03-Nov-2021

Dear reviewers and editor(s) of World Journal of Hepatology,

Thank you for considering this revised version of our Manuscript NO: 69918, "*Treatment of advanced hepatocellular carcinoma (HCC) in the second line: Time for more individualized treatment options?*".

We have responded to each item below and have provided a tracked version of our resubmission, addressing the points raised. Thank you for the thorough review, we truly appreciate the attention and detailed comments that have greatly improved our submission.

Sincerely,
Yi-Hsiang Huangon behalf of all co-authors.

Reviewer 1 Comments to the Author:

Manuscript titled Treatment of advanced HCC in the second line: Time for more individualized treatment options? Was found to be interesting and to the scope. The following comments are to improve the quality of the Work:

Abstract: the word baseline is repeated, Kindly remove.

> **RESPONSE:** Thank you for these positive, encouraging, and meaningful comments. We hope that our responses below have addressed your concerns and the revised manuscript has improved this work. The word baseline has been removed.

Introduction: treatment part; regorafenib drug should be mentioned before factors part.

> **RESPONSE**: We thank the reviewer for their suggestion. The introduction of the manuscript gives a general overview of HCC, while introducing first-line therapies (sorafenib, lenvatinib, atezolizumab, bevacizumab) to give the reader prior knowledge of treatments in the first-line setting. We then discuss factors (age, serum AFP, ethnicity) which may influence HCC development and patient outcomes. Subsequently, we introduce the aim of the review, which is to focus on the efficacy and safety using OS, PFS, and tolerability data for second-line treatments for patients with HCC. As regorafenib is a current second-line option for patients with HCC, it is

not introduced in the body of the manuscript until its own subsection (Subsection 2.1).

References: number of references should be updated.

RESPONSE: The reference list has been updated and all references have been checked to ensure their corresponding number matches with the in-text content.

Reviewer 2 Comments to the Author:

The manuscript entitled *"Treatment of advanced HCC in the second line: Time for more individualized treatment options?"* submitted to publication in the World Journal of Hepatology focuses on the second-line treatment options for advanced hepatocellular carcinoma (HCC) patients. There are many published papers focused on results of clinical trials of drugs for HCC systemic treatment. However, the submitted manuscript discusses only second-line therapy and, more importantly, available data on post-hoc pooled analyses of efficacy, safety, and patient reported outcomes as well as AFP response and age as predictive and prognostic factors in HCC patients. This distinguishes this manuscript from other papers and makes it of interest to the journal audience. However, there are some concerns and recommendations that can help to improve the quality of the manuscript.

RESPONSE: Thank you for these positive comments. We are glad that the main themes we were communicating are clear. We hope that our revisions in the manuscript have even further improved this work

Major Comment:

1. Title: a second part of the manuscript title does not reflect its content since personalized treatment options were not discussed. Instead, it is recommended to include in the title the subgroup analyses and post hoc analyses to improve treatment outcome.

RESPONSE: We thank the reviewer for this comment. The second part of the title "*Time for more individualized treatment options?*" is an underpinning theme of the manuscript. Current research efforts are aimed at identifying subgroups of HCC patients who will benefit from specific therapies, particularly after progression on first-line treatments. Identifying any predictive or prognostic factors prior to and

during systemic treatment of HCC is critical in determining optimal treatment patterns. Therefore, individualised treatment options are warranted. Our goal of the review was to communicate the available data for second-line treatment options for HCC, while highlighting the unmet need for personalized treatment options following progression in the first-line setting. Thus, we highlight this research gap and ask the question *"Time for more individualized treatment options?"*. We hope the reviewer understands our rational behind the chosen title.

2. Abstract: the same is for the Abstract. Moreover, not only ramucirumab and REACH and REACH-2 trials, but other drugs and trials discussed in the manuscript should be mentioned.

RESPONSE: We have now included in the abstract the other drugs and trials which have demonstrated clinically meaningful survival benefits in patients. The following text has been added to the abstract: "Although several phase III trials of regorafenib (RESORCE), ramucirumab (REACH/REACH-2), cabozantinib (CELESTIAL) have demonstrated clinically meaningful survival benefits in patients with the disease, the median overall survival (OS) of advanced HCC patients remains approximately 12 months after the start of systemic second-line therapy, with limited duration of response".

3. Key words: instead of "second line" there should be "second-line treatment"

RESPONSE: We have now added "second-line treatment" as a keyword

4. Introduction: it is recommended not to use subdivisions.

RESPONSE: We have removed the subdivisions from the introduction of the manuscript

5. The manuscript is not well-organized. There are some repeated discussions, especially as concerns REACH and REACH 2 trials. Further, it is recommended to discuss REACH 2 after REACH. 6.

