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Prognostic Impact and Risk Factors of Immune-Related Pneumonitis in Patients With Non–Small-Cell Lung Cancer Who Received Programmed Death 1 Inhibitors

Jun Fukihara,[1] Koji Sakamoto,[1] Junji Koyama,[1,3] Takayasu Ito,[1,4] Shingo Iwano,[2] Masahiro Morise,[1] Masahiro Ogawa,[4] Yasuhiro Kondoh,[3] Tomoki Kimura,[3] Naozumi Hashimoto,[1] Yoshinori Hasegawa[1]

Abstract

Pneumonitis is one of the adverse events of programmed death 1 (PD-1) inhibitors. We retrospectively evaluated prognosis and risk factors of pneumonitis in patients with non–small-cell lung cancer taking a PD-1 inhibitor. The overall survival time was significantly shorter in patients with pneumonitis than in those without. Pembrolizumab (vs. nivolumab) use and low serum albumin were risk factors for pneumonitis.

Introduction: Pneumonitis is one of the immune-related adverse events of programmed death 1 (PD-1) inhibitors that sometimes cause lethal outcomes. Although some recent reports have described PD-1 inhibitors as more effective in non–small-cell lung cancer (NSCLC) patients with immune-related adverse events than in those without, few data are available on the prognosis of those treated with PD-1 inhibitors who developed immune-related pneumonitis (IRP). Additionally, the robust risk factors of IRP have not been well elucidated. **Patients and Methods:** A retrospective review of patients with recurrent or advanced NSCLC who took a PD-1 inhibitor (nivolumab or pembrolizumab monotherapy) between January 2016 and March 2018 was undertaken. Radiologic findings such as unilateral infiltration were also defined as IRP as long as they were deemed relevant to PD-1 inhibitors. **Results:** Twenty-seven (16%) of 170 patients developed IRP. Although 22 (81%) of 27 patients with IRP recovered with drug cessation with or without corticosteroid therapy, 8-week landmark analysis showed the overall survival after administration of the PD-1 inhibitor was significantly shorter in patients with IRP than in those without (8.7 vs. 23.0 months, $P = .015$). Patients with IRP tended to not receive next-line treatment and choose best supportive care after cessation of PD-1 inhibitor therapy. In the multivariate analysis, pembrolizumab (vs. nivolumab) and low serum albumin were independent risk factors for IRP. **Conclusion:** Development of IRP was correlated with poor prognosis in patients with NSCLC. Further study is necessary for establishing the best prediction and management strategies for IRP.

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Introduction

Programmed cell death 1 (PD-1) inhibitors such as nivolumab and pembrolizumab exhibit significant clinical efficacy in the treatment of non–small-cell lung cancer (NSCLC). They are the standard agents for pretreated NSCLC patients,[1-3] and additionally, pembrolizumab improved survival when combined with

J.F. and K.S. contributed equally to this article, and both should be considered first author.

[1]Department of Respiratory Medicine
[2]Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
[3]Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto, Aichi, Japan
[4]Department of Respiratory Medicine, Handa City Hospital, Handa, Aichi, Japan

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Address for correspondence: Koji Sakamoto, MD, PhD, Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi, Japan 466-8560
E-mail contact: sakakoji@med.nagoya-u.ac.jp

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platinum-based chemotherapy in the first-line setting.[4,5] Despite such robust evidence for the effectiveness of PD-1 inhibitors, immune-related adverse events (irAEs) frequently prevent patients from taking the treatment continuously. A standard method of management for each irAE has not yet been well established, and information about their predictors or prognoses is limited.

Immune-related pneumonitis (IRP) is one of the relatively rare irAEs first reported in 3 patients with melanoma in 2015.[6] Subsequently, it was also described in 2 patients with NSCLC in 2016.[7] Its prevalence has been reported as 2.7% to 5.8% in patients with NSCLC in randomized controlled trials.[2,3] Although it is sometimes associated with death, development of IRP may reflect the extent of immune activity, and PD-1 inhibitors may therefore be more effective in NSCLC patients with IRP compared to those without IRP. To date, whether the development of IRP is an indicator of better antitumor response or outcome remains unclear. Given the fact that clinicians are frequently confronted with difficulty in reducing the dosage of corticosteroid and resuming administration of PD-1 inhibitors in patients with IRP because IRP tends to recur and is sometimes life-threatening, even if IRP can be correlated with a better overall response rate (ORR) and progression-free survival (PFS), difficulties in continuing optimal treatment may shorten survival.

Additionally, the characteristics of patients who are likely to develop IRP have not been well elucidated. Although some clinical parameters such as a combination of more than 2 immunocheckpoint inhibitors[8-10] or a history of radiotherapy[10,11] have been reported to be risk factors of pneumonitis, these results vary from report to report and are not universal.

The aims of this multicenter retrospective study were to evaluate the prognostic impact and risk factors of IRP through a review of the baseline clinical background of patients with recurrent or advanced NSCLC who took PD-1 inhibitors.

Patients and Methods

Study Design and Population

This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the institutional review boards of the 3 participating institutes (Nagoya University Hospital, no. 2018-0176; Tosei General Hospital, no. 724; and Handa City Hospital, no. 2018-010). Informed consent was waived because the data were collected retrospectively and analyzed anonymously.

