Original Article

Safety and feasibility of carboplatin and paclitaxel in combination with nintedanib for non-small cell lung cancer patients with idiopathic pulmonary fibrosis: a prospective pilot study

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Background: Idiopathic pulmonary fibrosis (IPF) is a risk factor for mortality in patients with lung cancer. Nintedanib has been known to slow down the decline of lung function and reduce IPF exacerbation. We aimed to explore the feasibility of adding nintedanib to chemotherapy for non-small cell lung cancer (NSCLC) patients with IPF.

Methods: Chemotherapy-naïve stage III or IV NSCLC patients with IPF were prospectively enrolled and received carboplatin plus paclitaxel with nintedanib. Primary endpoint was incidence of treatment-related acute exacerbation of IPF within 8 weeks after the last administration of chemotherapy. We initially planned to enroll 30 patients and consider it feasible when the incident rate is less than 10%. Secondary endpoint was progression-free survival (PFS), overall survival (OS), overall response rate (ORR) and disease control rate (DCR).

Results: After 27 patients were enrolled, trial was early terminated because 4 patients (14.8%) experienced exacerbation. Median PFS and OS were 5.4 months [95% confidence interval (CI): 4.6–9.3] and 15.8 months (95% CI: 12.2–30.1), respectively. ORR and DCR were 40.7% (95% CI: 24.5–59.2%) and 88.9% (95% CI: 71.9–96.1%), respectively. One patient discontinued trial treatment due to neuropathy.

Conclusions: Although the primary endpoint was not met, there might be a survival benefit. The addition of nintedanib to chemotherapy might be useful in selected population.

Keywords: Nintedanib; idiopathic pulmonary fibrosis (IPF); non-small cell lung cancer (NSCLC)

Submitted Sep 28, 2022. Accepted for publication Jan 31, 2023. Published online Apr 03, 2023.
doi: 10.21037/tlcr-22-699
View this article at: https://dx.doi.org/10.21037/tlcr-22-699

Introduction

Global Cancer Statistics showed that lung cancer is in the second place in the newly diagnosed cancers in 2020 (1). Although lung cancer is the leading cause of cancer related death, the outcome improved dramatically especially after the approval of the targeted therapy for the specific oncogenic driver mutation and immune checkpoint inhibitors in the last two decades. However, underlying interstitial pneumonia (IP) has been shown to be the risk factor for drug-related pneumonitis (2). Therefore, the lung cancer patients with underlying IP were excluded from most clinical trials, leading to the lack of data regarding the safety and efficacy of regimen of chemotherapy for non-small cell lung cancer (NSCLC) patients with IP (3-6). Nintedanib has been shown to slow down the decline of lung function and to reduce the risk of acute exacerbation in idiopathic pulmonary fibrosis (IPF) and progressive and fibrosing interstitial lung disease (PF-ILD) (7,8). In addition, anti-

tumor effect of nintedanib had been reported (9-11). In the present study, we aimed to evaluate the safety and feasibility of carboplatin and paclitaxel in combination with nintedanib. We present the following article in accordance with the TREND reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-699/rc).

Methods

Study design

This is a prospective pilot study conducted at two institutes in Japan. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine (approval No. 2015-269) and was registered by the UMIN-CTR (trial number: UMIN 000021591). All patients provided written informed consent before the study entry.

Patients eligibility

Eligible patients were 20 years of age or older; histological or cytological diagnosis of NSCLC; stage III, IV, or recurrence after surgery; cytotoxic chemotherapy-naïve; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; at least one measurable lesion; preserved organ function [i.e., aspartate aminotransferase and alanine aminotransferase <2.5× upper limits of normal (ULN); total bilirubin <1.5 mg/dL; serum creatinine <1.5× ULN; white blood cell count ≥3,000/mm^3; neutrophil count ≥1,500/mm^3; hemoglobin ≥9.0 g/dL; platelet count ≥100,000/mm^3; PaO_2 or SpO_2 at room air ≥60 Torr or 93%, respectively; life expectancy of more than 8 weeks from the initiation of protocol treatment. Eligible criteria of high-resolution computed tomography (HRCT) findings were based on the inclusion criteria adopted in INPULSIS trial (7). That is to say, the criteria A and B and C; or criteria A and C; or criteria B and C had to be met. HRCT findings were confirmed by at least one radiologist and two experienced pulmonologists. Key exclusion criteria were: severe or uncontrollable general condition; those who had already taken oral prednisolone of more than 10 mg per day or equivalent; symptomatic brain metastases; requiring drainage of pleural effusion or ascites; pregnant or nursing women; pleurodesis within a week.

