Peer Review File
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Reviewer A

Comment 1: Although the description of the CT pattern is provided, it would be helpful to know the extent of fibrosis for each patient prior to commencement of treatment. If CT quantification was performed, this would be useful to know.

Response 1: Unfortunately, we cannot perform CT quantification because we do not have the appropriate software.

Comment 2: The specific ILD diagnosis for each patient is not provided and this would be important information. There are concerns that in patients with underlying connective tissue diseases or disease of autoimmunity that the use of ICI may pose a risk of exacerbation. Similarly, much of the published literature on this topic pertains to use of ICI in IPF and so any information on other ILDs would be helpful for future clinical practice.

Minor comments:

1. It would be helpful to explicitly specify whether the respective patients received radiotherapy previously, from the current submission, the reader has to infer that none of the patients presumably received treatment before

Response 2:

None of the patients had a history of autoimmune disease and prior chest radiation therapy. This was an important point, so we added this information to the Table 1 and (p. 4, lines 91–92).

Case	Autoimmune disease	History of chest RT
1	None	None
2	None	None
3	None	None
4	None	None

All patients had no history of autoimmune disease or previous chest radiation therapy.

Comment 3: The baseline FVC and DLCO for the patients would be important information, and along the same line, the ILD-GAP stage or if all patients had a diagnosis of IPF, the GAP stage, would be useful to know, as it is well described that patients with more advanced disease tolerate cancer treatment worse.

Response 3: Case 4 had received laryngectomy due to laryngeal cancer, and pulmonary function tests could not be performed. Since only two cases had pulmonary function tests results immediately before treatment, we thought that it would be meaningless to list the ILD-GAP stage and the GAP stage.

In case 1 and case 2, pulmonary function tests were performed before and after treatment, so this information has been added to the newly created Table 2.

Table 2. Pulmonary function parameters before and after atezolizumab plus nintedanib treatment

Case	Before atezolizumab plus nintedanib treatment		After atezolizumab plus nintedanib treatment	
	Percent predicted FVC (%)	Percent predicted DLCO (%)	Percent predicted FVC (%)	Percent predicted DLCO (%)
1	103.0	38.0	118.5	47.0
2	67.4	44.7	62.8	49.3

FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide.

Added the following information of Case 1 (p. 5, lines 106–112).

Table 2 shows the changes in pulmonary function before and after atezolizumab plus nintedanib treatment. The percent predicted Forced vital capacity increased from 103.0% to 118.5%, and the percent predicted diffusing capacity of the lungs for carbon monoxide increased from 38.0% to 47.0%. Furthermore, her oxygenation ability improved, and home oxygen was discontinued. This improvement in pulmonary function may be influenced by tumor shrinkage caused by atezolizumab plus nintedanib treatment.

Added the following information of Case 2 (p. 5, lines 120–p.6, lines 123).

Regarding his pulmonary function, the percent predicted FVC decreased from 67.4% to 62.8%, but no decrease in the percent predicted diffusing capacity of the lungs for carbon monoxide was observed (Table 2). Tumor growth might have influenced the decrease in the percent predicted FVC.

Case 4 had a history of laryngeal cancer and there was an error in the age entry, so the information

was added and corrected. (p. 7, lines 149–153).

Case 4 was a 67-year-old man with squamous cell lung cancer in the upper right lobe underwent right lower lobectomy. However, four years later, at the age of 71 years, he relapsed with multiple bone metastases. He had a history of previous laryngectomy for laryngeal cancer (squamous cell carcinoma) 11 years ago. Based on the clinical course, it was determined that the patient had lung squamous cell carcinoma recurrence.

Comment 4: Whilst the authors acknowledge that further trials are needed to evaluate both the efficacy and safety of combination nintedanib and atezolizumab, it would be helpful if they could compare their findings with similar cases reported in the literature so that the reader would have a better understanding of the current landscape with regards to the literature on this topic.

