We thank the reviewers and editors for the critical assessment of our manuscript. Here are our point-to-point responses to the comments.

A) EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) **Science editor**:

The breakthrough in immunotherapy has completely changed cancer treatment and shows great potential to change PDAC treatment in the future. The authors focus on the tumor microenvironment in pancreatic ductal adenocarcinoma. The manuscript is well written and can be helpful for the readers to ameliorate the diagnostic and therapeutic approach for this scenario.

There is no figure legend in the picture.

Our response: Thank you for the comments. The original manuscript placed Figure Legend in a separate page before the Tables. In the revised manuscript, the Figure 1 and its figure legend are now in the same page.

The format of the table should be a three-line table.

Our response: Thank you for the comments. The Tables have been modified with the standard three-line format.

It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

Our response: Thank you for the comments. The manuscript has been revised with no more than 3 references from the same journal.

(2) **Company editor-in-chief**:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: https://www.referencecitationanalysis.com/.

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Our response: Thank you for the comments. A PowerPoint fine with decomposable Figure has been provided with the revised manuscript.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Our response: Thank you for the comments. The Tables have been modified with the standard three-line format.

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Our response: Thank you for the comments. The Figure is original and generated by the authors. We have not used a figure published elsewhere or that is copyrighted. We have added the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

B) REVIEWERS'S COMMENTS

Reviewer #1:

Specific Comments to Authors: *The paper is well structured and easy to follow. The methodology of the paper is not described.*

Our response: Thank you for the comments. We have included the Methodology in the revived manuscript (the last paragraph in the Introduction section). Specifically, we stated that "*In this review, we discuss the role of the tumor microenvironment and the latest advances in immunotherapy on pancreatic cancer through the search of peer-reviewed clinical and basic research articles related to this topic on PubMed, as well as the publicly accessible information on relevant clinical trials through ClinicalTrials.gov.*"

In my opinion the paper is too long for a minireview and is more suitable for World Journal of Gastrointest Oncology.

Our response: Thank you for the comments. We have followed the "Guidelines for Manuscript Preparation and Submission: Minireviews". There is currently no word limit specified for a Minireview article.

The legend for figure 1 is missing.

Our response: Thank you for the comments. The original manuscript placed Figure Legend in a separate page before the Tables. In the revised manuscript, the Figure 1 and its figure legend are now in the same page.

There are some typing errors.

Our response: Thank you for the comments. We have sent our revised manuscript to a professional company for English language editing, and have provided English Language Certificate from the company, American Journal Experts (AJE).

Reviewer #2:

Specific Comments to Authors: *This is a very good idea for a review article, since both tumor microenviroment in PDAC and immunotherapy are on the uprise as potential target and treatment*

options, and it is clear, that the authors have put a great deal of effort into writing this article. However, there are some fundamental flaws with this manuscript.

- The language is inconsistent regarding frases, abbreviations and uses "everyday language" too much.

Our response: Thank you for the comments. We have sent our revised manuscript to a professional company for English language editing, and have provided English Language Certificate from the company, American Journal Experts (AJE).

- The description of the different studies which the authors bases most of their review on, is messy, inconsistent and very hard to conclude anything from. - The composition of the manuscript could be made more streamlined - both for the readers but also for the general purpose of the article. Instead of explaining every type of pre-clinical and clinical studies regarding every type of target, therapy and vaccine, consider to compress it a little and focus on the overall picture for each of the subsections in the article. That would make the article much more useful as a an overview of the knowledge regarding PDAC, TME and immunotherapy for clinicians. Therefore, with some revisions, this could be a well written article of great interesest to most who deals with not only PDAC patients, but cancer patients in generel.

