Original Study

Real-World Efficacy of First-Line Pembrolizumab in Patients With Advanced or Recurrent Non–Small-Cell Lung Cancer and High PD-L1 Tumor Expression

Yuichi Tambo,[1] Takashi Sone,[1] Kazuhiko Shibata,[2] Kouichi Nishi,[3] Hiroki Shirasaki,[4] Taro Yoneda,[5] Tomoyuki Araya,[6] Kazumasa Kase,[7] Shingo Nishikawa,[1] Hideharu Kimura,[1] Kazuo Kasahara[1]

Abstract

To clarify the real-world efficacy and safety of first-line pembrolizumab, we assessed 95 consecutive patients with programmed death ligand 1 strongly expressed non–small-cell lung cancer in a retrospective multicenter trial. Nonadenocarcinoma and a large number of metastatic sites correlated with poor progression-free survival (PFS). PFS and overall survival (OS) were longer in patients with pembrolizumab-related adverse events; however, PFS and OS were shorter in patients with interstitial lung disease.

Background: In clinical trials, first-line treatment with pembrolizumab improved overall survival (OS) in patients with advanced non–small-cell lung cancer (NSCLC) with a programmed death ligand 1 (PD-L1) tumor proportion score of $\geq$ 50%. However, data on the efficacy of this treatment between clinical trials and actual clinical practice are inconsistent. **Patients and Methods:** Ninety-five patients with histologically diagnosed advanced or recurrent NSCLC and a PD-L1 tumor proportion score of $\geq$ 50% who received pembrolizumab as first-line treatment were consecutively enrolled onto this multicenter retrospective study from February 2017 to December 2018. Clinical data were collected from electronic medical records. We assessed the objective response rate, progression-free survival (PFS), OS, and immune-related adverse events (irAE), and determined their associations with clinical characteristics. **Results:** The objective response rate was 40.0%. The median PFS was 6.1 months, and OS did not reach the median. Multivariate analyses revealed that nonadenocarcinoma histology (hazard ratio, 1.78; 95% confidence interval, 1.05-3.03; $P = .015$) and $\geq$ 3 metastatic sites (hazard ratio, 3.97; 95% confidence interval, 1.97-8.01; $P < .001$) were independently correlated with poor PFS. Patients with irAE and patients without interstitial lung disease had significantly longer PFS (14.0 and 4.9 months, respectively; $P = .011$) than patients without irAE or patients with interstitial lung disease. **Conclusion:** The outcome of patients receiving first-line pembrolizumab treatment was worse in those with nonadenocarcinoma and with a large number of metastatic sites. Patients with irAE and without interstitial lung disease had a more favorable outcome.

Clinical Lung Cancer, Vol. 21, No. 5, e366-79

Keywords: First-line pembrolizumab, Immune checkpoint inhibitor, Immune-related adverse events, Real-world data, Tumor proportion score of more than 50%

[1]Department of Respiratory Medicine, Kanazawa University, Kanazawa, Japan
[2]Department of Medical Oncology, Kouseiren Takaoka Hospital, Takaoka, Japan
[3]Department of Respiratory Medicine, Ishikawa Prefectural Central Hospital, Kanazawa, Japan
[4]Department of Respiratory Medicine, Fukui-ken Saiseikai Hospital, Fukui, Japan
[5]Department of Respiratory Medicine, Komatsu Municipal Hospital, Komatsu, Japan
[6]Department of Respiratory Medicine, National Hospital Organization Kanazawa Medical Center, Kanazawa, Japan
[7]Department of Internal Medicine, Keiju Medical Center, Nanao, Japan

Submitted: Sep 14, 2019; Revised: Feb 1, 2020; Accepted: Feb 13, 2020; Epub: Feb 26, 2020

Address for correspondence: Yuichi Tambo, MD, Department of Respiratory Medicine, Kanazawa University Hospital, 1-13 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan
E-mail contact: yuichi.tambo@staff.kanazawa-u.ac.jp

1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2020.02.017

Introduction

Since the approval of anti−programmed death 1 (PD-1) or anti−programmed death ligand 1 (PD-L1) inhibitors as second-line treatment for non−small-cell lung cancer (NSCLC) in 2015, there has been a major paradigm shift in the use of immune checkpoint inhibitors (ICIs) for patients with NSCLC.[1-4] The PD-1 receptor is an ICI expressed on activated B and T cells that normally modulates excessive immune responses.[5,6] Binding of PD-1 to its ligands (PD-L1 and PD-L2) on tumor cells suppresses T cells through a negative feedback loop, leading to evasion of the immune response.[7-10]

Pembrolizumab is a highly selective humanized IgG4 monoclonal antibody against PD-1. In the KEYNOTE-024 trial reported in 2017, overall survival (OS) was found to be significantly better in the pembrolizumab-alone arm than in the platinum-combination therapy arm among patients with NSCLC who had a PD-L1 tumor proportion score (TPS) of $>$ 50% and who were receiving first-line treatment.[11] On the basis of this promising result, pembrolizumab has become the new standard primary treatment for patients with NSCLC and a PD-L1 TPS of $\geq$ 50%. Similarly, in the KEYNOTE-042 trial, significantly prolonged OS was observed in patients with NSCLC and a PD-L1 TPS of at least 50% in the pembrolizumab single-agent arm compared to that in patients in the platinum-combination chemotherapy arm.[12] Thus, combination therapy using platinum doublet chemotherapy and ICI treatment is now widely used as the primary treatment for advanced NSCLC on the basis of the results of the KEYNOTE-189, KEYNOTE-407, and IMpower 150 trials.[13-15]

However, there is still active discussion and debate regarding the most appropriate primary treatment for NSCLC with PD-L1 TPS $>$ 50%. First, there was a difference in the results of progression-free survival (PFS) and OS between the KEYNOTE-024 trial (10.3 and 30.0 months, respectively) and the KEYNOTE-042 trial (7.7 and 20 months, respectively), which is still not understood. Second, data on the efficacy and safety of primary treatment with pembrolizumab in patients with NSCLC and a PD-L1 TPS of $\geq$ 50% in clinical practice are often different from those obtained in clinical trials.

To clarify these issues, it is important to gather data related to primary treatment with pembrolizumab for patients with NSCLC and a PD-L1 TPS of $\geq$ 50%. Therefore, we performed this retrospective study to collect and analyze data on the efficacy and adverse events of pembrolizumab treatment in these patients.

Patients and Methods

Patient Selection

Patients for this retrospective multicenter trial were enrolled at Kanazawa University Hospital, Kanazawa Medical Center, Ishikawa Prefectural Hospital, Kouseiren Takaoka Hospital, Fukui-ken Saiseikai Hospital, Komatsu Municipal Hospital, and Keiju Medical Center from February 2017 to December 2018. Patients who met the following criteria were consecutively enrolled onto this study: patients with histologically diagnosed advanced or recurrent NSCLC who received treatment with anti−PD-1 or anti−PD-L1 antibodies (nivolumab, pembrolizumab, or atezolizumab). In this analysis, only data of patients with a PD-L1 TPS of $\geq$ 50% and who received pembrolizumab as the first-line treatment were extracted. The study design was approved by the institutional review board of each participating institution, and the research was conducted in accordance with the Declaration of Helsinki and the World Health Organization's *Guidelines for Good Clinical Practice*.

