Paris, 10th May 2018

Dear Editor,

We would like to thank you and the Reviewers for their very helpful comments and suggestions. We attach a revised version of our manuscript #39136 with tracked-in-red changes in the body of the text. Please find below the point-by-point responses to the Reviewer's comments.

Editor's revisions:

1. Please find enclose language certification.
2. Title: *Please do not use italics in the title.*

We removed the abbreviation. "Immune therapies in pancreatic ductal adenocarcinoma: where are we now?"

3. Please find enclose the audio file describing the final core tip.
4. Page 1: *No blank between "cancers" and "[3,4]" Please check throughout the article*

The blanks before references have been removed throughout the article.

5. References: PMID numbers, DOI names and coding system have been checked.
6. Illustrations, tables, abbreviations and italics: we followed formatting instructions.

Reviewer's code: 04008867

1. *Most comments/edits are just style or grammar.*

We have corrected errors in style or grammar and provided language certification.

2. *Figure 1: I don't think these diagrams are particularly helpful as is. They seem similar to the ones widely available through a Google search. The M2 macrophage is the role that is not so clear. You could do more with showing what that cell does in the microenvironment. Also add additional text in the caption.*

We provided detailed caption to make the Figure more informative: "Cells of the immune system express several surface molecules that are important for immune surveillance and regulation of the immune response.
TCR is expressed by T cells; it is an antigen-specific molecule that is unique to each T cell clone. MHC molecule is expressed by antigen-presenting cells (e.g. DC) and display a potential tumor antigen for recognition by the specific TCR.
Left panel: When an antigen presented in the context of MHC is recognized by the TCR, interaction of CD28 (expressed by T cell) with B7 (CD80/CD86) molecules provide a co-stimulatory signal leading to T-cell activation. However, depending on the conditions and microenvironment, these T cells can also express various levels of CTLA-4, a regulatory receptor (immune checkpoint) with a higher binding affinity for B7 than CD28. Therefore, when CTLA-4 is available at the cell surface, it successfully competes for binding with B7, removing the co-stimulatory signal and leading to T-cell downregulation. Tumor cells can then escape the T cell cytotoxic effect (immune evasion). CTLA-4 blockade affects the immune priming phase occurring in the lymph node, by supporting the activation and proliferation of a higher number of effector T cells, regardless of TCR specificity, and by reducing Treg-mediated suppression of T-cell responses.
Right panel: T cells also express PD-1 receptor, which has the potential to induce a programmed-death cascade in T cells that mistakenly react to host cells and thereby maintaining self-tolerance. PD-1 ligand, PD-L1, is used by tumor cells to engage the PD-1 receptor and switch off the reaction, inducing immune tolerance to the MHC-presented antigen. PD-L1 can also be expressed by stromal cells (e.g. M2 macrophages). PD-1 blockade works during the effector phase in peripheral tissues (tumor) to restore the immune function of "exhausted" T cells that have been turned off following extended or high levels of antigen exposure."

3. *Figure 2. What are the circles with blue, red, and orange outlines ? Is that supposed to represent immunogenicity ? Need more explanation in the caption*

We provided detailed caption to make the Figure more informative: "The circle outlines the three steps of the cancer-immunity cycle: (1) immunogenicity (yellow), (2) T-cell recruitment and (3) activation. PDAC resistance to immune therapy is due to the combination of several factors: (1) low tumor immunogenicity, with a low mutation rate and low neaoantigen burden compared to other tumors (e.g.

melanoma); (2) low T-cell recruitment and (3) activation: the dense desmoplastic stroma generates high interstitial pressure; this results in poor tumor perfusion and intra-tumor hypoxia, which in turn activates fibroblasts to release immunosuppressive cytokines (e.g. TGFβ, IL-6, CSF1 = "chemical barrier") that lead to the recruitment of immunosuppressive cells (M2 macrophages, TREG, MDSC) and exclusion and anergy of effector T cells."

