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Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non–Small-Cell Lung Cancer

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IMPORTANCE Immune-related adverse events (irAEs) have been associated with the efficacy of PD-1 (programmed cell death protein 1) inhibitors in patients with melanoma, but whether such an association exists for non–small-cell lung cancer (NSCLC) has remained unknown.

OBJECTIVE To evaluate the relation of irAEs to nivolumab efficacy in NSCLC.

DESIGN, SETTING, AND PARTICIPANTS In this study based on landmark and multivariable analyses, a total of 134 patients with advanced or recurrent NSCLC who were treated with nivolumab in the second-line setting or later between December 2015 and August 2016 were identified from a review of medical records from multiple institutions, including a university hospital and community hospitals. Data were updated as of December 31, 2016.

EXPOSURES The absence or presence of any irAE before the landmark date.

MAIN OUTCOMES AND MEASURES Kaplan-Meier curves of progression-free survival (PFS) according to the development of irAEs in 6-week landmark analysis were evaluated with the log-rank test as a preplanned primary objective. Overall survival (OS) was similarly evaluated. Multivariable analysis of both PFS and OS was performed with Cox proportional hazard regression models.

RESULTS In a cohort of 134 patients (median [range] age, 68 [33-85] years; 90 men [67%], 44 women [33%]), irAEs were observed in 69 of the 134 study patients (51%), including 12 patients (9%) with such events of grade 3 or 4, and 24 patients (18%) requiring systemic corticosteroid therapy. In 6-week landmark analysis, median PFS was 9.2 months (95% CI, 4.4 to not reached [NR]) and 4.8 months (95% CI, 3.0 to 7.5) (P = .04) whereas median OS was NR (95% CI, 12.3 to NR) and 11.1 months (95% CI, 9.6 to NR) (P = .01) for patients with or without irAEs, respectively. Multivariable analysis also revealed that irAEs were positively associated with survival outcome, with hazard ratios of 0.525 (95% CI, 0.287 to 0.937; P = .03) for PFS and 0.282 (95% CI, 0.101 to 0.667; P = .003) for OS.

CONCLUSIONS AND RELEVANCE Development of irAEs was associated with survival outcome of nivolumab treatment in patients with advanced or recurrent NSCLC. Further studies are needed to confirm our findings.

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Supplemental content

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The development of immunotherapy has improved treatment outcome for various types of cancer including non-small-cell lung cancer (NSCLC). Nivolumab and pembrolizumab, monoclonal antibodies that target PD-1 (programmed cell death protein 1), have been approved for the treatment of metastatic NSCLC on the basis of recent clinical trials demonstrating that these agents prolong survival compared with cytotoxic chemotherapy.[1-4] On the other hand, treatment with such immune-checkpoint inhibitors is accompanied by immune-related adverse events (irAEs).[5,6] The development of irAEs has been found to be associated with survival benefit in melanoma,[7-11] suggesting that an early onset of irAEs might be predictive of a better outcome of treatment with immune-checkpoint inhibitors and that the proper management of such events might be required to maximize the therapeutic effect of these drugs. The relation between irAEs and outcome of such treatment for patients with NSCLC has remained unknown, however.

We performed a multi-institutional retrospective study to investigate the irAE profile and its association with clinical activity for nivolumab in NSCLC with the use of landmark and multivariable analyses.

Key Points

Question Are immune-related adverse events associated with outcome of nivolumab treatment in patients with non–small-cell lung cancer (NSCLC)?

Findings In this multi-institutional medical record review including 134 patients with advanced or recurrent NSCLC treated with nivolumab monotherapy, landmark and multivariable analyses showed that immune-related adverse events were significantly associated with a better treatment outcome.

Meaning Early recognition and proper management of immune-related adverse events are important to maximize the therapeutic benefit of immune-checkpoint inhibitors in patients with NSCLC.

Methods

Data Collection

We reviewed the medical records of all patients with advanced or recurrent NSCLC who were treated with nivolumab at 4 participating institutions. The end of the follow-up period was December 31, 2016. The study was performed according to protocols approved by the institutional review board of each participating hospital.

