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Relationship between immune-related adverse events and the long-term outcomes in recurrent/metastatic head and neck squamous cell carcinoma treated with nivolumab

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ABSTRACT

Objectives: Immune-related adverse events (irAEs) have been shown to be associated with higher antitumor responses and a clinical benefit in non-small cell lung carcinoma, renal cell carcinoma, and melanoma patients. However, little is known regarding the association between irAEs and the clinical effect of nivolumab for recurrent/metastatic head and neck squamous cell carcinoma (R/MHNSCC).

Materials and methods: We evaluated 108 patients treated with nivolumab for R/MHNSCC at 2 participating institutions. IrAEs were identified and profiled. We analyzed the association of each immune-related adverse effect with the clinical outcome of the patients.

Results: Among 108 patients, the objective response rate (ORR) was 29.6% (32/108 patients), and the disease control rate (DCR) was 50.0% (54/108 patients). IrAEs were observed in 41 patients (38.0%). Patients with irAEs had a significantly higher ORR and DCR than those without irAEs (46.3% vs. 19.4%, $P = 0.004$ and 75.6% vs. 34.3%, $P < 0.001$, respectively). The median progression-free and overall survival rates in patients with irAEs were significantly longer than in those without irAEs.

Conclusions: There was a significant relationship between irAEs and efficacy in R/MHNSCC patients treated with nivolumab. Our results indicate that the development of irAEs may aid in the earlier prediction of anticancer effects in patients with recurrent or metastatic HNSCC during nivolumab monotherapy.

Introduction

Nivolumab, an anti-programmed death-1 (PD-1) antibody, is an immune checkpoint inhibitor (ICI), which are new cancer immunotherapy agents. The recent CheckMate 141 clinical trial reported that nivolumab was effective in extending the median overall survival (OS) in this patient population compared with standard chemotherapies. Based on these data, nivolumab has been approved for the treatment of patients with R/MHNSCC who demonstrate disease progression either during or after receiving platinum-based therapy [1]. The unique point of ICIs is that these drugs offer a clinical benefit even if they seem to be ineffective [2], and some patients show a persistent long-term effect even after stopping nivolumab therapy [3].

However, in some cases, ICIs have induced side effects known as "immune-related adverse events (irAEs)", which differ from the effects experienced with traditional chemotherapy and targeted therapy [4]. Recent reports have suggested that the occurrence of irAEs was related to higher antitumor responses and a clinical benefit in patients with non-small-cell lung carcinoma [5,6], melanoma [7], and renal cell carcinoma [8]. In addition, several previous reports have suggested that a better outcome after treatment with ICIs was associated with multiple irAEs [5], severe irAEs (grade ≥ 3) [9], the location of the manifested irAE (e.g. cutaneous irAEs) [7,8,10], and an early irAE onset (within two weeks of administration) [11].

The present study evaluated the association between the irAE profile and nivolumab efficacy in patients with R/MHNSCC.

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Materials and Methods

Patients

From April 2017 to August 2018, 108 patients with R/MHNSCC who were treated with nivolumab were retrospectively analyzed. The clinical characteristics of the patients are summarized in Table 1.

All tumors were histologically confirmed to be SCC. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 52 patients, PS 1 in 49 patients, PS 2 in 5 patients and PS 3 in 2 patients. Nivolumab was used as a first-line therapy in 59.2% (64/108 patients), a second-line therapy in 30.6% (33/108 patients), a third-line therapy in 9.3% (10/108 patients) and a fourth-line therapy in 0.9% (1/108 patients).

Patient follow-up lasted until death or until the cut-off date (June 30, 2019). The median follow-up interval was 7.5 months (range 0.3–27 months).

The evaluation of the response

The tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (version1.1) based on the findings of computed tomography which was performed every 8 to 12 weeks. Progressive disease (PD) was defined as a ≥ 20% increase in the sum of the diameters of the target lesions or the appearance of new metastatic lesions. Stable disease (SD) was defined as ranging from a < 30% decrease to a 20% increase in the tumor size on imaging. A partial response (PR) was defined as a ≥ 30% decrease in the sum of the diameters of target lesions. We evaluated the best overall response (BOR) of all patients as complete response (CR), PR, SD or PD. The objective response rate (ORR) corresponded to CR and PR, and the disease control rate (DCR) corresponded to CR, PR and SD. From the first day of treatment with nivolumab as the starting point, the overall survival (OS) was assessed up until death, and the progression-free survival (PFS) was assessed to the day of disease progression or death. The IrAEs were evaluated according to a protocol described in a previous study [4]. Toxicity was assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The study protocol was approved by the institutional review board of Kyushu University (reference number: 2019-239) and the Kyushu Cancer Center (reference number: 2019–58). All patients provided their informed consent for the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Table 1
The patients characteristics according to the development of immune-related adverse events (irAEs).

