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ORIGINAL PAPER

Tumor expression and usefulness as a biomarker of programmed death ligand 1 in advanced non-small cell lung cancer patients with preexisting interstitial lung disease

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Abstract

In non-small cell lung cancer (NSCLC) patients, the expression of tumor programmed death ligand 1 (PD-L1) is an important parameter for deciding the timing of the use of anti-programmed cell death 1 (PD-1) antibody. There has been increasing concern over the benefit of anti-PD-1 antibody in high-risk patients, such as those with preexisting interstitial lung disease (ILD). However, the status and value of PD-L1 as a predictive biomarker and the efficacy of anti-PD-1 antibody in NSCLC patients with preexisting ILD remains uncertain. We retrospectively reviewed the medical records of advanced/recurrent NSCLC patients who had undergone analysis of the tumor PD-L1 expression. We identified 358 patients with advanced/recurrent NSCLC who had undergone analysis of tumor PD-LI expression. Of these, 210 received anti-PD-1 antibody. Tumor-cell PD-L1 expression was similar between the groups with and without preexisting ILD (median, 35%; interquartile range, 0–70%; vs. median, 10%; interquartile range, 1–68%; $p = 0.66$). Of the 210 patients who received anti-PD-1 antibody, 14 patients had preexisting ILD. The progression-free survival (PFS) showed no significant difference between the patients receiving anti-PD-1 antibody with and without preexisting ILD (median PFS, 4.3 vs. 5.3 months; HR, 0.97; $p = 0.84$). Within the patients with preexisting ILD, the PFS was tended to be longer in the patients with tumor PD-L1 expression $\geq 50\%$ than in those with tumor PD-L1 expression $< 50\%$ (median PFS, 12.5 vs. 2.5 months; HR, 0.47; $p = 0.14$). The value of PD-L1 expression as a biomarker may be comparable between patients with and without preexisting ILD.

Keywords Non-small cell lung cancer · Immune checkpoint inhibitor · Nivolumab · Pembrolizumab · Interstitial lung disease · Programmed death ligand 1

Abbreviations

PD-1	Programmed cell death 1
PD-L1	Programmed death ligand 1
NSCLC	Non-small cell lung cancer
PFS	Progression-free survival
OS	Overall survival
ILD	Interstitial lung disease
RECIST	Response evaluation criteria in solid tumors
CT	Computed tomography
HR	Hazard ratio
CI	Confidence interval
EGFR	Epidermal growth factor receptor
ORR	Overall response rate
DCR	Disease control rate

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Introduction

Programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) checkpoint inhibitors, including nivolumab, pembrolizumab, and atezolizumab, are now established as standard therapeutic agents for advanced non-small cell lung cancer

(NSCLC). Treatment with PD-1/PD-L1 checkpoint inhibitors has been shown to provide longer progression-free survival (PFS) and overall survival (OS) in NSCLC patients [1]. On the other hand, the response rate remains at about 20% among advanced NSCLC patients receiving PD-1/PD-L1 checkpoint inhibitors [2–5]. The low response rate to PD-1/PD-L1 checkpoint inhibitors is a problematic. Therefore, the identification of a marker capable of predicting the response of patients to PD-1/PD-L1 checkpoint inhibitors is needed.

Subgroup analyses from several trials have suggested that a high level of PD-L1 expression on tumor cells may be associated with a greater magnitude of benefit in terms of the response rate and OS [2–4]. A recent phase III trial demonstrated that a percent tumor-cell PD-L1 expression of ≥ 50% was associated with a longer-term clinical benefit of first-line anti-PD-1 antibody treatment as compared to platinum-based chemotherapy in advanced NSCLC patients [6]. Therefore, the PD-L1 expression level on tumor cells has been regarded as one of the predictive biomarkers of the potential efficacy of anti-PD-1 antibody treatment. Clinically, decisions regarding the timing of the use of anti-PD-1 antibody (that is, whether it should be used as a first-line or later-line treatment) in patients with advanced NSCLC depends on the PD-L1 expression levels of the tumor cells.