Highlight box

Key findings

- The addition of nintedanib might not reduce exacerbation of idiopathic pulmonary fibrosis (IPF) in patients with non-small cell lung cancer (NSCLC).

What is known and what is new?

- There are few prospective studies regarding feasibility of addition of nintedanib on chemotherapy for NSCLC patients with IPF.
- Addition of nintedanib on carboplatin (CBDCA) plus paclitaxel (PTX) might not reduce the exacerbation, but might prolong prognoses compared to historical CBDCA plus PTX only.
- Baseline serum level of TGFβ1 negatively and YKL40 positively correlated with decline of diffusing capacity of the lung for carbon monoxide.

What is the implication, and what should change now?

- We might be thoughtful about the addition of nintedanib on chemotherapy in NSCLC patients with IPF.
- Some cytokines such as TGFβ1 and YKL40 might be useful for predicting the change in lung function in patients with IPF under chemotherapy as well.

Treatment and trial procedures

Enrolled patients received nintedanib (150 mg twice a day) for at least a week before initiation of chemotherapy. Chemotherapy consisted of carboplatin (CBDCA) (area under the curve of 6 on day 1) and paclitaxel (PTX) (200 mg/m^2 on day 1) every 3 weeks. Patients received chemotherapy up to 4 cycles or until the discontinuation criteria was met. After completion or discontinuation of chemotherapy, patients received nintedanib monotherapy until discontinuation criteria. Initiation of each cycle required the following criteria: ECOG PS 0 or 1; white blood cell count ≥1,500/mm^3; platelet count ≥100,000/mm^3; aspartate aminotransferase and alanine aminotransferase <100 IU/L; total bilirubin <1.5 mg/dL; serum creatinine <1.5 mg/dL; no infection and no non-hematologic toxicity of grade ≥3. When patients experienced grade 4 neutropenia, thrombocytopenia of grade ≥3, febrile neutropenia, or non-hematologic toxicity of grade ≥3, the dose of chemotherapy was decreased by one level (carboplatin: level 1=AUC 5, level 2=AUC 4; paclitaxel: level 1=160 mg/m^2, level 2=160 mg/m^2). Discontinuation criteria was defined as below: hematologic toxicity grade 4, not fulfilling criteria to initiate next cycle within 4 weeks after the scheduled date, progressive disease, unacceptable toxicity, death of any cause, not being able to reduce dose level further, rejection of further treatment, or the physicians' decision of discontinuation of the treatment.

The patients underwent the pulmonary function test

to evaluate vital capacity (VC) and diffusing capacity of the lung for carbon monoxide (DLco) every 8 weeks until treatment discontinuation due to adverse events or disease progression. HRCT was performed every 8 weeks until disease progression after completion of protocol treatment. Blood gas analysis was conducted within a week before the start of the trial treatment. Furthermore, 10 mL of blood sample was obtained by the start of trial treatment for cytokine analysis, such as IL-8, MMP-7, VEGF, CCL18, TGFβ1, and YKL-40, which were known to be involved in the pathogenesis of fibrotic lung diseases. Cytokine levels were measured according to manufacturer's protocol. IL-8, MMP-7, VEGF, and CCL18 were measured using Luminex Discover Assay® (R&D Systems, Inc.) (12). TGFβ1 was measured using TGFβ1 Single Plex Magnetic Bead Kit® (EMD MILLIPORE, Inc.) (13). YKL40 was measured using Human Cytokine/Chemokine Magnetic Bead Panel IV® (EMD Millipore, Inc.) (14).