Data Collection

Clinical data—including age, sex, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status (PS), stage, histology, history of palliative radiotherapy, and metastatic site (lymph nodes, liver, brain, bone, lung, malignant pleural effusion, malignant pericardial effusion, skin, and meningeal metastasis) at the time of commencing pembrolizumab treatment—were collected from electronic medical records and pharmacy databases. PD-L1 status was evaluated by immunohistochemistry using the PD-L1 IHC 22C3 pharmDx assay.[16]

Clinical responses were defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1.[17] PFS was determined from the date of commencing pembrolizumab therapy to the date of disease progression or death from any cause. OS was determined from the date of commencing pembrolizumab therapy to the date of death. Patients were followed until March 31, 2019. The presence of immune-related adverse events (irAE) was based on assessment by the treating physician, and the irAE were graded according to the Common Terminology Criteria for Adverse Events, version 4.0. The diagnosis of interstitial lung disease (ILD) was mainly based on radiographical findings and clinical course. In possible cases, ILD was diagnosed by bronchoalveolar lavage.

Statistical Analyses

OS and PFS were analyzed by the Kaplan-Meier method. The differences between patient groups according to each factor were compared by the log-rank test. $P \leq .05$ was regarded as statistically significant, and all comparisons were 2 sided. Cox regression analysis was used to calculate the hazard ratio of each factor with 95% confidence interval (CI). Multivariate analysis by the Cox regression model was performed using factors showing a significant effect on OS or PFS in the univariate analyses to detect independent prognostic factors. SPSS 20 for Windows (IBM, Armonk, NY) was used to conduct all analyses.

Results

Patient Characteristics

Of the 435 patients eligible for this study during the recruitment period, 95 patients were ultimately enrolled onto the study (Supplemental Figure 1 in the online version). The patient characteristics are summarized in Table 1. The median age was 72 years. Among the 95 patients, most were male, had an ECOG PS score of 0-1, had stage IV disease, were smokers, and had not received palliative radiotherapy. Fifty-nine patients (62.1%) were diagnosed with adenocarcinoma, and 19 patients (20.0%) had 3 or more metastatic sites. Only one of the patients had a driver mutation (*EGFR* mutation, *ALK* fusion gene, *ROS1* fusion gene), which was an uncommon *EGFR* mutation.

Clinical Effect and Adverse Events of Pembrolizumab

The objective response rate (ORR), disease control rate, and progressive disease rates are listed in Table 2.

Table 1 Baseline Demographic and Clinical Characteristics of 95 Patients

Characteristic	Variable	Value
Age (years)	—	72 (51-89)
Gender	Men	71 (74.7)
	Female	24 (25.3)
ECOG PS	0-1	74 (77.9)
	2	11 (11.6)
	3-4	10 (10.5)
Stage	Recurrence	29 (30.5)
	IV	66 (69.5)
Histology	Adenocarcinoma	59 (62.1)
	Nonadenocarcinoma	36 (37.9)
	Squamous-cell carcinoma	31 (32.6)
	adenosquamous carcinoma	1 (1.1)
	Combined small-cell lung cancer	1 (1.1)
	Other	3 (3.2)
Smoking	Never	17 (17.9)
	Smoker	77 (81.1)
	Unknown	1 (1.1)
Radiotherapy	Provided	18 (18.9)
	Not provided	77 (81.1)
No. of metastatic sites	<3	76 (80.0)
	≥3	19 (20.0)

Data are presented as n (%) or median (range).
Abbreviation: ECOG PS = Eastern Cooperative Oncology Group performance status.

The median follow-up time was 8.8 months. On the basis of 59 total events of progression or death, the median PFS was 6.1 months (95% CI, 3.64-8.56). The estimated percentage of patients who were alive and had no disease progression at 6 and 12 months was 50.9% and 35.7%, respectively (Figure 1A).

At the time of the analysis, 36 deaths had occurred. The OS did not reach the median. The estimated percentage of patients who were alive at 6 and 12 months was 78.3% and 58.3%, respectively (Figure 1B).

Treatment-related adverse events occurred in 40 patients (42.1%). The summary of irAE is listed in Table 3. We classified 40 patients with irAE into the group of irAE$^+$ and ILD$^-$ (n = 27), indicating patients with irAE but without ILD, and an ILD$^+$ group (n = 13). The discontinuation rate of pembrolizumab due to irAE was higher in the ILD$^+$ group compared to that in the irAE$^+$ and ILD$^-$ group (92.3% and 33.3%, respectively; $P < .001$)

Table 2 Response to Pembrolizumab

Response	N	%
CR	6	6.3
PR	32	33.7
SD	27	28.4
PD	23	24.2
NE	7	7.4
Total	95	100
ORR	38	40.0
DCR	65	68.4

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

Correlation Between Patient Characteristics and Response to Pembrolizumab

We investigated the correlation between patient characteristics and PFS or OS to explore potential biomarkers that could predict the effects of pembrolizumab. In the univariate Cox proportional hazards regression model of PFS, ECOG PS (0-1 vs. ≥ 2), histology (adenocarcinoma vs. nonadenocarcinoma), and number of metastatic sites (< 3 vs. ≥ 3) correlated with PFS (Table 4; Supplemental Figures 2A, 3A, and 4A, respectively, in the online version). Multivariate analyses revealed that histology (adenocarcinoma vs. nonadenocarcinoma) and number of metastatic sites (< 3 vs. ≥ 3) were independently correlated with PFS (Table 4). In the univariate Cox proportional hazards regression model of OS, histology (adenocarcinoma vs. nonadenocarcinoma) and number of metastatic sites (< 3 vs. ≥ 3) were correlated with OS (Table 5; Supplemental Figures 3B and 4B, respectively, in the online version). Multivariate analyses revealed that the number of metastatic sites (< 3 vs. ≥ 3) was the only factor independently correlated with OS in pembrolizumab-treated patients with advanced NSCLC (Table 5).

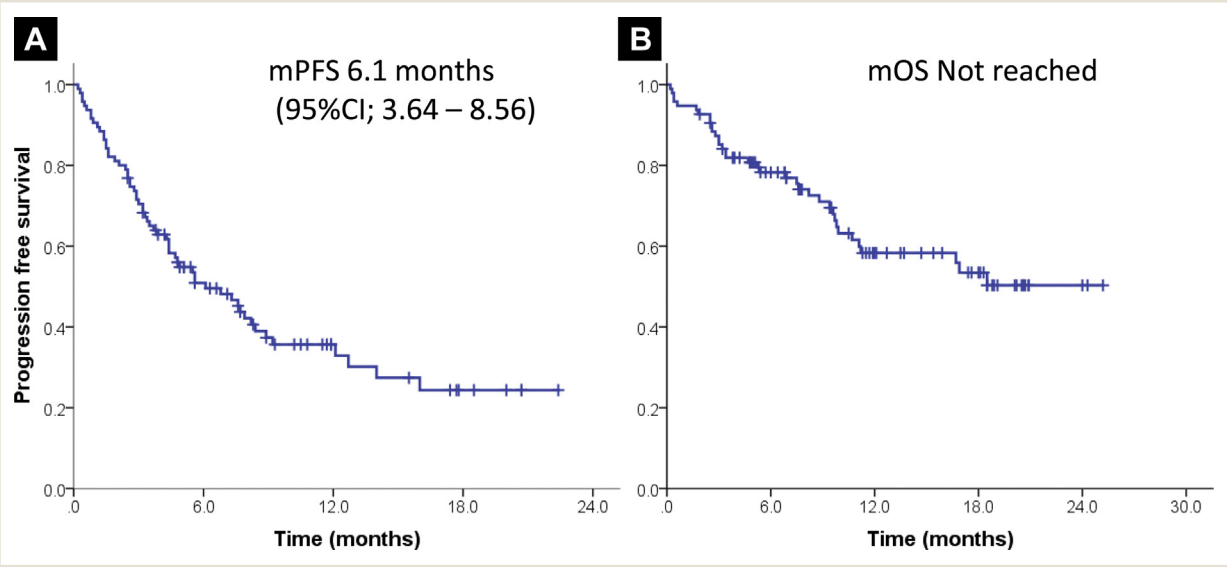
Correlation Between irAE and Response to Pembrolizumab