Interstitial lung disease (ILD) is characterized by damage to the lung parenchyma caused by chronic inflammation and progressive fibrosis [7]. It has been reported to be associated with an increased risk of lung cancer [8, 9]. The chronic inflammation associated with ILD probably accelerates the early stage of carcinogenesis. Indeed, approximately 15% of patients with lung cancer have been found to have preexisting ILD at the initial diagnosis [10, 11]. However, once tumors have progressed to malignancy, the impact of ILD on the tumor immune microenvironment and the expression of PD-L1 in tumor cells remains poorly understood.

According to a recent study, tumor PD-L1 expression in early-stage NSCLC is similar between patients with and without preexisting ILD [12]; however, the status in advanced NSCLC patients is still unclear. Moreover, the value of tumor PD-L1 expression as a predictive biomarker in advanced NSCLC patients with preexisting ILD receiving anti-PD-1 antibody treatment and the influence of preexisting ILD on the efficacy of anti-PD-1 antibody also remain unknown. Hence, we evaluated the tumor PD-L1 expression, and the association between tumor PD-L1 expression and the efficacy of anti-PD-1 antibody therapy in NSCLC patients with preexisting ILD.

Materials and methods

We retrospectively reviewed the medical records of patients with advanced or recurrent NSCLC registered between December 1, 2015 and March 31, 2018 at the National Cancer Center Hospital, Japan, in whom tumor PD-L1 expression had been analyzed. The end of the follow-up period was July 31, 2018. We obtained ethical approval from the National Cancer Center Hospital Japan, and patient confidentiality was maintained.

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, based on the findings of computed tomography (CT). PFS was defined as the interval between the first dose of anti-PD-1 antibody and the day of documentation of clinical or radiographic disease progression or death from all causes; in the absence of confirmation of disease progression or death, the data were censored on the last date that the patient was known to be alive. Most cases of preexisting ILD and immune-related pneumonitis were diagnosed only by CT. Retrospective radiologic review of the serial chest CT scans of all the patients was performed independently by two pulmonologists (R.S. and S.M.) and one radiologist (M.K.), none of whom had any knowledge of the patients' outcomes. In almost all the patients, the CT technique used was high-resolution CT, as a routine clinical practice. The chest CT images were reconstructed to 1–5-mm slice thickness. Preexisting ILD was diagnosed based on the findings of treatment CT, in accordance with the official guidelines of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society association [15].

PD-L1 expression in tumor specimens of the patients with NSCLC was analyzed using the commercially available PD-L1 immunohistochemistry 22C3 pharmDx assay (Dako) (Agilent Technology, North America) [16]. Positive PD-L1 expression in ≥ 1% of all the tumor cells was classified as a positive result, while positive PD-L1 expression in ≥ 50% of tumor cells was classified as strongly positive PD-L1 expression, consistent with the methodology used in other studies involving anti-PD-1 antibody treatment of NSCLC [1, 17, 18].

Statistical analysis

Dichotomous variables, such as the baseline characteristics, are expressed in numbers and percentages and were compared using Fisher's exact test. Continuous variables are represented as the median values and interquartile ranges and were analyzed using the Wilcoxon rank-sum test. PFS curves were constructed using the Kaplan–Meier method, and the statistical significances of differences between NSCLC patient groups with and without preexisting ILD were evaluated using the log-rank test, and hazard ratio (HR) and 95% confidence interval (CI). All p values were based on a two-sided hypothesis, and values of < 0.05 were considered as being indicative of statistical significance. All the

statistical analyses were performed using JMP Pro software, version 13.0.0 (SAS Institute, Cary, NC).

Results

Patient characteristics

A total of 358 patients with advanced or recurrent NSCLC who underwent analysis for tumor PD-L1 expression were reviewed in this study. The patient characteristics are summarized in Table 1. Of the 358 patients, 50 patients (14%) were 75 years old or over, 210 (59%) received treatment with anti-PD-1 antibody, and 28 (7.8%) had preexisting ILD (Fig. 1). There were significant differences between the patients with and without preexisting ILD in regard to the number of patients who were ≥ 75 years old (29% vs. 13%; $p = 0.029$), male (89% vs. 60%; $p = 0.0011$), and had squamous cell histology (54% vs. 15%; $p < 0.001$). There was also a significant difference in the number of patients between the tumor PD-L1 expression < 50% and ≥ 50% groups receiving anti-PD-1 antibody treatment (49% vs. 76%; $p < 0.001$).