A retrospective review of consecutive patients with recurrent or advanced NSCLC who took PD-1 inhibitors (nivolumab or pembrolizumab monotherapy) at 1 of the 3 participating institutes between January 2016 and March 2018 was undertaken. The doses of nivolumab and pembrolizumab were 3 mg/kg every 2 weeks and 200 mg every 3 weeks, respectively, until disease progression, intolerable toxicity, or patient refusal. Data were collected on patient survey forms. Follow-up was censored on September 2018, and 2 patients who were lost to follow-up within 6 weeks after administration of a PD-1 inhibitor for reasons other than death or development of IRP were excluded. Eventually, 27 of 170 patients developed IRP and were included.

Diagnosis of IRP

All diagnoses of IRP were made by 2 pulmonologists (J.F. and K.S.) and one chest radiologist (S.I.), all of whom are regularly engaged in clinical work with lung cancer and interstitial lung disease. In this study, not only traditional radiologic findings for drug-related pneumonitis, such as diffuse or patchy bilateral ground-glass opacities and/or consolidations, but also atypical findings, like unilateral shadows and an increase of radiation pneumonitis (Figure 1), were also defined as IRP, as long as those abnormal findings were deemed relevant to use of PD-1 inhibitors. Those with alternative diagnoses, including infectious pneumonia, were excluded.

Data Collection and Response Evaluation

The patient characteristics and test results at the time of commencing PD-1 inhibitors were collected from clinical charts. Additionally, that information was also collected on patients who developed IRP at the time of their IRP diagnosis. Clinical characteristics included Eastern Cooperative Oncology Group performance status, tumor histology, administered drug (nivolumab or pembrolizumab), treatment line, and, when appropriate, severity of IRP as evaluated by the Common Terminology of Criteria for Adverse Events version 4.0, as well as treatment details for IRP. Collected test results included findings from laboratory tests and chest computed tomography (CT). The extent of emphysema on CT was evaluated by the Goddard score[12] and was classified as mild or moderate/severe. Preexisting interstitial lung disease was also recorded. The dates of first administration and cessation of the PD-1 inhibitor, diagnosis of IRP, confirmation of disease progression, commencement of next-line treatment after the PD-1 inhibitor, and the last date of follow-up with survival status were also recorded.

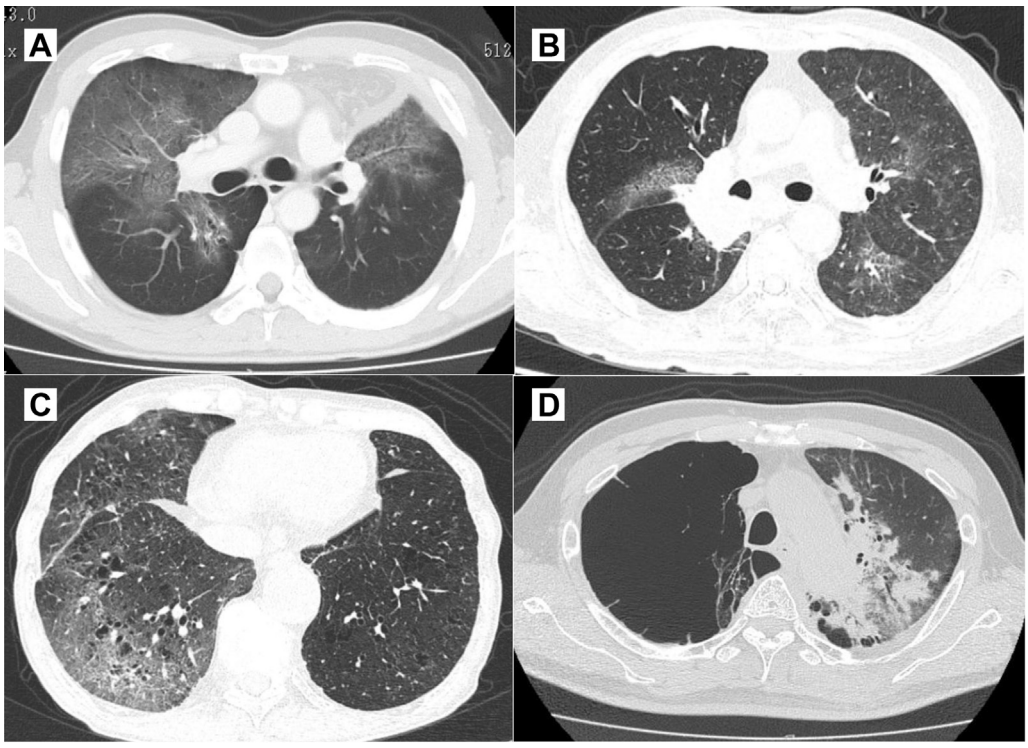
According to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[13] clinical responses to PD-1 inhibitors were classified as complete response, partial response, stable disease, progressive disease (PD), or not evaluable. Stable disease was defined as disease control maintained for at least 6 weeks, and all other responses were confirmed at least 4 weeks after the initial assessment. PD was defined as more than a 20% increase in the sum of the longest diameter of the target lesions, unequivocal progression of existing nontarget lesions, or appearance of any new lesions. The ORR and disease control rate (DCR) were defined as the best tumor responses of complete response + partial response, and complete response + partial response + stable disease, respectively.

Statistical Analysis

Continuous variables are presented as medians with interquartile range because all of them showed nonnormal distribution. Categorical variables are summarized by number of patients and percentages. To assess the differences of variables between subgroups, the Mann-Whitney *U* test or the Kruskal-Wallis test, as appropriate, was used for continuous variables, and the Pearson chi-square test was used for categorical variables.

