Reviewer's report

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

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Reviewer: Karen Pollok

Reviewer's report:

Zhang et al describe the molecular characterization of primary small cell carcinoma of the esophagus (PSCCE) specimens from 38 patients of Chinese decent. It is commendable that 38 specimens were available for analysis since PSCCE comprises less than 2% of all esophageal cancers. The new information presented is that a high incidence of PTEN mutations exist in PSCCE in this particular patient population. This has not been reported in the literature previously and warrants publication. There are some clarifications in data interpretation and revisions of sentence structure that need to be addressed prior to publication.

Major Compulsory Revisions:

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?

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?

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.

Minor Essential Revisions:

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.

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.

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.

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.

Page 4, figure 1 legend:
Change “immunereactivity” to “immunoreactivity.”

Page 7:
The authors state:
Moreover, there are no significant associations 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.

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 sufficient 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...

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

**Level of interest:** An article of importance in its field

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

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests.