Impact of Immune-related Adverse Events on Nivolumab Efficacy in Patients With Upper Gastrointestinal Cancer

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Abstract. *Background: The development of immune-related adverse events (irAEs) has been found to be associated with survival benefits in some cancers. However, data on the relation between irAEs and gastroesophageal adenocarcinoma (GEA) or esophageal squamous cell carcinoma (ESCC) are scarce. Patients and Methods: We retrospectively reviewed the data of 29 GEA and 21 ESCC patients treated with nivolumab. We investigated the impact of the development of irAEs in GEA and ESCC patients on best overall response and survival. Results: Patients with irAEs had significantly better best overall response, overall survival and progression-free survival than those without irAEs (p=0.007, p<0.001 and p=0.005, respectively). Multivariate analyses identified an Eastern Cooperative Oncology Group performance status ≥2 and the absence of an irAE as independent poor prognostic factors (p<0.001 and 0.016, respectively). Conclusion: The development of irAEs has the potential to predict survival outcomes in patients with GEA and ESCC treated with nivolumab.*

Gastroesophageal adenocarcinoma (GEA) and esophageal cancer show high malignant potential and poor prognosis, leading to the third and sixth leading cause of cancer-related mortality worldwide, respectively, and more than 1.2 million deaths altogether in 2020 (1). First-line doublet platinum-based chemotherapy is the standard of care for both advanced or recurrent GEA and esophageal squamous cell carcinoma (ESCC), with the addition of trastuzumab in human epidermal growth factor receptor 2-positive GEA (2).

The recent development of immunotherapy has improved treatment outcomes for various types of cancer including GEA and ESCC. Nivolumab and pembrolizumab, monoclonal antibodies that target programmed cell death protein 1 (PD-1), have been approved for the treatment of advanced or recurrent unresectable GEA and ESCC on the basis of recent clinical trials demonstrating that these agents prolonged survival compared with cytotoxic chemotherapy (2, 3). Conversely, treatment with such immune-checkpoint inhibitors (ICIs) is accompanied by immune-related adverse events (irAEs) (4). The development of irAEs has been found to be associated with survival benefits in melanoma and non-small cell lung cancer, suggesting that an early onset of irAEs might be predictive of a better outcome of treatment with ICIs, and that the prompt management of irAEs could prolong the therapeutic period and maximize the therapeutic effect of ICIs (4). However, data on the relationships between irAEs and therapeutic effects of ICIs in GEA or ESCC are scarce (5).

We hypothesized that the development of irAEs in patients with GEA and ESCC treated with ICIs may be predictive of their better survival compared with those without irAEs. In this regard, this study aimed to investigate the impact of irAEs on survival in patients with advanced or recurrent GEA and ESCC treated with nivolumab.

Patients and Methods

Patients. We retrospectively collected data from the electronic medical records of all patients with advanced or recurrent GEA and ESCC who were treated with nivolumab at the Department of Surgery, Hamamatsu University School of Medicine. Nivolumab was initially administered to patients with GEA in November 2017, and to patients with ESCC in October 2018 in our institute. The end of the follow-up period was April 24, 2021. All procedures were conducted in accordance with institutional and national standards

on human experimentation and with the Declaration of Helsinki of 1964 and its later versions. The ethics committee of Hamamatsu University School of Medicine approved this study. The board waived the requirement for written patient consent for the use of clinicopathological data, and all patients agreed to participate through an opt-out approach.

Procedure. Nivolumab was administered intravenously over 30 min at a dose of 240 mg every 2 weeks until disease progression assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, or unacceptable toxicity (6). Tumors were assessed using computed tomography per RECIST version 1.1 at baseline and every two months from the start of cycle 1 or at the development of symptoms. Adverse events were assessed throughout the treatment period and for 28 days after the end of treatment according to the National Cancer Institute Common Terminology Criteria for Adverse Event, version 5.0 (7).

