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Letter to the Editor

Development of endocrine immune-related adverse events and improved survival in advanced melanoma patients treated with nivolumab monotherapy

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To the Editor,

Immune checkpoint inhibitors (ICIs) are well known to cause inflammatory side-effects in various organ systems—including endocrine glands—by activating the immune system [1–3]. Among various immune-related adverse events (irAEs), endocrine irAEs often exhibit non-specific symptoms and require caution during evaluation. In recent years, a study of clinical biomarkers for ICIs was undertaken, with a few studies describing the correlation between irAEs and treatment efficacy [4–9]. However, no study has yet revealed the association between endocrine irAEs and the efficacy of nivolumab monotherapy in the treatment of melanoma. Therefore, we aimed to describe the profile of endocrine irAEs in 69 advanced melanoma patients treated with nivolumab monotherapy at our institution and investigate the correlation between endocrine irAEs and the efficacy of nivolumab.

Records of 73 unresectable Stage II/III or Stage IV melanoma patients who received nivolumab monotherapy at our institution from September 2014 to August 2018 were analysed retrospectively. Of those, only 69 patients were included in the analysis because two patients did not undergo response evaluation and two patients had pre-existing autoimmune thyroiditis. For evaluating the clinical subtypes of melanomas, we classified patients into four groups according to location of the primary tumour. Overall, 28 patients with non-acral cutaneous melanomas, 25 patients with mucosal melanomas, 14 patients with acral lentiginous melanomas, and two patients with uveal melanomas were identified and included in the study. All patients received nivolumab monotherapy at either 2 mg/kg every 3 weeks or 3 mg/kg every 2 weeks. Clinical data collected from patients included age and sex, clinical subtype, profile of endocrine irAEs, irAE grade, time from the initiation of nivolumab to the onset of irAEs, tumour response, overall survival (OS) and progression-free survival (PFS). To evaluate the tumour responses and irAEs, computed tomography was performed every 1–2 months, and endocrine studies were performed once a month. Unless subjective symptoms were observed, we measured endocrine hormones before treatment

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Table 1
Attributes of the patients with endocrine immune-related adverse events.

Case	Age/sex	Subtype	Endocrine irAE	Grade	Time to onset (days)	Best response	OS (days)	PFS (days)	Vital status
1	66F	Non-acral	Hypothyroidism	II	57	CR	963	963	Alive
			Hypopituitarism	III	106				
2	74M	Non-acral	Hypopituitarism	III	126	CR	382	382	Alive
3	64F	Non-acral	Hypothyroidism	II	168	PR	1549	1549	Alive
4	73F	Uveal	Type 1 Diabetes Mellitus	III	319	PR	1318	424	Alive
5	74F	Mucosal	Hypothyroidism	II	112	PR	989	989	Alive
6	80F	Non-acral	Hypothyroidism	II	105	PR	312	312	Alive
7	39M	Acral	Hypopituitarism	III	266	SD	627	504	Dead
8	80M	Mucosal	Hypopituitarism	III	182	SD	585	585	Alive
9	62F	Mucosal	Hypopituitarism	II	221	SD	447	252	Dead
10	59M	Mucosal	Hypopituitarism	III	185	SD	264	264	Alive
11	72F	Mucosal	Hypothyroidism	II	111	SD	199	199	Alive
12	78M	Mucosal	Hypothyroidism	II	147	PD	198	50	Dead
13	89F	Mucosal	Hypothyroidism	II	42	PD	246	91	Dead

F, female; M, male; irAE, immune-related adverse event; OS, overall survival; PFS, progression-free survival; non-acral, non-acral cutaneous melanoma; uveal, uveal melanoma; mucosal, mucosal melanoma; acral, acral lentiginous melanoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

initiation and every month thereafter. We defined hypopituitarism as deficient secretion of adrenocorticotropic hormone. An abnormally low level of pituitary hormones followed by hypothyroidism was considered hypopituitarism in this study. Tumour response was defined according to the Response Evaluation Criteria in Solid Tumours guidelines (version 1.1), and all endocrine irAEs were graded according to Common Terminology Criteria for Adverse Events (version 5.0). All statistical analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd.). The significance of differences in the baseline characteristics and tumour response was estimated using Welch's t-test and Fisher's exact test. OS was calculated from the initiation of nivolumab monotherapy to death from any cause or to the last follow-up. PFS was calculated from the initiation of nivolumab monotherapy to either disease progression, death from any cause, or the last follow-up. OS and PFS were analysed using the Kaplan–Meier method, and P-values of <0.05 were considered statistically significant. This study was approved by the Ethics committee of Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital.

Of the 69 patients who were evaluated, 13 developed endocrine irAEs (Table 1). Of the 56 remaining patients, two patients developed hypopituitarism during ipilimumab therapy after cessation of nivolumab therapy. Because hypopituitarism is observed more frequently in ipilimumab therapy than in nivolumab therapy [10], their irAEs were not regarded as nivolumab-induced endocrine irAEs. No hyperthyroidism was observed in this study. The median time from initiation of nivolumab monotherapy to the onset of endocrine irAE was 111 days for hypothyroidism, 183 days for hypopituitarism, 319 days for type 1 diabetes mellitus and 136 days (20 weeks) for all endocrine irAEs. In this study, although one patient (Case 12) developed hypothyroidism after nivolumab therapy, all other endocrine irAEs were observed during nivolumab therapy. All endocrine irAEs were grade II–III and were controlled with hormone replacement therapy.

