



Title	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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1 **A prospective phase II study of carboplatin and nab-paclitaxel in patients with advanced non-small**
2 **cell lung cancer and concomitant interstitial lung disease (HOT1302)**

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1 **Abstract**

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

7 **Patients and methods:** The enrolled patients had treatment-naïve, advanced NSCLC with ILD. Patients
8 received 100 mg/m² *nab*-paclitaxel weekly and carboplatin at an area under the concentration-time curve
9 of 6 once every 3 weeks for 4–6 cycles. The primary endpoint was the overall response rate (ORR);
10 secondary endpoints included toxicity, progression-free survival (PFS), and overall survival (OS).

11 **Results:** Thirty-six patients were enrolled between April 2014 and September 2017. Sixteen patients
12 (44.4%) had adenocarcinoma, 15 (41.7%) had squamous cell carcinoma (Sq), and 5 (13.9%) had non-
13 small cell carcinoma. The median number of cycles administered were 4 (range: 1–6). The ORR was
14 55.6% (95% confidence interval [CI]: 39.6–70.5). The median PFS and OS were 5.3 months (95% CI:
15 3.9–8.2) and 15.4 months (95% CI: 9.4–18.7), respectively. A greater proportion of patients with Sq
16 experienced improvements than did those with non-Sq: ORRs, 66.7% (95% CI: 41.7–84.8) vs. 47.6%
17 (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:
18 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
19 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
20 (5.6%) experienced grade ≥ 2 pneumonitis and 1 patient (2.8%) died.

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

23

24

25 Keywords: non-small cell lung cancer, interstitial lung disease, carboplatin, nab-paclitaxel, clinical trial

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27

1 **1. Introduction**

2 Lung cancer is the leading cause of cancer-related death worldwide, and non-small cell lung
3 cancer (NSCLC) accounts for more than 80% of all such cancers [1]. Drugs that target specific molecular
4 abnormalities within the tumor, such as *EGFR* mutations, *ALK* rearrangements, *ROS1* rearrangements,
5 and *BRAF* mutations are the preferred first-line therapies for patients with adenocarcinoma [2]. Immune
6 checkpoint inhibitors (ICIs) with or without cytotoxic chemotherapy are also effective. Pembrolizumab
7 monotherapy; pembrolizumab and platinum-based doublet combination; and atezolizumab, bevacizumab,
8 and platinum-based doublet combination have been shown to have superior effectiveness over their
9 counterparts, and have therefore been approved as first-line therapies in patients with advanced NSCLC
10 [3-6].

11 Interstitial lung disease (ILD) encompasses a diverse range of pulmonary fibrotic disorders
12 that affect the alveoli of the lung [7]. The most common such disorders are idiopathic interstitial
13 pneumonias (IIPs), which include such conditions as idiopathic pulmonary fibrosis (IPF) and idiopathic
14 nonspecific interstitial pneumonia [8, 9]. The prevalence of IPF among patients with lung cancer is
15 reported to be 2–8%, as the 2 diseases may share a common etiology [7]. Acute exacerbation of IIPs (AE-
16 IIPs), particularly of IPF, has long been a subject of investigation in Japan, and has recently also attracted
17 attention in Western countries [10]. A number of studies of the clinical and prognostic implications of AE-
18 IIPs, which is characterized by non-infectious acute respiratory deterioration that is often unpredictable
19 and fatal, have been performed. The incidence and mortality rates of AE-IIPs vary, ranging from 5% to
20 57% and from 20% to 86%, respectively, according to a recent consensus report [10]. Although the
21 pathogenesis of AE-IIPs remains unknown, treatment-related acute exacerbation of ILD (AE-ILD), which
22 mimics the clinical conditions of AE-IIPs, may occur as a complication of surgery, radiotherapy, and
23 chemotherapy in patients with lung cancer and pre-existing ILD. This condition is serious and often fatal
24 [11-16]. Thus, patients with concomitant advanced NSCLC and ILD have been excluded from most
25 clinical trials of chemotherapy, and there remains no standard treatment for such patients to date (even
26 while treatment options for NSCLC with driver gene aberrations such as *ALK* rearrangements, *ROS1*
27 rearrangements, and *BRAF* mutations continue to expand).