Response 4: Regarding the combination of nintedanib and atezolizumab, there is only one case report in which nintedanib was added to a patient who repeatedly developed drug-induced pneumonitis after receiving pembrolizumab and atezolizumab. The case is described in the discussion (lines 169–172). This is the first report of the combination of nintedanib and ICI in patients with NSCLC complicated by pre-existing ILD.

Reviewer B

Comment 1: The authors do a good job of describing prior anticancer therapy and subsequent therapies, but there is limited information regarding treatment course for nintedanib, was it continued after disease progression for patient 1? Was it permanently discontinued after GI hemorrhage for patient 3? Patient 4 developed pneumonitis but there is no description of how nintedanib was managed, or the course/progression of pneumonitis.

Response 1: Thank you for your advice. Case 1 continued to receive nintedanib after finishing atezolizumab. I have added the following text (p. 5, line 106).
Meanwhile, nintedanib was continued for managing ILD.

In Case 3, both nintedanib and atezolizumab were permanently discontinued. I have added the following text (p. 6, lines 146–147).
Nintedanib was permanently discontinued because of toxicity, and atezolizumab was not restarted.

In Case 4, nintedanib was also discontinued 3 weeks after discontinuing atezolizumab. I have added the following text (p. 6, lines 162–163).
Nintedanib was discontinued 3 weeks after the onset of pneumonitis at the attending physician's discretion.

Comment 2: Case 1- did the oxygen need change on nintedanib?

Response 2: She was able to finish her home oxygen therapy as her respiratory function improved. I have added the following text (p. 5, lines 102–103).
At that time, her respiratory condition improved, and home oxygen therapy was discontinued.

Comment 3: Case 3 with GI hemorrhage- what was the etiology? Was endoscopy performed? How was nintedanib managed? Inisitally held, then resumed at a lower dose? Or permanently discontinued?

Response 3: Added information about gastrointestinal endoscopy results. (p. 6, lines 141–143).
Upper and lower gastrointestinal endoscopy revealed an ulcer in the descending colon, which was thought to be the cause of the gastrointestinal hemorrhage.

Comment 4: It would helpful to have timelines detailing start of atezolizumab, nintedanib,

pneumonitis occurrence, toxicities from nintedanib and scan timepoints.

Response 4: The time series of the treatment progress of the four cases has been added as Figure 1. As a result, the figure number has changed. (Figure 1 to Figure 2, etc)

