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A prospective phase II study of carboplatin and *nab*-paclitaxel in patients with advanced non-small cell lung cancer and concomitant interstitial lung disease (HOT1302)

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ABSTRACT

Objectives: Patients with concomitant advanced non-small cell lung cancer (NSCLC) and interstitial lung disease (ILD) are excluded from most clinical chemotherapy trials because of the high risk of exacerbating the latter condition. This study prospectively investigated the efficacy and safety of albumin-bound paclitaxel (*nab*-paclitaxel) in combination with carboplatin in patients with both advanced NSCLC and ILD.

Patients and methods: The enrolled patients had treatment-naïve, advanced NSCLC with ILD. Patients received 100 mg/m^2 *nab*-paclitaxel weekly and carboplatin at an area under the concentration-time curve of 6 once every 3 weeks for 4–6 cycles. The primary endpoint was the overall response rate (ORR); secondary endpoints included toxicity, progression-free survival (PFS), and overall survival (OS).

Results: Thirty-six patients were enrolled between April 2014 and September 2017. Sixteen patients (44.4%) had adenocarcinoma, 15 (41.7%) had squamous cell carcinoma (Sq), and 5 (13.9%) had non-small cell carcinoma. The median number of cycles administered were 4 (range: 1–6). The ORR was 55.6% (95% confidence interval [CI]: 39.6–70.5). The median PFS and OS were 5.3 months (95% CI: 3.9–8.2) and 15.4 months (95% CI: 9.4–18.7), respectively. A greater proportion of patients with Sq experienced improvements than did those with non-Sq: ORRs, 66.7% (95% CI: 41.7–84.8) vs. 47.6% (95% CI: 28.3–67.6) (P = 0.254); median PFS, 8.2 months (95% CI: 4.0–10.2) vs. 4.1 months (95% CI: 3.3–5.4) (HR, 0.60 [95% CI, 0.30–1.20]; P = 0.15); and median OS, 16.8 months (95% CI: 9.8–not reached) vs. 11.9 months (95% CI: 7.3–17.4) (HR, 0.56 [95% CI, 0.24–1.28]; P = 0.17). Two patients (5.6%) experienced grade ≥2 pneumonitis and 1 patient (2.8%) died.

Conclusion: Weekly nab-paclitaxel combined with carboplatin showed favorable efficacy with acceptable toxicity in patients with both advanced NSCLC and ILD.

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1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide, and non-small cell lung cancer (NSCLC) accounts for more than 80% of all such cancers [1]. Drugs that target specific molecular abnormalities within the tumor, such as *EGFR* mutations, *ALK* rearrangements, *ROS1* rearrangements, and *BRAF* mutations are the preferred first-line therapies for patients with adenocarcinoma [2]. Immune checkpoint inhibitors (ICIs) with or without cytotoxic chemotherapy are also effective. Pembrolizumab monotherapy; pembrolizumab and platinum-based doublet combination; and atezolizumab, bevacizumab, and platinum-based doublet combination have been shown to have superior effectiveness over their counterparts, and have therefore been approved as first-line therapies in patients with advanced NSCLC [3–6].

Interstitial lung disease (ILD) encompasses a diverse range of pulmonary fibrotic disorders that affect the alveoli of the lung [7]. The most common such disorders are idiopathic interstitial pneumonias (IIPs), which include such conditions as idiopathic pulmonary fibrosis (IPF) and idiopathic nonspecific interstitial pneumonia [8,9]. The prevalence of IPF among patients with lung cancer is reported to be 2–8%, as the 2 diseases may share a common etiology [7]. Acute exacerbation of IIPs (AE-IIPs), particularly of IPF, has long been a subject of investigation in Japan, and has recently also attracted attention in Western countries [10]. A number of studies of the clinical and prognostic implications of AE-IIPs, which is characterized by non-infectious acute respiratory deterioration that is often unpredictable and fatal, have been performed. The incidence and mortality rates of AE-IIPs vary, ranging from 5% to 57% and from 20% to 86%, respectively, according to a recent consensus report [10]. Although the pathogenesis of AE-IIPs remains unknown, treatment-related acute exacerbation of ILD (AE-ILD), which mimics the clinical conditions of AE-IIPs, may occur as a complication of surgery, radiotherapy, and chemotherapy in patients with lung cancer and pre-existing ILD. This condition is serious and often fatal [11–16]. Thus, patients with concomitant advanced NSCLC and ILD have been excluded from most clinical trials of chemotherapy, and there remains no standard treatment for such patients to date (even while treatment options for NSCLC with driver gene aberrations such as *ALK* rearrangements, *ROS1* rearrangements, and *BRAF* mutations continue to expand).