28 In our previous retrospective study of patients with NSCLC and ILD, we found that a
29 solvent-based formulation of paclitaxel (*sb*-paclitaxel) in combination with carboplatin (*sb*-P/C) was the

1 most frequently used regimen [17]. Minegishi et al. reported favorable patient outcomes in their small
2 feasibility study of carboplatin and weekly *sb*-paclitaxel, with a response rate of 61% (11/18), a median
3 progression-free survival (PFS) and overall survival (OS) of 5.3 and 10.6 months, respectively, and a 1-
4 year survival rate of 22% [18]. However, carboplatin plus weekly *sb*-paclitaxel is not an approved
5 regimen in Japan.

6 The 130 nm albumin-bound formulation of paclitaxel (*nab*-paclitaxel) has shown promising
7 efficacy in both preclinical models and in clinical trials of patients with NSCLC. Compared to *sb*-
8 paclitaxel, *nab*-paclitaxel has several advantages such as a higher mean maximum serum concentration of
9 free paclitaxel, greater paclitaxel concentration delivery to tumors, and increased transport across
10 endothelial cell monolayers [19, 20]. In a large multicenter international phase III study (CA031), weekly
11 *nab*-paclitaxel in combination with carboplatin (*nab*-P/C) demonstrated a significantly higher overall
12 response rate (ORR) than did *sb*-P/C (33% vs. 25%; $P = 0.005$) based on an independent assessment.
13 Improvements of approximately 10% in PFS (median, 6.3 vs. 5.8 months; hazard ratio [HR], 0.902; 95%
14 confidence interval [CI], 0.767–1.060; $P = 0.214$) and in OS (median, 12.1 vs. 11.2 months; HR, 0.922;
15 95% CI, 0.797–1.066; $P = 0.271$) were observed in the *nab*-P/C arm versus the *sb*-P/C arm. Furthermore,
16 significantly fewer incidences of grade ≥ 3 neuropathy, neutropenia, arthralgia, and myalgia occurred in
17 the *nab*-P/C arm [21]. However, there is no information to date regarding the efficacy of *nab*-P/C
18 combination therapy in patients with concomitant NSCLC and ILD.

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

21

22 **2. Patients and Methods**

23 **2.1. Eligibility**

24 Eligible patients were those aged 20–74 years with histologically or cytologically confirmed
25 stage IIIB, stage IV, or postoperative recurrent NSCLC with ILD. Patients who received prior systemic
26 therapy for lung cancer were excluded, but those who experienced postoperative recurrence no sooner
27 than 1 year since the last administration of adjuvant chemotherapy were included. The following criteria
28 were also required for eligibility: an Eastern Cooperative Oncology Group performance status score of 0
29 or 1; clinically diagnosed ILD; adequate function of the bone marrow, liver, kidneys (creatinine clearance

1 ≥ 60 mL/min), and lungs (alveolar O₂ pressure ≥ 60 Torr); and at least 1 measurable lesion as defined by
2 the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).

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

13 **2.2. Study design and treatment**

14 This study was designed as a prospective, multicenter, single-arm phase 2 trial. The primary
15 endpoint was ORR; secondary endpoints included toxicity, PFS, and OS. Eligible patients received
16 carboplatin at a dose corresponding to an area under the curve (AUC) equal to 6 mg/mL/min (AUC=6) on
17 day 1 and *nab*-paclitaxel 100 mg/m² on days 1, 8, and 15 every 3 weeks for 4–6 cycles or until evidence
18 of disease progression or unacceptable toxicity manifested.

19 In the event of severe toxicities during a given cycle, the doses of carboplatin and *nab*-
20 paclitaxel were reduced in subsequent cycles. Such toxicities included grade 3 thrombocytopenia, grade 4
21 neutropenia, grade ≥ 3 febrile neutropenia, or other grade ≥ 3 nonhematological toxicities. Dose reduction
22 comprised of a decrease in carboplatin to an AUC of 5 mg/mL/min and a decrease in *nab*-paclitaxel to 75
23 mg/m² (level -1) followed by subsequent dose reductions comprising a decrease in carboplatin to an AUC
24 of 4 mg/mL/min and a decrease in *nab*-paclitaxel to 50 mg/m² (level -2). If patients required a third dose
25 reduction, the protocol treatment was terminated.

