

30th August 2022

Dear The Editors of Cancers,

RE: **cancers-1821556: 'Incorporating immunotherapy in the management of gastric cancer: molecular and clinical implications'**

We appreciate your willingness to consider an updated version and we would like to thank the reviewers for their effort and time spent on the paper and detailing views that have been very helpful. In doing so, we are sending you our revised version. More specifically, in response to the reviewers' specific comments:

Reviewer #1

We appreciate the reviewer's comments that: *'This is a well written paper'* and that *'...it is very straightforward and it summarizes almost everything related to the topic very clearly'*. Following the reviewer's suggestions, as explained below, we have clarified the issues that were raised in our revised version. More precisely:

1) The abstract and introduction prepare the reader for a review about immunotherapies in GC; however, significant part of the paper tackle GC etiology. I suggest rephrasing the aims of this review.

As suggested by the Reviewer, we have now rephrased the aims of this review by editing the abstract and the introduction accordingly.

2) Figure 2 is not coherent. It shows mode of entry for EBV, whereas for *H. pylori*, it shows the mode of action. I suggest illustrating both mode of entry and mode of action for EBV and *H. pylori*.

*We would like to thank the reviewer for this constructive suggestion. As requested, we have now implemented the changes. We agree that including both mode of entry and mode of action for *H. pylori* and EBV may indeed provide a clearer overview. (Line 277).*

3) Figure 3 is confusing and the "peptide" is not explained in the legend. I suggest dividing the figure into two panels; one showing the interaction between tumor cell and T-cell in normal state, and the other panel showing these cells in the presence of PD-1 and PD-L1 inhibitors.

Thank you for pointing this out. We have now edited Figure 3 accordingly, by dividing it into two panels. (Line 503).

4) The paper discusses thoroughly the effects of immunotherapy on GC in a biased way as the authors did not talk about the side-effects of such approach. Along with targeting the cancer, immunocomprimization can be very problematic. It is worth addressing the limitations and draw-backs of immunotherapy as well.

We would like to thank you for this observation and suggestion. To make this aspect clearer we have introduced the following paragraph at the beginning of paragraph 9 (Line 496):

"Over the last few years, immunotherapy has been actively incorporated as part of first and later lines of systemic treatment for advanced gastric cancer. PD-1 inhibitors have been shown to significantly improve efficacy in several large phase III trials when added to platinum-based chemotherapy, which has for many years been the standard of care in the first line setting for metastatic GC (Figure 3). In this section, we aim to present clinical research data that support a potentially prognostic, as well as predictive role for PD-L1 expression in gastric cancer, and finally present up to date results from large scale, phase III clinical trials, that have investigated the efficacy of PD-1/PD-L1 inhibitors in clinical practice. The description of toxicity of PD-1/PD-L1 inhibitors in gastric cancer trials is not within the scope of this work, as this has been extensively described elsewhere, and does not seem to differ to toxicity observed from the same agents in other tumour types."

5) The English in the abstract and introduction needs revision for sentence structure.

As suggested, we have now revised the English in the abstract and introduction.

Reviewer #2

We would like to thank the reviewer for the comment that this is: '*... a comprehensive and interesting review*' and that: '*The manuscript is of interest*'. We appreciate the reviewer's comments, which we addressed as described below:

1) I feel the manuscript has been organized and drafted mostly as a qualitative review, which is fine. I would, however, try to improve the methodology employed.

Following the Reviewer's suggestions to improve the methodology employed in this review, Please see the responses below for point 2, 3 and 4.

2) Please refer to the PICOTS criteria and frame populations, intervention(s), comparator(s), outcomes, timing, setting.

3) Please provide details of the search strategy employed in the present review paper,

4) Please provide details in the search strategy. I would suggest referring to the PRISMA criteria (please add a PRISMA flow-chart).

Thank you for your suggestions. This manuscript consists of a detailed narrative description of the most significant phase III clinical trials which have investigated a role for modern immunotherapy in the management of gastric cancer patients, in both previously treated, and treatment-naïve patients. We feel that the proposed PICOTS and PRISMA criteria are far more relevant for a manuscript that would aim to conduct a systematic review or meta-analysis, which is not the scope of our current review.

5) I would suggest reducing the textual part and add tables to wrap up the main findings and help the reader navigating the data presented.

Thank you for this comment. We have already included a table summarizing the results of the most significant large scale clinical trials of immunotherapy in gastric cancer. Due to the narrative nature of our manuscript, we feel that there is no effective way to reduce the textual part, and instead include this information in further tables embedded within the manuscript.

We believe that the manuscript is now significantly improved following the recommendations of the reviewers and that our paper is now hopefully acceptable for publication at Cancers. We would be happy to make any further changes required should you request them.

Yours truly,



Prof Georgios Giamas on behalf of the authors