Peer Review File
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Reviewer A

Comment 1: It needs to show information on PD-L1 expression and driver mutations in the table.
Reply 1: The authors have added columns with the available PD-L1 expression and molecular alterations for each patient to Table 2. Not all patients had PD-L1 testing performed, those who did not have "not available" listed. PD-L1 testing was not standard in June 2015 when our study began enrolling.
Changes in the text: Two additional columns were added to Table 2. One for PD-L1 expression and one for molecular alterations with actionable alterations bolded. Please note *ERBB2 (HER2)* mutations are not bolded as they were added to the NCCN guidelines following data collection. Methods have been updated on page 8, lines 117-119, describing the PD-L1 testing performed.

Comment 2: Specific details about the NGS method are necessary. Information such as whether it was targeted sequencing or exome sequencing, hybrid capture methods of amplicon-based sequencing. And the type of machine used for measurement should be provided.
Reply 2: Targeted sequencing was performed on tumor tissue in a CLIA certified laboratory for the purpose of clinical care. Testing was performed through Tempus, Foundation Medicine, Caris and Washington University Genomics and Pathology Services (CLIA 26D0698285). Cell-free DNA was performed on peripheral blood through Guardant or Inivata. Either testing was permitted for this study.
Changes in the text: We added a line describing that targeted sequencing was performed of clinically significant cancer genes on page 8, lines 115-117.

Comment 3: It is necessary to confirm and report whether any other genetic abnormalities were detected aside from mutations in the TP53, PDGFR-A, and FGFR1-3 genes.
Reply 3: The authors have added columns with the available PD-L1 expression and molecular alterations for each patient to Table 2. Not all patients had PD-L1 testing performed, those who did not have "not available" listed. PD-L1 testing was not standard in June 2015 when our study began enrolling.
Changes in the text: Two additional columns were added to Table 2. One for PD-L1 expression and one for molecular alterations with actionable alterations bolded. Please note *ERBB2 (HER2)* mutations are not bolded as they were added to the NCCN guidelines following data collection. Methods have been updated on page 8, lines 117-119, describing the PD-L1 testing performed.

Comment 4: Please verify the accuracy of the Abstract's PFS 95% CI (18>1.8?).
Reply 4: The authors have corrected the absence of the decimal point.
Changes in the text: On page 3 (abstract) line 46 a decimal point was added to amend 18 to 1.8.

Reviewer B

Comment 1: Whether patients included were tested for other actionable mutations, e.g. EGFR/ ALK, and whether those who had 3 TP53 mutations and adenocarcinoma with prolonged survival belonged in this category. It is well-observed that a number of patients with EGFR and TP53 mutations have naturally slow-growing disease.
Reply 1: The authors have added columns with the available PD-L1 expression and molecular alterations for each patient to Table 2. Not all patients had PD-L1 testing performed, those who did not have "not available" listed. PD-L1 testing was not standard in June 2015 when our study began enrolling.
Changes in the text: Two additional columns were added to Table 2. One for PD-L1 expression and one for molecular alterations with actionable alterations bolded. Please note *ERBB2 (HER2)* mutations are not bolded as they were added to the NCCN guidelines following data collection. Methods have been updated on page 8, lines 117-119, describing the PD-L1 testing performed.

Comment 2: Whether response rate correlated with survival in this small patient population.
Reply 2: We appreciate the reviewer's comment on this. Unfortunately, this small pilot study was not powered to answer this question.
Changes in the text: The authors have elected not to include this data in the manuscript due to the small population included in the study and inherent biases in such an analysis.