Endpoint

The primary end point of this study is the incidence of treatment-related acute exacerbation which occurred within 8 weeks after the last administration of chemotherapy. Acute exacerbation was defined by the following: worsening of dyspnea within days to weeks; evidence of abnormal gas exchange; new radiographic opacities; and an absence of an alternative explanation such as infectious disease, heart failure, or pulmonary embolism (15). The secondary endpoint is disease control rate (DCR), overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). We determined the data cutoff date to be June 30th, 2022.

Evaluation and statistical analysis

Because the incident rate of chemotherapy-related acute exacerbation has been reported to be 10–20%, this feasibility pilot study was planned to include 30 patients. Therefore, if less than 3 of 30 enrolled patients (≤10%) experienced acute exacerbation, we considered this trial to be feasible. ORR was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1). We estimated PFS and OS using Kaplan-Meier method. PFS was defined as the time from the initiation of treatment to disease progression. OS was defined as the time from enrollment to date of death. The patient, who was lost to follow-up or had not experienced neither PFS nor OS events by the date of data cut-off, was defined as a censored case. Serum cytokine levels of the patients with treatment-related exacerbation and those without were compared using Wilcoxon rank sum test. The correlation between baseline cytokine concentration and changes in the lung function was calculated using Spearman rank correlation. Statistical differences were considered significant if P values were less than 0.05. The statistical analysis was performed using JMP Pro 14.0 (SAS Institute Inc., Cary, NC, USA). Toxicities were evaluated based on the Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0.

Results

Patient characteristics

A total of 27 patients were enrolled in this trial between June 6, 2016 and June 16, 2021 from 2 institutions in Japan. All patients were diagnosed with IPF and lung cancer concomitantly. The baseline characteristics were shown in *Table 1*. The median age was 70 (range, 54–79), and male accounted for 81.4%. The median value (range) of Krebs von den Lungen-6 antigen (KL-6) and surfactant protein-D (SP-D) in serum was 615.5 (299–1,700) U/mL and 140.8 (33.5–887) ng/mL, respectively. Likewise, VC as percent of predicted (%VC) and DLco as percent of predicted (%DLco) was 84.2% (49.5–147.9%) and 69.1% (40.5–115.2%), respectively. Gender-Age-Physiology (GAP) score was 0–1 in 2 patients (7.4%), 2–3 in 16 (59.3%), and 4–5 in 9 (33.3%), respectively. There were no patients with oral corticosteroids, antifibrotic drug, or history of cardiovascular disease. The reason why we did not enroll patients with history of cardiovascular disease, was that we took account of inhibitory effect of nintedanib on VEGF.

Acute exacerbation

Of 27 patients, acute exacerbation occurred in 4 patients (14.8%). Because this study did not meet its primary endpoint of feasibility, this trial had been early terminated at July 2021. The days from start of trial treatment to acute exacerbation were 12, 29, 51, and 83 days, respectively (Figure S1).

Efficacy

Median PFS and OS [95% confidence interval (CI)] were

Table 1 Baseline characteristics

Characteristic	Values
Age (years)	70 [54–79]
Gender	
Male	22 (81.4)
Female	5 (18.6)
Smoking status	
Smoker	26 (96.3)
Never	1 (3.7)
Oral corticosteroids	0 (0)
Antifibrotic drug	0 (0)
ECOG performance status	
0	12 (44.4)
1	15 (55.6)
Histology	
Adenocarcinoma	15 (55.6)
Squamous	9 (33.3)
Others	3 (11.1)
PD-L1	
>50%	0 (0)
1–49%	3 (11.1)
Negative or unknown	24 (88.9)
Driver mutation	
EGFR	
Positive	0 (0)
Negative or unknown	27 (100.0)
ALK	
Positive	0 (0)
Negative or unknown	27 (100.0)
Clinical stage	
III	10 (37.0)
IV	12 (44.5)
Post operative recurrence	5 (18.5)
%VC	84.2 (49.5–147.9)
%DLco	69.1 (40.5–115.2)
KL-6 (U/mL)	615.5 (299–1,700)
SP-D (ng/mL)	140.8 (33.5–887)
LDH (U/L)	232.5 (157–714)
GAP score	
0–1	2 (7.4)
2–3	16 (59.3)
4–5	9 (33.3)

Data are expressed as n (%) or median (range). ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death 1-ligand 1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; VC, vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; KL-6, Krebs von den Lungen-6 antigen; SP-D, pulmonary Surfactant Protein-D; GAP, gender-age-physiology.