Characteristics	Number of patients (%)			P value
	Total (n = 108)	With irAEs (n = 41)	Without irAEs (n = 67)	
Age				
< 75 years	90 (83.3)	36 (87.8)	54 (80.6)	0.380
≧75 years	18 (16.7)	5 (12.2)	13 (19.4)	
Median (range)	66.0 (24–87)	64.0 (33–84)	67.0 (24–87)	0.127
Gender				0.021
Male	81 (75.0)	36 (87.8)	45 (67.2)	
Female	27 (25.0)	5 (12.2)	22 (37.8)	
ECOG PS				0.249
0–1	101(93.5)	40 (97.6)	61 (91.0)	
2–4	7(6.5)	1 (2.4)	6 (9.0)	
Primary site				0.050
Sinonasal truct	16 (14.8)	9 (22.0)	7 (10.4)	
Oral cavity	28 (25.9)	6 (14.6)	22 (32.9)	
Nasopharynx	6 (5.6)	2 (4.9)	4 (6.0)	
Oropharynx	19 (17.6)	9 (22.0)	10 (14.9)	
Hypopharynx	26 (24.1)	13 (31.6)	13 (19.3)	
Larynx	5 (4.6)	2 (4.9)	3 (4.5)	
External auditory canal	6 (5.6)	0 (0.0.)	6 (9.0)	
Others (salivary gland & primary unknown)	2 (2.8)	0 (0.0)	2 (3.0)	
PDL-1 expression				
+	29 (26.9)	9 (22.0)	20 (29.9)	0.245*
−	9 (8.3)	5 (12.2)	4 (6.0)	
Not Evaluated	70 (64.8)	27 (65.8)	43 (64.1)	
RT to locoregional site				0.287
Radiotherapy +	105 (97.2)	41 (100.0)	64 (95.5)	
Radiotherapy −	3 (2.8)	0 (0)	3 (4.5)	
Prior systemic therapy				0.844
Cetuximab containing therapy +	48 (44.4)	19 (46.3)	29 (43.3)	
Cetuximab containing therapy −	60 (55.6)	22 (53.7)	38 (56.7)	

RT: Radiotherapy.
* Test with the exception of "not evaluated".

Statistical analyses

All calculations were performed using the JMP 14 software program (SAS Institute, Cary, NC, USA). The OS and PFS were calculated using the Kaplan-Meier method and were evaluated with the log-rank test, and the categorical variables were analyzed using Fisher's exact test. Continuous variables were analyzed using the Mann-Whitney *U* test. The risk was expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Univariate and multivariate Cox proportional hazards regression models were used to assess the associations between potential confounding variables and the PFS and OS. A multivariable analysis was performed after adjusting for age, gender, and PS. Differences with a p value < 0.05 considered to be significant.

Results

Treatment efficacy

Among all patients, the ORR was 29.6% (32/108 patients), and the DCR was 50.0% (54/108 patients). The median OS for all patients was 13.0 months, and the median PFS was 3.7 months. The estimated 1-year OS and PFS rates were 54.4% and 24.4%, respectively (Fig. 1a, 1b).

IrAE profile

Forty-one cases (38%) experienced a total of 53 irAEs. The development of irAEs was more frequent in male patients than in female patients. However, other patient characteristics, including the age, PS, primary site, history of radiotherapy and history of cetuximab-containing therapy, were not significantly associated with irAE emergence (Table 1).

Table 2 summarizes the profiles of the 53 irAEs. The median time from the first day of nivolumab treatment to irAE onset was 8.6 weeks (range 0.1–50). The most typical pattern of irAEs was Grade 1 to 2 (42/53 events, 79.2%) and an onset after more than 2 weeks (40/53 events, 75.5%). Regarding the type of irAEs, endocrine irAEs were the most frequent (14/53 events, 26.4%), followed by skin AEs (11/53 events, 20.8%) and gastrointestinal AEs (8/53 events, 15.1%). The median time to the onset of irAEs and the distribution over time of individual irAEs are shown in Fig. 2.