27 **2.3. Baseline and treatment assessments**

28 Patient assessments, which included physical examination, complete blood counts, and
29 biochemistry analyses, were conducted once a week during each cycle of protocol treatment. Chest

1 radiography, computed tomography (CT) scans of the chest and abdomen, magnetic resonance imaging
2 studies of the brain, and bone scintigraphy or positron emission tomography-CT studies were performed
3 for baseline tumor assessment within 28 days before the initiation of the protocol treatment. Tumor
4 response was assessed at baseline and every 2 cycles using the RECIST version 1.1. If a patient was
5 documented as having a complete response (CR) or partial response (PR), confirmatory evaluation was
6 performed after an interval of at least 4 weeks. Stable disease (SD) required a minimum 8-week period
7 following enrollment in the study. Clinical response data were confirmed by extramural reviews.
8 Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse
9 Events (version 4.0).

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

22 23 **2.4. Statistical methods**

24 In the previous CA031 phase III study, *nab*-P/C demonstrated an ORR of 33%. Considering
25 the generally worse conditions of patients with advanced NSCLC who also have ILD, we set the
26 threshold and expected ORRs at 20% and 40%, respectively. Using the One Arm Binomial program
27 (Cancer Research and Biostatistics, Seattle, WA, USA), we estimated that 32 patients would be required
28 to produce a statistical power of 80% with a 1-sided type I error of 5%. Hence, the recruitment goal was
29 35 patients to allow for potential dropouts. Efficacy and safety analyses were planned for patients who

1 received at least 1 cycle of the treatment. Survival estimation was performed using the Kaplan-Meier
2 method. PFS was defined as the time from the date of enrollment to the date of the first occurrence of
3 disease progression or death from any cause; patients who had not experienced progression or death at the
4 data cutoff time were censored on the date of their last tumor assessment. OS was calculated from the
5 date of enrollment to the date of death from any cause; data were censored at the date of last follow-up if
6 the patient was confirmed to be alive. All statistical analyses were performed using JMP 14 (SAS Institute
7 Inc., Cary, NC, USA); a 2-tailed P-value <0.05 was considered significant.

8 9 **3. Results**

10 **3.1. Patient characteristics**

11 Between April 2014 and September 2017, a total of 36 patients were enrolled at 10
12 institutions of the Hokkaido Lung Cancer Clinical Study Group Trial (HOT) in Japan. All 36 patients
13 received the protocol treatment and were eligible for further analysis. Table 1 shows the baseline
14 characteristics of eligible patients. Sixteen patients (44.4%) had an adenocarcinoma, 15 (41.7%) had
15 squamous cell carcinoma (Sq), and 5 (13.9%) had non-small cell carcinoma. Only 1 patient (2.8%) was a
16 never smoker. Regarding the ILD pattern as shown on high-resolution CT, the number of patients with
17 UIP, probable UIP, indeterminate for UIP, and alternative diagnosis patterns were 12 (33.3%), 15 (41.6%),
18 5 (13.9%), and 4 (11.1%), respectively. Two patients who experienced recurrence after surgery had
19 pathological diagnoses of ILD: one had IPF and the other had non-specific interstitial pneumonia.

20 21 **3.2. Treatment delivery and efficacy**

22 A median of 4 cycles of treatment (range: 1–6 cycles) was administered; 23 patients (63.9%)
23 received at least 4 cycles (Table S1). The dose was reduced by 1 level for 19 patients (52.8%) and by 2
24 levels for 5 (13.9%). The reasons for discontinuing protocol treatment were the completion of ≥ 4 cycles
25 (13 patients, 36.1%), unacceptable toxicity without PD (12 patients, 33.3%), PD (9 patients, 25.0%), and
26 the investigators' decision (2 patients, 5.6%).