PFS and overall survival (OS) were measured from the date of first administration of the PD-1 inhibitor until the date of death or confirmation of PD for PFS and until the date of death for

Figure 1 Representative Images of Chest CT for Diagnosing Immune-Related Pneumonitis. (A, B) Diffuse/Patchy Bilateral GGOs. (C) Unilateral GGOs. (D) Increase of Radiation Pneumonitis



Abbreviations: CT = computed tomography; GGO = ground-glass opacity.

OS. The Kaplan-Meier method in 8-week landmark analysis was applied to estimate PFS and OS, and differences between groups were analyzed by a log-rank test. Given the lead-time bias due to the time-dependent nature of IRP, we performed landmark analysis. Because the median time from administration of PD-1 inhibitors and development of IRP has generally been reported to be 6.8 to 12.0 weeks[9,14-16] (and was 5.1 weeks with an interquartile range of 2.9 to 14.0 weeks in our cohort), 6 to 12 weeks after administration of PD-1 inhibitors was considered to be optimal for excluding very late onset IRP cases. To exclude patients who died too soon to evaluate the effectiveness of PD-1 inhibitors, we set the landmark no sooner than 6 to 8 weeks after initiation of PD-1 inhibitors, which is required to define stable disease according to the RECIST guidelines.[13] Eventually, 8-week landmark analysis, which is the same cutoff as a past report,[17] was carried out in patients with disease control or in patients who were alive at 56 days after administration of PD-1 inhibitors for PFS and OS, respectively, and values were compared between those with and without IRP that developed within the first 8 weeks. The ORR and DCR were evaluated not only for the total observation period but also at this landmark date in patients who were alive at the date. In addition, 6- and 12-week landmark analyses were performed as complementary evaluations. IRP developed after the landmark date was not counted in the landmark-based analyses.

A multivariate logistic regression model was used to evaluate predictors for IRP. To avoid multicollinearity, only one of the highly correlated variables (Spearman rank correlation coefficient ≥ 0.7) was entered the model, if present. A stepwise approach was adopted for variable selection. Receiver operating characteristic curve and the area under the curve were evaluated when continuous variables were detected as significant predictors of IRP after multivariate analysis to assess their diagnostic utility. The optimal cutoff value was defined as where the sum of sensitivity and specificity became highest.

All statistical tests were 2 sided, and $P < .05$ were considered statistically significant. Statistical analyses were carried out by SPSS 24.0 (IBM, Armonk, NY).

Results

Patient Characteristics

Twenty-seven (16%) of 170 patients developed pneumonitis. The median follow-up was 9.9 months (range, 0.5-31.5 months). Pembrolizumab was provided more frequently in patients with IRP than in those without (63% vs. 34%, $P = .004$). Other baseline characteristics were not significantly different between groups (Table 1). Patient characteristics at each participating institution are summarized in Supplemental Table 1 in the online version. There was no significant difference in frequency of IRP among the participating facilities.

Table 1 Patient Characteristics

Characteristic	Immune-Related Pneumonitis		*P*
	Yes (N = 27)	No (N = 143)	
Age (y)	67 (58-73)	70 (63-73)	.285
Gender			.944
Male	20 (74)	105 (73)	
Female	7 (26)	38 (27)	
Smoking (pack-years)	34.0 (10.0-58.0)	43.0 (12.0-60.0)	.578
ECOG PS			.275
0-1	21 (78)	123 (86)	
2-4	6 (22)	20 (14)	
Histology			.546
Squamous cell	8 (30)	51 (36)	
Non−squamous cell	19 (70)	92 (64)	
Drug			.004
Nivolumab	10 (37)	95 (66)	
Pembrolizumab	17 (63)	48 (34)	
Treatment Line			.095
First	8 (30)	23 (16)	
Second or higher	19 (70)	120 (84)	
Past thoracic RT	8 (30)	46 (32)	.795
Chest CT Findings			
Interstitial lung disease	4 (15)	12 (8)	.294
Moderate to severe emphysema	13 (48)	48 (34)	.147
Laboratory Findings			
WBC ($\times 10^3/mm^3$)	6.4 (5.1-11.0)	6.3 (4.8-8.1)	.221
NLR	4.2 (1.9-7.2)	3.1 (2.1-5.7)	.183
CRP (mg/dL)	1.74 (0.09-5.08)	0.68 (0.13-2.63)	.569
Albumin (g/dL)	3.5 (2.7-3.8)	3.7 (3.3-4.0)	.020
AST (U/L)	19 (15-26)	21 (16-26)	.458
ALT (U/L)	18 (10-26)	14 (10-20)	.207
Creatinine (mg/dL)	0.75 (0.51-0.93)	0.75 (0.65-0.89)	.482

Data are presented as n (%) or median (IQR).
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; NLR = neutrophil-to-lymphocyte ratio; WBC = white blood cell count.

Characteristics of IRP

The numbers of patients with grades 1, 2, 3, 4, and 5 IRP were 9, 7, 9, 0, and 2, respectively. The median duration from commencement of PD-1 inhibitor administration to development of IRP was 36 days. The most frequently observed radiologic finding was diffuse or patchy bilateral ground-glass opacity; however, some cases showed unilateral distributions. In cases of a history of radiotherapy, an increase in radiation pneumonitis was observed as one of the minor findings (5 of 8 cases). Seventeen of 20 patients taking corticosteroid therapy and 5 of 7 patients not receiving treatment other than cessation of PD-1 inhibitors improved, while 2 taking corticosteroid therapy had disease refractory to treatment and died (Table 2).

