Author's response to reviews

Title: High-incidence of PTEN mutations in Chinese patients with primary small cell carcinoma of the esophagus

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Author's response to reviews: see over
Dear Editors and Reviewers,

Thank you very much for your consideration and the reviewers for their helpful comments and advice. We would like to re-submit the revised manuscript entitled “High-incidence of PTEN mutations in Chinese patients with primary small cell carcinoma of the esophagus”, which has been rewritten and improved according to the comments of the reviewers. All changes are highlighted in red in the revised manuscript. Point-by-point responses to the comments are listed below this letter.

We shall look forward to hearing from you at your earliest convenience.

With best wishes,
Yours sincerely,

Ge Wang and Zhimin Zhang

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Following are our response to reviewers’ comments:

Reviewer #1: Professor Karen Pollok

Major Compulsory Revisions:
1. Q: Page 3: Please clarify this sentence. Whatever, it is logical to consider using EGFR mutations as a therapeutic modality in esophageal cancer treatment.

   The authors state that EGFR mutations are low in esophageal cancers but they still want to molecularly target? Do the authors mean to state that while this is an attractive target in other cancers, its incidence is low in esophageal cancers?

   A: Thank you very much for your question. Because whether the efficacy of the EGFR TKI gefitinib exist in patients of esophageal cancer remains unclear, this sentence we state here is not a accurate statement, and we have revised in the manuscript and added a sentence to clearly.
2. Q: Page 11, the authors state: Furthermore, the only one patient with PSCCE identified for EGFR mutation was L858R missense mutation in exon 21, which termed gefitinib-associated mutations. This suggests the gefitinib-based small molecular target therapy might be appropriately applied in treating PSCCE as well.
This statement is not clear regarding use of gefitinib-based therapy. Since only one patient had the L858R missense mutation, do the authors mean to say that gefitinib-based therapy would be appropriate for this patient but not other PSCCE patients that do not harbor this specific mutation?

A: Sorry for my carelessness. We mean to state that gefitinib-based therapy might be appropriate for PSCCE patients that harbor this specific mutation. We have revised in the manuscript.

3. Q: Page 14, the authors state:
Furthermore, EGFR mutations in PSCCE are rare but do exist, especially gefitinib associated mutations such as L858R, and thus the gefitinib-based gene target therapy but not KRAS and PIK3CA gene, should be included in this carcinoma treatment regimens.
The authors need to clarify this sentence. Please confirm that this is a more accurate statement: Furthermore, EGFR mutations in PSCCE are rare but do exist, especially gefitinib associated mutations such as L858R, and thus the gefitinib-based gene target therapy but not KRAS and PIK3CA gene, should be included in carcinoma treatment regimens for patients that harbor the L858R mutation.

A: Thank you very much for raising this important point. Sorry for my carelessness, and we have clarified the sentence according to your advice.

Minor Essential Revisions:

4. Q: Summary: The word data is plural. Datas should be “data”
The authors use the abbreviation ESCC. Please provide the complete term the first time the abbreviation is used.

A: Thank you very much for your question. We have revised in my manuscript and provide the complete term the first time the abbreviation is used.

5. Q: The authors comment: Whatever, PTEN is another target gene in esophageal cancer treatment.
One option for clarity purposes is to rephrase the sentence:
These data suggest that PTEN could be another target gene in esophageal cancer treatment.

A: Thank you very much for raising this important point. We have clarified the sentence according to your advice.

6. Q: The authors comment:
Given that targeting of the EGFR is a potentially interesting approach in the therapy of PSCCE,
the current lack of data on these genes mutations associated with EGFR in this tumor type, except a few case reports which lacks detailed description of the type of esophageal cancer investigated, we were motivated to investigate this topic in this study. Thus the distribution of these genes mutations in PSCCE still remains uncertain and this study which is the first in the world, to our knowledge will help to clarify.

These sentences need to be rewritten for clarity purposes.