In our previous retrospective study of patients with NSCLC and ILD, we found that a solvent-based formulation of paclitaxel (*sb*-paclitaxel) in combination with carboplatin (*sb*-P/C) was the most frequently used regimen [17]. Minegishi et al. reported favorable patient outcomes in their small feasibility study of carboplatin and weekly *sb*-paclitaxel, with a response rate of 61% (11/18), a median progression-free survival (PFS) and overall survival (OS) of 5.3 and 10.6 months, respectively, and a 1-year survival rate of 22% [18]. However, carboplatin plus weekly *sb*-paclitaxel is not an approved regimen in Japan.

The 130 nm albumin-bound formulation of paclitaxel (*nab*-paclitaxel) has shown promising efficacy in both preclinical models and in clinical trials of patients with NSCLC. Compared to *sb*-paclitaxel, *nab*-paclitaxel has several advantages such as a higher mean maximum serum concentration of free paclitaxel, greater paclitaxel concentration delivery to tumors, and increased transport across endothelial cell monolayers [19,20]. In a large multicenter international phase III study (CA031), weekly *nab*-paclitaxel in combination with carboplatin (*nab*-P/C) demonstrated a significantly higher overall response rate (ORR) than did *sb*-P/C (33% vs. 25%; P = 0.005) based on an independent assessment. Improvements of approximately 10% in PFS (median, 6.3 vs. 5.8 months; hazard ratio [HR], 0.902; 95% confidence interval [CI], 0.767–1.060; P = 0.214) and in OS (median, 12.1 vs. 11.2 months; HR, 0.922; 95% CI, 0.797–1.066; P = 0.271) were observed in the *nab*-P/C arm versus the *sb*-P/C arm. Furthermore, significantly fewer incidences of grade ≥3 neuropathy, neutropenia, arthralgia, and myalgia occurred in the *nab*-P/C arm [21]. However, there is no information to date regarding the efficacy of *nab*-P/C combination therapy in patients with concomitant NSCLC and ILD.

Based on this background, we conducted a multicenter prospective phase 2 study to evaluate the efficacy and safety of *nab*-P/C in patients with concomitant advanced NSCLC and ILD.

2. Patients and methods

2.1. Eligibility

Eligible patients were those aged 20–74 years with histologically or cytologically confirmed stage IIIB, stage IV, or postoperative recurrent NSCLC with ILD. Patients who received prior systemic therapy for lung cancer were excluded, but those who experienced postoperative recurrence no sooner than 1 year since the last administration of adjuvant chemotherapy were included. The following criteria were also required for eligibility: an Eastern Cooperative Oncology Group performance status score of 0 or 1; clinically diagnosed ILD; adequate function of the bone marrow, liver, kidneys (creatinine clearance ≥60 mL/min), and lungs (alveolar O_2 pressure ≥60 Torr); and at least 1 measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).

The exclusion criteria included ILD other than IIPs (*i.e.*, ILDs with a known etiology such as collagen vascular disease, pneumoconiosis, drug-induced pneumonitis, and others); a history of severe drug allergy; symptomatic central nervous system metastasis; presence of severe pleural, abdominal, or cardiac effusion; unstable comorbidities including cardiovascular disease, stroke, or gastric ulcer; a history of active double cancer; or ineligibility for other reasons as deemed by an investigator. This study protocol was approved by the institutional review board at each participating institution. All patients were required to provide written informed consent before enrollment. This trial was registered under the University Medical Hospital Information Network (UMIN) Clinical Trials Registry Identifier UMIN000012901.

2.2. Study design and treatment

This study was designed as a prospective, multicenter, single-arm phase 2 trial. The primary endpoint was ORR; secondary endpoints included toxicity, PFS, and OS. Eligible patients received carboplatin at a dose corresponding to an area under the curve (AUC) equal to 6 mg/mL/min (AUC = 6) on day 1 and *nab*-paclitaxel 100 mg/m^2 on days 1, 8, and 15 every 3 weeks for 4–6 cycles or until evidence of disease progression or unacceptable toxicity manifested.

