

Dear Editors,

Thank you for the recommendation of publication and for giving us the opportunity to revise this manuscript. Therefore, we have performed a revision of our manuscript, in the attempt to improve our work.

We hope that this revised version can meet the journal's quality requirements.

We thank you again greatly for your time and for the suggestions you provided.

Best regards

## Round-1

1 Reviewer

Thank you very much for your comments. Down below we report point by point our answers to your comments.

Comment 1) The author only "states" but not "comments", which should be the organic combination of "states" and "comments", that is, "states" is the basis of "comments", and "comments" is the extension and improvement of "states". Therefore, at the end of each segment, after the author introduces others' academic views and research results, the author also needs to briefly summarize the information, clarify your personal opinions, and put forward the necessity and theoretical value of further research in this field.

Answer: thank you very much for this kind suggestion. We revised the manuscript in order to clarify our point of view about the study results. Particularly, we added

- from line 161 to line 168 of chapter 2.1 "CHEMOTHERAPY"
- from line 39 to 44 of chapter 2.2 "TARGETED THERAPY"

Comment 2) Abbreviated terms have to be explained in full name when they first appear. The author should know that this is the foundation for writing. Clean up all abbreviations, including but not limited to the following: OS, PS, ORR, NAL-IRI, nab-paclitaxel, NTRK, BSC, OFF, FF, XELOX, FOLFOX, CapeOX, ECOG, etc.

Answer: we clarified all the abbreviations we used in the manuscript as you suggested

Comment 3) Supplement the standard of first-, second- and/or third-line therapy. Let the reader know clearly when to use what kind of treatment.

Answer: we explained the standard of first line treatment from line 13 to line 30 of chapter 2.1 "CHEMOTHERAPY". To date there isn't a standard of second line treatment and that was the point of this review. We tried to explain what could be the sequential therapies after a first line treatment as indicated from NCCN and EMA guidelines (see FIGURE 1). As for the third line treatment, only a small percentage of patients maintain a good performance status and receive a third line treatment.

Comment 4) The term "pancreatic cancer" is quite confusing in the manuscript. Such as: pancreatic adenocarcinoma (title), metastatic pancreatic ductal adenocarcinoma (PDAC) (paragraph 1 of Section 2.1), metastatic PDAC (section "1. Introduction"), PAC (no full name, 3.2 section), advanced pancreatic cancer (Section 2.2), metastatic PAC (paragraph 1 of section 3), MPDAC (Paragraph 3 of section 2.1), mPDAC (Section 4), etc. The author's expression of the terms should not change with the change of the literature, and the same manuscript should have consistent terminology

expression. Please unify the term. In addition, there should be a brief introduction to the classification of PAC.

Answer: we unified the term as PDAC (pancreatic ductal adenocarcinoma). Thank you for your note. This review is about metastatic adenocarcinoma in second line, as it's clarified by the title, so we don't think it's necessary to add an introduction to the classification of pancreatic cancer.

Comment 5) Table 1 is not so much a table as a figure. So, change it to a figure and add a figure legend. In addition, what mean does the last "clinical trials" on the left ? Figure 2 also needs to add a figure legend.

Answer: We changed table 1 to a figure and added a figure legend also for figure 2. We suggested the possibility of enrolling patients in "clinical trials", if available, as recommended by the NCCN guidelines , considering that we don't have strong evidence of benefit of a second line treatment.

Comment 6) The subheadings should be consistent, for example, in the "1) Second-line chemotherapy after treatment with FOLFIRINOX " section, a) is "gemcitabine in monotherapy", b) should be "gemcitabine based combination therapy", not "gemcitabine based treatment"; in the "2.2 TARGETED THERAPY " section, "Erlotinib" should correspond to "Larotrectinib and entrectinib" instead of " TRK inhibitors in TRK fusion-positive cancers: Larotrectinib and entrectinib", or change "Erlotinib" to "EGFR TI inhibitor: Erlotinib". Please check the full text and revise it.

Answer: we revised the manuscript as you suggested.

Comment 7) For "future directions", the author mentioned "increase of targeted therapies". What is the basis? Do you have the most promising therapeutic targets and drugs? Yes, what is it? Please be clear

Answer: In the section "future directions" we illustrated the most promising therapies under investigation in clinical trials.

Comment 8) Note that some expressions are not well, such as "44-48%" and "62-65%", the correct writing should be "44% - 48%" and "62% - 65%"; Table 2 has no table header.

Answer: we adjusted the expressions you underlined.

## 2 Reviewer

Comment : The authors report a review on second-line treatment of pancreatic adenocarcinoma. The topic is of interest. The manuscript requires revision for publishing. Complex sentences (more than 1 idea) should be simplified: 1 idea/1 sentence. Ex "To date, chemotherapy is still //, unfortunately providing //", "Precision médecine could be the key // and finally impacting Survival //". Standard requirements should be fulfilled: page numbering (and/or continuous line numbering).