There was no difference in PFS between pembrolizumab-treated patients with and without irAE at 7.9 (95% CI, 0.0-15.9) and 5.6 (95% CI, 3.5-7.7) months, respectively ($P = .068$; Figure 2A). OS was significantly longer in patients with irAE than in patients without irAE (not reached and 11.1; 95% CI, 2.1-20.1, respectively; $P = .033$, Figure 2B). Further analysis revealed that PFS was significantly shorter in patients with ILD than in patients with irAE and patients without ILD (irAE$^+$ and ILD$^-$) at 3.3 months (95% CI, 1.1-5.5) and 14.0 months (95% CI, 5.1-22.9), respectively (Supplemental Figure 5A in the online version). OS was also significantly shorter in patients with ILD than that in patients with irAE and without ILD (irAE$^+$ and ILD$^-$) at 16.7 months (95% CI, 2.4-31.0) and not reached, respectively (Supplemental Figure 5B in the online version).

The percentage of patients diagnosed with adenocarcinoma was significantly higher in the irAE$^+$ and ILD$^-$ group than in the irAE$^-$ or ILD$^+$ group; however, there were no significant differences between the two groups with regard to other factors (Supplemental Table 1 in the online version).

Patients in the irAE$^+$ and ILD$^-$ group had a longer PFS compared to those without irAE or with ILD (irAE$^-$ or ILD$^+$) at 14.months (95% CI, 5.1-22.9) and 4.9 (95% CI, 3.3-6.5) months, respectively ($P = .011$, Figure 2C). Similarly, patients with in the irAE$^+$ and ILD$^-$ group had a longer OS compared to patients in the irAE$^-$ or ILD$^+$ group (not reached and 11.2 months; 95% CI, 3.9-18.5, respectively; $P = .002$, Figure 2D). Landmark analysis performed to exclude a risk of immortal bias showed the same tendency, in which the patients in the irAE$^+$ and ILD$^-$ group had longer PFS and OS in each period (Supplemental Figure 6 in the online version).

Figure 1 Kaplan-Meier Survival Curves. (A) mPFS and (B) mOS in Patients Treated With Pembrolizumab as Frontline Therapy



Abbreviations: CI = confidence interval; mOS = median OS; mPFS = median progression-free survival.

Discussion

In our cohort, ORR and PFS in patients with advanced/recurrent NSCLC and a PD-L1 TPS of ≥ 50% was 40.0% and 6.1 months, respectively, and the OS did not reach the median. The ORR observed in this study was similar to those of the KEYNOTE-024 (44.8%) and KEYNOTE-042 (39.5%) trials. However, the PFS was shorter than those obtained in these two trials (10.3 and 7.1 months, respectively).[11,12,18] The difference in the results of this study and those of the KEYNOTE trials may be attributed to the fact that this study included cases of poor ECOG PS. When patients with a ECOG PS score of 2 or worse were excluded, the PFS was 7.9 months (Supplemental Figure 2A in the online version), which was equivalent to that of the KEYNOTE-042 trial.

Table 3 Summary of Immune-Related Adverse Events in Patients Treated With Pembrolizumab

Toxicity	Any Grade	Grade 3 or Higher
Any irAE	40 (42.1)	18 (18.9)
$irAE^{+}$ and ILD^{-}	27 (28.4)	
Dermatitis	13 (13.7)	4 (4.2)
Fever	5 (5.3)	1 (1.1)
Hepatitis	6 (6.3)	3 (3.2)
Pituitary and adrenal dysfunction	2 (2.1)	2 (2.1)
Cholangitis	2 (2.1)	2 (2.1)
Type 1 diabetes mellitus	2 (2.1)	1 (1.1)
Thyroid dysfunction	2 (2.1)	0
Arthritis	2 (2.1)	0
Myositis	1 (1.1)	1 (1.1)
Diarrhea	1 (1.1)	0
Peripheral neuropathy	1 (1.1)	0
Other	4 (4.2)	0
ILD^{+}	13 (13.7)	
Pneumonitis	13 (13.7)	7 (7.4)

Data are presented as n (%).
Abbreviations: ILD = interstitial lung disease; irAE = immune-related adverse event.

We showed that adenocarcinoma histology and a smaller number of metastatic sites were correlated with longer PFS. A smaller number of metastatic sites was also correlated with longer OS. Thirty-one patients (32.3%) with squamous-cell carcinoma were included in this study, which is a higher proportion than that included in the KEYNOTE-024 trial (18.8%) and is similar to that in the KEYNOTE-042 trial (38.1%). Although there are no published data of the response rate, PFS, or OS by histologic type, we consider that the outcome of patients with squamous-cell carcinoma and strongly expressed PD-L1 could be poor compared to patients with non−squamous-cell carcinoma. Notably, squamous-cell carcinoma is a well-known poor prognostic factor. Therefore, further investigation is needed to clarify the effect of pembrolizumab on patients with squamous-cell carcinoma.

In our study, a smaller number of metastatic sites was associated with a favorable antitumor effect of pembrolizumab. We used the number of metastatic sites rather than the specific metastatic site for this analysis for two reasons. First, the number of metastatic sites was considered to be related to the tumor burden. Second, in our cohort, there were no particular metastatic sites affecting PFS and OS except for bone metastasis (Supplemental Table 2 in the online version). We determined a cutoff of 3 metastatic sites for comparison because this cutoff had a greater impact on PFS and OS than other values tested (Supplemental Figure 7 in the online version). Huang et al[19] reported that the influence of the ratio of PD-

Table 4 Univariate and Multivariate Analysis of PFS in Patients Treated With Pembrolizumab

