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Nivolumab for advanced non-small cell lung cancer patients with mild idiopathic interstitial pneumonia: A multicenter, open-label single-arm phase II trial

Daichi Fujimoto[a,*], Makiko Yomota[b], Akimasa Sekine[c], Mitsunori Morita[d], Takeshi Morimoto[e,f], Yukio Hosomi[b], Takashi Ogura[c], Hiromi Tomioka[d], Keisuke Tomii[a]

[a] Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan
[b] Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan
[c] Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan
[d] Department of Respiratory Medicine, Kobe City Medical Center West Hospital, Kobe, Japan
[e] Clinical Research Center, Kobe City Medical Center General Hospital, Kobe, Japan
[f] Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan

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ABSTRACT

Objectives: The efficacy of nivolumab against metastatic non-small cell lung cancer (NSCLC) has been demonstrated; however, pneumonitis is relatively common and is a potentially life-threatening immune-related adverse event. Patients with idiopathic interstitial pneumonia (IIP) have a higher risk of pneumonitis and are generally excluded from clinical trials. Additionally, to date, a multicenter prospective trial for previously-treated NSCLC patients with IIP has not been performed. To fulfill this unmet medical need, we conducted a multicenter, open-label single-arm phase II trial to evaluate the efficacy and safety of nivolumab in NSCLC patients with mild IIP.
Materials and methods: Eligible patients had previously-treated, inoperable NSCLC with mild IIPs. Mild IIP was defined as a predicted vital capacity of at least 80% and possible usual interstitial pneumonia (UIP) or inconsistent with UIP pattern by chest high-resolution computed tomography. Primary end point was the 6 months PFS rate and secondary end point was the safety of this therapy.
Results: Eighteen patients were enrolled in this trial. Six months PFS rate was 56%, response rate was 39%, and disease control rate was 72%. There were no treatment-related deaths. One drug-related grade 3/4 non-hematologic event (grade 3 neurotoxicity) was observed. Two patients had grade 2 pneumonitis which improved by corticosteroid therapy.
Conclusions: Nivolumab could be an effective therapy for NSCLC patients with mild IIPs.

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases, with most cases already unresectable and metastatic at diagnosis [1]. Recently, the efficacy of programmed cell death 1 (PD-1) axis inhibitors was demonstrated in patients with advanced NSCLC [2–4]. However, pneumonitis can be a potentially life-threatening immune-related adverse event (irAE) in prospective trials with these inhibitors [5].

Interstitial lung disease (ILD) is characterized by damage to the lung parenchyma due to inflammation and fibrosis [6]. ILD, particularly idiopathic interstitial pneumonia (IIP) which is mainly characterized by idiopathic pulmonary fibrosis, has been shown to be associated with lung carcinogenesis [7]. Recent studies have revealed that IIP is relatively common among smokers in nonspecific populations and its prevalence appears to be increasing [8–10]. Approximately 10% of patients with NSCLC are also diagnosed with ILD [11,12], but these patients have generally been excluded from clinical trials owing to their

Abbreviations: NSCLC, non-small cell lung cancer; irAE, immune-related adverse events; IIP, idiopathic interstitial pneumonia; UIP, usual interstitial pneumonia; PD-1, programmed cell death 1; ILD, interstitial lung disease; AE-IIP, acute exacerbation of idiopathic interstitial pneumonia; ECOG, Eastern Cooperative Oncology Group; PS, performance status; %VC, vital capacity (as percent of predicted); RECIST, Response Evaluation Criteria in Solid Tumors

* Corresponding author at: Department of Respiratory Medicine, Kobe City Medical Center General Hospital, 2 Minatojima-Minamimachi, Chuo-ku, Kobe, 650-0047, Japan.
E-mail address: daichi@kcho.jp (D. Fujimoto).

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increased risk of pneumonitis. This makes it necessary to devise an optimal anticancer therapy for this patient group.

PD-1 axis inhibitors are only considered after careful assessment of the risk of pneumonitis, for which IIP severity is a major predictor [13]. Regarding IIP severity, a previous study demonstrated the relationship between poor pulmonary function and acute exacerbation in patients with idiopathic pulmonary fibrosis [14]. Furthermore, other studies demonstrated that low forced vital capacity and usual interstitial pneumonia (UIP) pattern on computed tomography (CT) were associated with chemotherapy-related pneumonitis in patients with ILD [15,16]. When considering these predictors of pneumonitis, the benefits of PD-1 axis inhibitors may outweigh their risks for pneumonitis in NSCLC patients with IIP who have relatively good pulmonary function and less severe interstitial pneumonia pattern on CT (i.e., mild ILD). From this point of view, we previously conducted a pilot trial revealing the short-term safety of nivolumab treatment for advanced NSCLC patients with mild IIP [17]. In this trial, six patients with mild IIPs did not develop pneumonitis within 12 weeks after the initiation of nivolumab treatment.