Comment 3: To say that Nintedanib has promising results in this study population is an overstatement with a 15% ORR and a 4.3 month PFS and 11 month OS. The drug is probably active in this population, but does not appear more effective than in a molecular unselected population.
Reply 3: Reference 16 (Reck, et al. *Annals of Oncology,* 2011) is a phase II study examining nintedanib as monotherapy in a molecularly-unselected metastatic NSCLC. The median PFS was 1.8 months and median OS was 5.5 months. One patient out of 73 had a partial response and there were no complete responses in the study. While the authors of this pilot study recognize the limitations of the small sample size and the caveats of cross-trial comparisons, our results do show a numerical improvement compared to the phase II study. Furthermore, our results with nintedanib monotherapy in a molecularly selected population were numerically similar to the phase III trials where nintedanib was combined with chemotherapy in a molecularly unselected population.
Changes in the text: The authors have made no changes to the text regarding this comment as these data are already provided. The results of phase I, II and III trials with nintedanib are demonstrated in lines 85-97 and in the discussion, comparisons are made between the pilot study and those results (lines 201-206 and 249-255).

Comment 4: The "new" findings of the study do not match the implication of the study. The study found that nintedanib monotherapy in molecularly selected patients are similar to nintedanib and chemo in an unselected population. If so, then the conclusion should not be to study nintedanib in combination with immunotherapy. The current study has nothing to do with adding immunotherapy.
Reply 4: The authors appreciate the reviewer's comments. Immunotherapy was approved for metastatic NSCLC amid the duration of our study. Current studies are examining the effect of combination nintedanib and immunotherapy and are ongoing in a molecularly unselected population. We await those results to determine if there is synergy in the combination and if a future line of inquiry using nintedanib and immunotherapy in a molecularly selected population would be fruitful.
Changes in the text: The authors have amended Highlight Box on page 5 and the Conclusions on page 15, line 273-278 to more accurately reflect the reasoning in discussing immunotherapy.

Comment 5: First Nintedanib has already been extensively studied, and has been studied in multiple small NSCLC populations. How do the findings here, for example, compare with prior phase I, II trials of Nintedanib monotherapy?
Reply 5: Reference 16 (Reck, et al. *Annals of Oncology,* 2011) is a phase II study examining nintedanib as monotherapy in a molecularly-unselected metastatic NSCLC. The median PFS was 1.8 months and median OS was 5.5 months. One patient out of 73 had a partial response and there were no complete responses in the study. While the authors of this pilot study recognize the limitations of the small sample size and the caveats of cross-trial comparisons, our results do show a numerical improvement compared to the phase II study. Furthermore, our results with nintedanib monotherapy in a molecularly selected population were numerically similar to the phase III trials where nintedanib was combined with chemotherapy in a molecularly unselected population.
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Comment 6: Approximately half to the study population had had 2 lines of treatment, which is not that

heavily-pretreated by today's standards for adenocarcinomatous or non-squamous NSCLC with actionable mutations.
Reply 6: We considered our population as heavily pre-treated as more than half of the patients received 3 or more lines of therapy (Lines 42-43 on page 3, lines 176-177 on page 10, line 202-203, page 12) and over half of patients did not have any actionable mutations.
Changes in the text: Actionable mutations were added in bold to a column in Table 2. Please note *ERBB2 (HER2)* mutations are not bolded as they were added to the NCCN guidelines following data collection.

Comment 7: But in comparison with the phase II study quoted in ref 16, the clinical benefit outcomes in this study are actually largely inferior in a molecularly-selected NSCLC population compared to an all-comers pre-treated NSCLC population. The conclusion I would draw from this data is that the pre-defined molecular markers for inclusion in this study do not actually predict for better clinical benefit from Nintedanib than without molecular selection.
Reply 7: Reference 16 (Reck, et al. *Annals of Oncology,* 2011) is a phase II study examining nintedanib as monotherapy in a molecularly-unselected metastatic NSCLC. The median PFS was 1.8 months and median OS was 5.5 months. One patient out of 73 had a partial response and there were no complete responses in the study. While the authors of this pilot study recognize the limitations of the small sample size and the caveats of cross-trial comparisons, our results do show a numerical improvement compared to the phase II study. Furthermore, our results with nintedanib monotherapy in a molecularly selected population were numerically similar to the phase III trials where nintedanib was combined with chemotherapy in a molecularly unselected population.
Changes in the text: The authors have made no changes to the text regarding this comment as these data are already provided. The results of phase I, II and III trials with nintedanib are demonstrated in lines 85-97 and in the discussion, comparisons are made between the pilot study and those results (lines 201-206 and 249-255).