Statistical Analysis

The difference in progression-free survival (PFS) curves estimated with the Kaplan-Meier method according to the absence or presence of any irAE in 6-week landmark analysis was evaluated with the log-rank test as a preplanned primary objective. Univariable and multivariable Cox proportional hazard regression models were adopted to determine hazard ratios. Multivariable analysis was performed with adjustment for age, sex, the number of prior treatment lines, smoking status, mutational status, and brain metastases. Taking into account the lead-time bias due to the time-dependent nature of irAEs, we performed 6-week landmark analysis including only patients manifesting disease control or those who were alive at 42 days after initiation of nivolumab therapy for PFS (n = 105) or overall survival (OS) (n = 130), respectively. Both analyses were carried out on the basis of this landmark assessment of irAEs that developed within the first 6 weeks. In addition, 4-week and 8-week landmark analyses were performed as complementary evaluations. Any irAE occurring after the landmark date was not counted in the landmark-based analyses. All *P* values were based on a 2-sided hypothesis, and those less than .05 were considered statistically significant. Detailed methods for data collection and statistical analysis are provided in eMethods in the Supplement.

Results

Patient Characteristics and irAE Profile

A total of 134 NSCLC patients treated with nivolumab were included in the study (eTable 1 in the Supplement). For 6-week landmark analysis, 29 patients were excluded because of disease progression or death before day 43 of nivolumab treatment for analysis of PFS (eTable 2 in the Supplement) and 4 patients were excluded because of death before this time for analysis of OS. The irAE profile is shown in **Table 1**.

Association of irAEs With Nivolumab Efficacy

Six-week landmark analysis showed that the overall response rate was significantly higher in patients with irAEs than in those without them (23 of 44 patients [52.3%] vs 17 of 61 patients [27.9%]; $P = .02$) and that the development of irAEs was significantly associated with increased PFS ($P = .04$) and OS ($P = .01$) (**Figure**). Similar results were obtained for 4-week and 8-week landmark analyses (eFigures 1 and 2 in the Supplement). Six-week landmark analyses for irAE subgroups revealed skin irAEs were significantly associated with increased PFS (eFigures 3 and 4 in the Supplement).

Multivariable analysis revealed that any irAE, skin irAEs, and endocrine irAEs were significantly associated with increased PFS at the 6-week landmark (**Table 2**). Any irAE and skin irAEs were significantly associated with increased OS, whereas endocrine irAEs were not, possibly because of the small number of patients with endocrine irAEs at this landmark and the insufficient follow-up time for OS.

Discussion

Our results have revealed that irAEs were associated with nivolumab efficacy in patients with NSCLC. Our landmark analyses—including the principal 6-week analysis, complemented by additional 4-week and 8-week analyses—minimized lead-time bias potentially associated with time-dependent factors

Table 1. Immune-Related Adverse Events According to Category and Grade

Category	Patients, No. (%)[a]				
	Total (n = 134)	Grade 1-2	Grade 3-4[b]	Systemic Steroid Therapy[c]	Weeks to Onset, Median (range)
Any	69 (51)	57 (43)	12 (9)	24 (18)	4.1 (0.3-36.2)
Skin	43 (32)				5.7 (0.4-36.2)
Rash[d]	33 (25)	31 (23)	2 (1)	3 (2)	
Pruritus	16 (12)	7 (5)	NA	NA	
Vitiligo	2 (1)	2 (1)	NA	NA	
Pneumonitis	6 (4)	3 (2)	3 (2)	6 (4)	10.8 (2.1-30.1)
Endocrine[e]	11 (8)	NA	NA	NA	4.6 (1.1-21.1)
Thyroiditis/hypothyroidism	10 (7)	10 (7)	NA	NA	
Hypophysitis	1 (1)	1 (1)	NA	1 (1)	
Gastrointestinal	12 (9)				8.9 (0.9-21.8)
Mucositis[f]	3 (2)	3 (2)	NA	NA	
Diarrhea/colitis[g]	10 (7)	10 (7)	NA	6 (4)	
Hepatobiliary	7 (5)				12.2 (2.1-19.1)
Hepatitis	5 (4)	NA	5 (4)	5 (4)	
Cholangitis	2 (1)	1 (1)	1 (1)	2 (1)	
Other	11 (8)				4.6 (0.3-28.1)
Fatigue	7 (5)	7 (5)	NA	3 (2)	
Appetite loss	4 (3)	4 (3)	NA	1 (1)	
Polyarthritis	1 (1)	1 (1)	NA	1 (1)	
Myasthenia gravis	1 (1)		1 (1)	1 (1)	

Abbreviation: NA, Not applicable.