Statistical analysis. Statistical analyses were performed using SPSS version 27.0 software (IBM Corp., Armonk, NY, USA). Categorical data were analyzed using Fisher's exact test or the chi-squared test as appropriate. Quantitative data were analyzed using the unpaired Student's *t*-test. Survival was analyzed using the Kaplan-Meier method and log-rank test. Univariate and multivariate comparisons of survival time were performed using Cox regression analysis. $p < 0.05$ was considered statistically significant.

Results

Patient characteristics and irAE profile. The characteristics of all study participants are shown in Table I. There were 29 patients with GEA (58.0%) including 3 esophagogastric junction carcinoma and 26 gastric cancer, and 21 patients with ESCC (42.0%). Of all the patients, 13 patients (26.0%) suffered from irAEs. Patients with irAEs had significantly better Eastern Cooperative Oncology Group (ECOG) performance status (PS) ($p=0.026$), later therapy line ($p=0.044$), greater number of administrations of nivolumab ($p=0.030$) and more pharmacotherapy after nivolumab ($p=0.008$) than those without irAEs. The irAE profile is shown in Table II. The most frequent irAE was pneumonitis.

Impact of irAE on best overall response (BOR) in patients treated with nivolumab. The BOR is shown in Table III. Of all patients, 7 (14.0%) had a stable disease and 36 (72.0%) had a progressive disease. No patients had complete or partial response to nivolumab. The tumor response was not evaluable in 7 patients (14.0%). The BOR rates were compared between patients with and without irAEs except for 7 patients with unevaluable tumor response. Patients with irAEs (*n*=9) had significantly better BOR than those without irAEs (*n*=34) ($p=0.007$).

Impact of irAEs on overall survival (OS) and progression-free survival (PFS) in patients treated with nivolumab. The Kaplan-Meier curves for OS of all 50 patients according to

Table I. *Clinicopathological characteristics*.

Characteristic	All patients	irAE (−)	irAE (+)	*p*-Value
Total	50	37 (74.0%)	13 (26.0%)	
Age (years)	71 (43-86)	71 (46-86)	74 (63-84)	0.261
<65	9 (18.0%)	8 (21.6%)	1 (7.7%)	
≥65	41 (82.0%)	29 (78.4%)	12 (92.3%)	
Gender				0.148
Male	39 (78.0%)	27 (73.0%)	12 (92.3%)	
Female	11 (22.0%)	10 (27.0%)	1 (7.7%)	
ECOG PS				0.026
≤1	39 (78.0%)	26 (70.3%)	13 (100%)	
≥2	11 (22.0%)	11 (29.7%)	0 (0%)	
Tumor location				0.275
Esophagus	21 (42.0%)	18 (48.6%)	3 (23.1%)	
Esophagogastric junction	3 (6.0%)	2 (5.4%)	1 (7.7%)	
Stomach	26 (52.0%)	17 (45.9%)	9 (69.2%)	
History of surgery				0.648
Yes	32 (64.0%)	23 (62.2%)	9 (69.2%)	
No	18 (36.0%)	14 (37.8%)	4 (30.8%)	
Histology				0.108
Squamous cell carcinoma	21 (42.0%)	18 (48.6%)	3 (23.1%)	
Adenocarcinoma	29 (58.0%)	19 (51.4%)	10 (76.9%)	
Number of organs with metastases				0.856
≤1	28 (56.0%)	21 (56.8%)	7 (53.8%)	
≥2	22 (44.0%)	16 (43.2%)	6 (46.2%)	
Site of metastases				
Lymph node	26 (52.0%)	17 (45.9%)	9 (69.2%)	0.148
Peritoneum	21 (42.0%)	15 (40.5%)	6 (46.2%)	0.724
Lung	11 (22.0%)	8 (21.6%)	3 (23.1%)	0.913
Liver	8 (16.0%)	6 (16.2%)	2 (15.4%)	0.944
Bone	5 (10.0%)	4 (10.8%)	1 (7.7%)	0.747
Therapy line				0.044
2nd	9 (18.0%)	8 (21.6%)	1 (7.7%)	
3rd	30 (60.0%)	24 (64.9%)	6 (46.2%)	
≥4th	11 (22.0%)	5 (13.5%)	6 (46.2%)	
Number of administrations				0.030
≤4	38 (76.0%)	31 (83.8%)	6 (46.2%)	
≥5	12 (24.0%)	6 (16.2%)	7 (53.8%)	
Pharmacotherapy after nivolumab				0.008
Yes	16 (32.0%)	8 (21.6%)	8 (61.5%)	
No	34 (68.0%)	29 (78.4%)	5 (38.5%)	

