

We are highly grateful to the comments on the manuscript, which showed the amount of time and thought invested into improving this work. Below are the comments and our response and indicators of where the corresponding revisions were made in the manuscript.

#### Reviewer 1

- At 'Author contributions', there is a name 'Chang J' who was not included in the author list. Is it a simple mistake?

**Response.** Thank you for pointing out this issue. As expected, inclusion of was a simple mistake. We have removed “Chang J” from the Author contributions section.

**Changes in the text.** TITLE PAGE, Author contributions.

- Can authors provide the reason why nivolumab was not selected as a second line treatment?

**Response.** Thank you for this comment. The reason for favoring MET inhibitor over immunotherapy after first-line chemotherapy does merit more discussion. Several factors went into the choice of crizotinib. Nivolumab was not covered by insurance in this setting back in May, which affects the economic burden on the patient. Also, there had been evidence suggesting reduced efficacy of immunotherapy in NSCLC patients carrying oncogenic drivers such as *EGFR* sensitizing mutations or *EML4-ALK* fusions. crizotinib was chosen over nivolumab after weighing these factors. We have added a brief justification for choosing crizotinib over nivolumab in the manuscript.

**Changes in the text.** OUTCOME AND FOLLOW-UP, paragraph 1, lines 9-13.

- page 3: 'poorly-differentiated' -> Because all other parts of the manuscript did not use a hyphen, it would be better to change it 'poorly differentiated' for consistency.

**Response.** We are grateful to the carefulness with which you examined our manuscript, which would really help improve the work. We have revised accordingly.

**Changes in the text.** CONCLUSION, line 1.

- page 7: 'Response Evaluation Criteria in Solid Tumors v.1.1' -> Because the authors used 'RECIST 1.1' three rows below, it would be better to change the sentence as 'Response Evaluation Criteria in Solid Tumors v.1.1 (RECIST 1.1)'

**Response.** Thank you. We apologize for the carelessness in this mistake. We have revised accordingly.

**Changes in the text.** OUTCOME AND FOLLOW-UP, paragraph 1, line 17.

- page 8: 'This is similar with the previous studies that ICIs are less effective in NSCLC with EGFR mutation or EML4-ALK fusion.' -> References should be provided.

**Response.** Again we are embarrassed for this negligence. The intended reference has been added in the revised manuscript.

**Changes in the text.** REFERENCES. reference no. 16.

#### Reviewer 2

1. (p.6, ll.1-4) Imaging examinations: There is no description of primary lung cancer.

**Response.** Thank you for pointing out this issue. We have added the description of the primary lung cancer in the imaging section, indicating its location in the right lower lobe of the lung.

**Changes in the text.** CASE PRESENTATION, *Imaging examinations*, lines 1-2.

2. (p.6, ll.5-10) Immunohistochemistry ... poorly differentiated NSCLC: This description should be made in more detail. What were the results of immunostaining of TTF-1, napsin A, CK5/6, p40? Although it is later described that histopathologic markers TTF-1, CK7, p40, and CDX2 were negative in p.8, l.7, these results only suggest that this tumor may not be adenocarcinoma derived from terminal respiratory unit, squamous cell carcinoma, invasive mucinous adenocarcinoma, and metastatic adenocarcinoma from the intestine. Evidence of poorly differentiated adenocarcinoma as they say is not sufficient. I suspect that this tumor may be putative large cell carcinoma, putative carcinosarcoma, and also may be neuroendocrine cell carcinoma. I hope the authors to present more information about the pathologic diagnosis and also representative histopathologic figure of the tumor.

**Response.** We have added the description of immunohistochemistry results in p.6. Regarding the representative histopathologic figure, we agree that such figures would help determine the tumor's histologic type. We have been asking our pathologist for these figures but unfortunately have not received a reply. We would therefore like to ask for a second round of revision, which hopefully allows us more time to track down these figures.

**Changes in the text.** CASE PRESENTATION, *Further diagnostic work-up*, lines 1-5.

3. (p.8, ll.20-21) This is similar with the previous studies that ...: Reference should be cited.

**Response.** We apologize for not including the intended reference. This mistake has been corrected in the revised manuscript.

**Changes in the text.** References, reference no. 16.

Reviewer 3

As stated by the authors in the introduction section, several cases and clinical studies have already been reported regarding the efficacy of crizotinib in targeting MET amplification, exon 14 skipping and certain rearrangements in NSCLC patients. I would like to see a review of all reported cases that discuss on the same problem.

An additional table with citing references would be appreciated to support that this is an unique rare case worth to be presented and published to raise the awareness of the clinician.

**Response.** We agree with this comment that summarizing the case reports of *MET*-altered NSCLC could help provide a more comprehensive background so readers could better appreciate the rarity of *MET* fusions. We have revised the manuscript to introduce the status quo on the efficacy of crizotinib in treating these patients. We also briefly introduce what has been learned about the prevalence of *MET* fusions in NSCLC.

Regarding the additional table, the suggested item is provided as Table 1 in the Table File, summarizing case reports of *MET* fusion-positive NSCLC patients.

**Changes in the text.** INTRODUCTION, lines 16-26. Table 1.

Please expand all abbreviations in the abstract section.

**Response.** Thank you for pointing out this issue. We have revised the abstract to make sure all abbreviations within were expanded.