Antitumor Response and Prognosis

All patients who developed IRP and 124 of 143 patients who did not develop IRP ceased to take PD-1 inhibitors during the study period; the remaining 19 patients continued to take PD-1 inhibitors at the time of censoring. The median duration of PD-1 inhibitor therapy was significantly shorter in those with IRP (Table 3). For 8-week landmark analyses, 50 patients were excluded because of disease progression or death before the landmark date for analysis of PFS, and 14 patients were excluded because of death before this time for analysis of ORR, DCR, and OS (Supplemental Table 2 in the online version). In addition to ORR and DCR, PFS in 8-week landmark analysis was not significantly different between groups (Table 4, Figure 2A). However, OS in 8-week landmark analysis was significantly shorter in those with IRP (8.7 vs. 23.0 months, $P = .015$, Figure 2B). Similar results were obtained for 6- and 12-week landmark analyses (Supplemental Table 3 and Supplemental Figures 1 and 2 in the online version). In particular, a rapid decrease in survival rates lasted in the first 10 months in those with IRP, while it was constantly more moderate in those without IRP. In patients with IRP, performance status at the time of cessation of the PD-1 inhibitor tended to be worse, and patients with IRP who received anticancer treatment were significantly fewer

Table 2 Details of Immune-Related Pneumonitis in 27 Patients

Characteristic	Value
CTCAE Grade	
1	9
2	7
3	9
4	0
5	2
Onset from drug initiation (d)	39 (19-70)
Major Chest CT Findings	
Diffuse or patchy GGO with or without consolidations	25 (93)
Bilateral	21
Unilateral	4
Boost of radiation pneumonitis	2 (7)
Treatment for Pneumonitis	
Corticosteroid therapy	20 (74)
Improved	17 (85)
Worsened and died	2 (10)
Not assessable	1 (5)
No treatment (drug cessation only)	7 (26)
Improved	5 (71)
Unchanged	1 (14)
Not assessable	1 (14)

Data are presented as n, n (%), or median (interquartile range).
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; CT = computed tomography; GGO = ground-glass opacity.

Table 3 Characteristics at Time of Cessation of PD-1 Inhibitors

Characteristic	Immune-Related Pneumonitis		*P*
	Yes (N = 27)	No (N = 124)	
Duration of drug administration (d)	36 (20-98)	76 (41-173)	.003
ECOG PS			.208
0-1	13 (48)	76 (61)	
2-4	14 (52)	48 (39)	
Reason for Cessation			
Disease progression	5 (19)	96 (77)	
Pneumonitis	21 (78)	0	
Other adverse event	1 (4)	12 (10)	
Deterioration of ECOG PS	0	7 (6)	
Other	0	9 (7)	
Next-Line Treatment			
Any anticancer agent	6 (21)	66 (54)	.003
Chemotherapy	6 (21)	55 (45)	
Tyrosine kinase inhibitors	0	9 (7)	
Immune checkpoint inhibitors	0	2 (2)	
Follow-up until disease progression	7 (25)	9 (7)	.005
Best supportive care	14 (54)	49 (39)	.252
Time to next-line treatment (d)	40 (17-152)	20 (12-33)	.098

Data are presented as n (%) or median (interquartile range).
Follow-up was selected when disease progression was not observed or when progression was only slight at time of cessation.
Time to next-line treatment was evaluated only in patients showing disease progression at time of cessation and who did not choose best supportive care.
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; PD-1 = programmed cell death 1.

than in those without IRP (Table 3). Alternatively, those with IRP more frequently chose only follow-up until remarkable disease progression occurred, or they tended to choose best supportive care. As a result, the period from cessation of the PD-1 inhibitor to administration of the next-line anticancer agent was longer in those with IRP, although the difference was not statistically significant (Table 3).

Risk Factors for IRP

Univariate analysis showed that use of pembrolizumab and low serum albumin were significantly correlated with development of IRP (Table 5). In the multivariate analysis, use of pembrolizumab (compared to nivolumab; odds ratio = 3.259; 95% confidence interval, 1.361-7.807; $P = .008$) and low serum albumin (for increase of 1.0 g/dL; odds ratio = 0.381, 95% confidence interval, 0.179-0.808; $P = .012$) were independent risk factors for IRP. In terms of serum albumin, the area under the curve was only 0.641 ($P = .020$) when it alone was adopted to predict IRP. The cutoff value was 2.75 mg/dL with low sensitivity of 25.9%, specificity of 95.8%, and positive and negative predictive values of 53.8% and 87.3%, respectively.

Discussion

In this study, we demonstrated that patients who developed IRP had a worse prognosis than those did not develop IRP, and we evaluated detailed clinical information that we thought might have influenced the worsened survival. Additionally, we for the first time illustrated that administration of pembrolizumab (vs. nivolumab) and low serum albumin are independent predictors of IRP.

In general, irAE has been found to be associated with better outcomes in melanoma.[18-22] When it comes to NSCLC, skin reactions were reported to predict a better response to nivolumab[23] and longer survival after pembrolizumab therapy.[24] Haratani et al[25] recently showed that any irAE was correlated with longer PFS and OS in patients with NSCLC, and similar results were also reported by other studies.[17,26,27] On the basis of these results, irAEs are generally regarded as predictors of better response to PD-1 inhibitors and longer survival in patients with NSCLC. However, the number of patients with IRP included in those reports is quite small, so it has not been clarified whether IRP can also affect outcome.