Age is presented as median (range). irAE: Immune-related adverse event; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

the incidence of irAEs are shown in Figure 1A. Patients with irAEs (*n*=13) had significantly better OS than those without irAEs (*n*=37) ($p<0.001$). Subgroup analysis revealed that patients with GEA and irAEs (*n*=10) had significantly better OS than those without irAEs (*n*=19) (Figure 1B, $p<0.001$). OS was comparable between patients with ESCC with irAEs (*n*=3) and those without irAEs (*n*=18) (Figure 1c, $p=0.309$).

Table II. *Immune-related adverse events according to category and grade.*

Category	Total (n=50)	Grade 1-2	Grade 3-4
Any	13 (26.0%)	9 (18.0%)	5 (10.0%)
Pneumonitis	5 (10.0%)	4 (8.0%)	1 (2.0%)
Endocrine			
Thyroiditis/ hypothyroidism	3 (6.0%)	2 (4.0%)	1 (2.0%)
Hypophysitis	1 (2.0%)	0 (0%)	1 (2.0%)
ACTH deficiency	1 (2.0%)	0 (0%)	1 (2.0%)
Gastrointestinal			
Diarrhea/colitis	3 (6.0%)	1 (2.0%)	2 (4.0%)
Mucositis	1 (2.0%)	0 (0%)	1 (2.0%)
Skin			
Rash	1 (2.0%)	1 (2.0%)	0 (0%)

ACTH: Adrenocorticotropic hormone.

Table III. *Best overall response to nivolumab.*

Best overall response	All patients	irAE (−)	irAE (+)	*p*-Value
Stable disease	7 (14.0%)	3 (8.1%)	4 (30.8%)	0.007
Progressive disease	36 (72.0%)	31 (83.8%)	5 (38.5%)	
Not evaluable	7 (14.0%)	3 (8.1%)	4 (30.8%)	

irAE: Immune-related adverse event.

Table IV. *Results of univariate and multivariate analyses showing factors affecting the overall survival.*

Variable	Univariate *p*-Value	Multivariate *p*-Value	Hazard ratio	95% CI
Age (≥65 *vs*. <65)	0.731	0.492	1.424	0.519-3.906
Sex (male *vs*. female)	0.428	0.566	1.357	0.478-3.861
Histology (squamous cell carcinoma *vs*. adenocarcinoma)	0.791	0.611	1.272	0.503-3.226
Number of organs with metastases (≥2 *vs*. ≤1)	0.547	0.613	1.279	0.492-3.322
ECOG PS (≥2 *vs*. ≤1)	<0.001	<0.001	17.931	4.964-64.773
irAE (no *vs*. yes)	<0.001	0.016	7.299	1.456-37.037

ECOG: Eastern Cooperative Oncology Group; PS: performance status; irAE: immune-related adverse event.

The Kaplan-Meier curves for progression-free survival (PFS) of all 50 patients according to the incidence of irAEs are shown in Figure 2A. Patients with irAEs (*n*=13) had significantly better PFS than those without irAEs (*n*=37) (*p*=0.005). Subgroup analysis revealed that PFS was significantly better in patients with irAEs than in those without irAEs in both GEA (*n*=10 *vs*. 19, Figure 2B, *p*=0.032) and ESCC (*n*=3 *vs*. 18, Figure 2C, *p*=0.012).

Prognostic factors predicting poor survival in patients treated with nivolumab. Univariate analysis revealed that an ECOG PS ≥2 and the absence of irAEs were clinically important factors affecting the OS of patients with GEA and ESCC treated with nivolumab. On multivariate analysis, an ECOG PS ≥2 [hazard ratio (HR)=17.931; 95% confidence interval (CI)=4.964-64.773; *p*<0.001] and the absence of irAEs [HR=7.299; 95% CI=1.456-37.037; *p*=0.016] were identified as independent poor prognostic factors (Table IV).