Characteristic	Variable	N	PFS	Univariate Analysis			Multivariate Analysis		
				HR	95% CI	*P*	HR	95% CI	*P*
Gender	Male	71	5.6	1			—	—	—
	Female	24	7.6	0.98	0.55-1.74	.940	—	—	—
Age	<70 y	39	4.8	1			—	—	—
	≥70 y	56	8.4	0.62	0.37-1.04	.067	—	—	—
Smoking	Never	17	6.1	1			—	—	—
	Smoker	77	6.8	0.95	0.48-1.89	.859	—	—	—
ECOG PS	0-1	74	7.9	1			1		
	≥2	21	3.4	2.15	1.25-3.72	.006	0.92	0.46-1.85	.817
Stage	Recurrence	29	6.1	1			—	—	—
	IV	66	6.8	0.90	0.56-1.67	.661	—	—	—
Histology	Adenocarcinoma	59	8.4	1			1		
	Nonadenocarcinoma	36	3.7	2.04	1.22-3.41	.004	1.78	1.05-3.03	.015
Radiotherapy	Provided	18	7.9	1			—	—	—
	Not provided	77	5.6	0.88	0.45-1.69	.768	—	—	—
No. of metastatic sites	<3	76	8.2	1			1		
	≥3	19	2.1	4.19	2.39-7.35	<.001	3.97	1.97-8.01	<.001

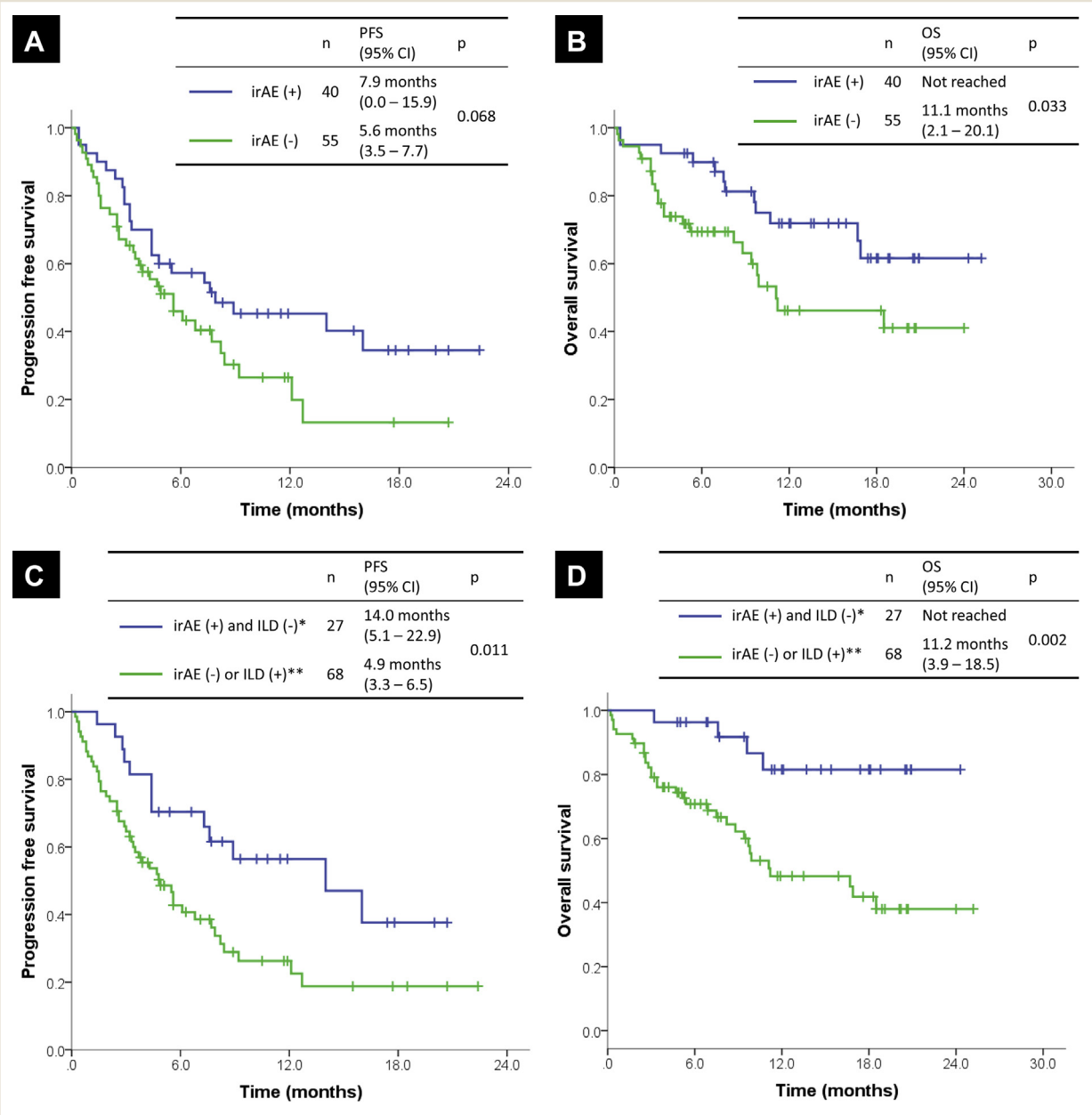
Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; PFS = progression-free survival.

Table 5 Univariate and Multivariate Analysis of OS in Patients Treated With Pembrolizumab

Characteristic	Variable	N	OS	Univariate Analysis			Multivariate Analysis		
				HR	95% CI	*P*	HR	95% CI	*P*
Gender	Male	71	NR	1			—	—	—
	Female	24	16.7	1.10	0.53-2.27	.808	—	—	—
Age	<70 y	39	16.9	1			—	—	—
	≥70 y	56	NR	0.93	0.48-1.80	.838	—	—	—
Smoking	Never	17	16.7	1			—	—	—
	Smoker	77	NR	0.67	0.31-1.48	.321	—	—	—
ECOG PS	0-1	74	NR	1			—	—	—
	≥2	21	11.1	1.88	0.92-3.82	.083	—	—	—
Stage	Recurrence	29	18.5	1			—	—	—
	IV	66	NR	1.02	0.51-2.05	.720	—	—	—
Histology	Adenocarcinoma	59	NR	1			1		
	Nonadenocarcinoma	36	9.9	1.97	1.02-3.79	.043	1.69	0.87-3.28	.123
Radiotherapy	Provided	18	NR	1			—	—	—
	Not provided	77	16.9	0.73	0.30-1.76	.887	—	—	—
No. of metastatic sites	<3	76	NR	1			1		
	≥3	19	3.4	3.96	1.99-7.89	<.001	3.61	1.80-7.26	<.001

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NR = not reached; OS = overall survival.

Figure 2 Kaplan-Meier Survival Curves of Patients With and Without irAE. (A) PFS and (B) OS in Patients With and Without irAE. (C) PFS in Patients With irAE (−) or ILD (+) and Patients With irAE (+) and ILD (−). (D) OS in Patients With irAE (−) or ILD (+) and Patients With irAE (+) and ILD (−). *irAE (−) Indicates Patients Without irAE; ILD (+), Patients With ILD. **irAE (+) Indicates Patients With irAE; ILD (−), Patients Without ILD



Abbreviations: CI = confidence interval; ILD = interstitial lung disease; irAE = immune-related adverse event; OS = overall survival; PFS = progression-free survival.

$1^{+}Ki67^{+}CD8$ T cells as a marker of exhausted T-cell reinvigoration to tumor burden of greater than 1.94, may be associated with the favor clinical outcome in pembrolizumab-treated patients with melanoma. These results suggested that in addition to PD-L1 expression, tumor burden is one of the most important factors for predicting the efficacy of pembrolizumab for patients with NSCLC and a PD-L1 TPS of $\geq$ 50%.