4. *Table 1. You should probably add a column, or include in this column, the intent of therapy (advanced PDAC would be palliative, and resected PDAC I'm guessing means adjuvant ? And if it's second-line vs. frontline therapy)*

We have specified "adjuvant" or "neoadjuvant" setting for resected PDAC and "first-line" or "pre-treated" for advanced PDAC.

Are you intentionally distinguishing between «No objective response »and «stable disease »? To be consistent, I would say, «Best response = progression of disease »to make it clear that the people with no objective response did worse than the one who had stable disease.

We have homogenized by considering only the objective response rate in all the studies.

I think you are missing the partial responses.

This information is not provided in the conference abstract (only data available from this study).

Reviewer's code: 00646291

1. *The quality of the review could benefit from restructuring the different sections indicating the introduction as number 1 and then the "Results of immune therapies in PDAC" was included in the section entitled "Methods" and the outcomes of the clinical trials were described in a separate section entitled "Results". The subsections "Reasons why checkpoint inhibitor (CPI) monotherapies failed to show any activity in PDAC" and "Research Challenges" could be combined in one section entitled "Discussion" and the "Rethink clinical trials" and "Conclusions " in a section entitled "Conclusions and future directions"*

Thanks for this valuable suggestion. We have restructured the sections as followed:

1) Introduction
2) Results: failure of immune monotherapies in PDAC
3) Discussion
3.1 Reasons why checkpoint inhibitor (CPI) monotherapies failed to show any activity in PDAC
3.2 Research challenges
4) Conclusions
4.1 Rethink current clinical trial approaches
4.2 Future directions

2. Minor comments

We have corrected errors in style or grammar and provided language certification.

Reviewer's code: 00742268

1. *Either quote or mention all MMR key genes: MMR machinery is encoded by four key genes.*

We mentioned all four MMR genes (page 5): "The MMR machinery is encoded by four key genes (MLH1, MSH2, MSH6, PMS2)"

2. *Context not very clear: Indeed, CXCL9 and CXLC10 secretion recruitment of unspecific lymphocytes may be driven by.*

We removed this sentence.

3. *Table 1: where applicable, the arms of the trials should be stated.*

We specified the arms of randomized trials.

4. *It should be stated how in practice `not good candidate patients` are handled in regard to include or exclude them from trials: Moreover, patients with heavily pre-treated, progressive, advanced PDAC are not good candidates for immune therapy...*

We rephrased this section to make it clearer (page 14): "In addition, patients with heavily pre-treated, progressive, advanced PDAC are not good candidates for immune therapy and this may partially account for failure of previous studies. These patients should possibly be excluded from immunotherapy clinical trials. Alternatively, positioning immune therapy as maintenance strategy following a course of induction chemotherapy (e.g. with FOLFIRINOX) seems to present several

advantages: (i) it allows the identification and exclusion of patients with rapid tumor progression, (ii) such a treatment may have induced immunogenic cell death and sensitized the tumor to CPI, and (iii) given that induction chemotherapy was not interrupted due to inefficacy, it could be reintroduced at disease progression. Taken together, these elements support the development of immune therapy as maintenance therapy in patients with controlled disease."

5. *Should be rephrased: Firstly, tumor immunogenicity is mandatory an efficient immune response.*

This sentence has been removed because it was redundant with the following sentence: "The "cancer-immunity cycle" theory defines three conditions that are required to obtain an effective anti-tumoral immune response[27]: tumor immunogenicity, T cell recruitment and activation."

6. It should be checked if in certain cases the official journal title abbreviations were used.

Abbreviations have been checked checked.

We hope that these revisions improve the manuscript such that you and the Reviewer now deem it suitable for publication in *World Journal of Gastroenterology*.

Once again, we thank you for your interest in our work and we are honoured that you have accepted to consider this review for publication in *World Journal of Gastroenterology*.

We remain at your disposal and we look forward to hearing from you at your earliest convenience,

Best regards,

Dr. Cindy Neuzillet