Baseline characteristics and tumour responses among 13 patients with endocrine irAEs and 56 patients without endocrine irAEs have been summarised in Table 2. Although older or female patients tended to develop

Table 2
Baseline characteristics and tumour response of patient groups.

Baseline characteristics and tumour response	With endocrine irAEs	Without endocrine irAEs
N	13	56
Age		
Mean	70.0	62.6
Range	39–89	21–82
Sex		
Female	8	20
Male	5	36
Clinical subtype		
Non-acral cutaneous	4	24
Mucosal	7	18
Acral	1	13
Uveal	1	1
Stage		
Stage II/III	5	11
Stage IV	8	45
Best response		
CR (n)	2	1
PR (n)	4	12
SD (n)	5	8
PD (n)	2	35
Response rate (%)	46.2	23.2
P	0.164	
Disease control rate (%)	84.6	37.5
P	0.004	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; irAEs, immune-related adverse events.

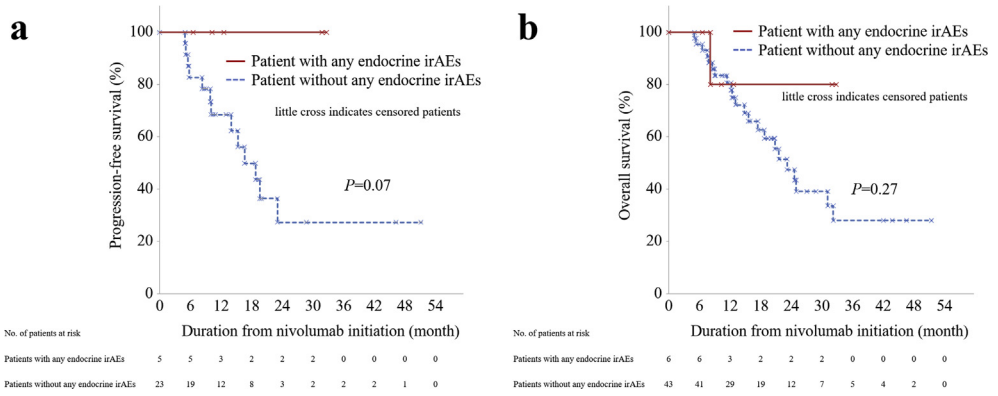

Fig. 1. Association of endocrine immune-related adverse events with progression-free survival and overall survival, the 20-week landmark analysis. (a) Progression-free survival of patients with or without any endocrine irAEs. (b) Overall survival of patients with or without any endocrine irAEs. irAEs, immune-related adverse events.

endocrine irAEs in this study, there was no significant difference in baseline characteristics. The response rate in patients with and without endocrine irAEs was 46.2% and 23.2%, respectively ($P = 0.164$). Disease control rate (DCR) in patients with and without endocrine irAEs was 84.6% and 37.5%, respectively ($P = 0.004$).

We performed a landmark analysis based on subgroups, where we excluded all patients who withdrew before the landmark point at 20 weeks, classified the remaining patients by the event that occurred during the period and performed survival analysis. Finally, 28 patients (5 in the endocrine irAE group and 23 in the non-endocrine irAE group) without disease progression for at least 20 weeks were included in the PFS analysis and 49 patients (6 in the endocrine irAE group and 43 in the non-endocrine irAE group) who survived longer than 20 weeks were included in the OS analysis. The 20-week landmark analysis showed a trend to a better PFS for patients with endocrine irAE, however, nothing significant for OS between the groups ($P = 0.07$ and 0.27; Fig. 1).

Recently, some studies revealed the association between endocrine irAEs and the efficacy of ICI therapy. Studies by Fujisawa *et al.* revealed that endocrine irAEs were associated with improved OS in melanoma patients treated with ipilimumab after progression with nivolumab therapy [5], while Haratani *et al.* found that endocrine irAEs were associated with improved PFS in non–small-cell lung cancer patients who received nivolumab therapy [6]. Moreover, other melanoma studies revealed the association between irAEs and the efficacy of nivolumab therapy [7–9]. In this study, a significant difference was observed in DCR between patients with and without endocrine irAEs. From the results of the 20-week landmark analysis, patients with endocrine irAEs tended to have better PFS than those without irAEs.

Limitations of this study include its retrospective nature and small sample size. In addition, because this study was conducted in a single centre in Japan, the translation of these experiences from Asian patients to European patients might be limited. Although the 20-week landmark was not useful for predicting the early clinical benefits, the occurrence of endocrine irAEs during nivolumab monotherapy in this study suggests its long-term efficacy. Moreover, since the 12-week landmark survival analysis in the study by Freeman–Keller *et al.* did not reveal the association between late-onset irAEs and the long-term efficacy [7], further large-scale studies are needed to verify these results.

Despite these limitations, to our knowledge, our study is the first to indicate the association between the occurrence of endocrine irAEs and the efficacy of nivolumab therapy in advanced melanoma patients. We have demonstrated that advanced melanoma patients with endocrine irAEs tended to have improved PFS in the 20-week landmark analysis. Our study indicates that endocrine irAEs during nivolumab monotherapy could be positive clinical biomarkers for the long-term efficacy of the therapy. Moreover, it would be worthwhile to evaluate whether the same is true in the adjuvant setting.

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Conflicts of interest statement

None declared.

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