We found that ECOG PS, as one of the most common prognostic factors for NSCLC, did not have an independent impact on PFS or OS. There are several potential explanations for this finding. First, there were only small number of cases with ECOG PS 2-4, and statistical power was insufficient to investigate the effect on survival. Second, the effects of ECOG PS may be different between patients receiving cytotoxic chemotherapy and molecular targeted

therapies and ICIs. Finally, the impact of the tumor burden on the response to ICIs may be stronger than that of ECOG PS.

The PFS and OS were both longer in patients with irAE induced by pembrolizumab than in those without irAE. In particular, irAE excluding ILD had a greater impact on PFS and OS in patients treated with pembrolizumab. In contrast, PFS and OS were shorter in patients with ILD than in those with other irAE. Some retrospective or prospective observational studies indicated that the development of irAE was associated with the survival outcome of patients with advanced or recurrent NSCLC after nivolumab treatment.[20-22] However, Ksienski et al[23] reported that patients who required treatment interruption due to irAE had a lower median OS compared to those treated continuously. Our results indicate that treatments other than single-agent pembrolizumab should be selected for patients at high risk of ILD because ILD strongly affects treatment discontinuation and may be related to poor PFS and OS.

ILD was more frequent in patients with nonadenocarcinoma, and irAEs other than ILD were more frequent in patients with adenocarcinoma in our cohort. However, there are few reports on the risk factors of ILD or irAE in treatment with ICIs.[24] Thus, it is necessary to search for not only patient background but also other irAE-related predictors, such as peripheral blood biomarkers.[25]

Our study has some limitations. First, although we consecutively collected the data of the patients, this study is retrospective in nature and thus subject to selection bias. Second, the data on irAE may be insufficient; in particular, there is a possibility that grade 1 irAEs were not correctly recorded and that the severity of the irAE was evaluated differently among investigators.

Conclusion

This study provides novel data on the real-world efficacy of first-line pembrolizumab in patients with advanced or recurrent NSCLC with a PD-L1 TPS of $\geq$ 50%, demonstrating a shorter PFS in patients with nonadenocarcinoma and large number of metastatic sites. PFS was longer in patients with irAE and without ILD compared to patients without irAE or with ILD. These results will further discussions on whether pembrolizumab is most appropriate as a single agent or in combination with other chemotherapeutic agents in the first-line treatment of patients with NSCLC and a PD-L1 TPS of $\geq$ 50%. Further investigations are required to identify clinical biomarkers that can reliably predict the response to pembrolizumab in this group of patients.

Clinical Practice Points

- Pembrolizumab improved OS in patients with advanced NSCLC, with a PD-L1 TPS of $\geq$ 50%, as first-line treatment. However, there are often difference in the data on the efficacy of this treatment between clinical trials and real-world data.
- This retrospective multicenter trial was conducted to clarify the real-world efficacy and safety of first-line pembrolizumab.
- The ORR was 40.0%. Median PFS was 6.1 months, and OS did not reach the median.
- Nonadenocarcinoma histology and 3 or more metastatic sites were correlated with poor PFS.
- PFS and OS were longer in patients with pembrolizumab-related adverse events; however, PFS and OS were shorter in patients with ILD.
- Obtaining real-world efficacy data of first-line pembrolizumab in patients with NSCLC and PD-L1 TPS of $\geq$ 50% is important for decision making regarding this treatment for patients with strong positive NSCLC.
- Further investigations are required to identify clinical biomarkers that can reliably predict the response to pembrolizumab in this group of patients.

Acknowledgments

We thank the patients, their families, and all the investigators for participating in this study.

Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

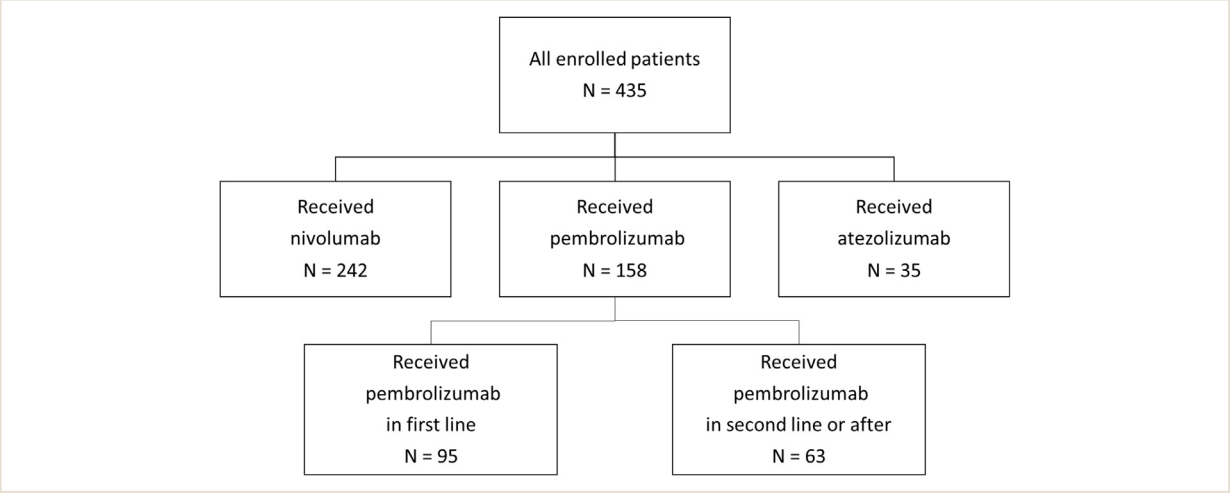
Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2020.02.017.

References

1. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med* 2015; 373:1627-39.
2. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *N Engl J Med* 2015; 373:123-35.
3. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1–positive, advanced non–small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387:1540-50.
4. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non–small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; 389:255-65.
5. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 2010; 236:219-42.
6. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012; 12:252-64.
7. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002; 8:793-800.
8. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci U S A* 2002; 99:12293-7.
9. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol* 2005; 23:515-48.
10. Freeman BGJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000; 192:1027-34.
11. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med* 2016; 375:1823-33.
12. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non–small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019; 6736:1-12.
13. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med* 2018; 378:2078-92.
14. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. *N Engl J Med* 2018; 379:2040-51.
15. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018; 378:2288-301.
16. Roach C, Zhang N, Corigliano E, et al. Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non–small-cell lung cancer. *Appl Immunohistochem Mol Morphol* 2016; 24:392-7.
17. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45:228-47.
18. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non–small-cell lung cancer with PD-l1 tumor proportion score of 50% or greater. *J Clin Oncol* 2019; 37:537-46.