Comment 8: In the Methods section, line 97-98, the sentence is ambiguous. What platform was used for cell-free DNA testing, or was next generation sequencing performed on both tumour tissue and cell-free DNA from peripheral blood?
Reply 8: Targeted sequencing was performed on tumor tissue in a CLIA certified laboratory for the purpose of clinical care. Testing was performed through Tempus, Foundation Medicine, Caris and Washington University Genomics and Pathology Services (CLIA 26D0698285). Cell-free DNA was performed on peripheral blood through Guardant or Inivata. Either testing was permitted for this study.
Changes in the text: We added a line describing that targeted sequencing was performed of clinically significant cancer genes on page 8, lines 115-117.

Comment 9: Line 126-127 also requires grammatical revision: "Patients on strong P-gp inhibitors and inducers were monitored closely for potential drug interactions."
Reply 9: The grammatical error has been corrected.
Changes in the text: We have revised the sentences on line 144-145 on page 9.

Comment 10: Similarly, in the Results section, line 197, "….its role in angiogenesis may contribute towards immunotherapy resistance,…"
Reply 10: The grammatical error has been corrected.
Changes in the text: We have revised the sentence on line 214-215 on page 12 to say "resistance".

Comment 11: Without being mislead by prior study references, ref 30 from line 277-229 was actually powered to look for exacerbation-free survival differences, and PFS and OS improvements could well be chance findings. The limitations of the study is well-written.
Reply 11: We appreciate the reviewer's comments and agree with the reviewer that the primary endpoint in Otsubo, et al. (Reference 30) was exacerbation-free survival and have modified the text below.

Changes in text: Page 14 line 248-249 was amended to include that the study was powered for exacerbation-free survival.

Comment 12: Putting OS and PFS on the same chart in Fig 2 creates an illusion of benefit, and is not commonly done in literature nor suitable.
Reply 12: The overall survival and progression free survival curves have been separated into two figures. Figure 2A and Figure 2B.
Changes in text: The curves have been illustrated on separate figures. Figure 2A demonstrates the progression free survival. Figure 2B demonstrates the overall survival. The figure legends have been modified to reflect this change. The manuscript has been revised on page 11 lines 184-185 to reflect this change.

Reviewer C

Comment 1: Did patients has any other driver mutations?
Reply 1: The authors have added columns with the available PD-L1 expression and molecular alterations for each patient to Table 2. Not all patients had PD-L1 testing performed, those who did not have "not available" listed. PD-L1 testing was not standard in June 2015 when our study began enrolling.
Changes in the text: Two additional columns were added to Table 2. One for PD-L1 expression and one for molecular alterations with actionable alterations bolded. Please note *ERBB2 (HER2)* mutations are not bolded as they were added to the NCCN guidelines following data collection. Methods have been updated on page 8, lines 117-119, describing the PD-L1 testing performed.

Comment 2: I think the authors should explain why they chose this dosage.
Reply 2: In the phase I dose escalation trials with nintedanib monotherapy, the maximum tolerated dose was defined to be 250 mg twice daily in Caucasians and 200 mg twice daily in Japanese patients with a manageable safety profile in advanced cancer patients. Based on the overall safety profile, the recommended phase II dose for nintedanib as monotherapy was 200 mg bid. This is the same dose used in both phase III studies, LUME-Lung 1 and LUME-Lung 2.
Changes in the text: A statement has been added to reflect the rationale of the dosing on page 9, line 142-143.