Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: This is an interesting study which propose a new and exciting target for the treatment of PDAC, as well as potentially more types of cancer, if validated in other studies. Therefore the value of the findings and topic of this paper is of great interest. However, several things have to be revised in order to make this paper acceptable for publication - I have tried to illuminate these things in the attached review of your paper, but overall concerns are; - Language level is not of high enough quality - A clearer aim is needed - Method section is very confusing and you have to find a lot of facts about how the study was conducted in the discussion section. - The statistics behind the number of samples you chose to evaluate is lacking - More than one part of the results section is a discussion - You lack a "strength and weaknesses" section were you illuminate the pros and cons of your study and critically evaluate your own work.

1. Language level is not of high enough quality

Answer: We have send our revised manuscript to the recommended professional English language editing company to polish the manuscript further. And we will provide a new language certificate along with the revised manuscript.

2. A clearer aim is needed

Answer: Thanks for your constructive advice, we have revised our aim to make it clearer. The revised aim is: To investigate the expression of CLDN18.2 in PDAC patients and then propose a new target for the treatment of PDAC.

3. Method section is very confusing and you have to find a lot of facts about how the study was conducted in the discussion section.

Answer: Thanks for your kindly advice, we have revised the method section and clarified different method and its aim to make it clearer. Besides, we have add the description of how the study was conducted in the discussion section.

4. The statistics behind the number of samples you chose to evaluate is lacking

Answer: Thanks for your kindly advice, the statistics about the samples we evaluated was listed in Table 1 and Table 2. We listed detailed statistics of the tumor samples, such as age, gender, localization and TNM category in table 2.

5.More than one part of the results section is a discussion

Answer: Thanks for your careful reminder, we have streamlined the results section to make it more clear and concise.

6. You lack a "strength and weaknesses" section were you illuminate the pros and cons of your study and critically evaluate your own work.

Answer: Very thanks for your advice, we have added this section at the end of manuscript to critically evaluate our work.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: Summary Xi et al. analyzed the expression of Claudin 18.2 in pancreatic ductal adenocarcinoma (PDAC). Although the authors showed increased expression level of Claudin 18.2 in PDAC, I cannot recommend this article for publication because it has extensive problems. Major points 1) Introduction; There is no evidence showed that chemotherapy with/without targeted therapy is the first-line treatment in PDAC. In NCCN guidelines, there is no evidence that the chemotherapy with targeted therapy

showed favorable prognosis (https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455). 2) The authors showed that the p53MVA and PD-1 inhibitor combination therapy is "pretty safe" regimen. However, as authors citated the article, there is many patients who suffered Grade1-2 adverse events albeit small sample size (Chung et al. Clin Transl Oncol. 2019 Mar;21(3):363-372. doi: 10.1007/s12094-018-1932-2) 3) Materials and methods [Scoring of CLDN 18.2 staining] The authors have not stated how many slides were used for IHC-score evaluation. Please clarify the number of slides used. 4) Results: Considering the heterogeneity of patients' characteristics shown in table 2, the authors should perform multivariate analysis to evaluate if the significant factors correlated to CLDN18.2 expression is independent factor. 5) Discussion; In the result section, the authors showed that there is no significant survival difference between CLDN18.2 high/low expression patients. I think it is a hard to say that the zolbetuximab is a potential treatment target on PDAC. If the authors would like to show the zolbetuximab is a candidate agent, the authors should show more basic evidence related to zolbetuximab.

1. Introduction; There is no evidence showed that chemotherapy with/without targeted therapy is the first-line treatment in PDAC. In NCCN guidelines, there is no evidence that the chemotherapy with targeted therapy showed favorable prognosis(https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455).

Answer: Thanks for your careful reminder, we have corrected this error. In NCCN guidelines, chemotherapy is the first-line treatment in unresectable PDAC.

2. The authors showed that the p53MVA and PD-1 inhibitor combination therapy is "pretty safe" regimen. However, as authors citated the article, there is many patients who suffered Grade1-2 adverse events albeit small sample

size (Chung et al. Clin Transl Oncol. 2019 Mar;21(3):363-372. doi: 10.1007/s12094-018-1932-2)

Answer: Thanks for your careful reminder, in our manuscript, we wrote that the p53MVA and PD-1 inhibitor combination therapy is "pretty safe" regimen. The reason for this is because the conclusion in this reference is that: "We have shown that the combination of p53MVA vaccine with pembrolizumab is feasible, **safe**, and may offer clinical benefit in select group of patients that should be identified through further studies". But as you said, there is many patients who suffered Grade1-2 adverse events albeit small sample size. So we have corrected our inappropriate words to make it more objectivity.

3. Materials and methods [Scoring of CLDN 18.2 staining] The authors have not stated how many slides were used for IHC-score evaluation. Please clarify the number of slides used.

Answer: Thanks for your kindly advice, we have modified this section according to your suggestion.

4. Results: Considering the heterogeneity of patients' characteristics shown in table 2, the authors should perform multivariate analysis to evaluate if the significant factors correlated to CLDN18.2 expression is independent factor.

Answer: Thanks for your constructive advice. According to your suggestion, we have performed multivariate analysis (using Principal effect analysis, homogeneity of variance test, and post hoc comparison) to evaluate if the significant factors correlated to CLDN18.2 expression is independent factor. We found that the significant factors including lymph node metastasis, distant metastasis, nerve invasion and stage correlated to CLDN18.2 expression are independent factors, respectively, P values are all less than 0.05. we have added this section to our manuscript.

5. Discussion; In the result section, the authors showed that there is no significant survival difference between CLDN18.2 high/low expression patients. I think it is a hard to say that the zolbetuximab is a potential treatment target on PDAC. If the authors would like to show the

zolbetuximab is a candidate agent, the authors should show more basic evidence related to zolbetuximab

Answer: Thanks for your constructive advice. In the result section, we showed that there is no significant survival difference between CLDN18.2 high/low expression patients, but when we used stratified analysis to test the impact of different CLDN18.2 expression on different cancer stages (AJCC), different N category and M category, the correlation was discovered. we found significant correlation of CLDN18.2 expression with survival in PDAC patients with stage III, stage IV and distant metastasis (Figure 3B to I). This suggests the CLDN18.2-positive patients with late stage and distant metastasis may have a poorer prognosis. So zolbetuximab may be a potential treatment target on PDAC, but the beneficiaries need to be screened. Of course, we are looking forward more large-scale studies will be conducted to further analyze CLDN18.2 expression in PDAC and provide more basic evidence related to zolbetuximab in the future.