Discussion

The development of irAEs has been found to be associated with survival benefits in melanoma, non-small cell lung cancer, renal cell carcinoma, and very recently in gastric cancer (5, 8-13). However, to date, the association between irAEs and the prognosis with esophageal cancer has remained unknown. In the present study, we first showed that the development of irAEs is associated with better PFS in patients with ESCC who received ICIs, and that the impact of irAEs could differ between GEA and ESCC. We previously performed a comprehensive characterization of genomic alterations in ESCC and esophageal adenocarcinoma (EAC), and showed that EAC was genetically different from ESCC and proved to be the same as gastric adenocarcinoma (14). In

the present study, patients with irAEs had better PFS than those without irAEs in both subgroups of GEA and ESCC. Although there was no significant difference in OS between patients with ESCC with and without irAEs (*p*=0.309), the number of patients with ESCC with irAEs (*n*=3) was too small to compare with those without irAEs (*n*=18) in this study. Taken together, our results suggest that the incidence of irAEs could be associated with better prognosis across cancer types. Moreover, patients with irAEs had a significantly better overall response compared to patients without irAEs, supporting the impact of irAEs on good prognosis.

The mechanisms underlying the association of irAEs with the outcome of treatment with PD-1 inhibitors are unknown. Previous studies showing an association of vitiligo with the outcome of immunotherapy in patients with melanoma have suggested that antigens shared between melanoma cells and normal melanocytes might contribute to this association (15-17). Whether gastric cancer or esophageal cancer cells share antigen with tissues affected by irAEs in patients with GEA or ESCC remains to be determined. In the present study, 10 of 29 patients with GEA (34.5%) and 3 of 21 patients with ESCC (14.3%) developed irAEs and patients with GEA tended to develop more irAEs than those with ESCC. It was
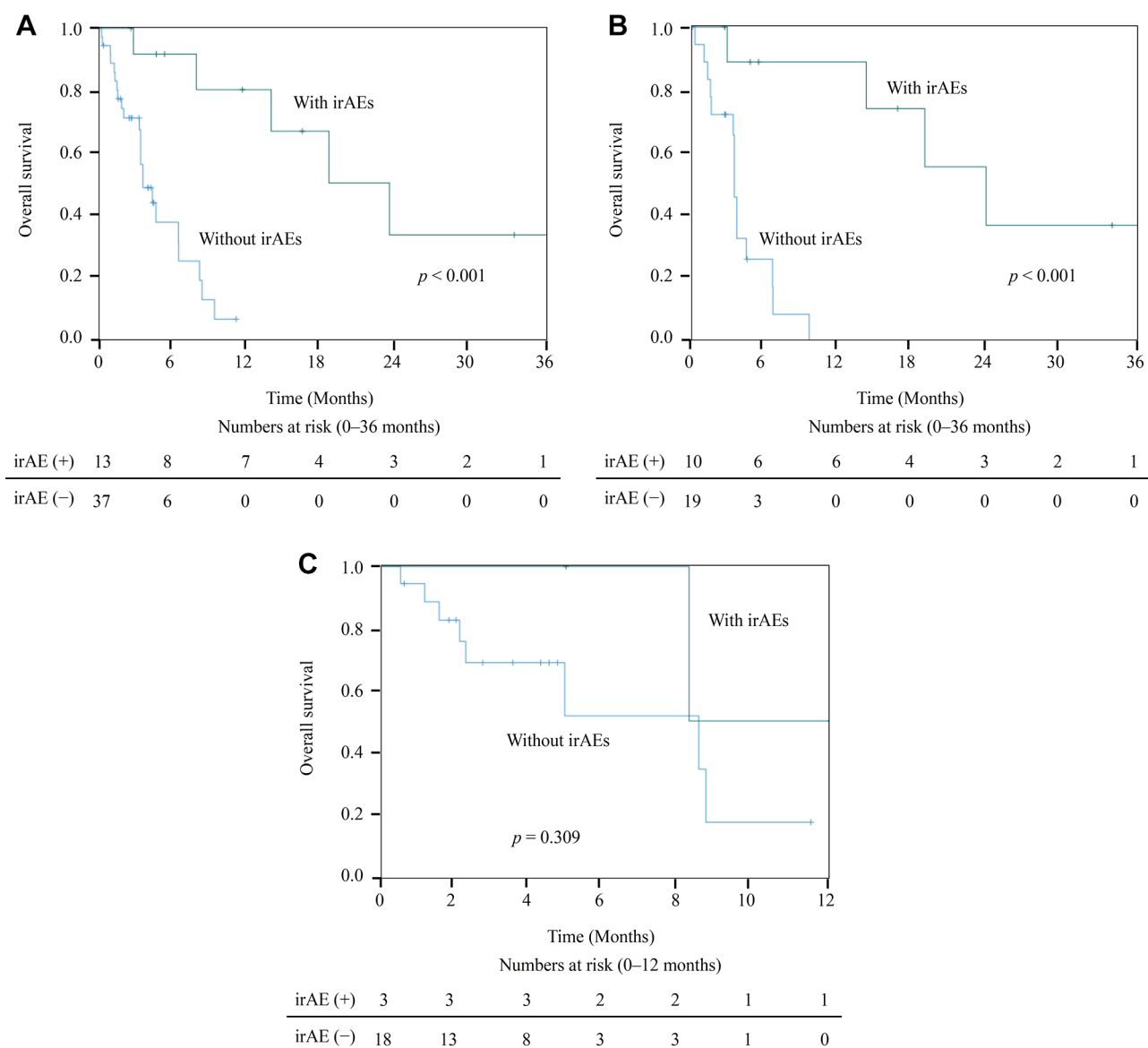
Figure 1. *Kaplan-Meier overall survival curves for (A) all patients, (B) patients with gastroesophageal adenocarcinoma and (C) patients with esophageal squamous cell carcinoma with and without immune-related adverse effects (irAEs).*