The tumor PD-L1 expression was not significantly different between the patients with and without preexisting ILD (median, 35%; interquartile range, 0–70%; vs. median, 10%; interquartile range, 1–68%; $p = 0.66$; Fig. 2A). The proportion of patients with positive (≥ 1%) and strongly positive (≥ 50%) PD-L1 expression was also not significantly different between the patients with and without preexisting ILD (PD-L1 ≥ 1%: 79% vs. 70%; $p = 0.24$; PD-L1 ≥ 50%: 46% vs. 36%; $p = 0.19$, respectively; Fig. 2B).

Of the 210 patients who received anti-PD-1 antibody treatment, 14 patients had preexisting ILD. Of the 14 patients receiving anti-PD-1 antibody who were diagnosed with preexisting ILD, 12 patients were diagnosed by HRCT, one patient was diagnosed based on the pathology results, and one patient was diagnosed only by 5-mm slice CT. The characteristics of the patients who received anti-PD-1 antibody treatment are summarized in Table 2. The median age was 61 years, 67%

Table 1 Baseline characteristics at the diagnosis ($n = 358$)

	All, *n* (%)	Preexisting ILD			PD-L1 expression on tumor cells		
		Yes, *n* (%)	No, *n* (%)	*p*	< 50, *n* (%)	≥ 50%, *n* (%)	*p*
Patients	358	28	330		226	132	
Age				0.029			0.26
Median (range)	62 (27–84)	68 (33–83)	62 (27–84)		64 (27–83)	60 (33–84)	
≥ 75 years old	50 (14)	8 (29)	42 (13)		29 (13)	21 (16)	
Gender				0.001			0.078
Male	223 (62)	25 (89)	198 (60)		134 (59)	89 (67)	
Histology				<0.001			0.059
Squamous cell	65 (18)	15 (54)	50 (15)		47 (21)	18 (14)	
Non-squamous cell	293 (82)	13 (46)	280 (85)		179 (79)	114 (85)	
Clinical stage				0.19			0.31
III/IV	291 (81)	25 (89)	266 (81)		186 (82)	105 (80)	
Recurrence	67 (19)	3 (11)	64 (19)		40 (18)	27 (20)	
Drug				0.22			<0.001
Receiving anti-PD-1 antibody	210 (59)	14 (50)	196 (59)		110 (49)	100 (76)	

ILD interstitial lung disease, *PD-L1* programmed cell death ligand 1, *PD-1* programmed cell death 1

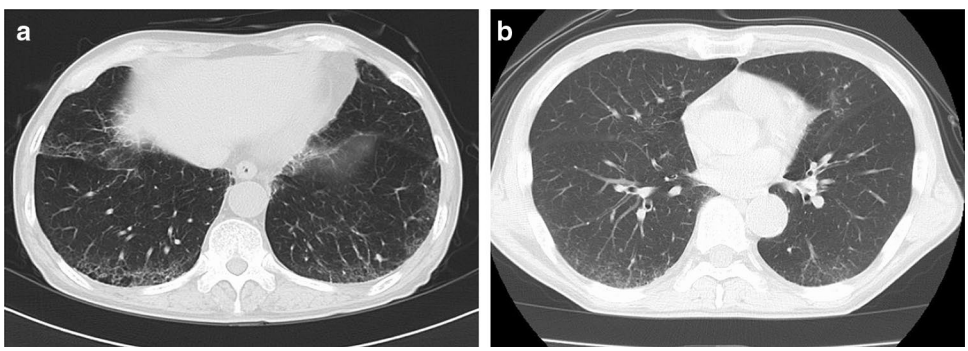

Fig. 1 Computed tomography scans of the chest in patients with preexisting interstitial lung disease reveal **a** subpleural distribution, honeycomb cysts, and bronchiectasis, and **b** ground glass abnormality

