**Peer Review File**

Article Information: https://dx.doi.org/10.21037/jgo-23-418

**Reviewer A**

There are still few large-scale papers on the relationship between PD-L1 expression and paclitaxel plus ramucirumab, and I think this is a valuable study.

1. Since the description of the patient's background is insufficient, please add it. (such as PS, history of gastrectomy, presence/absence of liver metastasis/peritoneal dissemination/ascites, HER2 status, MSI status)

Answer > I have added them to the baseline characteristics.

2. Please describe whether there is any difference in patient background for each PD-L1 expression.

Answer > I have added them to the baseline characteristics.

3. You mentioned that "In our study, 4 patients with a PD-L1 CPS of 10 or more received an ICI after treatment with ramucirumab plus paclitaxel, and 3 of those 4 patients discontinued the drug 170 after a few months due to disease progression. However, one patient maintained a PR for more than 2 years of continuous ICI treatment." Post-treatment after paclitaxel plus ramucirumab is related to OS, so please describe in more detail, including data from other cases. (How many patients received what kind of treatment in each PD-L1 group, etc.).

Answer > I have added them to the supplementary materials.

**Reviewer B**

Interesting hypothesis in connecting PDL1 expression and anti-VEGF agents. You may want to give some examples of GI cancers where anti-VEGF and anti-PD1 therapies are used together.

1. You may want to discuss TPS vs CPS, and also how there is discrepancy between the scoring from one pathologist to another, these issues have become hot topic.

Answer > The comparison between TPS and CPS was challenging due to insufficient our dataset. Instead, in this study, I have added a comment in the discussion section regarding the comparison of the PD-L1 CPS used in this research, which is 22C3, to the 28-8 used in the current nivolumab plus XELOX regimen.

"Lastly, it is important to note that the PD-L1 CPS diagnostic tool is 22C3. Since the PD-L1

CPS score has not been validated for each immunohistochemistry method, there is a possibility that the approval criteria for nivolumab plus XELOX may differ when relying on the PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako, Santa Clara, CA, USA)(8), which is currently in use. Specifically, the 28-8 assay is known to have a PD-L1 cutoff value higher than that of 22C3(1), thus necessitating additional studies to address this discrepancy."

2. The analysis is not clear on proving whether PDL1 is predictive of response, or merely prognostic regardless of anti-VEGF. Do you have patients who received other 2nd line chemo regimens, such as docetaxel, paclitaxel without anti-VEGF, ramucirumab alone, or irinotecan? If the same PDL1 CPS 10 cutoff is seen in ramucirumumab, then that would support your hypothesis. If the same PDL1 CPS cutoff is seen in other chemos, then perhaps CPS 10 is more prognostic, but if this is not seen, then it would support your hypothesis of predictive of response from ramucirumumab.

Answer > Through additional analysis, we found that there was no significant difference in survival outcomes when ICI was used after ram/taxol or when cytotoxic chemotherapy was employed, even at a PD-L1 CPS cutoff of 10. Therefore, we have added a discussion section to emphasize that PD-L1 CPS is a meaningful survival predictor when using ram/taxol (supplementary material attached).

"Moreover, when assessing the survival outcomes of patients who underwent immune checkpoint inhibitor (ICI) therapy or cytotoxic chemotherapy subsequent to second-line administration of ramucirumab plus paclitaxel, no significant disparity was observed between the two cohorts when categorized by a PD-L1 cutoff of 10. This implies that the PD-L1 CPS cutoff value of 10 might delineate a more distinctive demarcation among patients subjected to the ramucirumab plus paclitaxel. These findings suggest that a PD-L1 CPS cutoff of 10 might be a novel biomarker to predict the survival of patients who receive ramucirumab plus paclitaxel to treat AGC."

3. The study is influenced by one receiving nivolumab 1st line and 4 receiving ICI third line. I assume those 4 probably have high PDL1 score. Please include post-treatment ICI info in the results in addition to discussion.

Answer > I have added the content regarding post-treatment ICI to the discussion section.