In the event of severe toxicities during a given cycle, the doses of carboplatin and *nab*-paclitaxel were reduced in subsequent cycles. Such toxicities included grade 3 thrombocytopenia, grade 4 neutropenia, grade ≥3 febrile neutropenia, or other grade ≥3 nonhematological toxicities. Dose reduction comprised of a decrease in carboplatin to an AUC of 5 mg/mL/min and a decrease in *nab*-paclitaxel to 75 mg/m^2 (level -1) followed by subsequent dose reductions comprising a decrease in carboplatin to an AUC of 4 mg/mL/min and a decrease in *nab*-paclitaxel to 50 mg/m^2 (level -2). If patients required a third dose reduction, the protocol treatment was terminated.

2.3. Baseline and treatment assessments

Patient assessments, which included physical examination, complete blood counts, and biochemistry analyses, were conducted once a week during each cycle of protocol treatment. Chest radiography, computed tomography (CT) scans of the chest and abdomen, magnetic resonance imaging studies of the brain, and bone scintigraphy or positron emission tomography-CT studies were performed for baseline tumor assessment within 28 days before the initiation of the protocol treatment. Tumor response was assessed at baseline and every 2 cycles using the RECIST version 1.1. If a patient was documented as having a complete response (CR) or partial response (PR), confirmatory

evaluation was performed after an interval of at least 4 weeks. Stable disease (SD) required a minimum 8-week period following enrollment in the study. Clinical response data were confirmed by extramural reviews. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

A diagnosis of ILD was determined in accordance with American Thoracic Society/European Respiratory Society criteria [8,9] as assessed by each investigator before patient registration. Three pulmonologist (KS, MS, and SK) centrally reviewed all baseline chest high-resolution computed tomography scans and categorized each subject as having a usual interstitial pneumonia (UIP) pattern, probable UIP pattern, indeterminate for UIP pattern, or an alternative diagnosis pattern according to the criteria of the 2018 American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society clinical practice guideline [22]. AE-ILD was diagnosed according to the following criteria [10,13]: (1) subjective worsening of dyspnea within 1 month; (2) new ground-glass opacities or consolidation on chest CT and/or chest radiography; (3) hypoxemia with a decline of 10 mmHg or more in partial pressure of oxygen from the previous level; and (4) no clinical evidence of infection, pulmonary embolism, congestive heart failure, or pneumothorax that could explain the worsening of the patient's condition.

2.4. Statistical methods

In the previous CA031 phase III study, *nab*-P/C demonstrated an ORR of 33%. Considering the generally worse conditions of patients with advanced NSCLC who also have ILD, we set the threshold and expected ORRs at 20% and 40%, respectively. Using the One Arm Binomial program (Cancer Research and Biostatistics, Seattle, WA, USA), we estimated that 32 patients would be required to produce a statistical power of 80% with a 1-sided type I error of 5%. Hence, the recruitment goal was 35 patients to allow for potential dropouts. Efficacy and safety analyses were planned for patients who received at least 1 cycle of the treatment. Survival estimation was performed using the Kaplan-Meier method. PFS was defined as the time from the date of enrollment to the date of the first occurrence of disease progression or death from any cause; patients who had not experienced progression or death at the data cutoff time were censored on the date of their last tumor assessment. OS was calculated from the date of enrollment to the date of death from any cause; data were censored at the date of last follow-up if the patient was confirmed to be alive. All statistical analyses were performed using JMP 14 (SAS Institute Inc., Cary, NC, USA); a 2-tailed P-value < 0.05 was considered significant.

3. Results

3.1. Patient characteristics

Between April 2014 and September 2017, a total of 36 patients were enrolled at 10 institutions of the Hokkaido Lung Cancer Clinical Study Group Trial (HOT) in Japan. All 36 patients received the protocol treatment and were eligible for further analysis. Table 1 shows the baseline characteristics of eligible patients. Sixteen patients (44.4%) had an adenocarcinoma, 15 (41.7%) had squamous cell carcinoma (Sq), and 5 (13.9%) had non-small cell carcinoma. Only 1 patient (2.8%) was a never smoker. Regarding the ILD pattern as shown on high-resolution CT, the number of patients with UIP, probable UIP, indeterminate for UIP, and alternative diagnosis patterns were 12 (33.3%), 15 (41.6%), 5 (13.9%), and 4 (11.1%), respectively. Two patients who experienced recurrence after surgery had pathological diagnoses of ILD: one had IPF and the other had non-specific interstitial pneumonia.

