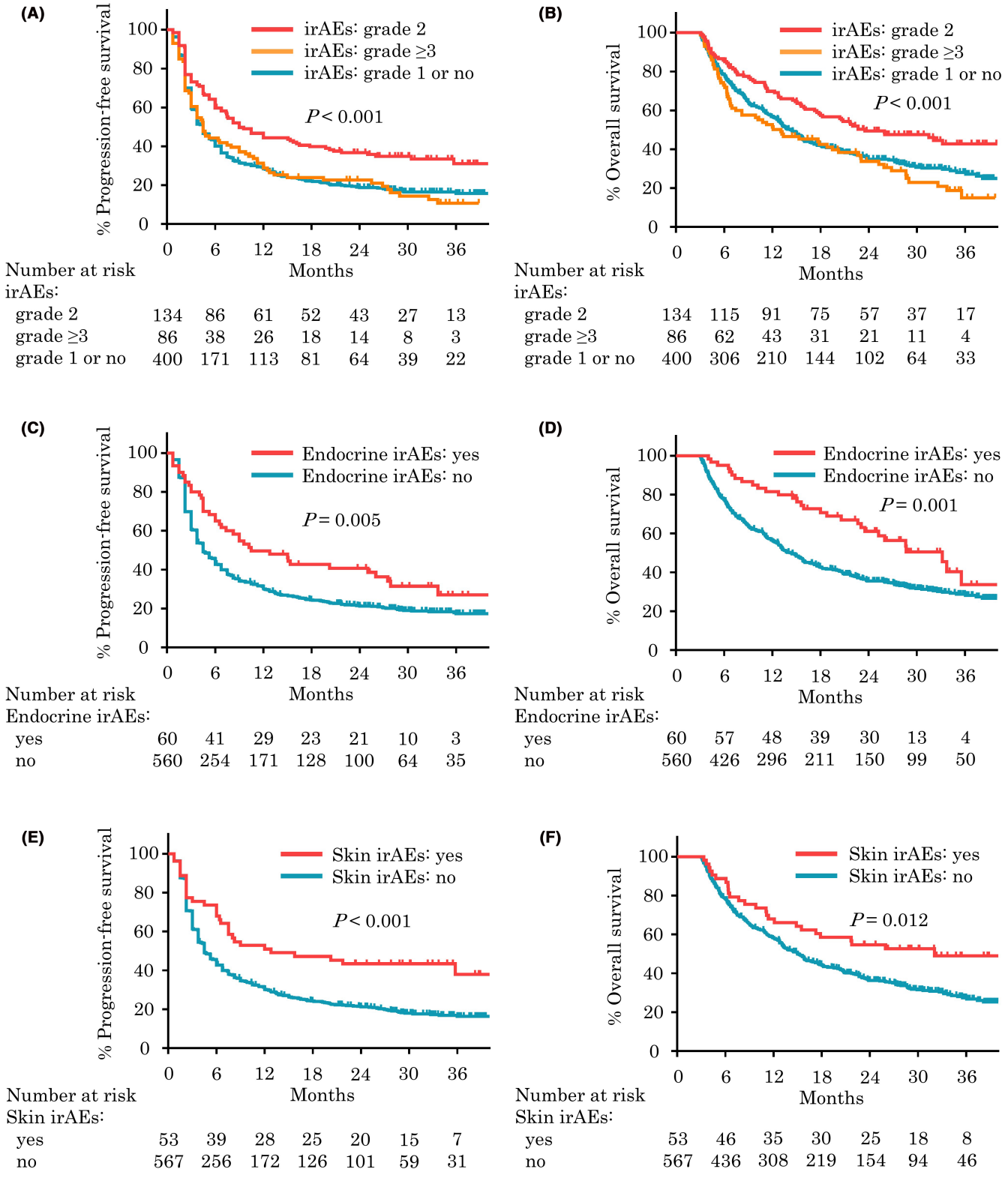


FIGURE 3 Kaplan-Meier plots analysis showing progression-free survival and overall survival for patients with grade 2 or ≥3 immune-related adverse events (irAEs) (A, B), endocrine irAEs (C, D), and skin irAEs (E, F) who survived longer than 3 months