5.4 (4.6–9.3) and 15.8 (12.2–30.1) months, respectively (*Figure 1A,1B*). DCR, ORR were 88.9% (95% CI: 71.9–96.1%), 40.7% (24.5–59.2%), respectively (*Table 2*). We compared the lung function between before treatment and after completion of induction chemotherapy and found no significant difference in %VC (P=0.48) (Figure S2).

Exploratory cytokine analysis

We conducted exploratory analysis of cytokines related to the pathogenesis of fibrotic lung diseases (Table S1). There was no significant difference between the patients who experienced treatment-related exacerbation and those who did not, regarding IL-8, MMP-7, VEGF, CCL18, TGFβ1, YKL40. We also evaluated the correlation between cytokine level and changes in lung function between before and just after completion of CBDCA+PTX (*Table 3*). TGFβ1 negatively correlated with the decline of DLco (r_s =–0.51, P=0.04) and YKL40 positively correlated with the decline of DLco (r_s =0.63, P=0.008).

Treatment-related adverse events

Major toxicities during treatment were presented in *Table 4*. No patients had grade 5 adverse events. Serious adverse events (grade 3–4) included neutropenia (44.4%). In particular, serious febrile neutropenia occurred in 22.9% patients. Liver dysfunction were seen in 74.1% patients. In addition, one patient discontinued the trial therapy after one cycle of chemotherapy due to serious neuropathy. Regarding nintedanib, drug holidays and dose reduction

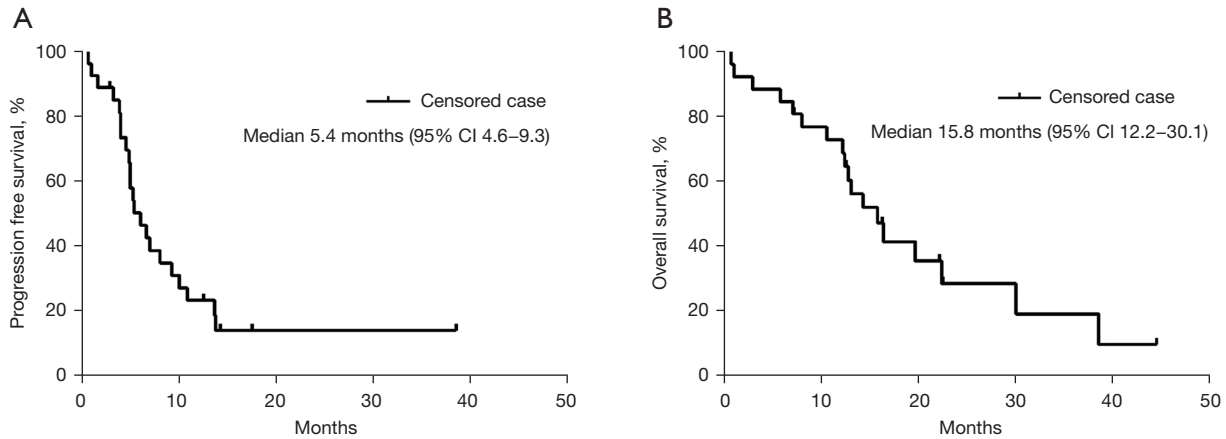

Figure 1 Survival analysis using Kaplan-Meier method. (A) Progression free survival. (B) Overall survival. CI, confidence interval.

Table 2 Best response to trial treatment

Best response	n	%
CR	0	0
PR	11	40.7
SD	13	48.1
PD	3	11.2
DCR	24	88.9 (71.9–96.1)
ORR	11	40.7 (24.5–59.2)

Data are expressed as n or % (95% confidence interval). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; ORR, overall response rate.