3.2. Treatment delivery and efficacy

A median of 4 cycles of treatment (range: 1–6 cycles) was administered; 23 patients (63.9%) received at least 4 cycles (Table S1). The dose was reduced by 1 level for 19 patients (52.8%) and by 2 levels for 5 (13.9%). The reasons for discontinuing protocol treatment were the completion of ≥4 cycles (13 patients, 36.1%), unacceptable toxicity without PD (12 patients, 33.3%), PD (9 patients, 25.0%), and the investigators' decision (2 patients, 5.6%).

Of the 36 patients, the response of 1 was not evaluable. Two patients achieved a CR while 18 had a PR; the ORR was 55.6% (95% confidence interval [CI]: 39.6–70.5%) (Table 2). Twelve patients maintained an SD, yielding a disease control rate of 88.9% (95% CI: 74.7–95.6%). Three patients experienced PD. After a median follow-up period of 14.1 months (range: 1.8–48.4 months), the median PFS and OS were 5.3 months (95% CI: 3.9–8.2 months) and 15.4 months (95% CI: 9.4–18.7 months), respectively (Fig. 1).

We also investigated the relationship between histology (Sq vs. non-

Table 1
Baseline characteristics.

	No. of patients	(%)
Sex		
Male	26	72.2
Female	10	27.8
Age, years		
Median	68.5	
Range	51–74	
ECOG performance status score		
0	13	36.1
1	23	63.9
Histology		
Adenocarcinoma	16	44.4
Squamous cell carcinoma	15	41.7
Non-small cell lung carcinoma	5	13.9
Stage		
IIIB	15	41.7
IV	18	50.0
Recurrence	3	8.3
Smoking status		
Ever	35	97.2
Never	1	2.8
HRCT pattern		
UIP	12	33.3
Probable UIP	15	41.6
Indeterminate for UIP	5	13.9
Alternative Diagnosis	4	11.1
%FVC		
Median	96.4	
Range	60.4–127.9	
%DLCO		
Median	73.1	
Range	34–99.7	
PaO2 (torr)		
Median	77.95	
Range	68.8–96.2	
SpO2 (%)		
Median	96	
Range	90–99	
KL-6 (U/mL)		
Median	781	
Range	183–6854	
WBC (/μL)		
Median	7895	
Range	4000–12500	
CRP (mg/dL)		
Median	0.54	
Range	0.03–13.77	
LDH (U/mL)		
Median	209.5	
Range	150–1653	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; PaO2, partial pressure of oxygen; SpO2, peripheral capillary oxygen saturation; WBC, white blood cells; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 2
Treatment outcomes.

Outcome	n	(%)
CR	2	5.6
PR	18	50.0
SD	12	33.3
PD	3	8.3
NE	1	2.8
ORR (CR + PR)	20	55.6
DCR (CR + PR + SD)	32	88.9

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

Sq) and treatment outcomes. A greater number of patients in the Sq group experienced good outcomes; however, there was no significant difference between the 2 groups (possibly owing to the small sample size). The ORR was 66.7% (95% CI: 41.7–84.8%) in the Sq group and 47.6% (95% CI: 28.3–67.6%) in the non-Sq group (P = 0.254). The median PFS was 8.2 months (95% CI: 4.0–10.2 months) in the Sq group vs. 4.1 months (95% CI: 3.3–5.4 months) in the non-Sq group (HR, 0.60 [95% CI, 0.30–1.20]); P = 0.15) (Fig S1a). The median OS was 16.8 months (95% CI: 9.8 months–not reached) in the Sq group vs. 11.9 months (95% CI: 7.3–17.4 months) in the non-Sq group (HR, 0.56 [95% CI, 0.24–1.28]; P = 0.17) (Fig S1b).