Clinical outcomes and the association of irAEs with nivolumab efficacy

The patients with irAEs had a significantly higher ORR and DCR than those without irAEs (46.3% vs. 19.4%, $P = 0.004$ and 75.6% vs. 34.3%, $P < 0.001$ respectively) (Table 3). All five cases with CR had irAEs. The patients with irAEs had a significantly longer median OS and PFS than those without irAEs (not reached (NR) [95% CI: NR-NR] vs.

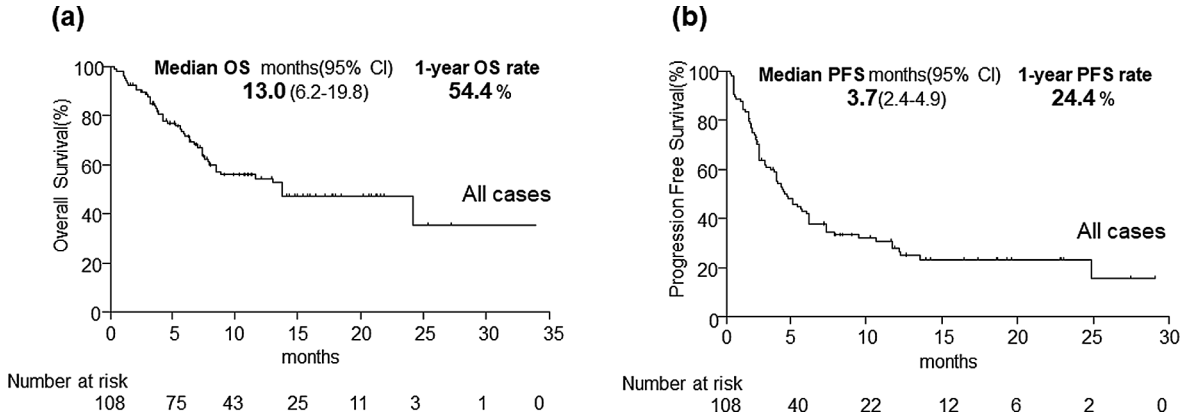

Fig. 1. Kaplan–Meier curves for the (a) overall survival and (b) progression-free survival in all patients.

Table 2
Profiles of irAEs.

Category	Number of events (%)				
	Total	Grade (1)(2)	Grade (3)(4)	Early (≦2w)	Later (＞2w)
Any	53	42 (79.2)	11 (20.8)	13 (24.5)	40 (75.5)
Endocrine	14 (26.4)	12 (22.6)	2 (3.8)	0	14 (26.4)
Hypothyroidism	12	12	0		12
Hypophysis	1	0	1		1
Hyperglycemia	1	0	1		1
Skin	11 (20.8)	10 (18.9)	1 (1.9)	2 (3.8)	9 (17.0)
Rash/Pruritus	11	10	1	2	9
Gastrointestinal	8 (15.1)	8 (15.1)	0 (0.0)	1 (1.9)	7 (13.1)
Diarrhea/Nausea	8	8	0	1	7
Hepatobiliary	6 (11.4)	3 (5.7)	3 (5.7)	4 (7.6)	2 (3.8)
Elevated hepatic enzymes	5	2	3	3	2
Cholangitis	1	1	0	1	0
Pulmonary	4 (7.6)	2 (3.8)	2 (3.8)	1 (1.9)	3 (5.7)
Interstitial pneumonia	4	2	2	1	3
Renal	4 (7.6)	4 (7.6)	0 (0.0)	2 (3.8)	2 (3.8)
Elevated creatinine	4	4	0	2	2
Other	6 (11.4)	3 (5.7)	3 (5.7)	3 (5.7)	3 (5.7)
Myositis/arthritis	2	1	1	2	0
Myocarditis	1	0	1	0	1
Encephalitis	1	0	1	0	1
Ophthalmoneuritis	1	1	0	0	1
Fever	1	1	0	1	0

