

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 69918

**Title:** Second-line treatment of advanced hepatocellular carcinoma: Time for more individualized treatment options?

**Provenance and peer review:** Unsolicited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 04770380

**Position:** Editorial Board

**Academic degree:** DSc, PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** Russia

**Author's Country/Territory:** Taiwan

**Manuscript submission date:** 2021-09-06

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-09-06 12:09

**Reviewer performed review:** 2021-09-15 20:08

**Review time:** 9 Days and 7 Hours

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|--------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| Language quality   | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion         | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
| Re-review          | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No   |

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| <b>Peer-reviewer<br/>statements</b> | Peer-Review: [ <input checked="" type="checkbox"/> ] Anonymous [ <input type="checkbox"/> ] Onymous<br>Conflicts-of-Interest: [ <input type="checkbox"/> ] Yes [ <input checked="" type="checkbox"/> ] No |
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## SPECIFIC COMMENTS TO AUTHORS

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.

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.
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.
3. Key words: instead of “second line” there should be “second-line treatment”.
4. Introduction: it is recommended not to use subdivisions.
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. 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



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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  $\geq 75$  years (48)". "Safety profiles of ramucirumab were comparable between  $< 65$  and  $\geq 65$ - $< 75$  age subgroups. The incidence of  $\geq$ Grade 3 treatment-related AEs was higher in ramucirumab arm than placebo arm in  $\geq 75$  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. 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. 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.

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**Peer-review model:** Single blind

**Reviewer's code:** 05935994

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Egypt

**Author's Country/Territory:** Taiwan

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**Reviewer accepted review:** 2021-09-16 04:35

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**Review time:** 6 Days and 6 Hours

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|---------------------------|---|
| <b>Scientific quality</b> | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| <b>Language quality</b>   | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>         | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority)<br><input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
| <b>Re-review</b>          | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No   |



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#### **SPECIFIC COMMENTS TO AUTHORS**

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. Introduction: treatment part; regorafenib drug should be mentioned before factors part. References: number of references should be updated.