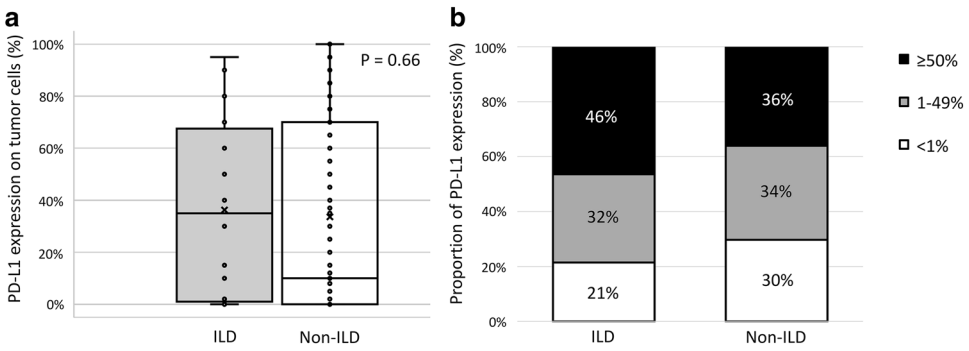

Fig. 2 Comparison of **a** programmed cell death ligand 1 expression on the tumor cells and **b** percent expression in the tumor cells of programmed cell death ligand 1 (< 1%, 1–49%, ≥ 50%) in NSCLC patients with and without preexisting interstitial lung disease. *PD-L1* programmed cell death ligand 1, *ILD* interstitial lung disease

Table 2 Baseline characteristics of the patients receiving anti-PD-1 antibody

	All, *n* (%)	Preexisting ILD		*p*
		Yes, *n* (%)	No, *n* (%)	
Patients	210	14	196	
Age				0.015
Median (range)	61 (30–83)	63 (33–83)	61 (30–83)	
≥75 years old	25 (12)	5 (36)	20 (10)	
Gender				0.024
Male	140 (67)	13 (93)	127 (65)	
ECOG PS				0.52
0–1	185 (88)	12 (86)	173 (88)	
Smoking status				0.22
Never-smoker	42 (20)	1 (7.7)	41 (21)	
Current or former smoker	165 (80)	12 (92)	153 (79)	
Histology				0.030
Squamous cell	40 (19)	6 (43)	34 (17)	
Non-squamous cell	170 (81)	8 (57)	162 (83)	
Clinical stage				0.46
III/IV	154 (73)	11 (79)	143 (73)	
Recurrence	56 (27)	3 (21)	53 (27)	
EGFR mutated	32 (19)	1 (13)	31 (19)	0.54
PD-L1 22C3 TPS subgroups				0.32
< 50%	110 (52)	6 (43)	104 (53)	
≥ 50%	100 (48)	8 (57)	92 (47)	
Prior thoracic radiotherapy	79 (38)	5 (36)	74 (38)	0.56
Treatment line				0.25
1	39 (19)	4 (29)	35 (18)	
2	171 (81)	10 (71)	161 (82)	
Anti-PD-1 antibody				0.50
Nivolumab	127 (60)	9 (64)	118 (60)	
Pembrolizumab	83 (40)	5 (36)	78 (40)	

PD-1 programmed cell death 1, *ILD* interstitial lung disease, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor, *PD-L1* programmed death ligand 1, *TPS* tumor proportion score

were male, 88% were Eastern Cooperative Oncology Group Performance Status 0–1, 20% were never-smokers, 19% had *epidermal growth factor receptor* (*EGFR*) mutations, and 19% received anti-PD-1 antibody treatment as first-line treatment. There were significant differences between the patients receiving anti-PD-1 antibody with and without preexisting ILD in regard to the number of patients who were ≥ 75 years old (36% vs. 10%; $p = 0.015$), male (93% vs. 65%; $p = 0.024$), and squamous cell histology (43% vs. 17%, $p = 0.039$).