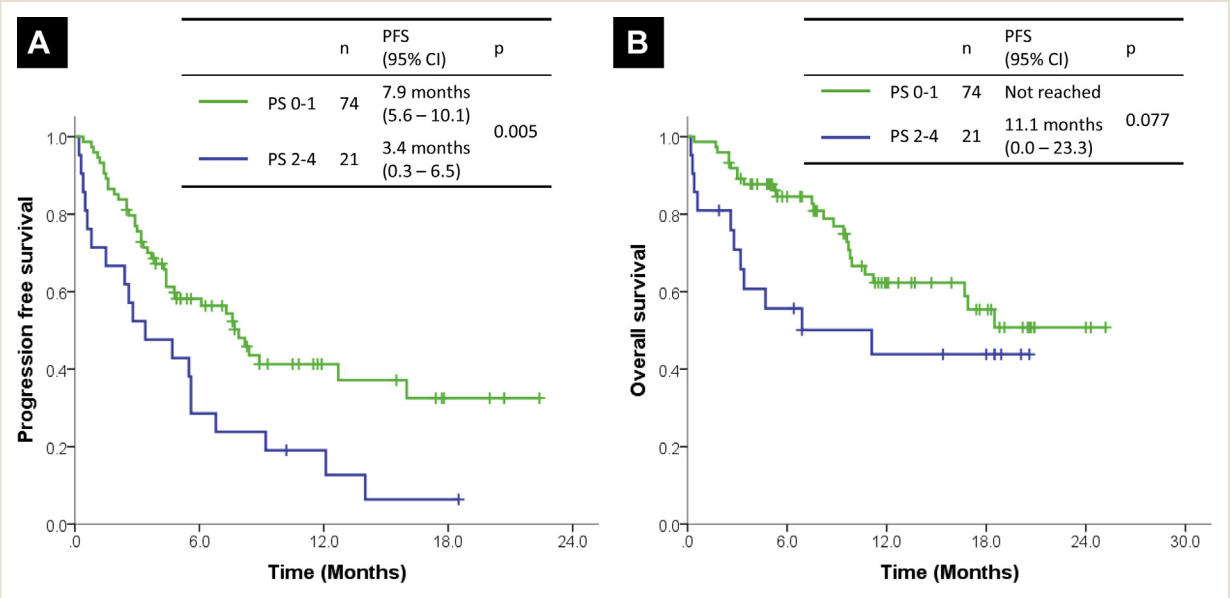
19. Huang AC, Postow MA, Orlowski RJ, et al. T-cell invigoration to tumour burden ratio associated with anti–PD-1 response. *Nature* 2017; 545:60-5.
20.. Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non–small-cell lung cancer. *JAMA Oncol* 2018; 4:374-8.
21. Teraoka S, Fujimoto D, Morimoto T, et al. Early immune-related adverse events and association with outcome in advanced non–small cell lung cancer patients treated with nivolumab: a prospective cohort study. *J Thorac Oncol* 2017; 12:1798-805.
22. Sato K, Akamatsu H, Murakami E, et al. Correlation between immune-related adverse events and efficacy in non–small cell lung cancer treated with nivolumab. *Lung Cancer* 2018; 115:71-4.
23. Ksienski D, Wai ES, Croteau N, et al. Efficacy of nivolumab and pembrolizumab in patients with advanced non–small-cell lung cancer needing treatment interruption because of adverse events: a retrospective multicenter analysis. *Clin Lung Cancer* 2019; 20:e97-106.
24. Kenmotsu H, Sakai F, Kato T, et al. Nivolumab-induced interstitial lung disease (ILD) in Japanese patients with non–small cell lung cancer: a study on risk factors using interim results of post-marketing all-case surveillance. *J Clin Oncol* 2017; 35(Suppl 15), abstract 9078.
25. Pavan A, Calvetti L, Maso AD, et al. Peripheral blood markers identify risk of immune-related toxicity in advanced non–small cell lung cancer treated with immune-checkpoint inhibitors. *Oncologist* 2019; 24:1128-36.

Supplemental Figure 1 **Flowchart Indicating Receipt of Drugs. Consecutive Patients Receiving Anti–PD-1/PD-L1 Antibody Were Enrolled Onto This Study. Of 435 Patients, 95 Patients With PD-L1 TPS Score ≥ 50% Who Received Pembrolizumab as First-line Therapy Were Extracted in This Analysis**



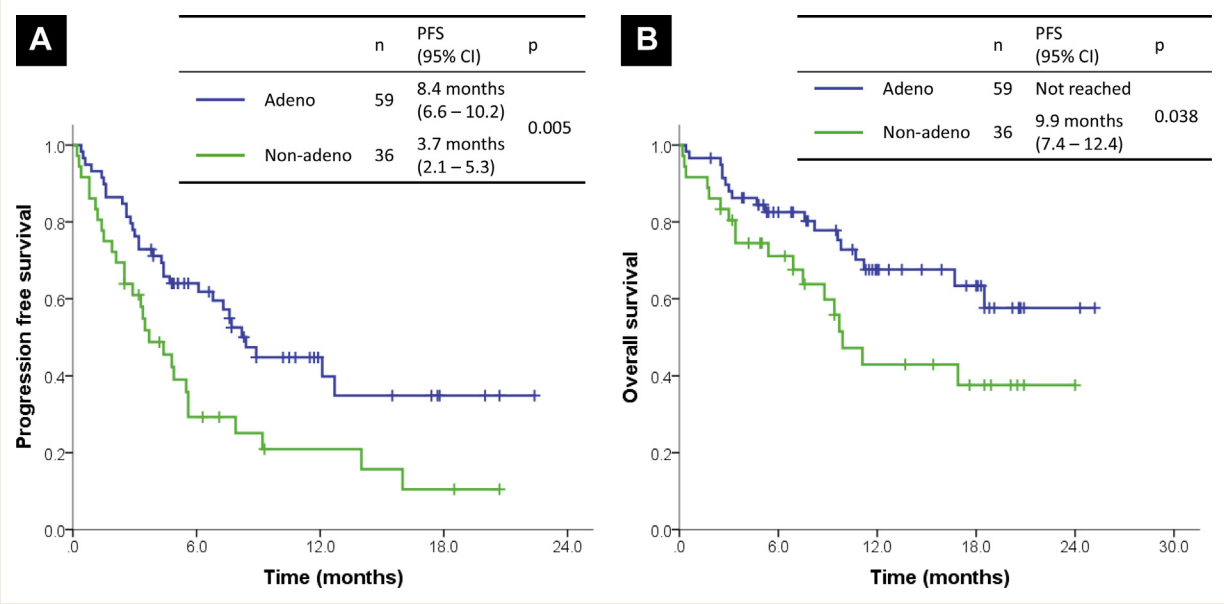
Abbreviations: PD-1 = programmed cell death 1; PD-L1 = programmed death ligand 1; TPS = tumor proportion score.