Based on this phase II trial, we hypothesized that PD-1 axis inhibitors are effective for NSCLC patients with mild IIP. Therefore, we performed a multicenter, open-label single-arm phase II trial to evaluate the efficacy and safety of nivolumab, a PD-1 inhibitor, in patients with advanced NSCLC and mild IIP.

2. Patients and methods

2.1. Patients

Patients were eligible for enrolment if they met the following criteria: histologically- or cytologically-proven inoperable stage III or IV NSCLC; prior treatment with at least 1 chemotherapy regimen; evaluable disease lesions; age ≥20 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS), 0–1; adequate organ function; and the presence of mild IIP (defined below). Patients were ineligible if they received systemic glucocorticoids or other immunosuppressive treatments; had active autoimmune disease; or had a history of pneumonitis for which they had received glucocorticoids. All study participants provided informed consent. The trial was approved by the Ethics Review Board or Institutional Review Board of each participating institute.

Preexisting ILD was diagnosed based on clinical features and high-resolution computed tomography (HRCT) results for the chest (pretreatment). All patients received HRCT before the initiation of nivolumab therapy, and the presence of ILD was evaluated by at least 2 pulmonologists. To diagnose patients with IIP, we excluded collagen vascular disease (CVD)-associated ILD, occupational lung diseases, and other alternative diagnoses. In particular, we screened for CVD-associated antibodies such as anti-SS-A, anti-SS-B, anti-scleroderma 70, anti-U1RNP, anti-aminoacyl-tRNA synthetases, and anti-neutrophil cytoplasmic antibodies. If patients with IIP had a predicted vital capacity (%VC) ≥80% and an HRCT image showed a possible UIP or inconsistent with UIP pattern, they were diagnosed with “mild” IIP (Fig. 1) [18]. The occurrence of pneumonitis both during and 4 weeks after the final administration of nivolumab was considered drug-related pneumonitis.

2.2. Study design

This was a multicenter, open-label phase II trial with the primary objective of investigating the efficacy of nivolumab therapy in NSCLC patients with mild IIP. The secondary objective was to determine the safety of this therapy. The 6 months progression free survival (PFS) rate was used as the primary endpoint in our trial because previous reports showed that the 6 months PFS of immune checkpoint inhibitors strongly correlates with overall survival (OS) [19,20]. A previous study showed that the 6 months PFS rate in previously-treated NSCLC patients with ILD receiving docetaxel was approximately 10% [21]. Additionally, the 6 months PFS rate was approximately 30% in Checkmate 057 trial [4]. Thus, the threshold 6 months PFS rate was set to 10% and the expected 6 months PFS rate, 30%.

We used Simon's two-stage design [22,23], and our null hypothesis, 6 months PFS rate is 10%, was tested against a one-sided alternative. In the first stage, 7 patients were recruited. If none of these patients achieved 6 months PFS, the study would be terminated. An additional 11 patients were then recruited (final total = 18). The null hypothesis would be rejected if 4 or more of the 18 patients could achieve 6 months PFS. Such design yielded a type I error rate (one-sided) of 0.1 and power of 0.8 when the true 6 months PFS rate was 30%. HRCT was performed every 4 weeks to screen for drug-related pneumonitis within 12 weeks after the commencement of nivolumab therapy. HRCT was then checked every 8 weeks. We used the Common Terminology Criteria for Adverse Events version 4.0 as the safety assessment. Clinical tumor assessment was performed using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Complete overall response rate (ORR) represents all cases with complete response (CR) and partial response (PR). The interval between the date of nivolumab treatment initiation and that of disease progression or death (PFS), or death alone (OS), was calculated for each patient.

2.3. Statistical analysis

All treated patients were included in the safety and efficacy analyses. The Kaplan-Meier method was used to estimate survival outcomes. Statistical analyses were performed using the JMP 11 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patients

Eighteen patients with a median age of 71.5 years were enrolled (Table 1). Most patients had stage IV disease (72%) and an ECOG PS of 1 (78%). The most common histology was adenocarcinoma (67%) and median (range) %VC was 92.2% (interquartile range: 83.3–104.6%). Fifteen patients displayed a possible UIP pattern while 3 had an