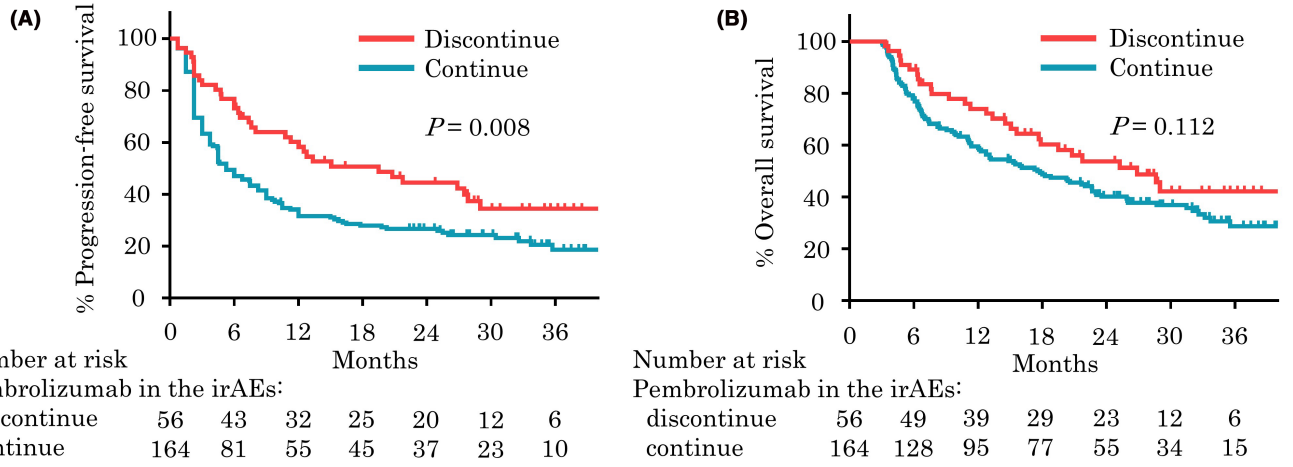


FIGURE 4 Kaplan-Meier plots analysis showing progression-free survival (A) and overall survival (B) for patients with immune-related adverse events (irAEs) who did and did not discontinue pembrolizumab

Although our landmark analysis did not fully resolve the immortal bias, by excluding patients with survival periods shorter than 3 months in the present study, this underling bias was reduced, thereby strengthening our findings. Three months seemed to be long enough as the setting of landmark because the median time of onset of overall irAEs is about 2 months, and majority of irAEs appears within 3 months, as previously reported.[22,23] The results were similar when the analysis was limited to patients who survived more than 6 months. To further emphasize the significance of irAEs as a predictor of efficacy to pembrolizumab, a sensitivity analysis was also performed. Because only about 20%-30% of all irAEs occur after 3 months of treatment,[22,24] a virtual cohort was created by randomly selecting 20% of patients from a cohort of patients who survived at least 3 months and had grade ≥2 irAEs and transferring them to a grade 1 or no irAE cohort. Despite the attempt narrowing the survival difference between the two cohorts, the presence of irAE was still shown to be a predictive factor.

A representative hypothesis explaining the relationship between ICI efficacy and irAEs is the cross-reactivity of epitopes common to the tumor and specific organ, and theoretically, hyperactivation of T cells induced by ICIs might result in better tumor responses and higher grades of irAEs.[25] Reports focusing on the association between the severity of irAEs and the efficacy of ICIs are scarce, but several studies including patients with UCs indicated that the development of grade ≥3 irAEs was an independent positive predictor of therapeutic efficacy, which could support the hypothesis.[16,26] Conversely, Zhou et al. conducted a meta-analysis of 30 studies mainly including patients with NSCLC or melanoma and identified favorable outcomes in patients with low-grade irAEs.[27] Kawai et al. evaluated 176 patients with UCs using time-dependent analysis, and the incidence of grade 1-2 irAEs was associated with good prognosis.[21]