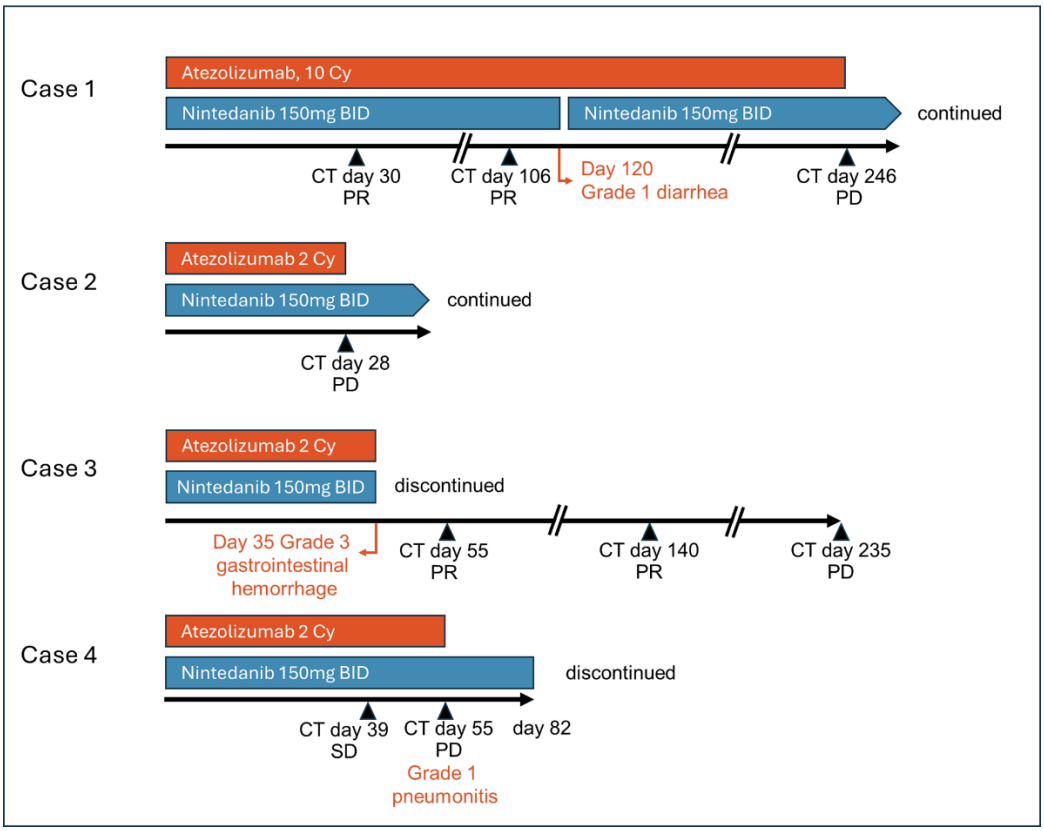

Figure 1 Clinical course of the four patients. CT, computed tomography; Cy, cycles; BID, twice daily; PR, partial response; SD, stable disease; PD, progressive disease.

Comment 5: Time of diagnosis of ILD and cancer plus atezolizumab start need to clarified in relationship to each other

Comment 10: Would be helpful to know for each patient if they received steroids or other interventions in the past for their ILD.

Response 5, 10: Our facility is a cancer center, so the first visit usually occurs when cancer is discovered. Four patients had pre-existing ILD at the time of first visit. There was no history of ILD treatment, corticosteroids, other immunosuppressants and antifibrotic agents. Added the following information (p. 4, lines 88–91).

All patients were diagnosed with pre-existing ILD at least before the initiation of first-line

systemic treatment and had never received any treatment for ILD, such as corticosteroids, other immunosuppressants, and anti-fibrotic agents.

Comment 6: Details about the severity of ILD, monitoring by pulmonology, previous treatments, PFT parameters and how they changed on nintedanib would be helpful.

Response 6: Case 4 had received laryngectomy due to laryngeal cancer, and pulmonary function tests could not be performed. Since only two cases had pulmonary function tests results immediately before treatment, we thought that it would be meaningless to list the ILD-GAP stage and the GAP stage.

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Table 2 shows the changes in pulmonary function before and after atezolizumab plus nintedanib treatment. The percent predicted Forced vital capacity increased from 103.0% to 118.5%, and the percent predicted diffusing capacity of the lungs for carbon monoxide increased from 38.0% to 47.0%. Furthermore, her oxygenation ability improved, and home oxygen was discontinued. This improvement in pulmonary function may be influenced by tumor shrinkage caused by atezolizumab plus nintedanib treatment.

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Case 4 had a history of laryngeal cancer and there was an error in the age entry, so the information was added and corrected. (p. 7, lines 149–153).

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carcinoma) 11 years ago. Based on the clinical course, it was determined that the patient had lung squamous cell carcinoma recurrence.

Comment 7: Did ILD improve for any of the patients?

Response 7: Although no improvement in ILD was observed on CT imaging, but pulmonary function status improved in Case 1. Added additional notes as presented in Response 6.

Comment 8: The method section should clarify how records were identified, how a diagnosis of ILD was identified - based on billing codes, PFTs, pulmonology review, etc.

Response 8: Added an information regarding determining whether it applies to IPF or PF-ILD (Table1, and p. 4, lines 82–84.)

Case	IPF or PF-ILD
1	PF-ILD
2	IPF
3	PF-ILD
4	PF-ILD

Based on the CT image findings and pulmonary function test results, a comprehensive judgment was made by one diagnostic radiologist (TH) and two pulmonologists (JS and TY) to determine whether the patient was compatible with IPF or PF-ILD.

Comment 9: In the method section it would be helpful to know which scans were reviewed - all scans? Only those prior to and while receiving atezolizumab? Were scans at diagnosis of ILD reviewed?