27 Of the 36 patients, the response of 1 was not evaluable. Two patients achieved a CR while 18
28 had a PR; the ORR was 55.6% (95% confidence interval [CI]: 39.6–70.5%) (Table 2). Twelve patients
29 maintained an SD, yielding a disease control rate of 88.9% (95% CI: 74.7–95.6%). Three patients

1 experienced PD. After a median follow-up period of 14.1 months (range: 1.8–48.4 months), the median
2 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),
3 respectively (Fig. 1).

4 We also investigated the relationship between histology (Sq vs. non-Sq) and treatment
5 outcomes. A greater number of patients in the Sq group experienced good outcomes; however, there was
6 no significant difference between the 2 groups (possibly owing to the small sample size). The ORR was
7 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
8 = 0.254). The median PFS was 8.2 months (95% CI: 4.0–10.2 months) in the Sq group vs. 4.1 months
9 (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
10 median OS was 16.8 months (95% CI: 9.8 months–not reached) in the Sq group vs. 11.9 months (95% CI:
11 7.3–17.4 months) in the non-Sq group (HR, 0.56 [95% CI, 0.24–1.28]; $P = 0.17$) (Fig S1b).

13 3.3. Safety

14 The major adverse events of all eligible patients are summarized in Table 3. The most
15 frequently reported hematological adverse event of grade ≥ 3 was neutropenia (23 patients, 63.9%);
16 however, none experienced febrile neutropenia. Non-hematological adverse events of grade ≥ 3 other than
17 pulmonary toxicity were minor; they included infection in 4 patients (11.1%), anorexia in 3 patients
18 (8.3%), and diarrhea and peripheral sensory neuropathy in 2 patients each (5.6%). One patient (2.8%)
19 experienced a grade 4 thromboembolic event (cerebral hemorrhage) during the second course of protocol
20 treatment, which may have been treatment-related despite having no thrombocytopenia at the time.
21 Regarding pulmonary toxicity, 2 patients (5.6%) experienced grade ≥ 2 pneumonitis and were treated with
22 steroids. One patient who underwent CT for the evaluation of treatment efficacy on day 90 of the protocol
23 treatment was found to have ground-glass opacity in the right upper lobe. He had no deoxygenation;
24 however, the physician in charge stopped the protocol treatment on safety concerns and commenced
25 prednisolone treatment (30 mg/day). The patient received no more anticancer treatment and died owing to
26 lung cancer progression on day 255 without any worsening of the ILD. This event did not meet the
27 criteria of AE-ILD, and was considered grade 2 pneumonitis. Another patient was also found to have an
28 enlarged ground-glass opacity lesion in the right upper lobe (compared to baseline) via CT performed on
29 day 43 of the protocol treatment (Figure S2a–d), with fever and deoxygenation observed on the following

1 day. The patient commenced antibiotics and steroid pulse treatment, but his general condition deteriorated
2 and he died of respiratory failure on day 55. This episode was considered AE-ILD and treatment-related
3 grade 5 pneumonitis (Table 3).

4 **3.4. Second-line therapy**

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

12 **4. Discussion**

13 To the best of our knowledge, ours is the first prospective phase 2 study of *nab*-P/C
14 combination therapy in patients with advanced NSCLC and concomitant ILD. Because of the risk of AE-
15 ILD occurrence, which occurs frequently following chemotherapy, there have only been 3 published
16 prospective trials that investigated the safety and efficacy of platinum doublet chemotherapy for patients
17 with NSCLC and ILD to date (Table 5). The first prospective feasibility study of carboplatin and weekly
18 *sb*-paclitaxel was performed by Minegishi et al., as mentioned earlier [18]. Two other groups (Sekine et al.
19 and Hanibuchi et al.) investigated combination carboplatin and S-1 [23, 24]. In terms of safety, the AE-
20 ILD rate among patients in our study (2.8%) was similar to those found in previous prospective studies
21 (5.6–9.5%), which demonstrated the feasibility of the *nab*-P/C combination in this setting. Furthermore,
22 our findings were consistent with those of 2 retrospective studies of *nab*-P/C combination therapy by
23 Niwa et al. [25] and Yasuda et al. [26], in which the AE-ILD rates were 0% (0/12) and 8.3% (1/12),
24 respectively. Most of these rates are better than those observed in previous retrospective studies [11-16],
25 which may be due to patient selection bias. Adverse events other than pneumonitis were also relatively
26 low in our study.