A: Thank you very much for your question. We have clarified these sentences according to your advice.

7. Q: Page 4, Clinical samples, the authors comment:

In the histopathologic examination of biopsy materials belonging to esophagus have taken endoscopically from the 38 patients.

This sentence should be revised for clarity:

Esophageal biopsies were obtained via endoscopy from 38 patients and histopathology performed.

A: Thank you very much for your question. We have clarified the sentence according to your advice.

8. Q: Page 4, figure 1 legend:

Change “immunereactivity” to “immunoreactivity.”

Page 7:

The authors state: Moreover, there are not significance of the association between PTEN mutations and clinical pathologic characteristics, e.g. gender, age, tumor location and TNM stage.

The sentence should be revised for clarity:

Moreover, there are no significant associations between PTEN mutations and clinical pathologic characteristics, e.g. gender, age, tumor location and TNM stage.

A: Thank you very much for your question. We have clarified the sentence according to your advice.

9. Q: The authors comment:

The reasons for the discrepancy were that there might be an ethnic difference in the distribution of the EGFR mutations in EC and the different sensitivity of technique for mutation detection.

The sentence should be revised for clarity:

Possible reasons for the discrepancy are that ethnic differences in the distribution of the EGFR mutations in EC may exist, and the sensitivity of technique used for mutation detection differ.

Page 13, the authors state:

First, the data presented here, such as treatment details survival and disease control etc, are not enough for us to draw firm conclusions about the mutations of these genes may serve as a
molecular classifier and their association with TKIs responsiveness in PSCCE and…
Is this what the authors wish to communicate?
First, the data presented here, such as treatment details, survival, and disease control are not sufficient to draw firm conclusions about whether the mutations of these genes can serve as a molecular classifier that correlates with TKIs responsiveness in PSCCE and…

A: Thank you very much for your question. We have clarified these sentences according to your advice.

10. Q: The axes in the amplification plots for PTEN mutations in Figure 2 are blurry and need to be improved.

A: Thank you very much for your question. We have improved the quality of Figure 2 in the manuscript according to your advice.

11. Q: **Quality of written English:** Needs some language corrections before being published

A: We have made correction on the English usage in our manuscript and have further revised by a native English speaking person.

**Reviewer #2: Professor Huaitian Liu**

1. Q: There are not significance of the association between PTEN mutations and clinical pathologic characteristics, e.g. gender, age, tumor location and TNM stage. PTEN with putative tumor suppressing is frequently mutated in many cancers. Do they test the association between PTEN mutations and tumor size? Zhang et al used #2 to assess the relationship between PTEN mutations and each of the clinical and pathologic parameters. Are all P values two-sided, and P < 0.05 was considered significant?

A: Thank you very much for raising this important point. We have not test the association between PTEN mutations and tumor size, because we have not the informations about tumor size of these patients. And we have added a sentence, “P-values < 0.05 were considered as statistically significant” to clearly define heterogeneity in table. 2.

2. Q: Page 13: It is necessary to point out that the incidence of PTEN mutation was relatively high among the male patients. Male 12/31(38.71%) vs Female 2/7 (28.57). It’s hard to draw the conclusion given relatively smaller number from female.

A: Thank you very much for raising this important point. We also considered this question in the course of analysis and we agree with your viewpoint very much. We have deleted the conclusion in the manuscript.

3. Q: Typos and other
Page 2: “Clinical–pathological datas” change to “Clinical–pathological data”
Page 11: 165–200/100,000 change to “165–200/100,000”
Page 11: “many publications report have indicated” change “many publications reports have
indicated”
Page 11: “which consistent with data” change to “which is consistent with data”
Page 13: “Our work” change to “our work”.

A: Thank you very much for your question, and your comments help us improve our manuscript. We have clarified these sentences according to your advice. Thank you very much!

4. Q: Quality of written English: Needs some language corrections before being published

A: We have made correction on the English usage in our manuscript and have further revised by a native English speaking person.