Comments to the Author

Reviewer #1:

Specific Comments to Authors:

1. Whether to introduce the clinical trials of immunotherapy for advanced liver cancer more comprehensively in the INTRODUCTION section of this article.

→ We would like to thank the reviewer for evaluating our manuscript and for their valuable comment. We additionally described the recently conducted clinical trials on advanced HCC treatments in the Introduction.

2. In the introduction of the disease, it is recommended to add whether there are inflammatory changes in the pulmonary CT before treatment. At the same time, whether the inclusion criteria had lung function requirements and whether the patient had lung function examination before treatment. It is suggested to compare the inflammatory changes of chest CT on the same level before and after treatment in the part of the chart.

→ We appreciate your advice. At baseline chest CT before treatment, there was no sign of inflammatory change, and only findings of interstitial lung abnormalities, such as minimal pulmonary fibrosis, were only shown. As recommended, we added this information in the Figure 4 legend as follows: The lung window of the transverse computed tomography (CT) scan obtained at the level of the left main pulmonary and main pulmonary trunk arteries shows the mixed areas of ground-glass opacity and bilateral consolidation with the anteroposterior gradient (B), compared to baseline CT which was scanned 3 and 4 days prior to atezolizumab and bevacizumab therapy and ARDS, respectively, (A) which demonstrated no inflammatory changes and minimal pulmonary fibrosis.

As recommended, we added the pulmonary function test results of our patient in page 7.

4. This case report is an elderly patient with many underlying diseases, with limited research significance and lack of post-treatment pulmonary pathological examination and related laboratory examination.

→ We agree with this opinion. We described the limitations of our case report in the Discussion section as follows; First, thorough post-treatment pulmonary pathological and laboratory examinations may have clarified the patient's diagnosis; however, a biopsy was not eligible because of the rapid course of the ARDS, and the family did not want an autopsy. Additionally, several serum biomarkers, such as Krebs von den Lungen-6 (KL-6), were related to the diagnosis of interstitial lung disease. If the results of the biomarkers were available, an acute exacerbation of interstitial lung disease could have been ruled out; unfortunately, these laboratory tests were not performed.

5. Atezolizumab is a commonly used drug in clinic, belonging to immune checkpoint inhibitors (ICIs). According to the instructions of the drug, whether single drug or combined with other anti-tumor drugs, the common adverse reactions in the lung include cough (20.8%), dyspnea (20.5%), and immune-associated pneumonia (frequency >1/100), so the innovation of this case report needs to be improved.

→ We appreciate your advice. Although respiratory symptoms such as cough, dyspnea and immune-associated pneumonia are well-known ICI-related adverse events, fatal ARDS with an extremely short duration from therapy, as was in our case, has not been reported. We also mentioned our study's limitation and point of view in last paragraph of the Discussion section as follows: although respiratory symptoms such as cough, dyspnea and immune-associated pneumonia are well-known ICI-related adverse events, fatal ARDS with an extremely short duration from therapy, as was in our case, has not been reported; therefore, our case report may be of value.

Reviewer #2:

Specific Comments to Authors: Cho et al reported a novel case of severe

pneumonitis following aterzolizumab-bevacizumab association. The manuscript is well written and documented. I have some minor comments: -

We would like to thank the reviewer for evaluating our manuscript and for their valuable comment.

1. It is not clear why a grant was required/used for this case report.

→ The grant was provided for the support of language editing services and manuscript submission.

2. This is not the first reported case of early and severe pneumonitis associated with aterzolizumab-bevacizumab as Endo et al. recently reported 2 fatal cases of pneumonia following Atezolizumab plus Bevacizumab, from which 1 occurred 5 days after the first infusion (Endo et al., Liver Cancer. 2022 Aug 16;11(6):572-575. doi: (1). eCollection 2022 Dec.). Thus, authors should add and discuss this recent paper in the discussion part.

→ We appreciate your advice. We additionally described the cases reported by Endo et al. at page 11.

3. Please indicate if the solid nodule in the right middle lobe was hypermetabolic or not in FDG-PET CT

→ Thank you for your important advice. We modified our description in the main manuscript as follows: A solid nodule in the right middle lobe also had mild focal hypermetabolic activity compared to the surrounding lung parenchyma with a maximum standardized uptake value of 1.0 in the section of Imaging examinations subsection.

We also added lung images of PET-CT indicating solid nodules in the right middle lobe in Figure 2, and added descriptions in the Figure Legend.

4. Please indicate received dose of bevacizumab in mg/kg (15 mg/kg?)

→ As requested, we indicated the received dose of bevacizumab at the Treatment subsection.

5. I am surprised concerning the very short interval from atezolizumab / bevacizumab infusion and pneumonia (3 days) as well as from admission to death (31h). In the literature, interval delay to anti-PDL1 associated pneumonitis rather ranged from 4-8 weeks after ICI infusion (Martins, F.; Sofiya, L.; Sykiotis, G.P.; Lamine, F.; Maillard, M.; Fraga, M.; Shabafrouz, K.; Ribi, C.; Cairoli, A.; Guex-Crosier, Y.; et al. Adverse effects of immune-checkpoint inhibitors: Epidemiology, management and surveillance. Nat. Rev. Clin. Oncol. 2019, 16, 563–580) **--> How authors could explain this point? They should more discuss this point and the fact that patient had no risk factors for severe ICI-associated pneumonitis (previous ILD especially, Cf Atchley and al., Immune checkpoint inhibitor-related pneu- monitis in lung cancer: real-world incidence, risk factors, and management practices across six Health Care Centers in North Carolina. Chest. 2021;160(2):731–42.).**

→ We appreciate this inspiring advice and agree with your opinion. Although the exact pathophysiologic mechanism of the rapid onset of ARDS is not clear, we proposed several hypotheses. The underlying ILAs and risk of combination therapy were additionally described in the Case Presentation (Imaging examinations) and Discussion sections as follows:

- Imaging examinations

[Chest CT showed] a 7-mm well-defined solid nodule suspected to be a metastatic nodule in the right middle lobe with interstitial lung abnormality (ILA) findings, such as bilateral subpleural reticulation and non-emphysematous cysts with traction bronchiectasis, respectively (Figure 1).

- Discussion

Furthermore, the presence of ILAs is associated with the risk of complications from medical interventions, such as chemotherapy and surgery. Chest CT done on our patient before atezolizumab and bevacizumab therapy showed ILA findings, which may have influenced the rapid onset of ARDS. Although our patient underwent combination therapy of ICI and TKI, a meta-analysis by Nishino et al. reported

significantly higher incidences of all-grade pneumonitis (6.6% vs 1.6%; P < .001) and grade 3 or higher pneumonitis (1.5% vs 0.2%; P = .001) in the ICI-combination therapy group than in the monotherapy group. Despite varying reported onset times of pneumonitis after treatment initiation (range, 9 days–19 months), the median time to onset is reported to be shorter when a combination therapy of ICIs is used.

6. Was a screening for infectious pneumonia performed? If yes, please provide the restrospective results to be sure that infectious pneumopathy was not a confounding factor for ARDS in this patient

→ Thank you for your useful advice. As requested, we added comments about how we could rule out infectious pneumonia in Outcome and Follow-up subsection.