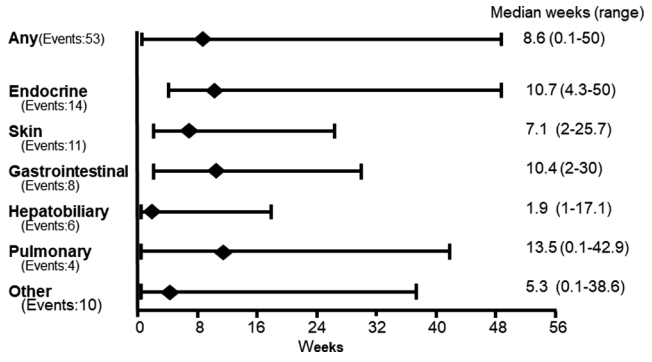

Fig. 2. Time to onset of immune-related adverse events (median with range).

Table 3
The bBest overall response according to the status of with or without irAE.

	Number of patients (%)			P value
	Total (n = 108)	With irAEs (n = 41)	Without irAEs (n = 67)	
ORR, n(%)	32 (29.6)	19 (46.3)	13 (19.4)	0.004
DCR, n(%)	54 (50.0)	31 (75.6)	23 (34.3)	< 0.001

7.2 months [95% CI: 6.2–8.7], $P < 0.0001$ and 8.0 months [95% CI: 2.8–13.2] vs. 3.0 months [95% CI: 1.8–4.2], $P = 0.008$, respectively) (Fig. 3a,3b).

The results of univariate and multivariate analyses regarding the prognostic factors influencing the 1-year OS and PFS or median OS and PFS among R/MHNSCC patients are summarized in Table 4. As described above, according to a multivariate analysis, the occurrence of irAEs and PS 0-1 status were independent prognostic factors (HR: 0.29 [95% CI: 0.13–0.61], $P = 0.0007$ and HR: 11.57 [95% CI: 3.77–33.09], $P < 0.0001$) of R/MHNSCC patients with nivolumab therapy.

Association between the type of irAEs and clinical outcomes

The PFS according to the number of irAEs (≥2 vs. 1), severity of irAEs (Grade ≥ 3 vs. < 3) and the onset of irAEs (early vs. later) was analyzed. However, there were no significant associations between the PFS and the number, severity or onset of irAEs.

We next evaluated the PFS based on the location of irAEs (i.e. endocrine vs. non-endocrine, or cutaneous vs. non-cutaneous, or gastrointestinal vs. non– gastrointestinal) in each group. Although there were no significant associations between the PFS and endocrine or cutaneous irAEs, the PFS was longer in patients with gastrointestinal irAEs than in those with non-gastrointestinal irAEs (gastrointestinal vs. non-gastrointestinal: NR [95% CI: NR-NR] vs. 6.0 months [95% CI: 2.2–9.8] $P = 0.041$) (Fig. 4). A multivariate analysis also confirmed that only gastrointestinal irAEs were significantly associated with a longer PFS (Table 5).

Discussion

The global phase III study "CheckMate 141 clinical trials" demonstrated that nivolumab improved the prognosis in R/MHNSCC patients compared with standard therapy [1]. That study showed that the ORR was 13.3%, and the 1-year OS rate was 36.0% in patients treated with nivolumab. It also mentioned that treatment-related adverse events