Supplemental Figure 2 **Kaplan-Meier Survival Curves by ECOG PS. (A) PFS in Patients With PS 0-1 and PS 2-4. (B) OS in Patients With PS 0-1 and PS 2-4**



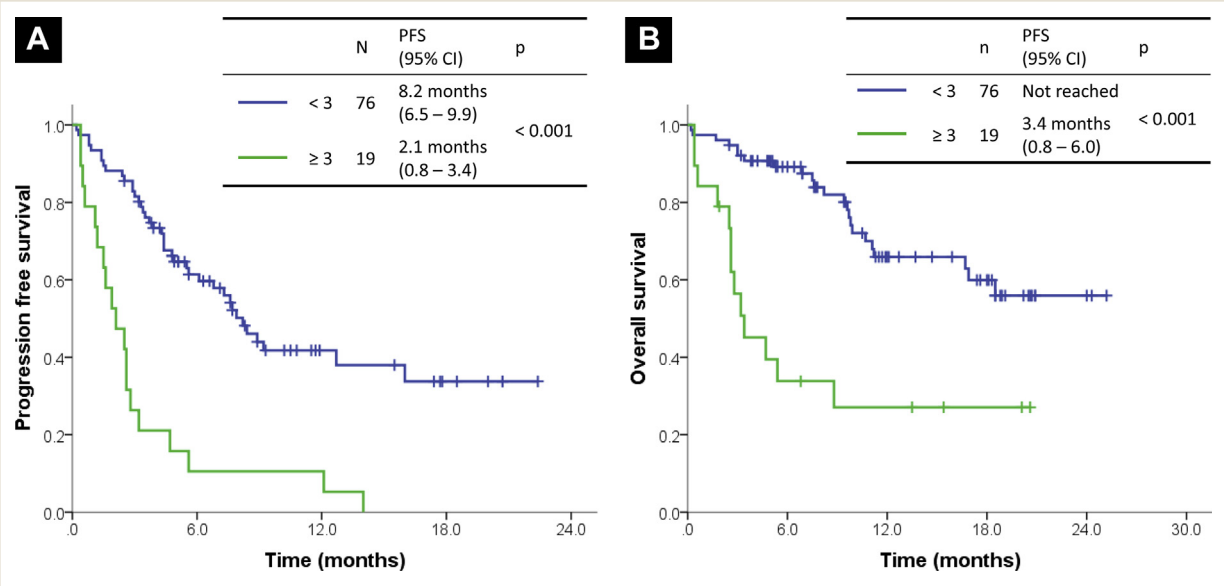
Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; OS = overall survival; PFS = progression-free survival.

Supplemental Figure 3 Kaplan-Meier Survival Curves by Disease. (A) PFS and (B) OS in Patients With adenocarcinoma and Nonadenocarcinoma



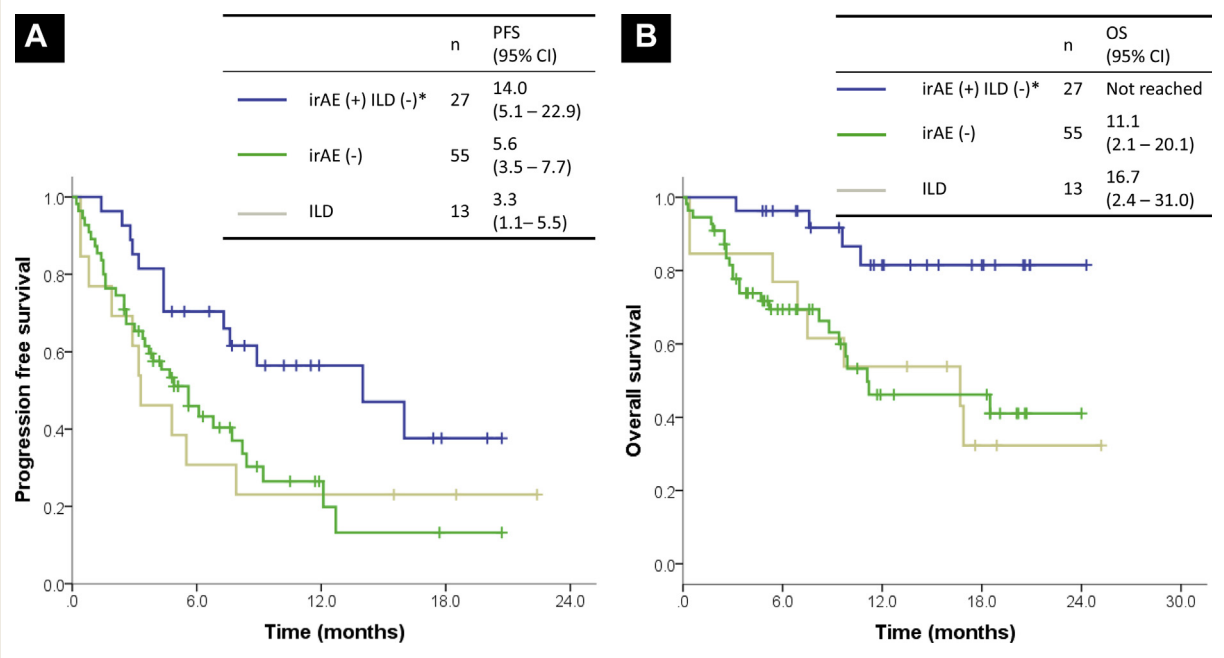
Abbreviations: CI = confidence interval; OS = overall survival; PFS = progression-free survival.

Supplemental Figure 4 Kaplan-Meier Survival Curves by Number of Metastatic Sites. (A) PFS and (B) OS in Patients With Number of Metastatic Sites < 3 and ≥ 3



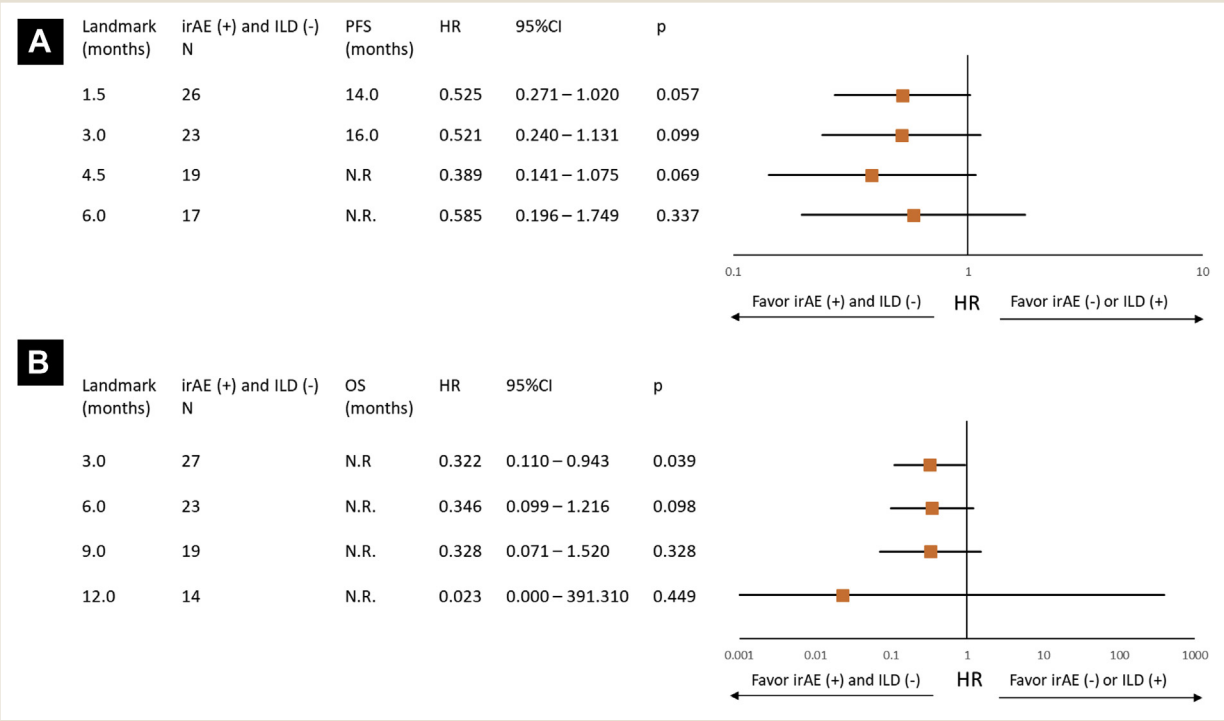
Abbreviations: CI = confidence interval; OS = overall survival; PFS = progression-free survival.