suggested that irAEs might affect favorable prognosis regardless of cancer type, even if the irAE incidence rates depend on the type of cancer.

Patients with irAEs had significantly greater number of administrations of nivolumab, and more post-nivolumab therapy than those without irAEs. Multivariate analyses revealed that ECOG PS ≥2 and the absence of an irAE were found to be significant poor prognostic factors. It is possible that irAEs could be managed more appropriately in patients with better PS, which increased the therapeutic opportunity after nivolumab and led to better outcomes. Adequate and

intensive management of irAEs appears to be important to enable continuous post-nivolumab therapy and prolong survival. Matsumoto *et al*. reported that patients with a good PS had a better PFS and OS than those with poor PS (18). Patients with good PS might undergo nivolumab as early as possible to have good prognosis.

This study has several limitations. Most importantly, it was a retrospective single-center investigation with a small number of patients; the number of patients with ESCC with irAEs was particularly small. Second, the follow-up time was not long enough to permit us to fully address the long-term
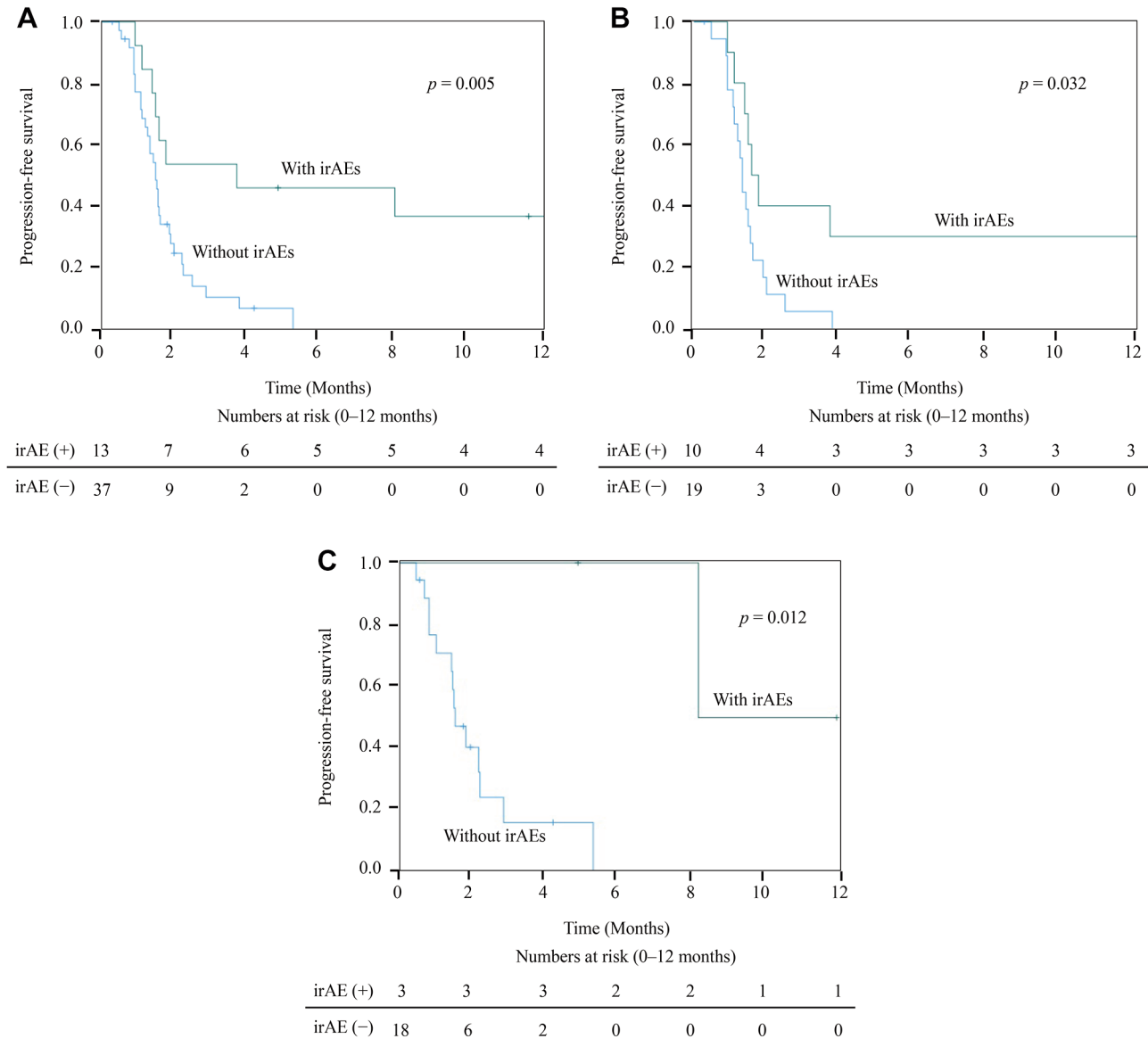
Figure 2. *Kaplan-Meier survival curves of progression-free survival for (A) all patients, (B) patients with gastroesophageal adenocarcinoma and (C) patients with esophageal squamous cell carcinoma with and without immune-related adverse effects (irAEs).*

survival outcome. Third, the study may not have detected irAEs that were not explicitly documented in the medical record. Further studies with larger cohorts will be needed to confirm an association between the development of irAEs and the efficacy of nivolumab.

In conclusion, the development of irAEs has the potential to predict survival outcomes in patients with GEA and ESCC treated with nivolumab. The development of irAEs should be monitored carefully after starting nivolumab treatment to ensure longer survival in patients with GEA and ESCC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

E.B and H.K drafted and wrote the manuscript. E.B, H.K and H.T were involved in study design and data interpretation. E.B, H.K, R.H, W.S, S.K, T.M, T.M and Y.H were involved in the acquisition of the data. E.B analyzed the data. All Authors read and approved the manuscript.

Acknowledgements

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