Response 9:

Typically, in oncology intervention trials, CT scans prior to trials entry are not checked. Trials in the second-line setting will not require submission of CT scans during first-line treatment. However, in this study, a previous CT was also reviewed to confirm the progress of fibrosis in the lungs. Therefore, I added the following information. (p. 4, lines 80–81).

All CT scans performed before the initiation of first-line systemic treatment to the end of the observation period were reviewed.

Comment 11: In the discussion, the authors describe a a phase two study of atezolizumab in ILD

patients that was terminated early due to 29% incidence of pneumonitis. The incidence of pneumonitis in this case series is 25%. The authors do not comment on this. Line 157 of "promising demonstration of the inhibitory effect of nintedanib on the onset of pneumonitis" is a bold given their rate is similar to that of the phase II study.

Response 11: "On the other hand, in a phase II study of atezolizumab for pretreated patients with NSCLC and ILD, pneumonitis was observed in 29.4%, 23.5% of whom experienced grade 3 or higher events; as a result, the study was terminated early [19]"
As shown in the underline, pneumonitis of Grade 3 or higher was observed in 23.5% of patients, so the trial was discontinued. Symptomatic pneumonitis was not observed in this study, so this is a difference, but we cannot overemphasize safety based on the report of 4 cases. Therefore, I added the following information. (p. 7, lines 171)
including one case (5.9%) of grade 5

Comment 13 (minor):

1) Post nintedanib images for case 2 are missing
2) Figure2b the lung windows should be included
3) Case 4 the scan alignment for the before and after are not the same level.
4) Lines 137-146 are largely a repeat of what was presented in the introduction regarding J-SONIC study. This does not need to be repeated in the discussion, especially since there was no immunotherapy given in this study.

Response 13-1: An CT images of Case 2 has been added to Figure 3.
Response 13-2: An CT lung windows of Case 3 has been added to Figure 3.
Response 13-3: The pneumonitis image in this case only showed a small ground-glass opacification in the right lung field, and the authors debated whether to classify it as Grade 1 pneumonitis or no pneumonitis (Grade 0). We think that this slice was the easiest to see with regard to the presence of ground-glass opacities. Slices for tumor evaluation regarding Case 4 have been added to Figure 4.
Response 13-4: We believe that the J-SONIC trial is important as a phase 3 trial of nintedanib for non-small cell lung cancer with ILD, so we would like to leave it as is. We appreciate your understanding.

Reviewer C

Comment: As a brief report, I think there is value in publishing this manuscript. It's hard to draw any firm conclusions, but the authors don't overstate the cases. The introduction and summary provide a nice summary of the current uncertainty around this issue.
Response: None.

Reviewer D

Comment 1: Abstract. Conclusions: In patients with NSCLC and pre-existing ILD, nintedanib might reduce the potential for ICI-induced pneumonitis and enhance the antitumor effect. Abstract might be beneficial to include a sentence that briefly summarizes the key findings of the study. This can provide readers with a quick overview of the research.

Response 1: It is important to note that 2 cases had PR and 1 case had asymptomatic pneumonitis, but these are already stated in the abstract. Besides, we believe it is important that treatment was possible in four cases without symptomatic pneumonitis. Therefore, I added the following text. (p2. line 33)

None of the patients experienced a worsening of respiratory symptoms.

Comment 2: Introduction. Nintedanib is a multi-kinase inhibitor that blocks vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–3, and platelet-derived growth factor receptors α and β, targeting the proangiogenic pathway downstream of vascular endothelial growth factor. It has been approved by the US Food and Drug Administration for the treatment of idiopathic pulmonary fibrosis (IPF), systemic sclerosis-associated ILD, and chronic fibrosing ILDs with a progressive phenotype [11–13]. Treatment with nintedanib reduced both the rate of forced vital capacity decline in patients with the foregoing conditions and the incidence of acute exacerbation of IPF. Although the Authors described in detail the findings from the included references, there are several relevant works/reviews, including most recently published which should be added and discussed by the Authors:

Response 2: Thank you for providing additional information. Added discussion citing references A and B. (p. 9, lines 214–218.)