The overall response rate (ORR) was similar in the patients with and without preexisting ILD (21% vs. 26%; $p = 0.51$; Table 3). The disease control rate (DCR) was also similar in the patients with and without preexisting ILD (57% vs. 54%; $p = 0.068$). The median PFS rates in the patients with and without preexisting ILD were 4.3 (95% CI 1.1–19) and 5.3 (95% CI 3.7–6.5) months, respectively (Fig. 3a), with no statistically significant difference between the two groups (HR, 0.97; 95% CI, 0.67–1.44; $p = 0.84$).

An additional survival analysis was performed for the patients with preexisting ILD classified according to the PD-L1 expression status. Although the difference was not statistically significant, the PFS in the group with strongly positive PD-L1 expression tended to be longer than that in the group with PD-L1 expression < 50% (median PFS, 12.5 vs. 2.5 months; HR, 0.47; 95% CI, 0.090–2.1; P = 0.14) (Fig. 3b).

The incidence of immune-related pneumonitis was significantly higher in the patients with preexisting ILD than in the patients without preexisting ILD (29% vs. 10%; $p = 0.037$) (Table 4). There were no significant differences in the incidences of grade ≥ 3 pneumonitis or death from treatment-induced pneumonitis between the two groups. Of the 24 patients with immune-related ILD, 19 required steroid treatment.

Discussion

This study demonstrated that the tumor PD-L1 expression status was comparable between advanced/recurrent NSCLC patients with and without preexisting ILD. Among

Table 3 Response to anti-PD-1 antibody

	Preexisting ILD		*p*
	Yes, *n* = 14	No, *n* = 196	
Best overall response, *n* (%)			
Complete response	0 (0.0)	1 (0.5)	
Partial response	3 (21)	49 (25)	
Stable disease	5 (36)	56 (29)	
Progressive disease	6 (43)	86 (43)	
Not evaluable	0 (0.0)	6 (3.1)	
Objective response, *n* (%; 95% CI)	3 (21; 7.6–48)	50 (26; 20–32)	0.51
Disease control, *n* (%; 95% CI)	8 (57; 33–79)	106 (54; 47–31)	0.52

PD-1 programmed cell death 1, *ILD* interstitial lung disease, *CI* confidence interval

Table 4 Lung toxicity of anti-PD-1 antibody

	All, *n* (%)	Preexisting ILD		*p*
		Yes, *n* (%)	No (%)	
Patients receiving anti-PD-1 antibody	210	14	196	
Pneumonitis				
Any grade	26 (12)	4 (29)	22 (11)	0.08
Grade ≥ 3	9 (4.3)	1 (7.1)	8 (4.2)	0.47
Grade 5	4 (1.9)	0 (0.0)	4 (2.0)	0.76
Requirement of steroid treatment	21 (81)	4 (100)	17 (77)	0.40

PD-1 programmed cell death 1, *ILD* interstitial lung disease

the patients treated with anti-PD-1 antibody, the PFS was similar between those with and without preexisting ILD. Our results support the contention that the tumor PD-L1 expression status is of value as a predictive biomarker even in NSCLC patients with preexisting ILD receiving treatment with anti-PD-1 antibody.

Previous studies have shown associations between strong tumor PD-L1 expression and male gender, advanced age, and squamous cell histology [13] [14]. These same clinical characteristics are also known to be associated with the presence of ILD among NSCLC patients [15, 16]. Because of this similarity in the risk factors for positive PD-L1 expression on tumor cells and preexisting ILD in NSCLC patients, it has been hypothesized that the chronic inflammation in ILD affects the tumor microenvironment and induces tumor tissue expression of PD-L1. However, the association between tumor-cell PD-L1 expression and the presence of ILD is still unclear. The present study demonstrated that some of the baseline characteristics (e.g., older age, male gender, and squamous cell histology) were significantly frequent in the patients with preexisting ILD. On the other hand, the distribution of these characteristics was not significantly different between the PD-L1 < 50% and ≥ 50% patient groups. Also, tumor-cell PD-L1 expression was similar between advanced/recurrent NSCLC patients with and without preexisting ILD. A recent study also showed that tumor PD-L1 expression was similar between stage I/stage II NSCLC patients with and without preexisting ILD [12]. These findings suggest that tumor PD-L1 expression is independent of the presence of underlying ILD.