[a] Percentages may add up to more than 100 because some patients experienced more than 1 event.

[b] Treatment-related death was not observed in the study cohort.

[c] High-dose steroid pulse therapy (methylprednisolone at 1 g/d) for 3 d followed by prednisolone (1 to 2 mg/kg) treatment for several weeks was administered in 4 patients (1 with cholangitis; 1, myasthenia gravis; 1, pneumonitis; and 1, hepatitis). Three patients (1 with cholangitis and 2 with colitis) were treated with infliximab after failure of steroid therapy.

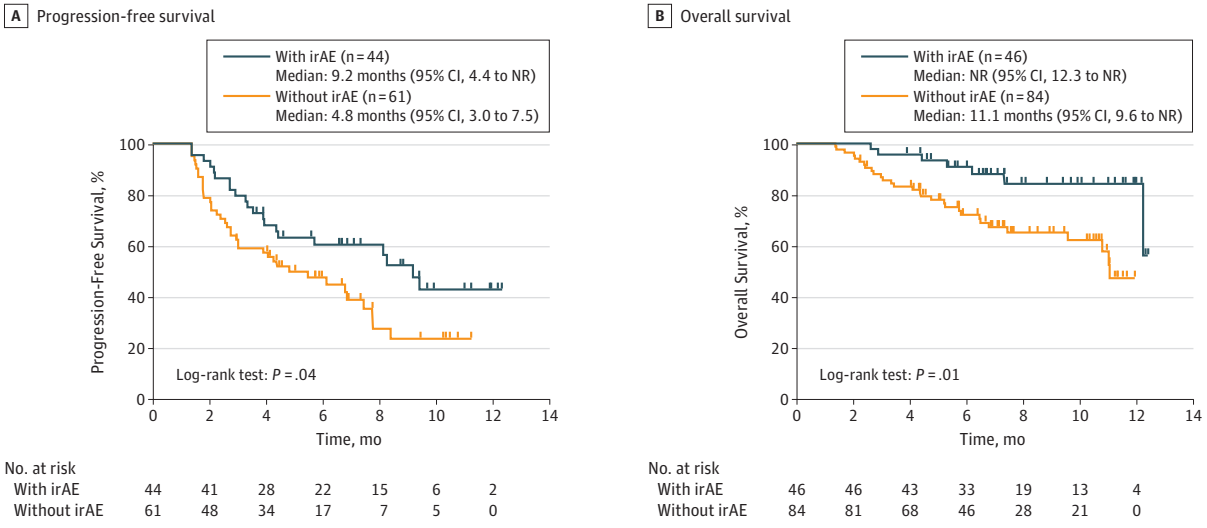
[d] Twenty-two patients were treated with topical corticosteroid therapy.

[e] All of these 11 patients received thyroid hormone replacement therapy after the onset of the immune-related adverse event.

[f] Each of these 3 patients was treated with topical corticosteroid therapy.

[g] Four patients required only temporary cessation of nivolumab therapy (not treatment with an immunosuppressive agent).

Figure. Analysis of Survival for Patients With or Without irAEs



Kaplan-Meier curves with 6-week landmark analysis for (A) progression-free survival (B) and overall survival in patients with or without irAEs. irAEs indicates immune-related adverse events; NR, not reached.

such as irAEs. The association of irAEs with nivolumab efficacy was further supported by multivariable analysis. Furthermore, given that our data are derived from multiple institutions including community hospitals, our findings should be applicable to a general NSCLC population.

