Our response to reviewers' comments

Reviewer #1:

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors provide a comprehensive review about pancreatic cancer immunology and immunotherapy options. In my view, the review is timely and although several aspects would deserve a deeper discussion, the most relevant aspects have been nicely pointed out and discussed in a comprehensive manner. As a suggestion, neoantigen discovery and its projection in personalized vaccination might be extended and references to NGS combined with immunopeptidomics analysis could be provided.

: We appreciate your comments that "the most relevant aspects have been nicely pointed out and discussed in a comprehensive manner."

Reviewer #2:

Conclusion: Minor revision

Specific Comments to Authors: The paper presents the current status of pancreatic cancer immunotherapy from the molecular mechanism to the clinical application level. The description of the article is systematic and comprehensive. It is a topic of interest to the researchers in this area. Yet some improvement was needed before acceptance for publication.

: We appreciate your consideration of our study as a topic of interest to the researchers.

My detailed comments are as follows: 1. The first section described the cellular composition of tumor microenvironment. A more general paragraph may be needed here to help readers understand the complex immune microenvironment of pancreatic cancer.

: As the reviewer recommended, we added a sentence before the cellular composition of tumor microenvironment to help readers understand the complex immune microenvironment of pancreatic cancer as follows.

"The pancreatic tumor microenvironment represents plentiful fibrotic stroma comprising a variety of cells and extracellular matrix components with blood vessels and nerves."

2. Based on the latest research results, the role of cancer-associated fibroblasts (CAFs) in panc

reatic cancer remains controversial[1]. The crosstalk of CAFs and infiltrating leukocytes was not highlighted, which makes the discussion of CAFs in this chapter slightly less logical. They were neither mention in any other part of immunotherapy applications in this article.

Reference: 1. Sahai, E., et al., A framework for advancing our understanding of cancer-associated fibroblasts. Nat Rev Cancer, 2020. 20(3): p. 174-186.

: The reviewer raised a good point. As reviewer recommended, we discussed the crosstalk of CAFs and infiltrating leukocytes with reference.

"Interference with T-cell function by CAF is mediated by immune crosstalk mediated by activation of transforming growth factor beta (TGF-β) and production of C-X-C motif chemokine 12 (CXCL12)."

We also added the application of CAF in Table 1 by adding following content. "CXCR4: receptor of CXCL 12."

3. The figures may be too simple for review articles. More display of cell interactions or immunotherapy methods may make the article easier for readers to understand.

: As the reviewer recommended, we added Figure 2 representing illustration of CAR T cells immunotherapy.

4. The benefits of GVAX were not mention in the description of current status of immunotherapy. The author even mentioned the lower overall survival of GVAX. More evidence may be needed to prove that GVAX is a promising immunotherapy method in the part of future prospects.

: We agree with the reviewer in that more evidence is needed to prove that GVAX is a promising immunotherapy. We change the sentence as follows.

"Although GVAX failed to improve the overall survival, other kind of vaccines might be effective in combination therapies by promoting the recruitment of T cells, resultantly enhancing the effect of immune check point inhibitors or other agents."

Reviewer #3:

Conclusion: Major revision

Specific Comments to Authors: This is a review about immunotherapy for pancreatic cancer. I

t addresses the role of immune cells in pancreatic cancer, tumor microenvironment, mechanis ms and efficacies of immunotherapeutic drugs in pancreatic cancer, and so on.

Several concerns are listed as follows.

1. Usually, pancreatic ductal adenocarcinoma is abbreviated as PDAC. The authors should cons ider this.

: Thank you for your meticulous evaluation. We changed the abbreviation of pancreatic d uctal adenocarcinoma from PDA to PDAC, as the reviewer recommended.

2. The description of the figures should be marked as Figure 1A or Figure 1B, instead of just describing as Figure 1 and Fig.1.

: Thank you for your kind suggestion. We clarified Figure 1A or 1B for easy readership i n the manuscript.

3. The manuscript looks more like a general science article, lacking a comprehensive and prof ound analysis of immunotherapy for pancreatic cancer. For example, it is full of hope for this treatment, but fails to recognize the challenges it faces.

: We agree with the reviewer in that current challenges regarding immunotherapy has de monstrated disappointing results. However, we think that we can remain hopeful that ag gressive pancreatic cancer will become a controllable disease with the aid of immunother apy, given the plentiful current trials. We already described about this in the future pros pects section.

4. Although clinical outcomes of immunotherapies in advanced pancreatic cancer are listed in Table 2, the agents are briefly introduced. The safety and efficacy of these drugs are not anal yzed in detail. The side effects of immunotherapeutic agents should not be underestimated, w hich should be recognized and managed properly in daily clinical practice.