3.3. Safety

The major adverse events of all eligible patients are summarized in Table 3. The most frequently reported hematological adverse event of grade ≥3 was neutropenia (23 patients, 63.9%); however, none experienced febrile neutropenia. Non-hematological adverse events of grade ≥3 other than pulmonary toxicity were minor; they included infection in 4 patients (11.1%), anorexia in 3 patients (8.3%), and diarrhea and peripheral sensory neuropathy in 2 patients each (5.6%). One patient (2.8%) experienced a grade 4 thromboembolic event (cerebral hemorrhage) during the second course of protocol treatment, which may have been treatment-related despite having no thrombocytopenia at the time. Regarding pulmonary toxicity, 2 patients (5.6%) experienced grade ≥2 pneumonitis and were treated with steroids. One patient who underwent CT for the evaluation of treatment efficacy on day 90 of the protocol treatment was found to have ground-glass opacity in the right upper lobe. He had no deoxygenation; however, the physician in charge stopped the protocol treatment on safety concerns and commenced prednisolone treatment (30 mg/day). The patient received no more anticancer treatment and died owing to lung cancer progression on day 255 without any worsening of the ILD. This event did not meet the criteria of AE-ILD, and was considered grade 2 pneumonitis. Another patient was also found to have an enlarged ground-glass opacity lesion in the right upper lobe (compared to baseline) *via* CT performed on day 43 of the protocol treatment (Fig. S2a–d), with fever and deoxygenation observed on the following day. The patient commenced antibiotics and steroid pulse treatment, but his general condition deteriorated and he died of respiratory failure on day 55. This episode was considered AE-ILD and treatment-related grade 5 pneumonitis (Table 3).

3.4. Second-line therapy

Twenty-four patients (66.7%) underwent second-line therapy per standard practice after the protocol treatment; the regimens are shown in Table 4, with S-1 the most preferred treatment. Three patients (12.5%) achieved PR, 5 (20.8%) had SD, 15 (62.5%) had PD, and 1 (4.2%) was not evaluable. Three patients (12.5%) were reported to have AE-ILD, and 1 died of causes that were possibly treatment-related according to the investigator.

4. Discussion

To the best of our knowledge, ours is the first prospective phase 2 study of *nab*-P/C combination therapy in patients with advanced NSCLC and concomitant ILD. Because of the risk of AE-ILD occurrence, which occurs frequently following chemotherapy, there have only been 3 published prospective trials that investigated the safety and efficacy of platinum doublet chemotherapy for patients with NSCLC and ILD to date (Table 5). The first prospective feasibility study of carboplatin and weekly *sb*-paclitaxel was performed by Minegishi et al., as mentioned earlier [18]. Two other groups (Sekine et al. and Hanibuchi et al.) investigated combination carboplatin and S-1 [23,24]. In terms of safety, the AE-ILD rate among patients in our study (2.8%) was similar to those found in previous prospective studies (5.6–9.5%), which demonstrated the feasibility of the *nab*-P/C combination in this setting. Furthermore, our findings were consistent with those of 2 retrospective studies of *nab*-P/C combination therapy by Niwa et al. [25] and Yasuda et al. [26], in which the AE-ILD rates were 0% (0/12) and 8.3% (1/12), respectively. Most of these rates are better than those observed in previous retrospective studies [11–16], which may be due to patient selection bias. Adverse events other than pneumonitis were also relatively low in our study.

Regarding efficacy, the ORR in our study was 55.6%, which met the primary endpoint. In their prospective trial, Minegishi et al. reported an