RESPONSE: We thank the reviewer for the comment. The rationale for discussing REACH-2 prior to REACH is that the REACH-2 was the pivotal phase III clinical trial

that led to the approval of ramucirumab treatment in hepatocellular carcinoma. A pre-planned subgroup analysis of REACH showed that patients with elevated AFP values (AFP ≥400 ng/ml) benefited from ramucirumab treatment. These results suggested that ramucirumab had an increased efficacy with increasing values of baseline AFP. This was subsequently confirmed in the pivotal phase III trial REACH-2. We therefore believe it is more practical that we communicate the REACH-2 data to the reader prior to REACH.

6. Upon discussion of age as a prognostic factor in RESORCE, CELESTIAL and other trials it should be noticed that "cabozantinib improved OS and PFS vs placebo in patients with previously treated advanced HCC irrespective of age category (30)". "In the post-hoc analysis, ramucirumab showed a survival benefit across age subgroups with a tolerable safety profile, supporting its use in advanced HCC with elevated AFP, irrespective of age, including ≥75 years (48)". "Safety profiles of ramucirumab were comparable between <65 and ≥65-<75 age subgroups. The incidence of ≥Grade 3 treatment-related AEs was higher in ramucirumab arm than placebo arm in ≥ 75 age subgroup. A trend toward a delay in the deterioration of symptoms in FHSI-8 for ramucirumab arm was observed in all age subgroups (51). The adverse events such as hypertension is unlikely resulted from HCC or systemic treatment.

RESPONSE: We thank the reviewer for their feedback and their acknowledgement of age as an important prognostic factor which we hope was communicated clearly. Cabozantinib and ramucirumab demonstrated clinically meaningful survival benefits irrespective of age category, indicating that the adverse events observed did not directly translate into reduced efficacy which is important information for patients and clinicians. While it is true that some HCC patients on systemic treatment may not present with hypertension, it is a frequent adverse event for tyrosine kinase inhibitors such as lenvatinib (Motzer et al., 2016) and sorafenib (Wu et al., 2008).

7. References: should be carefully checked. Some Refs were incorrectly used, for example, Ref. (13) should be checked since it is a paper on pembroliumab KEYNOTE-240 trial as a second-line HCC therapy; Ref. (33) is about sorafenib, not regorafenib

RESPONSE: Reference 13 and Reference 33 have been updated with the correct citations. All other references have been checked thoroughly to ensure all numbered references correspond to the in-text content.

8. Grammar should be checked: there should be "alpha-fetoprotein" but not alpha fetal protein" (throughout the text); liver-directed, first-line, second-line, age-dependent, and well-tolerated etc. should be written with dash.

RESPONSE: Thanks for your comments, we had revised.

EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

This review written by Rajappa S, et al. was well-written and informative. But several issues remained to be addressed. The manuscript should be revised according to the reviewers' comments. Furthermore, in clinical practice, ICIs or lenvatinib were also used as the first-line treatment. Authors should discuss the second-line treatment after those regimens.

RESPONSE: Thank you for your positive feedback and recommendations to improve the quality of our manuscript. To the best of our knowledge, drugs in the second-line setting have so far only been tested after sorafenib failure/intolerance. There are currently no phase III trial (mature) data to inform the choice of second-line therapy in HCC patients that received alternative front-line regimens like atezolizumab + bevacizumab or Lenvatinib. ESMO updates suggest, as there is no evidence for any particular drug, it is recommended that all the currently approved first- and second-line agents could be considered as second-line therapy. The IMbrave251 trial is ongoing to investigate atezolizumab with lenvatinib or sorafenib vs lenvatinib or sorafenib alone in HCC previously treated with atezolizumab/bevacizumab (NCT04770896).

Overall, there is limited literature on second-line treatments following first-line systemic therapy with ICIs or lenvatinib. A retrospective analysis by Koroki et al (2021) found that sorafenib may not be a candidate for use as a post-treatment therapy following lenvatinib, however, regorafenib demonstrated potential as an appropriate post-treatment agent after lenvatinib. We have now added information on second-line treatments following lenvatinib to the results section, under section 2.12 RESORCE, suggesting that clinical trials assessing the potential of regorafenib as

well as other therapies, as a post-treatment therapy following lenvatinib are warranted.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, 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.

RESPONSE: We thank the editor-in-chief for conditionally accepting the manuscript and we hope that our revisions are satisfactory.

Citations

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Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, Jassem J, Zolnierek J, Maroto JP, Mellado B, Melichar B, Tomasek J, Kremer A, Kim HJ, Wood K, Dutcus C, Larkin J. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol. 2015 Nov;16(15):1473-1482. doi: 10.1016/S1470-2045(15)00290-9. Epub 2015 Oct 22. Erratum in: Lancet Oncol. 2016 Jul;17 (7):e270. Erratum in: Lancet Oncol. 2018 Oct;19(10):e509. PMID: 26482279.

Wu S, Chen JJ, Kudelka A, Lu J, Zhu X. Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. Lancet Oncol. 2008;9(2):117-123. doi:10.1016/S1470-2045(08)70003-2