27 Regarding efficacy, the ORR in our study was 55.6%, which met the primary endpoint. In
28 their prospective trial, Minegishi et al. reported an ORR of 61.1% with carboplatin and weekly *sb*-
29 paclitaxel [18], while Sekine et al. and Hanibuchi et al. reported identical ORRs of 33.3% with

1 combination carboplatin and S-1 [23, 24]. Two small retrospective studies of *nab*-P/C found that this
2 combination produced ORRs of 55.6% and 67%, respectively [25, 26]. Our results validated the favorable
3 response of *nab*-P/C combination therapy in a prospective, multicenter setting, and our patients' median
4 PFS and OS were similar to those previously found in the 3 aforementioned prospective studies (PFS:
5 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:
6 11.8–14.9 months) [25, 26]. Based on these results, platinum doublet combination therapy appears to be
7 as effective in patients with NSCLC and ILD as in those in NSCLC alone, although the risk of AE-ILD is
8 moderately increased.

9 The prevalence of Sq histology is relatively high among patients with NSCLC and
10 concomitant ILD, the combination of which is generally a smoking-related comorbidity. Kojima et al.
11 reported that the prevalence of Sq histology was higher among patients with NSCLC who also had IIPs
12 than among those who did not (40.2% vs. 22.7%, $P < 0.0001$) in their single-institution study of 1170
13 patients with resected NSCLC [27]. Unlike adenocarcinoma, treatment options other than immune
14 checkpoint inhibitors for Sq are relatively limited; therefore, the development of novel treatments for this
15 subgroup of patients is a critical unmet need. In a subsequent analysis of the pivotal CA031 phase 3 trial,
16 Socinski et al. found that combination *nab*-P/C produced a 68% improvement in response over
17 combination *sb*-P/C among patients with Sq histology, with ORRs of 41% vs. 24% (response rate ratio
18 1.680; 95% CI 1.271–2.221; $P < 0.001$) [29]. Consistent with such previous findings, our study showed
19 improved ORR, PFS, and OS among patients with Sq histology, who comprised 41.7% of our cohort. The
20 anticancer mechanisms of *nab*-P/C in patients with Sq are unknown, but greater access to the bloodstream
21 owing to the central location of the tumor may render Sq tumors more susceptible to differences in drug
22 concentrations in the blood [28]. Furthermore, the albumin-binding protein osteonectin is known to be
23 overexpressed in lung cancer and is a poor prognostic factor. The albumin-binding property of
24 osteonectin might increase the amount of *nab*-paclitaxel in tumor cells, thereby increasing the agent's
25 efficacy [29]. However, this ought to be verified experimentally, as we did not investigate osteonectin
26 expression in our patients' tumor samples.

27 With respect to its mechanism, *nab*-paclitaxel acts based on the enhanced permeability and
28 retention (EPR) effect, and exhibits lower toxicity than non-EPR-based agents owing to its low perfusion
29 into organs like the kidney and heart [30, 31]. Furthermore, paclitaxel is one of the most potent

1 immunogenic inducers of cell death, and has already been used in combination with ICIs in a pivotal
2 phase 3 study of patients with squamous NSCLC [5, 32]. Like pancreatic cancer, squamous-cell cancers
3 are ‘stromal cancers’ that produce high levels of interstitial fluid pressure; EPR drugs can overcome this
4 pressure better than their non-EPR counterparts [31, 33]. This might also explain the reason for *nab*-
5 paclitaxel’s relatively better efficacy in patients with Sq than in those with non-Sq in our study. Maeda et
6 al. revealed that vascular mediators such as nitric oxide, bradykinin, and carbon monoxide augment the
7 EPR effect [30, 34]. We investigated the relationship between the predicted carbon monoxide diffusion
8 capacity of the lungs (below versus above the median values) and treatment outcomes, but found no
9 significant differences in ORR, median PFS, or median OS, possibly owing to the small number of
10 subjects.