Suresh et al[28] have recently reported poor prognosis in NSCLC patients with IRP through a single-center study. Using a Markov model, they suggested that IRP consistently worsened survival regardless of its recovery or time to development, although no specific reason was identified. According to the results from our multicenter study, the efficacy of PD-1 inhibitors in short-term outcomes such as ORR, DCR, and PFS was not significantly worse, while OS was significantly worse in patients with IRP. In

Table 4 Treatment Efficacy of PD-1 Inhibitors

Characteristic	Immune-Related Pneumonitis		*P*
	Yes	No	
For Total Observation Period			
No. of patients	27	143	
CR/PR/SD/PD/NE	0/8/7/10/2	0/34/48/59/2	
ORR	32%	24%	.403
DCR	60%	58%	.863
At 8-Week Landmark Point			
No. of patients	14	142	
CR/PR/SD/PD/NE	0/6/5/3/0	0/36/72/33/1	
ORR	43%	25%	.159
DCR	79%	77%	.878

Abbreviations: CR = complete response; DCR = disease control rate; NE = not valuable; ORR = overall response rate; PD = progressive disease; PD-1 = programmed cell death 1; PR = partial response; SD = stable disease.

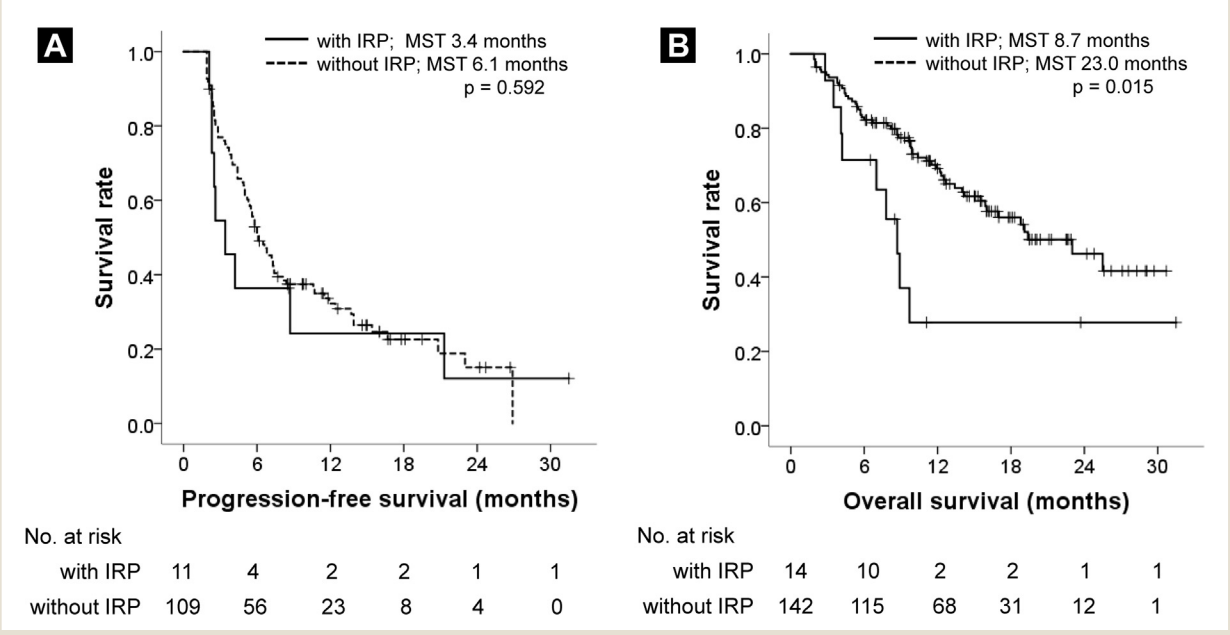
particular, the decline of the survival rate in those with IRP lasted for 10 months from administration of PD-1 inhibitors. This may be partly because patients with IRP, unlike those with skin reactions or thyroid dysfunction, are usually forced to quit taking PD-1 inhibitors, considering the possibility of fatal respiratory failure due to continuing the therapy. In addition, patients with IRP tended to reject, and their physicians tended to hesitate or delay, commencement of aggressive anticancer therapy as a result of prolonged steroid therapy for IRP, abrasive respiratory symptoms, and deteriorating performance status. These issues might cause a rapid decrease in the survival rate, one lasting long after the administration of PD-1 inhibitors, in those with IRP.

Considering these effects of IRP on prognosis, accurate prediction of IRP is important. Past reports have demonstrated that combinations of more than 2 immunocheckpoint inhibitors,[8-10] first-line therapy,[29] tumor histology,[16,30] history of radiotherapy,[10,11] and preexisting pulmonary fibrosis[31,32] were risks for IRP. Most of those factors, however, are not consistently predictive for IRP in different patient cohorts. In our cohort as well, none of the above-mentioned factors was a significant predictor for IRP.

In this study, administration of pembrolizumab was an independent risk factor for IRP. Few data are currently available comparing differences between pembrolizumab and nivolumab in the prevalence and predictive value of IRP in a real-world cohort. Although several past meta-analyses based on randomized controlled trials for NSCLC demonstrated that pembrolizumab developed grade 3 to 5 adverse events more frequently than nivolumab,[33,34] no significant risk of IRP was detected with pembrolizumab compared to nivolumab.[8,33,34] However, although earlier treatment was not a risk for IRP in the univariate analysis of this study, pembrolizumab may reflect it because a previous study indicated it to be a risk for IRP.[29] Further validation is warranted to confirm this result.