Older patients with IPF have been reported to have significantly higher rates of adverse events, such as diarrhea, nausea, and elevated liver enzymes [24]. Conversely, other studies have reported a decrease in FVC in patients who discontinued nintedanib treatment but not in those who reduced its dose [25]. Therefore, adverse events should be appropriately managed to obtain better clinical outcomes.

Comment 3: We retrospectively reviewed consecutive140 patients who were diagnosed with NSCLC and treated with atezolizumab at XXX Hospital in Japan between April 2018 and December 2021. Among those patients, four with pre-existing ILDs who also received nintedanib treatment were analyzed. One diagnostic radiologist (TH) and one pulmonologist (JS) evaluated baseline chest computed tomography (CT) findings according to the clinical practice guideline

jointly published by the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association with discrepancies being resolved by consensus discussion [16]. Pneumonitis was graded based on the US National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0 [17]. All four patients were treated with atezolizumab monotherapy at 1200 mg every 3 weeks and nintedanib 150 mg twice daily. The data cut off was 30 April 2022. Please, add information on inclusion and exclusion criteria.

Response 3: No specific exclusion criteria were set. Added information regarding inclusion criteria to Method. (p. 4, lines 71–73).

The inclusion criteria included patients with histologically or cytologically confirmed NSCLC, those with investigator-diagnosed PF-ILD (including IPF), and those receiving nintedanib before or concurrently with atezolizumab treatment.

Comment 4: Several retrospective studies have reported that, compared with other patients having NSCLC, those with pre-existing ILD more often develop ICI-induced pneumonitis [7, 8]. The discussion section needs to be improved. It is necessary to clarify the observations obtained and compare them with previous or similar studies.

Response 4: I understand what you are pointing out. However, this is the first report of only four cases. In a Phase 2 study of Atezolizumab for NSCLC with pre-existing ILD, pneumonitis was observed in 29.4%, 23.5% of whom experienced grade 3 or higher events; as a result, the study was terminated early. On the other hand, our report did not identify symptomatic pneumonitis. However, we would not like to overemphasize safety based on a case series of only 4 patients. We add following discussion (p. 8, lines 196–200).

A single-arm phase II trial of atezolizumab in patients with NSCLC with pre-existing ILD showed that 23.5% developed severe pneumonitis of grade 3 or higher, and the study was discontinued [19]. Although the results showed that nintedanib could be combined with atezolizumab while suppressing symptomatic pneumonitis, safety cannot be overemphasized based on a case series of only four patients.

Comment 5: Conclusions Combined treatment with nintedanib and an ICI—for example, atezolizumab—has the potential to be effective in both ameliorating the risk of drug-induced pneumonitis and enhancing the antitumor effect of the ICI. However, the effect of such combination treatment on the incidence of pneumonitis remains unclear, and data about the incidence and management of adverse events are lacking. Prospective clinical trials of this

combination treatment are therefore needed. Please, underline the novelty of the study and the possible clinical implications.

Response 5: The text was added as follows in Conclusion. (p. 10, line 229–238).
Although ICIs have transformed the treatment landscape of NSCLC, patients with pre-existing ILD are not able to gain full clinical benefits from ICIs because of the risk of developing pneumonitis. Combined treatment with nintedanib and an ICI—for example, atezolizumab—has the potential to be effective in both ameliorating the risk of drug-induced pneumonitis and enhancing the antitumor effect of the ICI. In this study, the clinical courses of four patients with NSCLC and pre-existing ILD treated with both nintedanib and atezolizumab at our institution were investigated. Despite having a small sample size, this case series is the first to report the co-administration of nintedanib and atezolizumab in patients with both NSCLC and pre-existing ILD. In this study, a partial response was observed in two patients who received nintedanib combined with atezolizumab. However, the effect of such combination treatment on the incidence of pneumonitis remains unclear, and data about the incidence and management of adverse events are lacking. Prospective clinical trials of this combination treatment are therefore needed.