Some previous studies did not detect a significant association of irAEs with survival outcome in patients with melanoma, especially with regard to PFS because of the exclusion of many patients who experienced disease progression before the landmark date.[10,12] Nevertheless, our 6-week landmark analysis re-

Table 2. Cox Proportional Hazard Regression Analysis of the Effect of irAE Development on Progression-Free Survival and Overall Survival

Survival	Univariable Hazard Ratio (95% CI)	*P* Value	Multivariable Hazard Ratio (95% CI)[a]	*P* Value
PFS (6-week landmark)				
Any irAE	0.567 (0.325-0.960)	.04	0.542 (0.295-0.971)	.04
Skin irAEs	0.509 (0.264-0.916)	.02	0.476 (0.232-0.912)	.03
Endocrine irAEs	0.389 (0.064-1.248)	.13	0.237 (0.037-0.842)	.02
OS (6-week landmark)				
Any irAE	0.305 (0.114-0.683)	.003	0.285 (0.102-0.675)	.003
Skin irAEs	0.240 (0.058-0.668)	.004	0.209 (0.049-0.618)	.003
Endocrine irAEs	0.461 (0.026-2.148)	.39	0.504 (0.027-2.629)	.47

Abbreviations: irAE, immune-related adverse event; OS, overall survival; PFS, progression-free survival.

[a] Covariables included sex (male vs female), age (≥75 vs <75 y), the number of prior treatment lines (≥2 vs <2), smoking status (current or former vs never), mutational status (positive for *EGFR* mutation or *ALK* fusion vs negative for these genetic alterations), and brain metastasis (yes vs no).

vealed a significant difference in both PFS and OS between patients with NSCLC with or without irAEs, suggestive of a robust association between such events and survival. Setting the landmark at 6 weeks for a study of patients with NSCLC treated with a PD-1 inhibitor seems reasonable because such individuals tend to experience disease progression earlier or at a higher rate compared with patients with melanoma. Of note, our early landmark analyses before routine response evaluation also suggest that an early onset of irAEs might be predictive of response or durable clinical benefit in patients with NSCLC treated with PD-1 inhibitors.

The mechanisms underlying the association of irAEs with outcome of treatment with PD-1 inhibitors are unknown. Previous studies showing an association of vitiligo with outcome of immunotherapy in patients with melanoma have suggested that antigens shared between melanoma cells and normal melanocytes might contribute to this association.[7,9,11] Whether lung cancer cells share antigens with tissues affected by irAEs in patients with NSCLC remains to be determined. A recent study[13] suggested that OS is prolonged in NSCLC patients receiving immunotherapy who develop immune-related thyroiditis compared with those without thyroiditis. Another study suggested an association between skin irAEs and improved OS in patients with NSCLC treated with nivolumab.[14] Our multivariable analysis at the 6-week landmark showing increased PFS or OS according to the presence of endocrine or skin irAEs are consistent with these previous findings.

Limitations

There are some limitations to our study. First, the study was retrospective in nature, so information bias cannot be excluded. Second, our multivariable analysis could not include all potential confounding factors because of the limited number of covariates available for the sample size. Third, the follow-up time was not long enough to allow us to fully address long-term survival outcome. Fourth, the various types of irAE, with the exception of those affecting skin, were not common, thus limiting our evaluation of which type of irAE most strongly contributes to the association with treatment outcome. The association between non-skin irAEs and nivolumab efficacy thus remains inconclusive and warrants further study with larger cohorts.

Conclusions

Our findings indicate that irAEs are associated with nivolumab efficacy in patients with NSCLC. As far as we are aware, our study is the first to reveal an association of irAEs with the efficacy of PD-1 inhibitors in NSCLC with landmark and multivariable analyses. Further studies with larger numbers of patients and longer follow-up times are needed to validate our findings.

ARTICLE INFORMATION

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Study concept and design: Haratani, Hayashi, Nakagawa.
Acquisition, analysis, or interpretation of data: Haratani, Hayashi, Chiba, Kudo, Yonesaka, Kato, Kaneda, Hasegawa, Tanaka, Takeda, Nakagawa.
Drafting of the manuscript: Haratani, Hayashi.
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Administrative, technical, or material support: Yonesaka, Kato, Kaneda, Hasegawa, Tanaka, Takeda.
Study supervision: Hayashi, Nakagawa.

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