Supplemental Figure 5 Kaplan-Meier Survival Curves by irAE and ILD. (A) PFS and (B) OS in Patients With irAE (+) and ILD (−), irAE (−), and ILD (+). *irAE (+) Indicates Patients With irAE; ILD (−), Patients Without ILD



Abbreviations: CI = confidence interval; ILD = interstitial lung disease; irAE = immune-related adverse event; OS = overall survival; PFS = progression-free survival.

Supplemental Figure 6 Landmark Analysis of Survival by irAE and ILD. Landmark Analysis of (A) PFS and (B) OS Comparing Patients With irAE (+) and ILD (−) and Patients With irAE (−) or ILD (+)

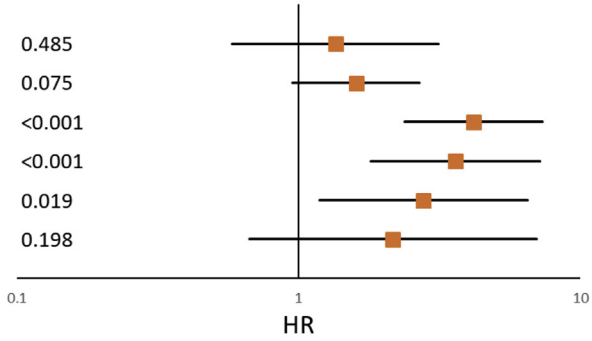


Abbreviations: CI = confidence interval; HR = hazard ratio; ILD = interstitial lung disease; irAE = immune-related adverse event; OS = overall survival; PFS = progression-free survival.

Supplemental Figure 7 Landmark Analysis of Survival by Number of Metastatic Sites. HR for (A) PFS and (B) OS in Each Cutoff of Number of Metastatic Sites

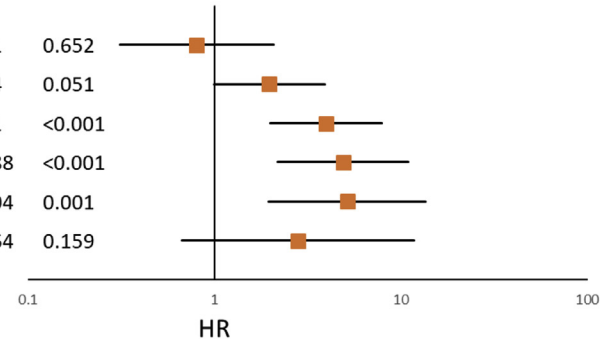
A

No. of Metastatic site	N	PFS (months)	HR	95%CI	p
≥ 1 (vs <1)	83	6.1	1.351	0.580 – 3.146	0.485
≥ 2 (vs <2)	48	4.7	1.601	0.954 – 2.685	0.075
≥ 3 (vs <3)	19	2.1	4.187	2.387 – 7.345	<0.001
≥ 4 (vs <4)	10	1.9	3.599	1.801 – 7.194	<0.001
≥ 5 (vs <5)	6	1.1	2.771	1.184 – 6.486	0.019
≥ 6 (vs <6)	3	1.1	2.164	0.669 – 7.003	0.198



B

No. of Metastatic site	N	OS (months)	HR	95%CI	p
≥ 1 (vs <1)	83	N.R.	0.804	0.312 – 2.071	0.652
≥ 2 (vs <2)	48	11.2	1.969	0.996 – 3.894	0.051
≥ 3 (vs <3)	19	3.4	3.963	1.990 – 7.891	<0.001
≥ 4 (vs <4)	10	2.6	4.903	2.187 – 10.988	<0.001
≥ 5 (vs <5)	6	2.6	5.173	1.967 – 13.604	0.001
≥ 6 (vs <6)	3	2.8	2.805	0.669 – 11.764	0.159



Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Supplemental Table 1 Patient Characteristics by irAE and ILD Status

Characteristic	Variable	Total (N = 95)	irAE$^-$ or ILD$^+$ (N = 68)	irAE$^+$ and ILD$^-$ (N = 27)	*P*
Age	<70 y	39 (41.1)	29 (42.6)	10 (37.0)	
	≥70 y	56 (58.9)	39 (57.4)	17 (63.0)	.306
Gender	Male	71 (74.7)	50 (73.5)	21 (77.8)	
	Female	24 (25.3)	18 (26.5)	6 (22.2)	.667
ECOG PS	0-1	74 (77.9)	51 (75.0)	23 (85.2)	
	2-4	21 (22.1)	17 (25.0)	4 (14.8)	.281
Stage	Recurrence	29 (30.5)	20 (29.4)	9 (33.3)	
	IV	66 (69.5)	48 (70.6)	18 (66.7)	.708
Histology	Adenocarcinoma	59 (62.1)	38 (55.9)	21 (77.8)	
	Nonadenocarcinoma	36 (37.9)	30 (44.1)	6 (22.2)	.047
Smoking	Never	17 (17.9)	14 (20.6)	3 (11.1)	
	Smoker	77 (81.1)	53 (77.9)	24 (88.9)	.438
	Unknown	1 (1.1)	1 (1.5)	0 (0)	
Radiotherapy	Provided	18 (18.9)	12 (17.6)	6 (22.2)	
	Not provided	77 (81.1)	56 (82.4)	21 (77.8)	.608
No. of metastatic sites	<3	76 (80.0)	51 (75.0)	25 (92.6)	
	≥3	19 (20.0)	17 (25.0)	2 (7.4)	.053

Data are presented as n (%).
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; ILD = interstitial lung disease; irAE = immune-related adverse event.

Supplemental Table 2 Patient Characteristics by Metastatic Site

Metastatic Site	Site Positive or Negative	N	PFS				OS			
			Median (Months)	HR	95% CI	*P*	Median (Months)	HR	95% CI	*P*
Lung	–	62	7.7	1			NR	1		
	+	33	5.6	1.275	0.747-2.118	.389	16.7	1.412	0.731-2.727	.304
Liver	–	87	7.3	1			NR	1		
	+	8	1.5	2.085	0.943-4.611	.069	4.7	2.078	0.731-5.905	.170
Bone	–	62	8.2	1			NR	1		
	+	33	3.7	2.199	1.298-3.724	.003	9.8	2.198	1.128-4.278	.021
Adrenal	–	82	6.8	1			NR	1		
	+	13	4.4	1.719	0.890-3.321	.107	8.2	1.967	0.858-4.507	.110
Effusion	–	73	7.6	1			18.5	1		
	+	22	4.3	1.399	0.787-2.487	.252	11.1	1.642	0.806-3.347	.172
Lymph node	–	82	7.3	1			NR	1		
	+	13	3.5	1.350	0.635-2.868	.436	16.7	1.235	0.512-2.975	.639
CNS	–	75	5.6	1			NR	1		
	+	20	8.2	0.859	0.455-1.622	.640	NR	0.918	0.402-2.097	.839

Abbreviations: CI = confidence interval; CNS = central nervous system; NR = not reached; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.