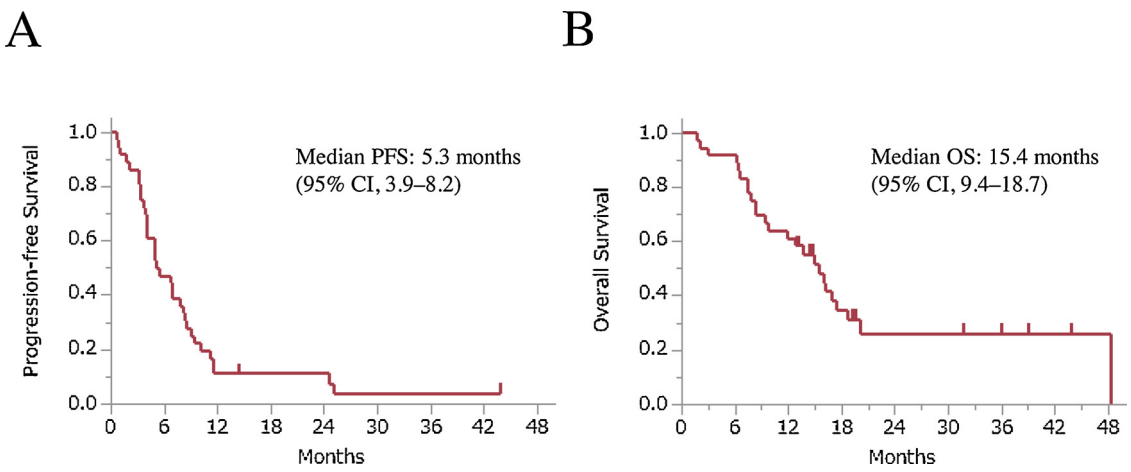

Fig. 1. Kaplan-Meier curves of (A) progression-free survival (PFS) and (B) overall survival (OS). CI, confidence interval. The median PFS, median OS, and 1-year survival rate were 5.3 months, 15.4 months, and 61.1%, respectively.

Table 3
Safety profiles.

	G1	G2	G3	G4	G5	All grades (N)	All grades (%)	≥G3 (N)	≥G3 (%)
Leukopenia	7	9	17	1	0	34	94.4	18	50.0
Neutropenia	7	4	9	14	0	34	94.4	23	63.9
Anemia	10	13	13	0	0	36	100.0	13	36.1
Thrombocytopenia	6	8	6	1	0	21	58.3	7	19.4
Pneumonitis*	34	1	0	0	1	36	100.0	1	2.8
PS deterioration	22	9	0	1	0	32	88.9	1	2.8
Fatigue	13	6	1	0	0	20	55.6	1	2.8
ALT increased	18	1	1	0	0	20	55.6	1	2.8
AST increased	18	1	0	0	0	19	52.8	0	0.0
Anorexia	10	4	3	0	0	17	47.2	3	8.3
Alopecia	8	8	0	0	0	16	44.4	0	0.0
Nausea	11	3	0	0	0	14	38.9	0	0.0
Creatinine increased	12	1	0	0	0	13	36.1	0	0.0
Peripheral sensory neuropathy	2	6	2	0	0	10	27.8	2	5.6
Hyperbilirubinemia	9	0	0	0	0	9	25.0	0	0.0
Constipation	3	5	0	0	0	8	22.2	0	0.0
Fever	6	1	0	0	0	7	19.4	0	0.0
Infection	0	2	4	0	0	6	16.7	4	11.1
Weight loss	3	1	0	0	0	4	11.1	0	0.0
Diarrhea	2	0	2	0	0	4	11.1	2	5.6
Thromboembolic event	0	1	0	1	0	2	5.6	1	2.8
Rash	2	0	0	0	0	2	5.6	0	0.0
Myalgia	2	0	0	0	0	2	5.6	0	0.0
Mucositis oral	1	1	0	0	0	2	5.6	0	0.0
Hiccups	1	1	0	0	0	2	5.6	0	0.0
Edema limbs	1	0	1	0	0	2	5.6	1	2.8
Insomnia	1	0	0	0	0	1	2.8	0	0.0
Hematuria	0	0	1	0	0	1	2.8	1	2.8
Dysgeusia	1	0	0	0	0	1	2.8	0	0.0
Arthralgia	1	0	0	0	0	1	2.8	0	0.0

* G1 pneumonitis at baseline is required by the inclusion criteria. G, grade; PS, performance status; ALT, alanine transaminase; AST, aspartate transaminase.

Table 4
Second-line therapy.

