Author’s response to reviews

Title: High incidence and early onset of nivolumab-induced pneumonitis: four case reports and literature review

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Author’s response to reviews:

Dr. Mingzhou Guo

Editor, BMC Pulmonary Medicine

Re: Manuscript reference number PULM-D-17-00560R1

“High incidence and early onset of nivolumab-induced pneumonitis: four case reports and literature review“
January 5, 2018

Dear Dr. Mingzhou Guo:

Thank you for your letter concerning the decision and comment on our manuscript (PULM-D-17-00560R1). Based on the comments from the reviewers and the opinion from the associate editor, we revised our manuscript and gave a detailed description in “Response to reviews”. We hope that our manuscript is now acceptable for publication in BMC Pulmonary Medicine.

Sincerely,

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Reviewers’ comments:

Sulev Koks (Reviewer 1): I think this manuscript is very interesting and useful for practioners. It’s case report describing side effect of a new biologics.

As this side-effect is very common and present mansucript provides very detailed information, publishing of it is important for clinicians.

I do not have any critical comments.

Author’s response:
We sincerely appreciate the comment of Dr. Sulev Koks.

Miaozhu Li (Reviewer 2): In principle, I appreciate this work, but several major issues need to be addressed before it can reach the requirement for publication.

Here, I list my specific concerns for the manuscript below:

Major

Discussion and Conclusion: P9, Line 19 - Line24

1. I believe a 20% incidence rate for such adverse reactions means it might worth investigating, while we could not rule out the possibility that this is due to chance or other demographic factors since the sample size (20) is indeed small. I would suggest the authors add some extra discussions on why the 20 samples collected in the study which are representative for the population in general (so you might not need a large number of samples) and why such patterns shown in this data are particularly interesting.

Author’s response:

Thank you for your comment. We agree with the small scale study in this report. Unfortunately, we could undergo only 20 patients who were treated with nivolumab in our institute from October 2014 to July 2017, and as a result, all of them were retrospectively investigated in this report. On the other hand, patients with nivolumab-induced pneumonitis had many clinical characteristics such as its severity and CT scan image patterns similar to those reported previously. Thus, high incidence and early onset in four patients who had common clinical characteristics shown in this report were considered to be discriminative.

According to the reviewer’s comment, we added the following description in the section of “Introduction”:

Of 20 patients with malignant tumor who were treated with nivolumab from October 2014 to July 2017 at Tokyo Medical University Hachioji Medical Center, we encountered four cases of nivolumab-induced pneumonitis

2. Following the above question, is it possible to give more detailed information on the patient demographics of all the 20 samples in the study, in addition to the current four patients? I think this might help us see if the four patients are demographically different from the population and explain the unexpected high incidence rate of nivolumab-induced
pneumonitis. Family history, history of the illness or other complications might also influence the susceptibility to pneumonitis. It would be interested to know the effects of those risk factors if the authors also present them.

Author’s response:

Thank you for your comment. We agree with the importance of information of all 20 patients. However, there were no significant differences in demographical characteristics of the CT scan prior to nivolumab initiation between patients with and without nivolumab-induced pneumonitis. Notably, patients with pre-existing interstitial pneumonia are commonly known to highly develop drug-induced pneumonitis, whereas four patients with developed nivolumab-induced pneumonitis had no pre-existing interstitial pneumonia. Furthermore, in statistical analyses, there were no significant differences in clinicopathological characteristics between patients with and without nivolumab-induced pneumonitis, although data were not shown.

According to the reviewer’s comment, we added the following description in the section of “Discussion and Conclusion”:

All four patients had no pre-existing interstitial pneumonia as a potential risk factor for drug-induced pneumonitis. Furthermore, in statistical analyses (data not shown), there were no significant differences in clinicopathological characteristics between patients with and without nivolumab-induced pneumonitis.

In contrast, these four patients had some characteristics that were different from patients with nivolumab-induced pneumonitis in the previously published reports (Table 1).

P8 - P10

3. The three paragraphs included in this section are not organized reasonably logical. It seems to be easy for the readers to lose track of the point on discussion. I would suggest breaking them into smaller paragraphs. For each paragraph, start with a leading sentence pointing out a specific factor (such as age, early onset pattern) to discuss, focus on analyzing that particular aspect of interest and develop the arguments progressively, and conclude with a finishing sentence to emphasize the implications.

Author’s response:

We appreciate your comment. As described previously, there were no significant differences in clinicopathological characteristics between patients with and without nivolumab-induced pneumonitis. Furthermore, the comparison of the characteristics of nivolumab-induced pneumonitis between four patients in this report and those previously published reports were discussed in the section of “Discussion and Conclusion”.
To clarify the distinctive characteristics between both patient groups, we modified the writing structure in the section of “Discussion and Conclusion”: The paragraph was newly created from the sentence of “These cases had some characteristics that were different from the previously published reports (Table 1).” Furthermore, this sentence was replaced with “In contrast, these four patients had some characteristics that were different from patients with nivolumab-induced pneumonitis in the previously published reports (Table 1).”

4. I guess it can be useful to discuss if such immune-related adverse reactions are population (race/gene) specific, in addition to the other factors (age, previous treatment, etc.) since this would be an important factor to consider in pharmacovigilance and trial design. Maybe it is still an open problem for such drugs, but I would expect to see at least some discussions or evidence from previous studies on this.