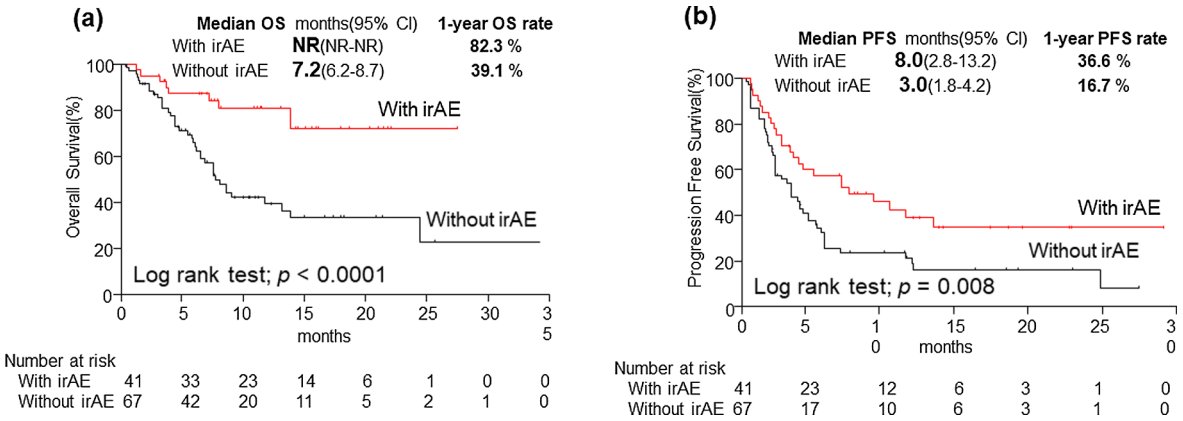

Fig. 3. Kaplan–Meier curves for the (a) overall survival (b) progression-free survival in patients with or without irAEs.

Table 4
Univariate and Multivariate analysis analyses of clinical factors associated with the OS and PFS.

Clinical factor	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age								
< 75 years (n = 90)	0.73 (0.35–1.36)	0.338	0.42 (0.17–0.91)	0.026	1.42 (0.64–2.80)	0.366	0.85 (0.33–1.96)	0.714
≧75 years (n = 18)								
ECOG PS								
0–1 (n = 101)	5.62 (2.28–11.96)	**0.0006**	11.67 (3.95–31.80)	**< 0.0001**	12.80 (4.81–30.92)	**< 0.0001**	11.57 (3.77–33.09)	**< 0.0001**
2–4 (n = 7)								
Radiotherapy to locoregional site								
Radiotherapy + (n = 105)	0.68 (0.25–2.80)	0.544	1.46 (0.52–6.10)	0.512	0.28 (0.10–1.15)	0.072	0.60 (0.21–2.57)	0.445
Radiotherapy - (n = 3)								
Prior systemic therapy								
Cetuximab containing therapy + (n = 48)	1.39 (0.89–2.19)	0.151	1.56 (0.97–2.51)	0.067	1.30 (0.73–2.32)	0.373	1.46 (0.79-2.75)	0.229
Cetuximab containing therapy - (n = 60)								
IrAEs								
With irAEs (n = 41)	0.53 (0.32–0.85)	**0.0081**	0.53 (0.31–0.86)	**0.01**	0.26 (0.12–0.52)	**< 0.0001**	0.29 (0.13–0.61)	**0.0007**
Without irAEs (n = 67)								

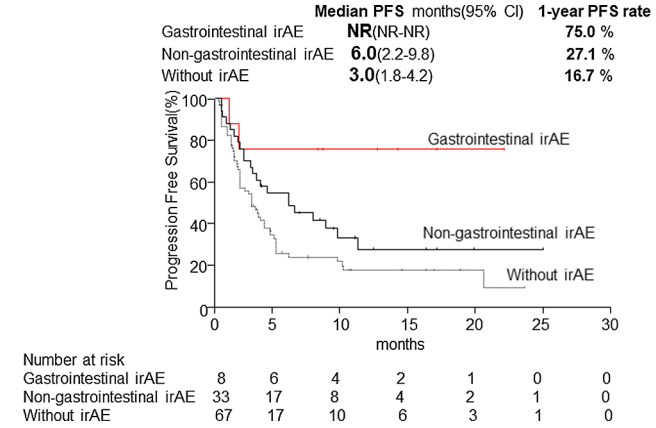

Fig. 4. Kaplan–Meier curves for the progression-free survival in patients with gastrointestinal or non-gastrointestinal irAEs or in those without irAEs at all.

occurred in 58.9% of patients (Grade ≥ 3 in 13.1%) [1]. In contrast, Kiyota et al. reported that the ORR and OS appeared better in the Asian population than in other populations according to the CheckMate 141 subgroup analysis when the efficacy of nivolumab in the Asian population receiving nivolumab was compared with the global results [12]. The present study indicated that the ORR was 29.6%, and the 1-year OS rate was 54.4%. These results were favorable compared to those of the

Table 5
Univariate and Multivariate analysis analyses of the effect of irAE development location on PFS.

location of irAEs	PFS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Endocrine (n = 14)	0.72 (0.35–1.44)	0.353	0.56 (0.35–1.47)	0.369
Non-endocrine (n = 27)				
Cutaneous (n = 11)	0.61 (0.27–1.41)	0.249	0.65 (0.28–1.52)	0.319
Non-cutaneous (n = 30)				
Gastrointestinal (n = 8)	0.23 (0.06–0.92)	**0.038**	0.23 (0.06–0.94)	**0.040**
Non-gastrointestinal (n = 33)				

"CheckMate 141 clinical trials" and consistent with the Asian subgroup analysis. These observations suggest that nivolumab may be effective for HNSCC in the Asian population.