Regimen	n	(%)
S-1	12	50.0
Vinorelbine	4	16.7
Docetaxel	3	12.5
Pemetrexed	1	4.2
Nivolumab	1	4.2
Nab-paclitaxel	1	4.2
Carboplatin/*nab*-paclitaxel	1	4.2
Carboplatin/paclitaxel	1	4.2
Total	24	100.0

ORR of 61.1% with carboplatin and weekly *sb*-paclitaxel [18], while Sekine et al. and Hanibuchi et al. reported identical ORRs of 33.3% with combination carboplatin and S-1 [23,24]. Two small retrospective studies of *nab*-P/C found that this combination produced ORRs of 55.6% and 67%, respectively [25,26]. Our results validated the favorable response of *nab*-P/C combination therapy in a prospective, multicenter setting, and our patients' median PFS and OS were similar to those previously found in the 3 aforementioned prospective studies (PFS: 4.2–5.3 months; OS: 9.7–12.8 months) [18,23,24] and 2 retrospective studies (PFS: 5.1–5.8 months; OS: 11.8–14.9 months) [25,26]. Based on these results, platinum doublet combination therapy appears to be as effective in patients with NSCLC and ILD as in those in NSCLC alone, although the risk of AE-ILD is moderately increased.

The prevalence of Sq histology is relatively high among patients with NSCLC and concomitant ILD, the combination of which is generally a smoking-related comorbidity. Kojima et al. reported that the prevalence of Sq histology was higher among patients with NSCLC who also had IIPs than among those who did not (40.2% vs. 22.7%, $P < 0.0001$) in their single-institution study of 1170 patients with resected NSCLC [27]. Unlike adenocarcinoma, treatment options other than immune checkpoint inhibitors for Sq are relatively limited; therefore, the development of novel treatments for this subgroup of patients is a critical unmet need. In a subsequent analysis of the pivotal CA031 phase 3 trial, Socinski et al. found that combination *nab*-P/C produced a 68% improvement in response over combination *sb*-P/C

Table 5
Summary of prospective trials.

Author	N (study design)	Regimen	Primary endpoint	ORR (%)	mPFS (months)	mOS (months)	1-year survival (%)	AE-ILD (%)
Minegishi et al. [18]	18 (single-center)	CBDCA + wPTX	Incidence of AE-ILD	61.1	5.3	10.6	22.2	5.6
Sekine et al. [24]	21 (single-center)	CBDCA + S-1 (every 3 weeks)	Incidence of AE-ILD	33.3	4.2	9.7	33.3	9.5
Hanibuchi et al. [25]	33 (multicenter)	CBDCA + S-1 (every 4 weeks)	ORR	33.3	4.8	12.8	51.4	6.1
Present study	36 (multicenter)	CBDCA + *nab*-PTX	ORR	55.6	5.3	15.4	61.1	2.8

Abbreviations: N, number; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival; AE-ILD, acute exacerbation of interstitial lung disease; CBDCA, carboplatin; wPTX, weekly paclitaxel; nab-PTX, the 130 nm albumin-bound formulation of paclitaxel.

among patients with Sq histology, with ORRs of 41% vs. 24% (response rate ratio 1.680; 95% CI 1.271–2.221; P < 0.001) [29]. Consistent with such previous findings, our study showed improved ORR, PFS, and OS among patients with Sq histology, who comprised 41.7% of our cohort. The anticancer mechanisms of *nab*-P/C in patients with Sq are unknown, but greater access to the bloodstream owing to the central location of the tumor may render Sq tumors more susceptible to differences in drug concentrations in the blood [28]. Furthermore, the albumin-binding protein osteonectin is known to be overexpressed in lung cancer and is a poor prognostic factor. The albumin-binding property of osteonectin might increase the amount of *nab*-paclitaxel in tumor cells, thereby increasing the agent's efficacy [29]. However, this ought to be verified experimentally, as we did not investigate osteonectin expression in our patients' tumor samples.

With respect to its mechanism, *nab*-paclitaxel acts based on the enhanced permeability and retention (EPR) effect, and exhibits lower toxicity than non-EPR-based agents owing to its low perfusion into organs like the kidney and heart [30,31]. Furthermore, paclitaxel is one of the most potent immunogenic inducers of cell death, and has already been used in combination with ICIs in a pivotal phase 3 study of patients with squamous NSCLC [5,32]. Like pancreatic cancer, squamous-cell cancers are 'stromal cancers' that produce high levels of interstitial fluid pressure; EPR drugs can overcome this pressure better than their non-EPR counterparts [31,33]. This might also explains the reason for *nab*-paclitaxel's relatively better efficacy in patients with Sq than in those with non-Sq in our study. Maeda et al. revealed that vascular mediators such as nitric oxide, bradykinin, and carbon monooxide augment the EPR effect [30,34]. We investigated the relationship between the predicted carbon monoxide diffusion capacity of the lungs (below versus above the median values) and treatment outcomes, but found no significant differences in ORR, median PFS, or median OS, possibly owing to the small number of subjects.