**Changes in the text.** ABSTRACT, lines 1, 11, 12, and 14.

Wordings need to be corrected: Introduction: “The mesenchymal-epithelial transition factor gene (MET),” should be changed to “The mesenchymal-epithelial transition (MET) gene,”

**Response.** We apologize for this mistake. The corresponding text has been revised.

**Changes in the text.** INTRODUCTION. Paragraph 1, line 1.

The expansion of RECIST is not properly demonstrated in the outcome and follow-up section.

**Response.** We agree with this comment and have revised the manuscript to appropriately expand this abbreviation.

**Changes in the text.** OUTCOME AND FOLLOW-UP, paragraph 1, line 17.

Besides, the authors stated that “However, the disease progressed afterwards in May, 2019 as per RECIST 1.1.” A more detailed description of how the disease progressed afterwards is recommended, as this finally leads to mortality of the case.

**Response.** We have added Figure 2C to illustrate how the cancer progressed after response to crizotinib, before starting nivolumab therapy.

**Changes in the text.** OUTCOME AND FOLLOW-UP, paragraph 1, lines 19-22.

Please add a section in discussion section describing the potential side effects of crizotinib.

**Response.** Thank you for this comment. We have added in DISCUSSION descriptions of potential side effects of crizotinib, as suggested.

**Changes in the text.** DISCUSSION, paragraph 4.

Please modify figure 2 by inserting arrows to point the tumor mass in both panels. An additional panel indicating the disease progression after May, 2019 is suggested if available for comparison.

**Response.** We found both suggestions highly helpful. Regarding the indicator arrows, figure 2 has been accordingly modified. Radiologic images after May 2019 were also appended to Figure 2 for comparison.

**Changes in the text.** Figure 2.

We are grateful for the chance of a second review, which allowed more time for us to wait for our pathologist to provide us previous images and perform more experiments. We believe that the manuscript has benefit from the additional evidence for addressing the review and will address each comment below.

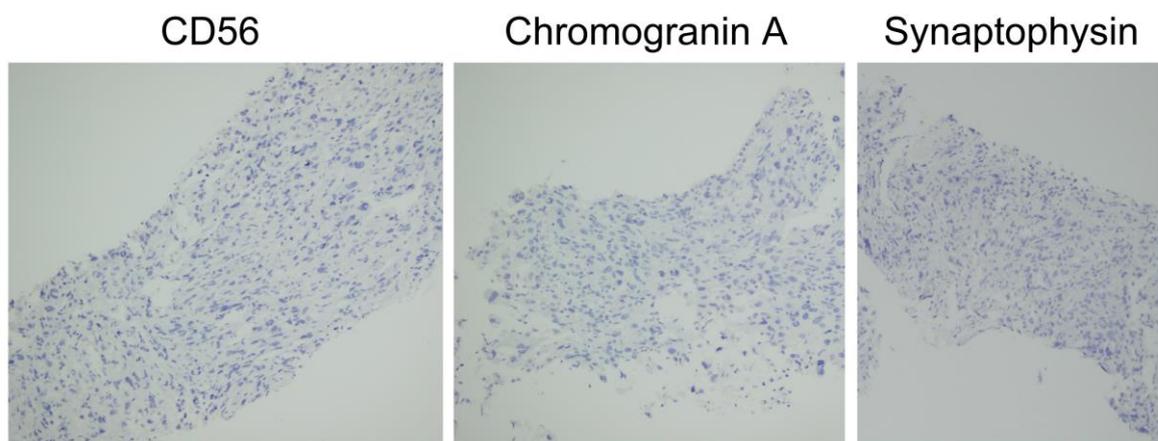
The authors responded to my previous comments to some extent. They say that they cannot receive a full reply from their pathologists. After understanding the situation, I want to point out some issues.

**Comment.** 1. AE1/AE3 (+) ... S-100 (-) (p.6, ll.3-4): Results of neuroendocrine markers, such as chromogranin, synaptophysin, and CD56, should be presented to exclude the possibility of neuroendocrine carcinoma/small cell carcinoma. By the way, CK18 (+) is described twice.

**Response.** Thank you for this comment. Our pathologist has completed immunohistochemistry staining of these makers, all of which were negative (please see figures below). We have added description of these results to the pathologic findings in the manuscript.

Also, the second “CK18 (+)” has been deleted.

**Changes in the text.** Page 6, line 2.



**Comment.** Other minor points. 2. chromatography (p.3, l.15): This may be “tomography.”

**Response.** Thank you for pointing out this mistake. We have corrected it in the text.

**Changes in the text.** Page 6, line 12.

**Comment.** 3. even received (p.3, l.17): despite receiving

**Response.** We have corrected this mistake in the text.

**Changes in the text.** Page 3, line 18.

**Comment.** 4. Table 1: References of text and Table 1 should be unified.

**Response.** Thank you for pointing out this issue. The inconsistent numbering was probably because Table 1 was originally uploaded as a separate file from the main text. We have fixed this issue by including the table in the main text file.

**Changes in the text.** Table 1 (pages 14-15).

**Comment.** 5. Figure 2A is not referred to in the text.

**Response.** We apologize for the carelessness. We have added main text reference to Figure 2A (now Figure 3A after inserting a histologic figure as Figure 1).

**Changes in the text.** Page 7, line 1.

**Comment.** 6. Base the (p.6, l.14): Based on the Additional comment: If histological figures get available, please show them.

**Response.** Thank you for raising this issue. We agree that presentation of histologic findings is important to the manuscript. The relevant hematoxylin and eosin staining results have been added as Figure 1 with corresponding legends.

**Changes in the text.** Page 5, line 27. Page 13, lines 2-3.