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

26 Recently, the oral intracellular inhibitor nintedanib (which targets multiple tyrosine kinases
27 such as vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived
28 growth factor receptor) was shown to slow IPF disease progression, as measured by the reduced decline
29 in forced vital capacity, in 2 phase 3 trials (IMPULSIS-1 and IMPULSIS-2) [37]. Based on the results of

1 these trials, a randomized phase 2 trial consisting of combination *nab*-P/C with and without nintedanib in
2 patients with advanced NSCLC and concomitant IPF has been initiated [38]. Though the inclusion criteria
3 differ slightly (our study included patients with IIPs other than IPF), our data support the usefulness of
4 combination *nab*-P/C as a backbone chemotherapy in this setting.

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

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

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

1

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4

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6

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9

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1 **Figure legends**

2

3 Fig. 1

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

7

8 Fig. S1

9 Kaplan-Meier curves of (A) progression-free survival (PFS) and (B) overall survival (OS) according to
10 histology (Sq vs. non-Sq). CI, confidence interval; NR, not reached; Sq, squamous cell carcinoma; non-
11 Sq, non-squamous cell carcinoma. The median PFS, median OS, and 1-year survival rate of patients with
12 Sq/non-Sq histologies were 8.2/4.1 months, 16.8/11.9 months, and 80.0/47.6%, respectively.

13

14 Fig. S2

15 Computed tomography images of the patient who experienced AE-ILD. The baseline images are shown in
16 (A) and (B); images acquired at the onset of AE-ILD are shown in (C) and (D). AE-ILD, acute
17 exacerbation of interstitial lung disease.

18

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	
PaO ₂ (torr)		
Median	77.95	
Range	68.8–96.2	
SpO ₂ (%)		
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.

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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

2

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD,

3

progressive disease; NE, not evaluable; ORR, overall response rate; DCR, disease control rate

4

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

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

4

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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/ <i>nab</i> -paclitaxel	1	4.2
Carboplatin/paclitaxel	1	4.2
Total	24	100.0

Table 5. Summary of prospective trials

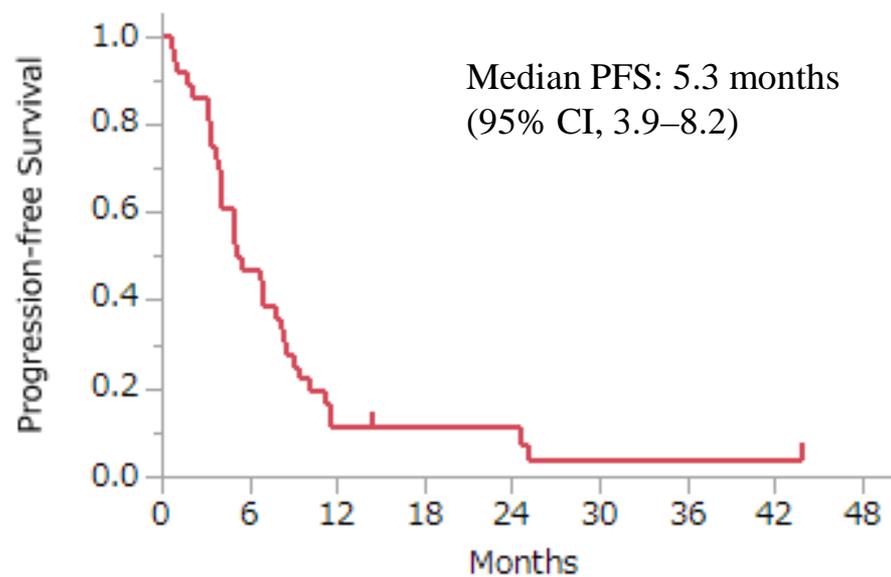
Author	N (study design)	Regimen	Primary endpoint	ORR (%)	mPFS (months)	mOS (months)	1-year survival (%)	AE-ILD (%)
Minegishi et al. [18]	18 (single-center)	CBDCA + wPTX	Incidence of AE-ILD	61.1	5.3	10.6	22.2	5.6
Sekine et al. [24]	21 (single-center)	CBDCA + S-1 (every 3 weeks)	Incidence of AE-ILD	33.3	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 + <i>nab</i> -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

1
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Fig. 1

A



B