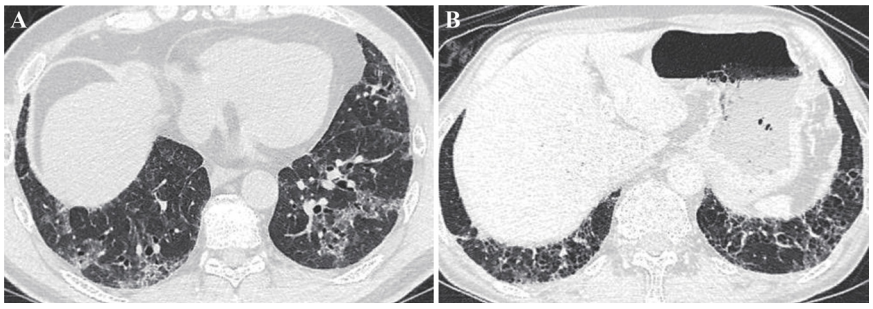

Fig. 1. High-resolution computed tomography images. (A) Image showing ground glass abnormality (a greater extent than reticular abnormality) (inconsistent with usual interstitial pneumonia [UIP] pattern). (B) Image showing a subpleural basal predominant reticular shadow and traction bronchiectasis without a honeycomb pattern (i.e., a possible UIP pattern).

Table 1
Patient characteristics.

Patient characteristics	n (%) (N = 18)
Age (years)	
Median (IQR)	71.5 (68.5-76.3)
Sex	
Male	17 (94)
Female	1 (6)
Smoking status	
Never	0 (0)
Current or former	18 (100)
Performance status	
0	4 (22)
1	14 (78)
Histology	
Adenocarcinoma	12 (67)
Squamous cell carcinoma	4 (22)
NSCLC-NOS	2 (11)
Treatment line	
Second	12 (67)
Third	4 (22)
Fourth	2 (11)
Patterns of ILD	
Possible UIP	15 (83)
Inconsistent with UIP	3 (17)
Vital capacity (percent of predicted)	
Median (IQR)	92.2 (83.3-104.6)
Stage	
III	5 (28)
IV	13 (72)
PD-L1 status	
≥50%	3 (17)
< 50%	9 (50)
Not investigated	6 (33)

ILD, interstitial lung disease; IQR, interquartile range; UIP, usual interstitial pneumonia; NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

inconsistent with UIP pattern. Median follow-up was 14.2 months (range, 2.7–32.1).

3.2. Efficacy

ORR was 39%; two patients achieved CR and 5 achieved PR. Furthermore, 33% of patients (n = 6) had stable disease (SD), while 28% (n = 5) had progressive disease (PD). The Kaplan-Meier curves for PFS are shown in Fig. 2. Six-month PFS rate was 56% (10/18), and median PFS was 7.4 months (95% CI: 1.8–16.8). There was no censoring case for the 6-month-PFS of nivolumab therapy. At the time of analysis, five patients continued to achieve disease control by nivolumab therapy. This included the 2 censored cases just after the 6 months mark. The Kaplan-Meier curves for OS are shown in Fig. 3. Median OS was 15.6 months (95%CI: 14.4-NR) and at the time of

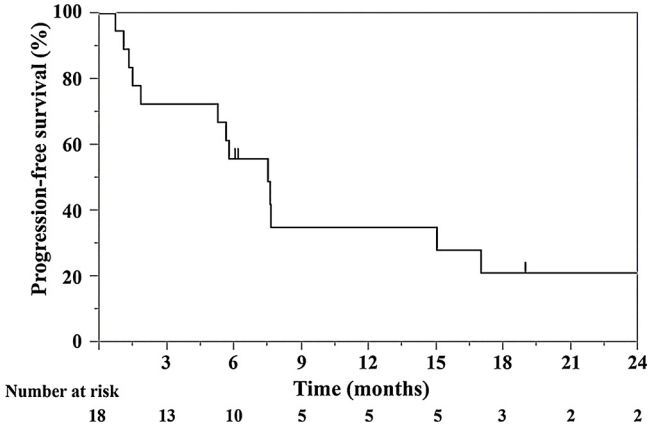

Fig. 2. Kaplan-Meier curves of progression-free survival.

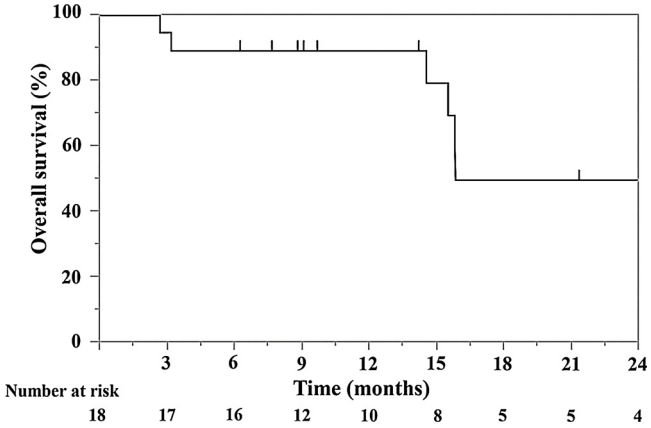

Fig. 3. Kaplan-Meier curves of overall survival.

analysis, OS data were limiting as only 6 events (33%) had occurred before the cutoff date for data collection.