To date, several reports have described the groups in whom nivolumab is most effective using real-world data. In the context of a changing immune environment, previous reports showed that a high PD-L1 expression correlated with an improved efficacy of ICIs [13], and the tumor antigen release elicited by radiotherapy was considered to have led to the activation of anticancer immune responses [14,15]. It was also reported that using an anti-epidermal growth factor receptor

(EGFR) antibody (e.g. cetuximab) may disrupt the effect of nivolumab, as the inhibition of EGFR causes the downregulation of PDL-1 expression and immune escape in cancer [16–18]. Although we could not find any correlation between the effects of nivolumab and the history of radiotherapy or cetuximab therapy in the univariate and multivariate analyses of the present study, we must consider that this interaction may occur when both treatments are administered concurrently. In fact, multiple ongoing clinical trials are investigating the combination of anti-PD1 antibodies with chemoradiotherapy (NCT02952586, NCT3040999, NCT02999087, NCT03349710, NCT03258554), and the combination of anti-PD1 inhibitors with cetuximab and RT (NCT03258554) [19].

Our findings showed that the patients with irAEs had a significantly higher ORR and a longer PFS and OS than those without irAEs, and the development of irAEs was associated with a survival benefit in patients with R/MSCC treated with nivolumab. Our results were consistent with those of previous studies of malignant tumors, including head and neck cancer [20], lung cancer [5,6], melanoma [7], and renal cell cancer [8].

Adverse events of antitumor agents usually progress to dose-limiting toxicities or result in the interruption of antitumor therapy, so patients who show such side effects generally have a poor prognosis. In contrast, the irAEs of ICIs typically indicate an encouraging response and a clinical benefit for the treated patients. It has been suggested that tumor neoantigens and normal tissue antigens might cross-react in the patients with irAEs and this active immune status may have been the cause of the meaningful outcome obtained in our study [21].

Regarding the pattern and type of irAEs, although previous reports have indicated that the development of multiple irAEs [5], an early irAE onset (within two week) [11] or a severe grade (≥ 3) [9] are associated with the clinical outcome, we found no evidence supporting any of these associations. In contrast, our multivariable analysis showed that only gastrointestinal irAEs were significantly associated with a longer PFS. Several reports have shown that a longer PFS or OS after treatment with ICIs is associated with irAEs in specific organs, and the occurrence of specific irAEs might depend on the type of cancer [5,7,8,10,22]. For example, the occurrence of cutaneous irAEs only correlated with a better outcome in melanoma patients [7], whereas gastrointestinal and endocrine irAEs had a statistically significant association with a longer PFS in lung cancer patients [5]. The mechanism underlying this correlation is not well understood. However, these findings suggest that cancer cells and the tissues in which irAEs occur are very similar in makeup [5], or the modulation of the PD-1 pathway may cause typical cutaneous changes similar to graft-versus-host-disease (GVHD) [23,24]. As the skin and gastrointestinal tract are the organs that develop GVHD most frequently, if we consider irAEs to indicate an excessive immunoreaction, then cutaneous and/or gastrointestinal irAEs may be associated with a good prognosis.

Several limitations are associated with this study, including its retrospective nature, small sample size and insufficient examination of the PD-L1 expression. Given these limitations, we intend to accumulate a larger number of R/MHNSCC patients and their associated data over a long follow-up period. We believe that the present investigation is a useful stepping stone for our next study, with further confirmation of our findings warranted.

Conclusion

In conclusion, the major finding of this study is suggested to be that unique immune toxicities, commonly described as irAEs, are significantly associated with improved treatment outcomes, including the survival, and tumor response in R/MHNSCC patients receiving nivolumab therapy. We believe that the development of irAEs may aid in the earlier prediction of an anticancer effect in patients with recurrent or metastatic HNSCC during nivolumab monotherapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial in-terests or personal relationships that could have appeared to influence the work reported in this paper.

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