Although no report is available supporting our result that low serum albumin predicts IRP, it has been reported to be a risk for developing acute respiratory distress syndrome.[35,36] Decreased oncotic pressure due to hypoalbuminemia and lung damage/inflammation are considered to induce pulmonary edema. Given

Figure 2 Kaplan-Meier Curves of Patients Who Did and Did Not Develop Immune-Related Pneumonitis at 8-Week Landmark Analysis. (A) Progression-free Survival. Median Survival Time Was Not Significantly Different Between Groups. (B) Overall Survival. Median Survival Time Was Significantly Shorter in Patients Who Developed Immune-Related Pneumonitis



Abbreviations: IRP = immune-related pneumonitis; MST = median survival time.

Table 5 Predictors of Development of Immune-Related Pneumonitis

Characteristic	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (y)	0.980	0.939-1.023	.347			
Gender, male	1.034	0.405-2.640	.944			
Smoking (pack-years)	0.994	0.981-1.007	.362			
ECOG PS, 0-1	0.569	0.205-1.083	.280			
Histology, squamous	0.760	0.311-1.857	.547			
Drug, pembrolizumab	3.365	1.431-7.909	.005	3.259	1.361-7.807	.008
Treatment line, first	2.197	0.859-5.617	.100			
Past thoracic RT, yes	0.888	0.362-2.178	.795			
Abnormal CT findings, yes	1.530	0.669-3.500	.313			
WBC ($\times 10^3/mm^3$)	1.090	1.000-1.188	.051			
NLR	1.060	0.993-1.131	.080			
CRP (mg/dL)	1.090	0.993-1.197	.071			
Albumin (g/dL)	0.367	0.176-0.768	.008	0.381	0.179-0.808	.012
AST (U/L)	0.987	0.949-1.028	.538			
ALT (U/L)	1.017	0.992-1.041	.185			
Creatinine (mg/dL)	1.356	0.414-4.445	.615			

Evaluated by stepwise logistic regression analysis using all variables described in this table.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CRP = C-reactive protein; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; NLR = neutrophil-to-lymphocyte ratio; OR = odds ratio; RT = radiotherapy; WBC = white blood cell count.

the fact that elevated baseline white blood cell count and C-reactive protein concentration were significantly correlated with low serum albumin in calculation of the correlation coefficient (but insufficient for judging multicollinearity; data not shown), systemic inflammation and low serum albumin might elevate the risk for IRP as well. Further studies are necessary to verify this hypothesis.

The incidence of IRP has been reported to be around 5%, based on past clinical trials[2,3] and most other reports. Some reports, however, demonstrated a higher incidence of 13% to 19%,[16,17,33,34] which is consistent with our results. This large difference may be partially due to the frequency of scanning chest CT scans in our routine clinical practice, as well as the high prevalence of patients with potential risks for IRP who took PD-1 inhibitors outside clinical trials, such as low performance status with systemic inflammation, though firm risk factors have not been confirmed. Additionally, we also need to be careful with the interpretation of radiologic findings. Drug-related pneumonitis generally shows diffuse/multifocal bilateral ground-glass opacities, consolidations, interlobular septal thickening, or centrilobular nodules on chest CT,[37] and these findings are sometimes classified on the basis of similar CT patterns for interstitial pneumonia. In terms of IRP induced by PD-1 inhibitors, Nishino et al[14] reported that, like some other drug-related pneumonitis, the most common CT pattern was "organizing pneumonia pattern," and "acute interstitial pneumonia pattern" was associated with more severe respiratory disorder. However, they also reported some cases of unilateral distribution of CT findings, which is possible but is a relatively rare finding in drug-related pneumonitis. Similarly, in our study, unilateral infiltration was observed in 14% of patients with IRP. Moreover, other atypical findings, such as peritumoral infiltrations (data not shown) or increases of radiation pneumonitis, are also observed in some cases, which are difficult, and sometimes impossible, to be distinguished from "pseudo-progression" and true radiation pneumonitis, respectively. The incidence of IRP can be altered on the basis of whether those interpreting the data consider these atypical findings to be compatible with IRP.

There are several limitations to our study. First, the retrospective study design and small number of patients limit the generalizability of the results. However, the number of patients included in this study is larger than in past reports regarding the prognosis of irAEs, which included 40 to 140 patients with NSCLC who were treated with PD-1 inhibitors.[17,23-27] Second, because the timing for chest CT and other systemic image examinations was not predefined, detection of IRP and treatment effect might possibly be delayed by not taking images at the proper time point. However, most patients in our study underwent chest CT at least once in 6 to 12 weeks as a part of routine follow-up. We could therefore collect sufficient data for evaluating the treatment effect and the development of IRP from almost all patients. This was partly due to excellent accessibility to CT scans and other imaging studies at our institutions in Japan. Third, most patients with remarkable preexisting interstitial pneumonia were excluded as candidates for PD-1 inhibitors through the daily clinical practice. This prevented us from evaluating the effect of associated interstitial pneumonia on IRP. Furthermore, because we did not predefine how to treat IRP, the treatment strategy was up to each clinician and therefore varied; this could affect the prognosis of IRP. However, because most patients with IRP recovered after administration of corticosteroids, the number of the cases of undertreatment should be small. We also did not evaluate the significance of other factors such as irAEs other than IRP, baseline pulmonary function, and the level of tumor programmed cell death ligand 1 expression, which are not routinely recorded or examined in usual clinical practice.

Conclusion

Unlike past reports on the prognosis of irAEs, IRP was correlated with poor prognosis in patients with NSCLC. Administration of pembrolizumab and baseline low serum albumin were independent predictors of IRP. Further study is needed to detect firm predictors of IRP and establish the best care strategy for patients who develop IRP to overcome the poor prognosis.