3.3. Safety

There were no treatment-related deaths. Instead, one drug-related grade 3/4 non-hematologic event (grade 3 neurotoxicity) was observed but there were no grade 4 hematologic adverse events (Table 2). The patient who developed grade 3 neurotoxicity discontinued therapy after achieving improved symptoms with corticosteroids, and at the time of analysis, the achievement of disease control continued even after discontinuation. Three patients developed toxicity leading to the discontinuation of nivolumab therapy (2 patients with Grade 2 pneumonitis and a patient with Grade 3 neurotoxicity).

3.4. Cases that developed pneumonitis

Two patients had grade 2 pneumonitis. One patient was a 77-year-old male current smoker with adenocarcinoma and possible UIP (%VC = 103.8%), who developed grade 2 pneumonitis 27 days after starting nivolumab therapy. This patient opted to discontinue therapy after pneumonitis improved with corticosteroids therapy. Tumor stability lasted 21 months (i.e., at the time of analysis even after the discontinuation). The other patient was a 67-year-old male former smoker with squamous cell carcinoma and possible UIP (%VC = 128.8%), who developed grade 2 pneumonitis 35 days after starting nivolumab therapy. This patient also opted to discontinue therapy after pneumonitis improved with corticosteroids therapy; tumor progression was observed 4 months after the discontinuation of nivolumab.

Table 2
Treatment-related adverse events (N = 18).

Event	Grade		
	1	2	≥3
Treatment-related			
Nausea	2	2	0
Fatigue	6	1	0
Diarrhea	1	1	0
Stomatitis	0	1	0
Leukopenia	0	1	0
Anemia	1	0	0
Thrombocytopenia	1	0	0
Immune-mediated			
Pneumonitis	0	2	0
Dysthyroidism	2	1	0
Colitis	0	0	0
Nephritis	0	0	0

4. Discussion

To the best of our knowledge, this is the first multicenter prospective trial to demonstrate the efficacy and long-term safety of nivolumab for advanced NSCLC patients with mild IIP.

We revealed the remarkable efficacy of nivolumab and met the primary endpoint. The 6 months PFS rate was 56%, response rate was 39% and disease control rate was 72%. Therefore, the response achieved in our subjects was better than that of previous studies with nivolumab [3,4]. This may have been due to the favoring characteristics of NSCLC patients with ILD. Most patients with NSCLC and ILD had a history of smoking; these patients had lower *EGFR* and higher *KRAS* mutation rates [24,25]. In previous PD-1 inhibitor trials, patients with a smoking history tended to experience better outcomes [2,4]. Furthermore, PD-1 inhibitors were less effective in patients with *EGFR* mutations but higher in those with *KRAS* mutations [4,26].

In our trial, 2 patients developed pneumonitis (11%) while in previous trials with PD-1 axis inhibitors for advanced NSCLC, 7–9% of patients developed pneumonitis in the Japanese cohort [27,28]. To add, the proportion of pneumonitis caused by nivolumab therapy in recent retrospective Japanese cohort study was approximately 10% [29,30]. Based on these results, nivolumab could be a treatment option for advanced NSCLC patients with mild IIP, and exhibits a safety profile similar to that found in patients without ILD.

To date, a multicenter prospective trial has not been performed with NSCLC patients with ILD who have undergone previous treatments. Previous retrospective studies showed that 2nd-line docetaxel and pemetrexed monotherapy present substantial risks in NSCLC patients with ILD [21,31]. While these studies included non-selected ILD patients, standard cytotoxic chemotherapies to NSCLC patients with ILD who have had previous treatments appear to carry higher toxicity risks. Additionally, in non-ILD patients, 2nd-line nivolumab led to a statistically superior survival benefit compared to docetaxel. Taken together, nivolumab could be a better option for previously-treated NSCLC patients with mild IIP.

Although our findings are of special interest, the study had some limitations. First, the classification of IIPs was not performed as patients did not receive surgical lung biopsy. Second, the present study was too small to draw definitive conclusions regarding the efficacy and safety of nivolumab. However, our findings suggest that nivolumab is a potential option to treat NSCLC patients with mild IIP, but future large-scale clinical trials are required to confirm our results.

In conclusion, nivolumab was demonstrated to be clinically active for NSCLC patients with mild IIP and thus, could be an effective treatment option for these patients.

Conflicts of interest

Dr. Fujimoto has received lecture fees from Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb K.K. Dr. Morimoto has received consultant fee from Bristol-Myers Squibb K.K. All remaining authors have declared no conflicts of interest.

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