Author’s response:

Thank you for the comment. We agree with the possibility that the ethnicity is associated with the susceptibility of drug-induced pneumonitis. Meanwhile, clinical factors of affected four patients such as age and sex were shown in Table 1, and the limited number of affected patients with the heavy treatment history and many treatment regimens failed to clarify the influence of previous treatment, even in the statistical analysis.

However, according to the reviewer’s suggestion, we added the following description in the section of “Discussion and Conclusion” and the citation [12]:

As the previous study suggests higher incidence of drug-induced pneumonitis in Japanese patients, the ethnicity also may impact on nivolumab-induced pneumonitis [12].

Minor

1. page 2 line 26. arised -> occurred
2. page 3 line 39. meta-analytic study -> meta-analysis
3. page 4 line 19. nivolmab -> nivolumab
4. page 5 line 56. As 4th-line treatment -> As a fourth-line treatment
5. page 7 line 56. in pyriform sinus -> in the pyriform sinus
6. page 9 line 27. male sex and smoking history -> male gender and smoking history
7. page 9 line 39. sex -> gender
8. page 10 line 22. similar wide range -> similarly wide range

Author’s response:

Thank you for your notice. According to the comment, we changed all words.

Michael A. Jantz (Reviewer 3): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

1. Abstract, line 24: change "Twenty percent of patients..." to "In our series, 20% of patients who were treated with nivolumab developed pneumonitis, all of which arised approximately 2 weeks after the initiation of nivolumab treatment. Prompt recognition of the nivolumab-induced pneumonitis allowed for successful resolution.

Author’s response:

Thank you for the comment. According to your suggestion, we changed the description as you indicated. The word, “arised” was replaced with “occurred” as the reviewer 1 indicated.

2. Abstract line 31: change "presented predominant" to "demonstrated predominantly"

Author’s response:

Thank you for the comment. According to your suggestion, we changed the description as you indicated.

3. Background, line 46: Change this to Furthermore, this report showed that pneumonitis related to nivolumab monotherapy occurred in 4.1% (1.4-8.5%) of patients with NSCLC with all grades and 1.7% (0-3.4%) with ≥ grade 3 toxicity while pneumonitis occurred in 1.5% (0-1.9%) of patients with MM at all grades and 0.1% (0-0.3%) with ≥ grade 3 toxicity.

Author’s response:

Thank you for the comment. According to your suggestion, we changed the description as follows: Furthermore, this report showed that pneumonitis related to nivolumab monotherapy occurred in 4.1% (1.4-8.5%) of patients with NSCLC with all grades and 1.7% (0-3.4%) with ≥
grade 3 toxicity, while pneumonitis occurred in 1.5% (0-1.9%) of patients with MM at all grades and 0.1% (0-0.3%) with ≥ grade 3 toxicity.

4. Background, line 58: Delete "On the other hand"

Author’s response:

Thank you for the comment. According to your suggestion, we deleted the description as you indicated.

5. Patient 1, line 49: change "MM metastasized..." to "The patient developed metastasis..."

Author’s response:

Thank you for the comment. According to your suggestion, we changed the description as you indicated.

6. Patient 2, line 36: remove PLE

Author’s response:

Thank you for the comment. According to your suggestion, we deleted the description as you indicated.

7. Patient 2, line 58: can remove "for lung cancer (rT2aN2M1b; PLE, OSS)"

Author’s response:

Thank you for the comment. According to your suggestion, we changed the description to “for lung cancer (rT2aN2M1b)”. The description of the clinical stage based on the TNM staging was left because a re-evaluation changed the stage at the time of nivolumab initiation.

8. Patient 2: Please add information about the patient's respiratory failure

Author’s response:

Thank you for the comment. According to your suggestion, we added the description of “pneumonitis-induced” in front of “respiratory failure” as information.
9. Patient 3, line 46: can delete PLE, PUL

Author’s response:

Thank you for the comment. According to your suggestion, we deleted the description as you indicated.

10. Patient 3, line 9: can delete PLE, PUL, BRA, OSS, ADR

Author’s response:

Thank you for the comment. According to your suggestion, we deleted the description as you indicated.

11. Patient 4, line 56: Change "The biopsy of tumor lesions..." After biopsy of lesions in the pyriform sinus of the hypopharynx, the patient was diagnosed with a hypopharyngeal squamous cell carcinoma (cT3N2cM0).

Author’s response:

Thank you for the comment. According to your suggestion, we changed the description as you indicated.

12. Patient 4: please add information about the patients respiratory insufficiency

Author’s response:

Thank you for the comment. According to your suggestion, we changed the description to show the cause of respiratory insufficiency as follows: respiratory insufficiency caused by nivolumab-induced pneumonitis (grade 3).

13. Discussion, line 14: Change "On the other hand, four..." to "In contrast, four..."

Author’s response:

Thank you for the comment. According to your suggestion, we changed the description as you indicated.
14. Discussion, line 5: The authors state that the severity of pneumonitis was mild in all patients but 3 patients were described as having grade 3 pneumonitis which is severe. Please clarify.

Author’s response:

Thank you for the comment. We agree with your suggestion. According to your indication, we changed the description of “The severity of pneumonitis was mild” to that of “Pneumonitis in our report was promptly ameliorated”.

15. Discussion, line 24: change "including predominant COP patterns" to "with COP pattern being the most common"

Author’s response:

Thank you for the comment. According to your suggestion, we changed the description as you indicated.

All changes and additional descriptions were underlined in the manuscript.