Table 3 Correlation between baseline cytokine level and decline of lung function just after completion of carboplatin and paclitaxel

Cytokine	Reduction rate of VC (%)		Reduction rate of DLco (%)	
	r_s	P value	r_s	P value
IL-8 (pg/mL)	−0.10	0.68	−0.04	0.86
MMP-7 (pg/mL)	−0.14	0.56	−0.24	0.34
VEGF (pg/mL)	−0.29	0.23	−0.41	0.09
CCL18 (pg/mL)	0.08	0.72	−0.14	0.58
TGFβ1 (pg/mL)	−0.11	0.66	−0.51	0.04
YKL40 (ng/mL)	0.14	0.58	0.63	0.008

IL-8, interleukin 8; MMP-7, Matrix Metalloproteinase-7; VEGF, vascular endothelial growth factor; CCL18, Chemokine (C-C motif) ligand 18; TGF-β, transforming growth factor β; YKL-40, human Chitinase-3 like 1 protein; VC, vital capacity; DLco, diffusing capacity of the lungs for carbon monoxide; r_s, spearman correlation coefficient.

were needed in 9 patients (33.3%). Adverse events during nintedanib maintenance therapy were shown in *Table 5*. Twenty patients received nintedanib maintenance therapy. Of these, 18 (90%) patients experienced any of adverse events. Discontinuation of nintedanib due to adverse events during maintenance therapy was needed in 2 (10%) patients. Although liver dysfunction and diarrhea were frequently observed, neither was high grade.

Discussion

Recently, remarkable advancement in the treatment for non-resectable locally advanced or metastatic NSCLC has been made. However, as is the case with most clinical trials excluding the patients with concomitant IP, lung cancer with IP has been completely left behind in the real world as well. There have been limited articles regarding chemotherapy for NSCLC with IP (3-6). Generally, almost all antitumor agents except for S-1, nab-paclitaxel or PTX are recognized to be less tolerable for lung cancer with IP. Nintedanib inhibits multiple tyrosine kinase such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) (16). In INPULSIS trial, nintedanib was shown to reduce the decline of lung function and the incidence of exacerbation (7). In addition, a recent article described the effect of addition of nintedanib to CBDCA+nab-paclitaxel

Table 4 Adverse events

Adverse event	Grade 1–2	Grade 3	Grade 4	Grade 5
Neutropenia	2 (7.4%)	5 (18.5%)	17 (25.9%)	0
Thrombocytopenia	16 (59.3%)	5 (18.5%)	0	0
Anemia	21 (78%)	4 (15%)	1 (4%)	0
Febrile neutropenia	0	5 (18.5%)	2 (7.4%)	0
Nausea	11 (40.7%)	3 (11.1%)	0	0
Anorexia	16 (59.3%)	5 (18.5%)	0	0
Liver dysfunction	17 (63.0%)	3 (11.1%)	0	0
Diarrhea	4 (14.8%)	4 (14.8%)	0	0
Neuropathy	23 (88.9%)	3 (11.1%)	0	0

Data are expressed as n (%).

Table 5 Adverse events in patients during nintedanib maintenance therapy

Adverse event	Grade 1–2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Anorexia	1 (5.0)	2 (10.0)	0 (0)	0 (0)
Liver dysfunction	9 (45.0)	3 (15.0)	0 (0)	0 (0)
Diarrhea	7 (35.0)	2 (10.0)	0 (0)	0 (0)