Our response: Thank you for the comments. We have been trying to provide a comprehensive review on tumor microenvironment and immunotherapy in pancreatic cancer. We are happy that our manuscript has been recognized by you for its potential interest "*to most who deals with not only PDAC patients, but cancer patients in general***". Also, additional favorable comments have been made by Reviewer #1: "***The paper is well structured and easy to follow***", Reviewer #3: "***This review provides a reference for immunotherapy in the treatment of pancreatic ductal adenocarcinoma. It has guiding significance to clinical work.***", and the Science Editor: "***The manuscript is well written and can be helpful for the readers to ameliorate the diagnostic and therapeutic approach for this scenario.***"**

Reviewer #3:

Specific Comments to Authors: *Manuscript Number: 75137 Title: Tumor Microenvironment in Pancreatic Ductal Adenocarcinoma: Implications in Immunotherapy. Pancreatic ductal adenocarcinoma (PDAC) occurs in the exocrine compartment of the pancreas and accounts for approximately 90% of pancreatic malignancies, making it the most common pancreatic tumor. Due to lack of early diagnosis and limited response to treatment, PDAC remains a highly aggressive and lethal malignancy, the fourth leading cause of cancer-related death worldwide. The difficulty in treating pancreatic cancer is at the cellular and genetic levels. Mutations in pancreatic tumors can lead to genetic instability, tumor growth and resistance to therapy. In addition to typical molecular markers, including oncogenic KRAS mutations and inactivation of the tumor suppressor genes CDKN2A/P16, TP53, and SMAD4, PDACs frequently contain mutations involved in multiple cellular signaling pathways. Molecular heterogeneity may account for its resistance to chemotherapy. In addition, pancreatic cancer stem cells account for approximately 1% of all pancreatic cancer cells, have the ability to self-renew, and exhibit chemoresistance. Immunotherapy has emerged as one of the most promising treatment options for advanced solid tumors, including lung, kidney, bladder, liver, and colorectal cancers. Unfortunately, PDAC is significantly resistant to*

immunotherapy, and so far, most phase I/II clinical trials of PDAC have failed to demonstrate the ideal clinical efficacy of immunotherapy. Notably, microsatellite instability (MSI), one of the predictive biomarkers for immune checkpoint blockade therapy, was detected in only a very small number of PDAC patients (less than 1%). On the other hand, emerging evidence suggests that the tumor microenvironment (TME) in PDAC is a key component of immunotherapy resistance. Despite advances in translational research, PDAC remains a highly lethal malignancy. Recent breakthroughs in immunotherapy have revolutionized cancer treatment and show great potential to transform the treatment of PDAC in the future. However, PDAC is less effective for various immunotherapies than other types of cancer. TME is considered a fundamental barrier to treatment resistance. To overcome this resistance, further research into innovative therapeutic strategies is required. This review provides a reference for immunotherapy in the treatment of pancreatic ductal adenocarcinoma. It has guiding significance to clinical work. Overall, I think this is a worthy review that has important implications. The manuscript can be accepted and published in World Journal of Gastroenterology.

Our response: Thank you for the comments. We greatly appreciate the positive feedback from the expert reviewer. As you have pointed out, we have been trying to provide a reference for immunotherapy in the treatment of pancreatic ductal adenocarcinoma, an unmet clinical need. We hope this article could guide further clinical trials to explore more effective therapy for pancreatic cancer.

We thank the reviewers for the critical assessment of our manuscript. Here are our point-to-point responses to the reviewers' comments. REVIEWERS' COMMENTS Reviewer #1: Specific Comments to Authors: The authors have done a great job revising this manuscript, especially regarding language and formate of the paper. It is now easy to read, relevant and can be used as a tool for clinicians every to get a better understanding and knowledge about the role of immunotherapy and TME in PDAC. Our response: Thank you for the comments. We greatly appreciate the positive feedback from the expert reviewer. To polish the language, we have sent our revised manuscript to a professional company for English language editing. We have also modified the table format and updated the reference list. Reviewer #2: Specific Comments to Authors: I re-reviewed the paper. It was difficult to compare the first version with new version. The modified phrases were not highlighted. However, it seems that the authors did not made any modifications in order to shorten the paper and compress it and focus on overall picture. Our response: Thank you for the comments. We are providing a Word file to highlight the changes we have made for the revision (as compared to the original version). As demonstrated in this file, we have provided significant language editing (by a professional English language editing company) and revision to the manuscript. Given the significant advances in tumor environment and the large number of ongoing clinical trials for pancreatic cancer, we think shortening the paper would obviously compromise the goal of this review paper which aims to paint an overall picture of immunotherapy in the treatment of pancreatic ductal adenocarcinoma.