In the present study, we were able to identify low-grade irAEs as a positive predictor of the efficacy of pembrolizumab in patients with UC, using different analysis methods and a larger cohort of patients. A prior study mentioned that patients with severe irAEs tended to require stronger immunosuppressants or modification of the treatment schedule to manage these events, and irAEs themselves can be fatal, which could have influenced the outcome.[8] In the present study, no irAE-related deaths occurred, and patients with severe irAEs were more likely to discontinue pembrolizumab because of these events than patients with low-grade irAEs. However, discontinuation of pembrolizumab because of irAEs was instead associated with better prognosis despite the short duration of treatment, and this trend was observed irrespective of the severity of irAEs. Our findings indicated that ICI efficacy might be affected more by the onset of irAEs than the duration of treatment, and therefore, modification of the treatment schedule might have less influence than expected. Although whether immunosuppressants reduce the therapeutic efficacy of ICIs is unclear,[8,15] the use of these treatments is one possible hypothesis to explain the inferiority of outcomes in patients with severe irAEs than in those with milder irAEs; however, we could not fully evaluate this in this study, representing a study limitation.

The relationship between the sites of irAEs and efficacy of ICIs was also previously reported in various types of cancer. In a meta-analysis evaluating different categories of irAEs, endocrine and skin irAEs were linked to significantly longer PFS, whereas gastrointestinal, pulmonary, and hepatic irAEs had no effect on survival.[27] Recently, the development of cutaneous irAEs and their subtypes were suggested to be protective against mortality in patients treated with PD-1 or PD-L1 therapy.[28] In patients with UC, endocrine irAEs were associated with higher ORR and longer PFS.[16] Although why specific irAEs positively affect therapeutic efficacy remained unknown, the prior report mentioned that the manageability of events differs among the types of irAEs.[11] Our results suggested the endocrine and skin irAEs are positive prognostic factors for the outcomes of pembrolizumab in patients with UC. The proportion of severe

irAEs was lower for endocrine and skin irAEs, supporting the idea that less severe irAEs contribute to better prognosis. Although some studies suggested that the number of irAEs (single or multiple) was associated with the therapeutic efficacy of ICIs,[11,26] we detected no difference in the present study.

This study had multiple limitations. First, selection bias attributable to the retrospective setting could exist, and comparisons between patients with and without irAEs are inevitably associated with the immortal time bias, as we previously mentioned. The time to irAE onset represents useful data, but we could not collect this information in this study. Second, we did not include grade 1 irAEs as low grade irAEs in our analysis, although it does not fit the general definition. However, regarding AEs as truly immune related or not is often challenging especially in lower grades, and it was difficult to collect all grade 1 irAEs retrospectively and accurately separate them from no irAEs, which may lead to bias. In addition, regarding grade 1 and grade 2 irAEs as same group may also lead to overestimation of the prognosis of grade 2 irAEs, because management of irAEs is usually different between two groups. To reduce these biases for analyzing clinically significant irAEs, patients were divided into three groups (grade ≤1, 2, and ≥3) in this study. Third, this study lacked a central review of imaging and pathology, as well as toxicity, and prognostic oncological biomarkers such as PD-L1 were not assessed. Fourth, the management of irAEs, including the usage of immunosuppressants or corticosteroids and the decision to discontinue ICIs, was not standardized in our study. We could not evaluate the impact of immunosuppressants on ICI efficacy owing to heterogeneity. Additionally, promptly treated irAEs might be considered lower-grade events, and vice versa. Nevertheless, this is the largest real-world analysis to investigate the association between irAEs and the efficacy of pembrolizumab in advanced UC.

In conclusion, the occurrence of irAEs, particularly low-grade irAEs, was a positive predictor of therapeutic efficacy in patients with platinum-pretreated advanced UC receiving pembrolizumab. The discontinuation of pembrolizumab because of irAEs, which frequently occurred in patients with severe irAEs, was associated with favorable objective responses. The severity of endocrine and skin irAEs was low, and these events were numerically related with good clinical outcomes.

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DISCLOSURE

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Reviewer Board: The research protocol was approved by the Institutional Review Board (IRB) of Kyoto University Graduate School of Medicine (approval number R1783) and the local IRB at each participating institute.

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

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