on the prevention of IPF exacerbation (17). The phase 3 randomized trial could not demonstrate the significant difference in exacerbation-free survival in intention to treat (ITT) population (hazard ratio 0.89, 90% CI: 0.67–1.17, P=0.24). In the present study, we selected CBDCA+PTX regimen and found no significant effect of addition of nintedanib to chemotherapy. With respect to lung function, no significant decline of %VC was observed during the observation period. We assume that addition of nintedanib to chemotherapy might suppress decline of lung function to some extent. While both previous phase III trial and our study could not show the reduction in exacerbation of IP, our study firstly demonstrated that some serum cytokines might be useful for predicting change in lung function in patients with IPF receiving chemotherapy as well. Meanwhile, anti-tumor activity of nintedanib has been also well recognized. Reck and colleagues demonstrated that docetaxel and nintedanib prolonged PFS compared with docetaxel only in the second-line setting for NSCLC (median 3.4 *vs.* 2.7 months, P=0.0019) (9). In addition, Hanna and colleagues demonstrated nitedanib plus pemetrexed prolonged PFS compared with pemetrexed only in preciously treated setting (median 4.4 *vs.* 3.6 months, P=0.0435) (18). However, in our study, median PFS and OS was 5.4 and 15.8 months, which were not so different from the previous study evaluating the feasibility of CBDCA + weekly PTX for NSCLC with IP (PFS 5.3 months and OS 10.6 months). As for safety profile, it is noticeable that more patients experienced serious events of liver dysfunction compared to previous randomized trial including CBDCA+PTX, which might be attributable to combination with nintedanib (3,5,6). Compared with previous studies regarding efficacy and safety of chemotherapy for NSCLC with IP, the baseline %VC was worse in our patients (3-6). In addition, GAP score was also relatively higher. The patients with more advanced disease at enrollment might be associated with the high exacerbation rate in the present study in spite of addition of nintedanib. Our study showed that the addition of nintedanib to chemotherapy may not suppress the exacerbation, as shown in the previous study (17). As for efficacy, OS and PFS was comparable to those in a recent study (17). In comparison with CBDCA+PTX only, our study indicated that adjunctive nintedanib may be associated with longer OS (OS: 10.6 *vs.* 15.8 months). We show subsequent anti-tumor therapies in Table S2. Five patients received immunotherapy as a single agent in third line. However, we are not sure whether immunotherapy affected OS.

In this study, we evaluated serum levels of cytokine involved in the pathogenesis of ILD. Of these, we found that the decline of DLco was negatively correlated with TGFβ1 and positively with YKL40. TGFβ1 has been considered to

be released from injured alveolar epithelial cells and promote differentiation of fibroblast to myofibroblast, leading to extracellular matrix deposition (19). Although our results did not agree to this theory, there is a report consistent with our result. Zakaria and colleagues reported that serum level of TGFβ1 was inversely correlated with modified British Medical Research Council (mMRC) scale and positively with 6-minute walk distance (20). TGFβ1 does not always exist in the active form and the function depends on the expression of TGFβ receptors in the lung (21). This might explain discrepancy between our result and pathophysiological role of TGFβ1. YKL40 is a glycoprotein belonging to chitinase family, which has been demonstrated to contribute tissue remodeling (22). In IPF patients, serum level of YKL40 was demonstrated to be inversely correlated with %VC and %DLco from a cross-sectional point of view. Considering the relationship between longitudinal changes of lung function and baseline serum level of TGFβ1 and YKL40, these cytokines might be predictive of the outcome of NSCLC patients with ILD as well.

There are some limitations. First, this is a small-sized prospective study due to early termination. Second, although our patients were comparable with UIP, definite diagnosis based on surgical lung biopsy was not acquired. Moreover, we diagnosed IPF based on HRCT finding adopted in INPULSIS criteria. These criteria include probable UIP, which was recommended to perform BAL in ATS/ERS/JRS/ALAT Clinical Practice Guideline 2018 (23). That is to say, we could not completely exclude the contamination of other ILD types.

Conclusions

Our study could not demonstrate the effect of nintedanib added to chemotherapy on the prevention of acute exacerbation in NSCLC patients with IPF. However, nintedanib might be associated with longer PFS and OS. This regimen might be an option in selected population.

Acknowledgments

We thank the patient for giving consent to this research.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-699/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-699/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-699/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-699/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine (approval No. 2015-269) and was registered by the UMIN-CTR (trial No. UMIN 000021591). All patients provided written informed consent before the study entry.