Some clinical trials have demonstrated that the PFS of NSCLC patients with strongly positive tumor PD-L1 expression is longer than that of patients not showing strongly

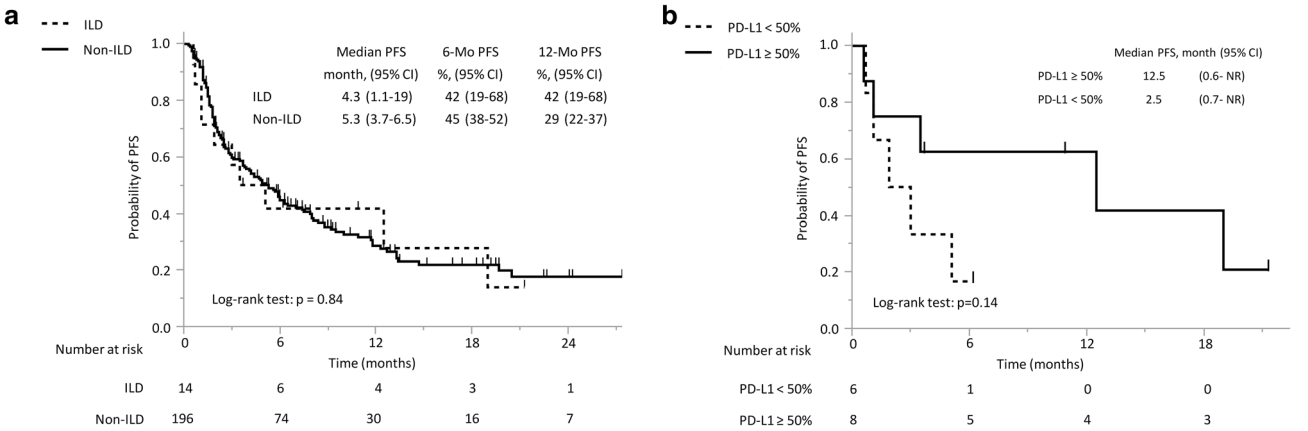

Fig. 3 Kaplan–Meier curves of progression-free survival **a** in NSCLC patients with and without preexisting interstitial lung disease, **b** in NSCLC patients with preexisting interstitial lung disease with tumor PD-L1 expression < 50% and ≥ 50%. *PFS* progression-free survival, *ILD* interstitial lung disease, *Mo* month, *CI* confidence interval, *PD-L1* programmed cell death ligand 1, *NR*, not reached

positive tumor PD-L1 expression. [17] PD-L1 expression on tumor cells is a potential predictive biomarker of the efficacy of anti-PD-1 antibody treatment. [2] [3] Therefore, PD-L1 expression test is currently used as clinical decision-making tool for adopting the use of anti-PD-1/PD-L1 antibody in advanced/recurrent NSCLC patients. In our study, we showed that the PFS in the PD-L1 ≥ 50% group was longer as compared to that in PD-L1 < 50% group, even among patients with preexisting ILD, although the difference was not statistically significant. Therefore, PD-L1 expression may be useful as a predictive biomarker of the efficacy of anti-PD-1 antibody treatment in NSCLC patients, regardless of the presence of preexisting ILD. Moreover, anti-PD-1 antibody treatment for NSCLC patients with preexisting ILD showed a similar efficacy as that seen in patients without preexisting ILD, suggesting that anti-PD-1 antibody could be considered as a treatment option for NSCLC patients with preexisting ILD.