Although second-line therapy is the standard of care for patients with advanced NSCLC, data regarding the efficacy of such treatments in these patients with NSCLC and ILD are very limited. Therefore, we investigated the outcomes of our patients who received second-line therapy after completing the protocol treatment. In the East Asia S-1 Trial in Lung Cancer, which was a large phase 3 trial that compared S-1 with docetaxel, S-1 was shown to be non-inferior to docetaxel in the second, third, and fourth-line settings; grades 3–4 febrile neutropenia occurred in 5 of the 569 patients (0.9%) in the S-1 group and in 75 of 560 patients (13.4%) in the docetaxel group [35]. Ozawa et al. retrospectively compared the frequencies of chemotherapy-related lung injury in patients with NSCLC and concomitant ILD who received S-1 to those who received docetaxel, and found significantly less such injury in the S-1 group (2 of 60 patients [3%]) than in the docetaxel group (16 of 89 patients [18%]) [36]. S-1 monotherapy was the preferred regimen after protocol treatment in our present study. As Sekine et al. reported, the AE-ILD rate tends to increase during second-line therapies and beyond [23]. Considering the favorable results obtained with *nab*-P/C and carboplatin/S-1 combinations, the optimal sequence of chemotherapy for both regimens should be further tested in order to improve the OS of this patient population.

Recently, the oral intracellular inhibitor nintedanib (which targets multiple tyrosine kinases such as vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor) was shown to slow IPF disease progression, as measured by the reduced decline in forced vital capacity, in 2 phase 3 trials (IMPULSIS-1 and IMPULSIS-2) [37]. Based on the results of these trials, a randomized phase 2 trial consisting of combination *nab*-P/C with and without nintedanib in patients with advanced NSCLC and concomitant IPF has been initiated [38]. Though the inclusion criteria differ slightly (our study included patients with IIPs other than IPF), our data support the usefulness of combination *nab*-P/C as a backbone chemotherapy in this setting.

Our study had several limitations. First, since the number of included patients was small and all were of Japanese ethnicity, it is difficult to draw any generalizable conclusions. Only 36 patients were accrued over 3 years because patients with NSCLC and ILD are mostly heavy-smokers, and therefore tend to have other concomitant smoking-related comorbidities (*e.g.*, cardiovascular disease) that make them ineligible for trial recruitment. Second, most ILD diagnoses were based on clinical and radiographic findings, not pathologic ones; this is a general shortcoming in terms of patients with advanced lung cancer and concomitant ILD. Since the majority of patients are diagnosed with both diseases simultaneously, there is little or no time to definitively diagnose ILD in this patient population given the urgency of managing the cancer. As Ryerson et al. reported, making a definitive diagnosis of ILD is often difficult, even for specialists [39]. We included a relatively larger population of patients with NSCLC and ILD to maximize the generalizability of the outcomes observed with the combination therapy, which might have affected the incidence of AE-ILD.

Very recently, Fujimoto et al. performed a small phase 2 study of nivolumab as a second-line therapy in patients with NSCLC who had mild IIP [40]. Among the 18 patients they investigated, the 6-month PFS rate (their primary endpoint) was 56%. Two patients had grade 2 pneumonitis that improved with corticosteroid therapy, and no treatment-related deaths occurred. ICIs combined with cytotoxic chemotherapy are now standard treatments for most advanced NSCLCs. Given the difficulties in treating this disease, it would be prudent to investigate ICI/chemotherapy combinations in patients with NSCLC exhibiting mild IIP in a larger, randomized trial.

In conclusion, ours is the first prospective phase 2 study of weekly *nab*-paclitaxel in combination with carboplatin in patients with advanced NSCLC and concomitant ILD. The treatment showed improved efficacy with acceptable toxicity in this patient population. Considering the fact that a substantial proportion of patients with advanced NSCLC and concomitant ILD has been excluded from consideration when developing standard therapies, further exploration of this treatment regimen should be performed in a large randomized phase 3 trial.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.09.020.

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