Dear Editors and Reviewers,

Thank you for giving us a chance to revise and improve the quality of our article. We have read the reviewers'comments carefully and have made revision in the paper. We have tried our best to revise our manuscript according to the comments.Here, we would like to explain the changes briefly.

Reviewer#1

Comments: This Letter to the Editor comments on the results of an article published in the World Journal of Gastroenterology by Nishimoto A in 2022. All the comments are pertinent and would interest the journal readers.

Answer: Thanks for your comments.

Reviewer#2

Comments: A very good comment regarding the paper of Nishimoto.

Answer: Thanks for your comments.

Reviewer#3

Comments: I appreciate the opportunity reviewing the manuscript on pancreatic cancer. In this letter to editor, the authors discussed the merits of the combination of gemcitabine and targeted drugs, which may offer additional benefits to patients. The manuscript is generally well-written and the only thing needs clarification is to elaborate the reasons why gencitabine+ erlotinib had shorter median OS compared to gencitabine monotherapy in the LAP07 trial (11.9mo vs. 13.6 mo). Is it due to higher adverse effects, such as myelosuppression, or neutropenic fever? Additionally, combination therapy, especially combination with high-cost target drugs, could represent significant financial toxicicity to patients who are uncovered or underinsured. Therefore, in real-world studies, choice of combination therapy is usually

confounded by multiple factors, introducing slection bias that favor the combination therapy. Authors should mention the descrepancies in real-word practice and RCT findings, and should be cautious in interpreting somehow encouraging results from observational studies.

Answer: We try to elaborate the reasons why gencitabine combined with targted durgs had shorter median OS compared to gencitabine monotherapy sometimes.The exact mechanism by which the combination of drugs could be less effective than gemcitabine alone is difficult to explain and may be related to the greater toxicity of combination drugs.An open-label, multicenter, randomized phase II trial evaluated gemcitabine plus afatinib versus gemcitabine alone for metastatic pancreatic cancer. Median overall survival was 7.3 months with gemcitabine plus afatinib versus 7.4 months with gemcitabine alone. Adverse events like diarrhea and rash were more frequent with gemcitabine plus afatinib.And in this study, the combination therapy proved to be more toxic to humans.At the same time, we also add that other drugs other than erlotinib have similar results in combination with gemcitabine to discuss our views. This avoids selection bias and error in a single trial, and the conclusion is that although most combinations have good effects on pancreatic cancer, there are cases in which gemcitabine alone is more effective.

In all, we found these comments are quite helpful. And special thanks to you for your good comments again.I wish this revision will be acceptable for publication in your journal.Thank you for your consideration. I am looking forward to hearing from you.

Yours Sincerely,

Zhe Liu

Email: Liuzhe4321@126.com