Reviewer's report

Title: Co-mutations of TP53 and KRAS Serve as Potential Biomarkers for Immune Checkpoint Blockade in Squamous-Cell Non-small Cell Lung Cancer: A Case Report

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Reviewer: Jiehui Deng

Reviewer's report:

In this manuscript, the authors reported the treatment of a squamous cell NSCLC patient who has KRAS/TP53 co-mutation showed partial response to pembrolizumab combined with gemcitabine. This particular case showed consistent result with what observed in the previous clinical studies, based on the premise that KRAS/TP53 co-mutated squamous lung cancer patient tumors have high PD-L1 expression, high TMB and thus response to anti-PD1 treatment (Wang et al, 2018, PMID: 28039262). This case report is interesting and meaningful in terms of understanding whether and which patient will respond to immune checkpoint blockade, however, it is not very clear at this point, whether this patient responses to the treatment because of PD-L1 level or tumor mutational burden (TMB). It seems neither one is the answer, since this patient has weak PD-L1 expression in the tumor and low TMB of 3.2 mutations/Mb. Which makes this case study even more interesting in terms of the underlining mechanism. Below are detailed comments for this manuscript:

1. The authors claimed this patient has weakly stained PD-L1 (line 31), and MMR-related genes were strongly stained by IHC. This is critical data for the study and should be shown in the figures.

2. For the TMB analysis, more detailed description and criteria of how the TMB number was culled. The method and standard for the TMB analysis is critical for interpretation of the result.

3. There are only few oncogenic driver genes including KRAS, TP53, EGFR, STK11 were mentioned for the NGS sequencing of patient genome. What are the other genes included in this 416 genes panel? Any DNA repair related genes that related to tumor mutation burden included?

4. The authors need to clarify what is the similarity and differences of this patient sample comparing with previous reported cases that also have KRAS/TP53 mutation. More importantly, what could be the potential explanation that this patient responded to immune checkpoint blockade.
5. This patient responded to gemcitabine when combined with pembrolizumab, but not rh-endostain combined with docetaxel. The authors should discuss the differences between these chemotherapy drugs and clinical usage. Furthermore, whether the effect observed is simply come from anti-PD1 treatment or due to the use of different chemotherapy drug.

6. In the conclusion, the authors claimed KRAS/TP53 co-mutation to be predicting factor for responses to anti-PD1 treatment. Since the authors only reported one case, there is not enough evidence to confirm KRAS/TP53 co-mutation as response marker to immune checkpoint blockade.

**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.

Yes

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

No

**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.

Not relevant to this manuscript

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