

ANSWERS TO REVIEWERS



June 05, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17205-review.docx).

Title: Second line systemic therapies for hepatocellular carcinoma: reasons for the failure

Author: Marcello Maida¹, Massimo Iavarone², Maurizio Raineri³, Calogero Cammà¹, Giuseppe Cabibbo¹

Name of Journal: *World Journal of Hepatology*

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The manuscript has been improved according to the suggestions of reviewers:

- 1) Format has been updated
- 2) Revision has been made according to the suggestions of the reviewer

- **REVIEWER #1**

This is well written. I would add your own thoughts as to what is next. Trials utilizing personalized genetic profiles? I would reference and briefly clarify BCLC for readers accustomed to other classifications. I would also mention the futility of any treatment in those with high CPT scores.

Answer: We clarified the potential contribution of the genetic signature in a new brief paragraph, reporting also, as an example, a RCT that recently pointed out the role of genetic expression in predicting outcome in advanced stage HCC patients that receive systemic therapy (page 6, line 7-14). We briefly described the BCLC staging classification (page 3, lines 14-24), adding a comment regarding the futility of any treatment in patients in BCLC D (page 3, lines 25-28).

- **REVIEWER #2**

The authors comment on a difficult situation in the management of HCC. All of the second-line trial fail for patients with tumor progression on sorafenib. The manuscript is well-written. However, the authors do not propose their own recommendations, either for clinical practice or for the design of future second-line clinical trial. Though the authors briefly mention genetic signature can be incorporated in future clinical trial, the statement is vague and not clear. Can the authors add a paragraph to express their recommendation?

Answer: we added a proposed algorithm for the management of patients after discontinuation of sorafenib in clinical practice and proper suggestions for inclusion in II line RCTs (page 7, lines 15-27), adding a specific figure (Figure 1).

As reported above, we clarified the potential contribution of the genetic signature in a new

brief paragraph, reporting also, as an example, a RCT that recently pointed out the role of genetic expression in predicting outcome in advanced stage HCC patients that receive systemic therapy (page 6, line 7-14).

- **REVIEWER #3**

So far sorafenib is still the only recommendation means for advanced stage patients in BCLC system, which is supported by the grade 1iA evidence of EBM. In view of the limitations of AEs and efficacy of sorafenib, more other molecular targeted drugs were applied into trials. Unfortunately, to date, no better drugs were found. The authors reviewed a series of related trials in recent 7 years and focused on analyzing the reason of failure. Importantly, they pointed out the design limitation of the head-to-head test and prognostic heterogeneity in patients who fail to the therapy of sorafenib. It may be the main reason for the failure of second-line treatment. Furthermore, they predict the future feasible solutions such as hierarchical design of second-line trials, genetic signature and expectations therapy. The authors provide us comprehensive understanding and in-depth analysis in this field. It is of great interest and significance either for basic researchers or for clinicians. It is an extremely valuable article. I proposed to priority publishing.

Answer: We thank the reviewer for comments.

3) References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

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