Response to reviewers

Dear Editor and Reviewers,

Thank you for offering us an opportunity to improve the quality of our submitted manuscript "**Case report: Response of Cholangiocarcinoma with Epigastric Metastasis to Lenvatinib plus Sintilimab**". We appreciated very much the reviewers' constructive and insightful comments. In this revision, we have addressed all of these suggestions. We hope the revised manuscript has now met the publication standard of your journal.

We highlighted all the revisions in yellow colour.

On the next pages, our point-to-point responses to the queries raised by the reviewers and editors are listed.

Reviewer's Comments

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript describes a case report of a stage IV cholangiocarcinoma (CCA) with liver and abdominal wall metastases that received palliative surgery and two cycles of combining Lenvatinib with Sintilimab. They found different responses of the intrahepatic and extrahepatic metastases to the same therapy. While the content seems interesting, the authors perhaps should elaborate on the differences in molecular targets of lenvatinib (a multiple receptor tyrosine kinase inhibitor) with Sintilimab (PD1) in extra- and intrahepatic CCA. This information may unravel the background behind this phenomenon. Also, there are some redundant sentences on Page 9. "Conversely, the immune microenvironment of extrahepatic tumors may be in an immune-activated state, making them more susceptible to attack by activated immune cells and the anti-angiogenesis effects of targeted immune drugs. This can ultimately lead to tumor regression. "

Response: We are extremely grateful for your suggestions. The differences in molecular targets in extra- and intrahepatic CCA between lenvatinib and Sintilimab are as follows:

Lenvatinib can inhibit tumor angiogenesis by targeting VEGF and FGF to exert anti-tumor effects[26]. Sintilimab, an IgG4 immunoglobulin that binds to PD-1, acts as an immune checkpoint inhibitor by selectively blocking the interaction between PD-1 expressed on activated T cells and its ligands, programmed cell death 1 ligand 1 (PD-L1) or programmed cell death 1 ligand 2 (PD-L2), expressed on immune cells and tumor cells. In studies involving

cholangiocarcinoma samples，PD-L1 expression was found to range from 9% to 72%, and from 46% to 63% in extrahepatic metastases[27-29]. Haffner found that although PD-L1 expression was rare in primary tumors, it exhibited increased rates in metastatic tumors[30]. Kim found that positive expression of PD-L1 expression in tumors was associated with significantly prolonged progression-free survival (PFS)[31]. This variability may elucidate the disparate responses of intrahepatic and extrahepatic tumors to targeted immunotherapy in the current case, potentially stemming from differences in the expression rates of molecular targets between the primary and metastatic tumors. However, further investigation, including molecular profiling and immune checkpoint molecule detection, is warranted for definitive confirmation. Unfortunately, the patient declined these tests due to financial constraints.

The redundant sentences on Page 9 have been deleted.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The case report and discussion of different responses of the intrahepatic and extrahepatic cholangiocarcinoma metastases to combining Lenvatinib with Sintilimab treatment are interesting. There are some issues:

1. How high is the levels of CA199 before and after Lenvatinib with Sintilimab? Is the CA199 level improved after the treatment?

Response: Thank you very much for your comment. Pre-targeted immunotherapy CA19-9 1000U/mL, CA19-9 decreased to 105.5U/mL after targeted immunotherapy.

2. Is the epigastric metastasis related to seeding of the surgical would?

Response: We are much obliged to you for your comment. During laparoscopic surgery, we considered that biliary leakage might lead to metastasis of Trock hole. Therefore, pre-treatment was performed during the operation. That is, the lower segment of the common bile duct was directly closed with endoscopically cut and closed, and then the upper segment of the bile duct was temporarily closed with blocking forceps. Subsequently, bilioenterostomy was performed, and the blocking forceps were released after the anastomosis was completed. There was no biliary leakage after surgery. Therefore, surgery is less likely to cause epigastric metastasis, and the location of the patient's epigastric metastasis is not consistent with the surgical incision.

3. There is a typo in Page 7: "visplatin".

Response: Thank you very much for pointing out the typo. "visplatin"has been corrected to cisplatin.

4. In page, "Conversely, the immune microenvironment of extrahepatic tumors may be in an immune-activated state, making them more susceptible to attack by activated immune cells and the anti-angiogenesis effects of targeted immune drugs. This can ultimately induce tumor regression" is repeated.

Response: Thank you so much for your careful check. Redundant sentences were removed.

5. The H&E pathological picture in Figure 3 (epigastric tumor biopsy) is in low quality. Please give a high power of view of the tumor glands and cancer cells in higher resolution.

Response: Thanks for your comments. High quality H&E pathological picture

have been provided.

6. Since there is a treatment effect in epigastric tumor, it would be better to show the PDL-1 staining (tumor cells or inflammatory cells) results and the amount of tumor infiltrating lymphocytes in the epigastric biopsy specimen.

Response: We strongly agree with the reviewer's opinion, but the patient declined genetic testing and molecular targeting for financial reasons.

7. Informed consent and/or IRB approval for case reporting (not surgical consent) are not included in the submitted files.

Response: We are very sorry for our negligence. An informed consent for case reports has been provided.

Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: To Authors I congratulate the authors for Case report: Response of Cholangiocarcinoma with Epigastric Metastasis to Lenvatinib plus Sintilimab name's article. Best regards.

Response: We appreciate the reviewer's positive evaluation of our work.

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 manuscript has been peer-reviewed, and it' s ready for the first decision.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, 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. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/. Uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom

right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

Response:

Dear company editor-in-chief:

We sincerely appreciate your suggestions. We have re-polished the manuscript, and the polishing certificate has been uploaded to the system as required. We applied the Reference Citation Analysis to check the article and address the questions raised by the reviewers. After careful considering your questions, we have given serious answers and improved our manuscript. The figures in the manuscript were also rearranged and re-uploaded as required. We would be greatly appreciated if the revised manuscript can meet your requirements.