Answer: Thank you very much for your suggestion. We revised the manuscript in order to simplify our sentences.

## 3 Reviewer

Comment: The present review describes the controversial and unsolved topic of second-line treatment of advanced pancreatic cancer. I think that this review is well-written and suitable for publication in World Journal of Gastroenterology. I believe the paper will be of interest to the readership of World Journal of Gastroenterology and would recommend it for acceptance after the minor point listed below are addressed. Minor 1.Introduction section: Please spell out the PDAC.

Answer: thank you very much for appreciating our work and for your suggestion that we followed.

#### 4 Reviewer

Comment: I would like to congratulate the authors for an extremely well-written and thorough review on second-line treatment of pancreatic adenocarcinoma. The authors do a phenomenal job of reviewing the current literature on this topic and also highlight future directions in the field. I have only minor edits to suggest for this excellent review: 1. Grammar can be improved. Reduce redundancy as there seem to be some repetition in initial paragraph 2. Use only standard abbreviation and please mention full form along with the abbreviation in first use. 3. Consider adding the following citation in the section of targeted therapy or future directions as this review from JAMA oncology highlights future prospects of germline mutations in PDAC. This citation should be a great addition to your well written review. "Rainone M, Singh I, Salo-Mullen EE, Stadler ZK, O'Reilly EM. An Emerging Paradigm for Germline Testing in Pancreatic Ductal Adenocarcinoma and Immediate Implications for Clinical Practice: A Review. JAMA Oncol. 2020;6(5):764–771. doi:10.1001/jamaoncol.2019.5963"

Answer: We appreciate very much your kind comment and your fair suggestions. We improved our manuscript following your advice and we have added the reference you suggested.

Rainone M, Singh I, Salo-Mullen EE, Stadler ZK, O'Reilly EM. An Emerging Paradigm for Germline Testing in Pancreatic Ductal Adenocarcinoma and Immediate Implications for Clinical Practice: A Review. JAMA Oncol. 2020;6(5):764–771. doi:10.1001/jamaoncol.2019.5963

#### Round-2

Dear Editor,

thank you to giving us the opportunity to revise the manuscript. We appreciate all the comments made by the Reviewers. Therefore, we have performed a revision of our manuscript, in the attempt to improve our work.

We hope that this revised version can meet the journal's quality requirements. We thank you again greatly for your time and for the suggestions you provided.

#### ANSWERS TO THE REVIEWERS.

Comment 1. To clarify the concept, the author used the term "pancreatic adenocarcinoma" in the title, the term "pancreatic cancer" in the beginning of the abstract, and the term "pancreatic ductal adenocarcinoma (PDAC)" in the Core tip section. The meanings of the three terms are not really the same, which is why I hope the author will give a classification of pancreatic cancer. The author should distinguish the relationship between the three terms. The term "pancreatic adenocarcinoma" is also called "pancreatic cancer" by many scholars, so they are the same ones concept. Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic adenocarcinoma (pancreatic cancer), accounting for about 80% - 90%.

Answer: we added this classification in the Introduction. "Adenocarcinoma is the most common type of exocrine (non-endocrine) pancreatic cancer, accounting for over 90 percent of pancreatic cancer diagnoses. In most cases it originates from the pancreatic ducts (ductal adenocarcinoma), in a smaller percentage of cases it can originate from the acini (acinar cell carcinoma). Rarer forms of pancreatic cancer are squamous cell carcinoma, adenosquamous carcinoma and colloid carcinoma."

2. In subtitle "2. CURRENT CLINICAL PRACTICE IN SECOND LINE METASTATIC PAC" and "3.2 Increase of targeted therapies" section. The abbreviated term "PAC" should be changed to PDAC. Similarly, the "MPAC" in "3. FUTURE DIRECTIONS" section should be changed to mPDAC.

Answer: Thank you for these corrections, we edited the manuscript as you suggested.

3. In the third natural paragraph of "2.1 CHEMOTHERAPY "section, what is the abbreviation MPACT? There should be an explanation.

Answer: the explanation is "Metastatic Pancreatic Adenocarcinoma Clinical Trial" we added it in the manuscript.

4. "In conclusion, ..... on the first-line treatment used . Within the 5FU-based regimens," , there is an extra space after the word "used". Similarly, in the second paragraph of "larotrectinib and entrectinib" section, the word "sustainability" is followed by the same thing, while the word "contexts" is followed by a blank space.

Answer: Thank you, we eliminated the extra spaces.

ANSWER to EDITORS'S COMMENT: 1. We replied point by point to reviewer's comments 2, We eliminated reference number 20 and rearranged the correct order 3, We provided the decomposable figure of figures and organized them into a PowerPoint file. We provided the text in figure(s) in text boxes. 4. We uploaded all the files