Peer Review File

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Reviewer A

① **The classification for UIP/IPF is based on which methodology? Patients with UIP/IPf have a median age well above seventy years of age, therefore please specify the clinical phenotype of patients under 65 years of age. Or is this a cohort of chronic ILD? Please provide data on histology of ILD/BAL and IPAF features.**

① Response:

We are grateful for reviewer's kind comments. We did not specified the demand of BAL or TBLB regarding ILD beforehand. We absolutely enrolled the patients based on chest HRCT findings adopted in INPULSIS trial. 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.

A: Definite honeycomb lung destruction with basal and peripheral predominance

B: Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance

C: Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

However, criteria other than "A and B and C" were comparable to probable UIP in ATS/ERS/JRS/ALAT Clinical Practice Guideline 2018. Probable UIP is recommended to perform BAL. This time around, we performed neither BAL nor lung biopsy to avoid the risk of exacerbation. Therefore, we could not completely exclude the contamination of some other ILD type. We newly described this regard in line 218-221, page 13, and added the reference No.23.

② **The basic lung cancer histology described in the manuscript is not matched with standard IHC and molecular phenotyping – please provide TTF-1 status for nonsquamous NSCLC and PD-L1 status for all patients. Molecular phenotyping is a standard of care and please provide molecular status on driver mutations of all patients.**

② Response

We are grateful for reviewer's comments. We conducted TTF-1 staining in accessible specimen, not all patients, because some patients were diagnosed with only cytology specimen. Please

refer to the supplemental table shown below. Considering the standard treatment option in advanced NSCLC, we should pursue the PD-L1 or driver mutation status in all the patients. However, particularly in patients with ILD, TKI or immune checkpoint inhibitor are generally avoided at least as a first line treatment. As such, we did not check these molecular phenotypings in most patients. Of 27 patients, status of EGFR and ALK had been clarified in 3 and 2 patients, respectively. All of these clarified patients were negative for EGFR and ALK. Other driver mutations were not acquired. It is difficult to demonstrate all of the driver status because driver status had not been specified in the protocol in advance and most patients (18 of 27 patients) had already deceased. Likewise, regarding PD-L1, negative or unknown were observed in 24 patients, one of which was negative. 1-49% was observed in 3 patients, and 50% or more were not seen in any patients. We additively described these regards in Table 1.

supplemental table. Status of TTF-1 staining in patients with non-squamous cell carcinoma

Histology	TTF-1 (+), n (%)
Adenocarcinoma, n=15	9 (60)
others, n=3	0 (0)

Data were expressed as n (%).

③ **The clinical chararacterization of the patients who had an exacerbation is most important to assess risk scores for ILD/NSCLC patients with advanced stage to optimize treatment goals and options. Please add clinical profiles – histology and course of the disease of lung cancer. The treatment length of nintedanib should be added by using a swimmer plot.**

③ Response

We are grateful for reviewer's comment. We demonstrated each time course of 4 patients with acute exacerbation in Figure S1. We described this in line 141, page 8. We also added the legend in line 271-274, page 16.

④ **Finally, please describe in detail the adverse events during the maintainance therapy with nintedanib.**

④ Response

We are grateful for reviewer's comment. We described this regard in line 162-166, page 9-10,

and in Table 5.

⑤ In summary the detailed description which underlying ILD is the NSCLC comorbidity is critical -therefore the treatment of the ILD cohort before or concurrent to the chemotherapy should be detailed – use of oral steroids – antifibrotic drug and cardiovascular medications in those who had an exacerbation. Please provide time of diagnosis of ILD.
Please provide data on supportive measures such as O2 therapy.

⑤ Response
We are grateful for reviewer's comments. This study did not include patients receiving oral corticosteroids. We described this regard in Table 1. Although we did not describe in exclusion criteria, we did not enroll patients already taking antifibrotic drug. Likewise, taking into account the inhibitory effect of nintedanib on VEGF, we did not enroll patients with history of cardiovascular disease. As for oxygen therapy, we enrolled patients with PaO_2 ≧60 Torr or SpO_2 ≧ 93% as shown in method section. As such, this study did not enroll patients with oxygen therapy. We described these regards, except for oxygen therapy, in line 134-136, page 8 and in Table 1. As for timing of diagnosis of ILD, we added the description in line 128, page 8. That is to say, ILD were newly diagnosed in all the patients concomitantly with lung cancer in this cohort.

⑥ The references in the literature section should be updated to 2022 and harmonized
⑥ Response
We are grateful for reviewer's comment. We exchanged reference No. 2, 15, and 22 for the new ones.

Reviewer B
① Did you also include patients with chemo-/immunotherapy?
① Response
We are grateful for reviewer's comment. Seventeen patients received subsequent chemotherapy. Of these, 5 patients received immunotherapy as a single agent. In our study, no one received combination of chemotherapy and immunotherapy. We described this regard in line 199-201, page 12, and in Table S2.

Reviewer C

①However, one mistake in the manuscript need to be corrected:
"2.3 Treatment and trial procedures
… 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=160mg/m2 , level 2=160mg/m2 95)…"
I assume the fist reduced dose level of paclitaxel is 180 mg/m2.

① Response
We are grateful for reviewer's comment. In our protocol, we determined both first and second dose reduction to be 160mg/m^2. It is not a mistake.

② What was the rationale for avoiding the concomitant administration of chemotherapy and nintedanib?
② Response
We are grateful for reviewer's comment. We avoided the concomitant administration of nintedanib and chemotherapy in case we could not distinguish which agent lead to adverse events such as nausea, anorexia, or liver dysfunction. Beforehand, we aimed to confirm the tolerability of nintedanib, then tried to administer chemotherapy.

③ Finally, the units of the PFS and OS curves were in days. It is more appropriate to report in months.

③ Response
We are grateful for reviewer's comment. We corrected the data to be "months" in Figure 1.

Re-review comments

Reviewer A
The manuscript in its revised version is still very limited in its data quality and the authors did not provide an in depth analysis of the required suggestions

The recent publication about this topic deals with this issue and we hope that there is not overlap and should be commented on.

Kohei Otsubo, Junji Kishimoto, Masahiko Ando, Hirotsugu Kenmotsu, Yuji Minegishi, Hidehito Horinouchi, Terufumi Kato, Eiki Ichihara, Masashi Kondo, Shinji Atagi, Motohiro Tamiya, Satoshi Ikeda, Toshiyuki Harada, Shinnosuke Takemoto, Hidetoshi Hayashi, Keita Nakatomi, Yuichiro Kimura, Yasuhiro Kondoh, Masahiko Kusumoto, Kazuya Ichikado, Nobuyuki Yamamoto, Kazuhiko Nakagawa, Yoichi Nakanishi, Isamu Okamoto
Nintedanib plus chemotherapy for nonsmall cell lung cancer with idiopathic pulmonary fibrosis: a randomised phase 3
European Respiratory Journal 60 (6) 2200380; DOI: 10.1183/13993003.00380-2022 Published 15 December 2022

Response

We appreciate reviewer's comment. As stated in page line 175-180, page 10, our study and suggested trials have in common that addition of nintedanib to chemotherapy does not reduce exacerbation. Although some biomarkers for predicting decline of lung function in general IPF population are known, predictive biomarkers in IPF patients under chemotherapy are unknown. YKL-40 and TGF-β might be useful for predicting change in lung function even in these patients as well. We assume that this is new findings. We add this regard in line 182-184, page 11.