

July 26, 2019

To the Editor

World Journal of Gastrointestinal Oncology

**RE: Submission Number ID 02441332: Targeted agents for second-line treatment of advanced hepatocellular carcinoma**

Dear Editor,

On behalf of all the authors, I would like to thank you and the Reviewers for the review and the opportunity to revise and resubmit our manuscript entitled "Targeted agents for second-line treatment of advanced hepatocellular carcinoma".

We have addressed the editorial and the Reviewers' comments in the manuscript. Below, we provide detailed responses addressed in the manuscript.

We look forward to your reply and hope that you will find the revised manuscript suitable for publication in World Journal of Gastrointestinal Oncology.

I remain available to answer any questions or additional comments.

Sincerely,

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**Responses to reviewer comments**

*We thank both reviewers for their kind comments and evaluations*

Reviewer: 1

Comments to the Author

The title reflects clearly the main subject and the abstract is quite good at summarising the article. Authors review very well the background, in a concise manner leading to introduce appropriately the relevance of their review. The review as such covers very well what it is relevant for any oncologist treating patients with HCC. They described very well the trials supporting those medications. Overall this article offers a well-written overview of the second line options for this difficult disease, highlighting the relevant points clearly. Tables are quite illustrative and the references are appropriate. Overall the quality of the article is very high

Reviewer: 2

Comments to the Author

I have made minor comments in the manuscript itself. In general this paper describes each phase 3 trial for 2L advanced HCC in detail and accurately. However, a key aspect missing is greater depth in determining the sequence of 2L therapy. How are they going to choose between ramucirumab cabozantinib and regorafenib in the 2L setting. This should be discussed in the text even if there is no straight answer.

*Response: We discussed this very important point in **page 17**. While we already stated that clinical factors informing treatment choices should include the first-line therapy adopted, tolerance, duration of response to that treatment, for clarity sake, we also suggest to consider inclusion and exclusion criteria provided by each clinical study protocol as an additional aid for the selection of the most adequate second-line agent. For instance, poor tolerability of prior sorafenib excludes an individual patient from treatment with regorafenib. Similarly, low AFP levels clearly contraindicate ramucirumab. In view of a treatment sequencing that includes up to three lines, consistent with CELESTIAL study, one may consider cabozantinib as a third-line treatment.*

*Also, in the manuscript, the Reviewer made some minor comments regarding language corrections. These have been addressed along the manuscript itself.*

### **Responses to Editor's comments**

We would like to confirm that:

- The manuscript has been revised according to the CrossCheck report;
- Authors' contributions have been added to the manuscript;

- All tables are original and therefore a permission document from the copyright holder is not requested.