Clinical Practice Points

- irAEs induced by PD-1 inhibitors are generally regarded to be associated with effectiveness of PD-1 inhibitor therapy and better prognosis.
- Although IRP induced by PD-1 inhibitors sometimes causes lethal outcome, only a few studies have focused on the prognosis of pneumonitis.
- The characteristics of patients who are likely to develop pneumonitis have also not been well elucidated.
- In this retrospective study, despite most patients with NSCLC who developed pneumonitis recovering with drug cessation and/or corticosteroid therapy, development of pneumonitis was significantly associated with shorter OS after administration of the PD-1 inhibitor.
- Patients with pneumonitis tended to be reluctant to take next-line treatment and instead chose best supportive care after cessation of PD-1 inhibitor therapy.
- Pembrolizumab use (compared with nivolumab) and low serum albumin were significant risk factors for pneumonitis.
- Further study is needed to detect firm predictors of pneumonitis and to establish the best care strategy for patients who develop pneumonitis to overcome the poor prognosis.

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Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online versionat https://doi.org/10.1016/j.cllc.2019.07.006.

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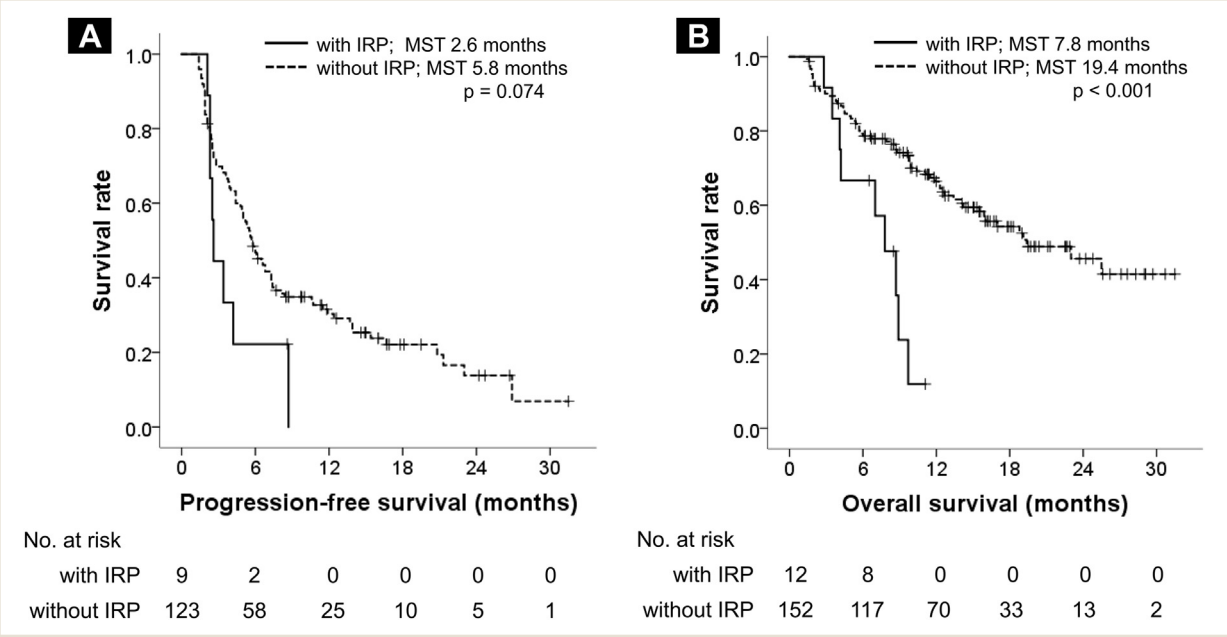
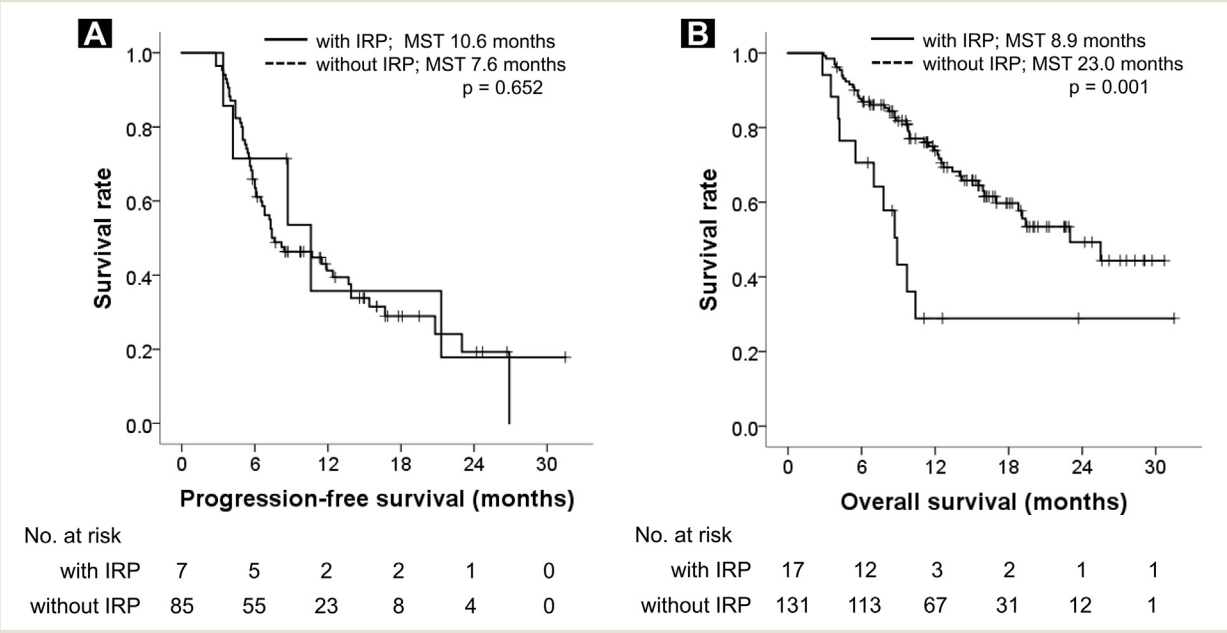
Supplemental Data

