Reviewer’s report

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

Version: 1 Date: 02 Jan 2018

Reviewer: Miaozhu Li

Reviewer's report:

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.

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.

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.

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.

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

Date: Jan 1, 2018

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Unable to assess
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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