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Cite this article as: Makiguchi T, Tanaka H, Okudera K, Taima K, Tasaka S. Safety and feasibility of carboplatin and paclitaxel in combination with nintedanib for non-small cell lung cancer patients with idiopathic pulmonary fibrosis: a prospective pilot study. Transl Lung Cancer Res 2023;12(4):719-726. doi: 10.21037/tlcr-22-699

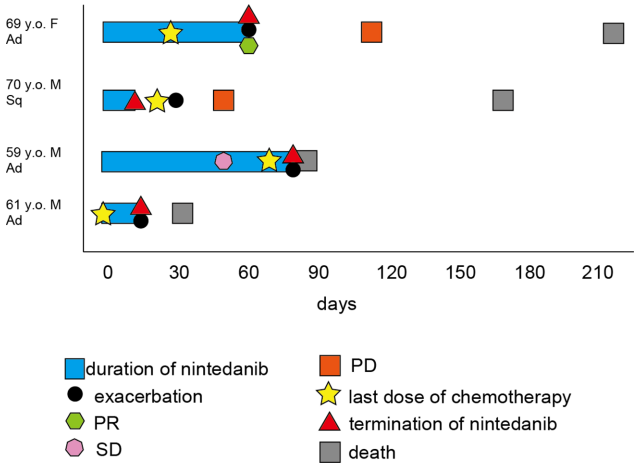

Figure S1 Swimmer plot of patients with acute exacerbation. Each time course of 4 patients were shown. Horizontal axis indicates days from start of trial treatment. y.o, year old; M, male; F, female; Ad, adenocarcinoma; Sq, squamous cell carcinoma; PR, partial response; SD, stable disease; PD, progressive disease.

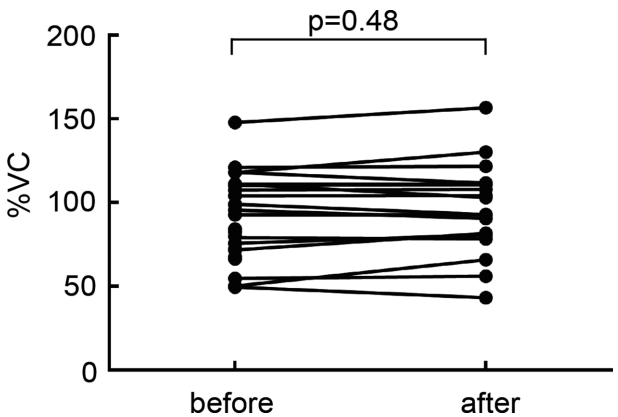

Figure S2 The comparison of predicted value of vital capacity between before and after the trial treatment.

https://dx.doi.org/10.21037/tlcr-22-699

Table S1 Exploratory cytokine analysis

	All patients	Exacerbation-experienced patients (n=4)	No exacerbation (n=23)	P value
IL-8 (pg/mL)	39.3±74.4	20.0±12.6	41.9±78.9	0.93
MMP-7 (pg/mL)	9392.1±11224.1	17200.0±26767.8	8034.3±6178.1	0.73
VEGF (pg/mL)	78.6±107.5	109.1±92.1	73.3±111.0	0.13
CCL18 (pg/mL)	51464.4±20769.8	44610.0±10870.5	52656.5±21992.7	0.68
TGFβ1 (pg/mL)	15547.5±12478.5	20745.4±12589.1	14602.5±12516.1	0.24
YKL40 (ng/mL)	224.6±254.8	161.0±116.3	234.2±270.3	1.0

IL-8: Interleukin 8, MMP-7: Matrix Metalloproteinase-7, VEGF: vascular endothelial growth factor, CCL18: Chemokine (C-C motif) ligand 18, TGF-β: transforming growth factor β, YKL-40: human Chitinase-3 like 1 protein. Data are expressed as mean ± SD.

Table S2 Subsequent anti-tumor therapy following trial treatment

	n
Second line	17
S-1	15
DTX+RAM	1
VNR	1
Third line	7
DTX	1
PEM	1
atezolizumab	3
nivolumab	2

DTX: docetaxel, RAM: ramucirumab, VNR: vinorelbine, PEM: pemetrexed.

https://dx.doi.org/10.21037/tlcr-22-699