: We totally agree with the reviewer in that the safety and efficacy of immunotherapeutic s. We already described the adverse events in the manuscript as follows.

anti-CTLA-4: The common adverse events include enterocolitis, inflammatory hepatitis, an d dermatitis. Algorithmic use of corticosteroids or other immunosuppressants can readily control these adverse events without any apparent loss of antitumor activity.

anti-PD-1 or anti-PD-L1: Adverse events associated with single-agent anti-PD-1 or anti-PD-L1 antibodies are uncommon, but they can include the development of fatigue, diarrhea, rash, and pruritus in 15 to 20% of patients.

CAR-T: Adverse events of CAR T cell therapy include cytokine release syndrome and neurotoxicity.

However, we also added adverse events in Table 2 as reviewer's recommendation.

Please, refer to Table 2 - Adverse events column.

5. Recently, immunotherapy has not only been limited to unresectable or stage IV pancreatic cancer, but also played an important role in neoadjuvant or adjuvant therapy. The information is also very important.

: We agree with the reviewer in that immunotherapy has a role in neoadjuvant and adjuvant therapy. We added following sentence in the Vaccine-based immunotherapy section.

"Zheng et al. recently reported that GVAX-induced intratumoral lymphoid aggregates correlated with survival following treatment with a neoadjuvant and adjuvant vaccine in patients with resectable PDAC[ref]". [ref]: Zheng et al. Clin Cancer Res 2020.

6. Lack of literature annotation in Table 1.

: Table 1 represents mechanisms of various immunotherapeutics. They are mostly described in the manuscript. We'll appreciate the reviewer to permit the current form of Table 1 for better visualization.

7. Existing literature on immunotherapy for pancreatic cancer is relatively limited. Thus, attentions should be paid to ongoing clinical trials or studies, which are not introduced or summarized in the manuscript.

: We totally agree with the reviewer in that ongoing clinical trials are important. As reviewer recommended, we added following sentence regarding ongoing clinical trials.

"For expecting future management of PDAC, attentions should be paid ongoing clinical trials. From a plethora of ongoing clinical trials, well-organized tables regarding hopeful trials are also available in other review articles[ref]." [ref]: Nevala-Plagemann et al. Nat Rev

Clin Oncol 2020, Mizrahi et al. Lancet 2020.

Reviewer #4:

Conclusion: Accept (General priority)

Specific Comments to Authors: This review is well written.

: We appreciate your comments that "This review is well written."

Reviewer #5:

Conclusion: Major revision

Specific Comments to Authors: The authors report the role of immune cells in the developm ent of pancreatic cancer, the tumor microenvironment, the cancer immunity cycle, the mechani sms and efficacies of immunotherapeutic drugs in pancreatic cancer, and the response criteria for use in trials aimed at testing immunotherapeutics in a narrative review.

Major comments 1. The authors should report how they selected the literature utilized for thi s review. In particular, this information should be reported in a specific section.

: Thank you for your meticulous evaluation. Although our study was a narrative review, we decided to add following sentences for clarifying the literature review strategy as revi ewer's recommendation.

"Literature review strategy

The PubMed database was used to search publications related to immunotherapy for pan creatic cancer employing the following keywords: ("pancreatic cancer", OR "pancreatic ade nocarcinoma") and ("immunotherapy" OR "vaccine" OR "antibody"). Pertinent articles publ ished in the English language literature were reviewed. All of the references were manuall y verified, and all reference lists in the retrieved articles were scrutinized to identify any additional articles that might have been missed by the PubMed search."

2. A Figure reporting the possible role of immunotherapy in clinical setting is highly appreciat ed.

: Thank you for your good suggestion. However, the role of immunotherapy is summarized in the Table 1 and Table 2. Instead, we added Figure 2 representing illustration of CAR T cells immunotherapy.

3. In the section entitled Response criteria for use in trials testing immunotherapeutics the authors stated on the last line that a full description of this issue is beyond the scope of this article. I agree with their statement but a brief explanation should be done.

: As the reviewer recommended, we added following sentences for iRECIST explanation.

"The category of new lesions is an important difference between RECIST 1.1 and iRECIST. According to RECIST 1.1, new lesions result in progression without the necessity of size measurement. In contrast, iRECIST states that new lesions will be categorized as unconfirmed progression, and then followed. Confirmed progression in iRECIST is only assigned if additional new lesions appear at next assessment or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target)."

4. In the section Future prospects the authors report that artificial intelligence can also be applied for aiding selection of target or protocol in an individual patient from numerous combination of a variety of cancer therapies. I do not agree with this conclusion that should be deleted of better explained.

: We agree with the reviewer in that the use of artificial intelligence in the field of immunotherapy may not be an evidence-based approach. We deleted that sentence as the reviewer recommended.

Science editor:

Issues raised: (1) The column should be minireviews; (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (3) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200

×). Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the r eference source in the references list. If the author fails to properly cite the published or cop yrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Re-Review: Required. 7 Recomm endation: Conditional acceptance.

: First of all, we appreciate science editor for giving us this revision. We responded point -by-point to the reviewers' comments and revised manuscript. The figures are our origina l figures, although we take into account the literature. We provided powerpoint file of fi gures.