Supplemental Figure 1 **Kaplan-Meier Curves of Patients Who Did and Did Not Develop Immune-Related Pneumonitis at 6-Week Landmark Analysis. (A) Progression-free Survival. Median Survival Time Was Not Significantly Different Between Groups. (B) Overall Survival. Median Survival Time Was Significantly Shorter in Patients Who Developed Immune-Related pneumonitis**



Abbreviations: IRP = immune-related pneumonitis; MST = median survival time.

Supplemental Figure 2 **Kaplan-Meier Curves of Patients Who Did and Did Not Develop Immune-Related Pneumonitis at 12-Week Landmark Analysis. (A) Progression-free Survival. Median Survival Time Was Not Significantly Different Between Groups. (B) Overall Survival. Median Survival Time Was Significantly Shorter in Patients Who Developed Immune-Related pneumonitis**



Abbreviations: IRP = immune-related pneumonitis; MST = median survival time.

Supplemental Table 1 Patient Characteristics by Institute

Characteristic	Institute			*P*
	NUH (N = 82)	TGH (N = 49)	HCH (N = 39)	
Pneumonitis, developed	12 (15)	9 (18)	7 (18)	.822
Age (y)	67.0 (59.0-73.0)	70.0 (64.0-73.0)	70.0 (65.0-73.0)	.152
Gender, male	57 (70)	34 (70)	34 (87)	.089
Smoking (pack-years)	38.5 (4.0-56.7)	44.3 (13.2-57.5)	46.0 (26.0-60.0)	.242
ECOG PS, 0-1	65 (79)	47 (96)	32 (82)	.033
Histology, squamous cell	22 (27)	21 (43)	16 (41)	.113
Drug, pembrolizumab	28 (34)	13 (27)	24 (62)	.002
Treatment Line				
First	12 (15)	5 (10)	14 (36)	.004
First or second	43 (52)	33 (67)	29 (74)	.043
Past thoracic RT, yes	24 (29)	20 (41)	10 (26)	.251
HRCT Findings				
Interstitial lung disease	5 (6)	7 (14)	4 (10)	.293
Moderate to severe emphysema	18 (22)	18 (37)	25 (64)	< .001
Laboratory Findings				
WBC ($\times 10^3/mm^3$)	6.4 (4.8-8.4)	5.8 (4.6-7.6)	6.4 (5.5-9.1)	.113
NLR	3.1 (2.1-5.2)	3.6 (1.9-5.8)	3.8 (2.2-7.2)0.95 (0.14-4.88)	.450
CRP (mg/dL)	0.66 (0.11-2.51)	0.59 (0.14-3.43)	3.6 (3.1-4.0)	.322
Albumin (g/dL)	3.7 (3.4-4.0)	3.7 (3.1-4.0)	22 (19-27)	.842
AST (U/L)	20 (16-25)	21 (16-26)	16 (10-21)	.496
ALT (U/L)	14 (9-21)	16 (11-22)	0.75 (0.62-0.83)	.502
Creatinine (mg/dL)	0.77 (0.61-0.93)	0.74 (0.65-0.90)	0.75 (0.62-0.83)	.752

Data are presented as n (%) or median (interquartile range).
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; ECOG PS = Eastern Cooperative Oncology Group performance status; HCH = Handa City Hospital; HRCT = high-resolution computed tomography; NLR = neutrophil-to-lymphocyte ratio; NUH = Nagoya University Hospital; RT = radiotherapy; TGH = Tosei General Hospital; WBC = white blood cell count.

Supplemental Table 2 Number of Cases Analyzed in Each Landmark Analysis

Landmark	Total Cases	Disease Progression or Death Before Landmark Date	Cases Analyzed for PFS	Death Before Landmark Date	Cases Analyzed for ORR, DCR, and OS
6-Week Landmark					
IRP developed	15	6	9	3	12
IRP not developed	155	32	123	3	152
8-Week Landmark					
IRP developed	18	7	11	4	14
IRP not developed	152	43	109	10	142
12-Week Landmark					
IRP developed	21	14	7	4	17
IRP not developed	149	64	85	18	131
No Landmark					
IRP developed	27	NA	27	NA	27
IRP not developed	143	NA	143	NA	143

Abbreviations: DCR = disease control rate; IRP = immune-related pneumonitis; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Supplemental Table 3 Efficacy of PD-1 Inhibitors in Each Landmark Point

Characteristic	Immune-Related Pneumonitis		*P*
	Yes	No	
6-Week Landmark			
No. of patients	12	152	
CR/PR/SD/PD/NE	0/4/5/3/0	0/38/84/29/1	
ORR	33%	25%	.534
DCR	75%	81%	.627
12-Week Landmark			
No. of patients	17	131	
CR/PR/SD/PD/NE	0/6/1/10/0	0/34/48/49/0	
ORR	35%	26%	.415
DCR	41%	63%	.090

Abbreviations: CR = complete response; DCR = disease control rate; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.