"However, one patient maintained a PR for more than 2 years of continuous ICI treatment(Supplementary table 1 and figure 2). And, It was apparent that patients who demonstrated a response lasting beyond a span of 2 years showed a notably elevated PD-L1 CPS score of 80."

4. Please include numbers at risk in the x axis for figures 1 and 2 to show the sample size clearly.

Answer > I have included the "Numbers at risk" section.

**Reviewer C**

The main findings are that ORR, PFS, and OS seem to improve with high (vs low) PDL1 expression, and this becomes more pronounced at the CPS 10 cutoff. However, there are only 18-19 pts with CPS 10+. The results seem a bit unstable. The authors should do a better of reporting the precise numbers and statistical variation.

1. The authors should include a CONSORT diagram of the number of pts that are in their database for gastric cancer, and how they arrived at the 117 eligible pts – showing the reason for exclusion and number of exclusion. The denominator of the original number is not reported.

Answer > I have added the CONSORT diagram related to the 543 patients who received ramucirumab plus paclitaxel as a practice, and among them, 117 patients who underwent PD-L1 testing, in the supplementary material.

2. Were responses confirmed vs unconfirmed? This should be reported in the manuscript.

Answer > The response has been confirmed.

3. Need to report 95% CI for all their ORR data. I see 95% CI for the PFS and OS data.

Answer > I have included the 95% confidence intervals.

4. For all the KMs, the HRs with 95% CI's should be reported within the graphic itself, just as they report the p value and median OS. The 95% CI for the median OS should also be reported within the graphic itself. Without the confidence intervals, the graphic can be a bit misleading. Also, need to add two rows beneath each set of curves showing the number of pts still remaining at each time point.

Answer > I have also added the 95% confidence intervals to the Kaplan-Meier curve.

**Reviewer D**

Choi et al. investigated the prognostic relevance of the PD-L1 expression status in the effect of ramucirumab (Ram) plus paclitaxel (Pac) for the 2nd-line treatment of advanced gastric cancer. They reported that the PD-L1 expression level of > 10% by combined positive score (CPS) can be a predictor of good response to the Ram/Pac therapy.
This study can be a good pilot study of response predictor of the 2nd-line Ram/Pac therapy. To improve the manuscript, I have some comments.
Major points;

1. (l.86) A total of 501 samples were collected for PD-L1 expression analysis. On the other hand, a number of patients was 117. Please specify how PD-L1 status was

determined by using plural samples per patient.

Answer > I have removed the item related to sample count as there was an error in it.

2. (ll.106) PFS was determined from the start of Ram/Pac therapy to disease progression or death from any cause, which is not appropriate. It should be from the start of Ram/Pax therapy to disease progression or cancer-specific death.
3. (ll.107) OS was determined from the start of Ram/Pax therapy to death from any cause, which is not appropriate. It should be from the start of Ram/Pax therapy to cancer-specific death.

Answer > I have made the necessary revisions to the PFS section.

4. (Tables 2 and 3, Figures 1 and 2) The authors compared tumor response and survival curves between PD-L1 CPS <1 and >= 1, between < 5 and >= 5, and between < 10 and >= 10. When I compare tumor response rate between < 1 (5/31) and >= 10 (6/18) in Table 2, there is no statistical significance by Fisher's exact test (p = 0.286). Although the authors managed to get a statistical significance by devising a statistical process, I cannot help thinking that the effect of PD-L1 expression may be limited. How about comparing among CPS < 1, 1 =< CPS < 10 and CPS >= 10?
5. (Table 2) A sum of patients responded and not responded is 101. What were the results of the remaining 16 patients?

Answer > We were unable to perform response evaluation due to reasons such as transferring patients to other hospitals or loss to follow-up.

Minor points;
6. (l.130) Among the 19: This must be 18.
7. (l.137) p = 0.92: This must be 0.93.
8. Please explain associations between CPS and clinicopathologic parameters, such as histologic grade.

Answer > I have made all the necessary corrections to the all minor points.