Preexisting ILD is a potential risk factor for pneumonitis in patients receiving cytotoxic chemotherapy and molecular target therapy. [18] [19] It is reported that approximately 10% of NSCLC patients with preexisting ILD die because of treatment-related pneumonitis, whereas only 3% of those without preexisting ILD die of treatment-related pneumonitis [18]. On the other hand, it has been reported that pneumonitis associated with immune checkpoint inhibitor use occurs in about 5% of NSCLC patients [20, 21]. Pneumonitis induced by immune checkpoint inhibitor treatment differs from that induced by chemotherapy and molecular target therapy, both in terms of the radiological appearance and clinical outcomes. Immune checkpoint inhibitors cause immune-related adverse events in many organs, induced by T cell hyperactivation. In most cases, such adverse events can be well managed by counteracting the lymphocyte activation with steroids [22, 23]. The same treatment is also valid for immune-related pneumonitis. According to previous reports, most patients developing immune-related pneumonitis can be successfully treated with corticosteroids [20]. Our study showed that preexisting ILD was associated with a higher incidence of treatment-induced pneumonitis in NSCLC patients. In the preexisting ILD group, all the patients who developed pneumonitis received steroid treatment. Of note, the incidences of grade ≥ 3 pneumonitis and death from treatment-induced pneumonitis were similar between NSCLC patients with and without preexisting ILD. Based on these findings, the careful observation and early management of pneumonitis may be important for patients with preexisting ILD who receive anti-PD-1 antibody treatment.

The present study had several limitations. First, this study was conducted based on a retrospective review of medical records. The potential for selection bias exists because our study was conducted at a single institution and we included patients who had undergone analysis for tumor PD-L1 expression. Indeed, the preexisting ILD rate in our study was lower than that reported in previous studies (7.8% in our study vs. approximately 15% in previous reports) [10, 11]. This could be attributable to avoidance of administration of anti-PD-1 antibody treatment to patients with severe ILD at our institution. In addition, the interval between the time of biopsy and staining for PD-L1 was variable. Second, our sample size was too small to allow reliable determination of the factors associated with the efficacy and safety of the treatment. Finally, the diagnosis of preexisting ILD and treatment-related pneumonitis is not routinely confirmed by histopathology in clinical practice. Despite these limitations, our study revealed that strong tumor PD-L1 expression was associated with the efficacy of anti-PD-1 antibody treatment in NSCLC patients with preexisting ILD in the real-world setting.

Conclusion

Our study indicates that the PD-L1 expression status may be a useful predictive biomarker even in NSCLC patients with preexisting ILD receiving anti-PD-1 antibody treatment, and that the efficacy of anti-PD-1 antibody in NSCLC patients with preexisting ILD was comparable to that in those without preexisting ILD. We suggest that anti-PD-1 antibody therapy is a good addition to the treatment options for NSCLC patients with preexisting ILD, taking into account the tumor PD-L1 expression status. To meet the unmet medical needs of NSCLC patients with preexisting ILD, additional prospective studies are needed to determine the efficacy and safety of treatment with ICIs.

Compliance with ethical standards

Conflict of interest SM has served on speakers' bureaus for Taiho Pharmaceutical and Ono Pharmaceutical. YG has had consulting/advisory roles for Taiho Pharmaceutical; has served on speakers' bureaus for Taiho Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, MSD; and has received research funding from Taiho Pharmaceutical, Bristol-Myers Squibb, and Ono Pharmaceutical. SK has received research funding from Ono Pharmaceutical and has received honoraria from Ono Pharmaceutical, and Bristol-Myers Squibb. HH has received research funding from MSD, Bristol-Myers Squibb, Ono Pharmaceutical, and Taiho Pharmaceutical. YF has received research funding from MSD and has served on speakers' bureaus from MSD, Taiho Pharmaceutical, Bristol-Myers Squibb, and Ono Pharmaceutical. NY has had consulting/advisory roles for Taiho Pharmaceutical; has served on speakers' bureaus for Ono Pharmaceutical, Bristol-Myers Squibb, MSD; and has received honoraria from Ono Pharmaceutical, and MSD. NY has received research funding from Taiho Pharmaceutical, Bristol-Myers Squibb, and Ono Pharmaceutical and has served on speakers' bureaus from Bristol-Myers Squibb, and Ono Pharmaceutical. YO has

received research funding and honoraria from Taiho Pharmaceutical, MSD. All remaining authors have declared no conflict of interest.

Ethical approval This study was approved by National Cancer Center Hospital Japan and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study involved retrospective analysis of existing data with no patient intervention or interaction.

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