April 26, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2977-review.doc).

**Title:** Mechanisms of resistance to sorafenib and the corresponding strategies in hepatocellular carcinoma

**Author:** Bo Zhai, Xueying Sun

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

**ESPS Manuscript NO:** 2977

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

1. **For Reviewer 1**

Have language polishing done.

1. **For reviewer 2**

This is a good review on the resistance of sorafenib. However, as detailed below, a number of recent studies have not been taken into account, which should be corrected.

Comments 1: Page 4: replace “sorafenib was shown to have a limited median time of symptomatic progress and a lower partial response rate due to drug resistance” by ”sorafenib was shown to result in a limited increase in median time to symptomatic progression and a low partial response rate due to drug resistance” .

Response: Done.

Comment 2: Replace everywhere “sorefanib-resistance “ by “sorafenib resistance”

Response: Done.

Comment 3: Page 4: indicate the range of IC50 values for sorafenib in vitro

Response: As there were different cell lines in two separate studies, it is hard to include the detailed data in the review. We carefully checked this sentence and have made revision as below: “The IC50 values of growth inhibition of different HCC cell lines by sorafenib in vitro showed big variations”.

Comment 4: Replace “Sorafenib executes its anti-tumor activity partially through targeting the Raf-1 and B-Raf by inhibiting the RAF/MEK/ERK signaling pathways” by “Sorafenib executes its anti-tumor activity partially through targeting the Raf-1 and B-Raf, thus inhibiting the RAF/MEK/ERK signaling pathways“. The inhibition of pERK is a consequence of the effect on Raf, thus the “moreover” is not justified

Response: Thanks for the comment. Now it has been corrected.

Comment 5: Page 5: The correlation between pERK levels and response to sorafenib has not been confirmed. This has not been formally published but has been presented at several meetings and discussed by JM LLovet (see for instance Villanueva GASTROENTEROLOGY 2011;140:1410–1426) .

Response: Thanks for the comment. This part has been revised accordingly.

Comment 6: Replace “appraised” by “assessed”

Response: Done.

Comment 7: Replace “muddy” by “of uncertain value”.

Response: Done.

Comment 8: Page 6: replace “unattached” by “unscathed”.

Response: Done.

Comment 9: JAK is not inhibited but activated by the mentioned receptors.

Response: Corrected.

Comment 10: Page 8: replace “Emerging evidence suggests that EMT is involved in and targeting EMT…” by “Emerging evidence suggests that EMT is involved in resistance and and that targeting EMT…”.

Response: The sentence is an elliptical one. It has been revised to “Emerging evidence suggests that EMT is involved in, and targeting EMT can reverse, the resistance of antitumor drugs”.

Comment 11: Replace “The above studies indicate that EMT is involved in the resistance to sorafenib in HCC” by “The above studies indicate that EMT may be involved in the resistance to sorafenib in HCC”

Response: Done.

Comment 12: Page 10 : the results of the phase II study of brivanib have not been confirmed in a large phase II study, the results of which having been presented in major liver and cancer meetings recently. Thus, the paragraph should be modified.

Response: Thanks for the comment. The paragraph has been modified. Unfortunately, the authors do not have the information of recent conferences. The latest results for brivanib in HCC clinical trials were obtained from the website of Bristol-Myers Squibb, the manufacturer of brivanib.

Comment 13: The chapter on tivantinib should be partly rewritten. Indeed, a major finding of this study was to show that only patients with high levels of Met prior treatment benefited from the treatment, indicating that Met could be a predictive biomarker in this case.

Response: Thanks for the comment. This chapter has been modified.

1. **For reviewer 3**

Comment 1: The title may be good as "Mechanisms and the strategies of resistance to sorafinib in hepatocellular carcinoma".

Response: Thanks for the comment. However, the title suggested by the reviewer is also not clear as the article aims to discuss the mechanisms of resistance to sorafenib, and the corresponding strategies to overcome the resistance in hepatocellular carcinoma. Therefore, we would like to add “corresponding” before “strategies”. The revised title will be “Mechanisms of resistance to sorafenib and the corresponding strategies in hepatocellular carcinoma”.

Comment 2: Please check these sentences because their meanings are not clear:

1)...has also drawn attention as sorafenib, as a multilkinase inhibitor, targets several ...

2) ...The parallel PI3K/Akt pathway remains unattached, when sorafenib targets the MAPK pathway and tyrosine kinases by inhibiting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Ret and c-kit...

3) ...Emerging evidence suggests that EMT is involved in and targeting EMT can reverse the resistance of antitumor drugs.

4) In "CONCLUSION" section, the second sentence "The primary resistance of hepatocellular carcinoma (HCC) to sorafenib..." should be "The primary resistance of HCC to sorafenib..."

Response:

1. It has been revised.
2. “unattached” has been changed to “unscathed” following the comment by reviewer 2.
3. The sentence is an elliptical one. It has been revised to “Emerging evidence suggests that EMT is involved in, and targeting EMT can reverse, the resistance of antitumor drugs”.
4. Corrected.
5. **For reviewer 4**

This article is well-structured and very informative. However, there are some concerns that may require the authors’ attention.

Comment 1: In regard to combination therapies involving sorafenib, randomized phase II trials of doxorubicin plus sorafenib vs. doxorubicin, and a phase III trial of sorafenib plus erlotinib vs. sorafenib have already been reported. As for second-line treatment, a phase III trial of brivanib versus placebo has been reported. In addition, phase III trials such as everolimus or ramucirumab, and randomized phase II trials, such as axitinib or GC33 are presently ongoing. The authors should comment on these trials.

Response: Thanks for the comment. The results of clinical trials and the ongoing trials mentioned above, and some recent reports on bevacizumab and erlotinib are all included in the revised manuscript.

Comment 2: No tables or figures are included in this manuscript. Tables and figures illustrating the study findings make it easier to understand the contents of a manuscript.

Response: Two tables are added to the manuscript.

All the changes made the manuscript according to the comments by reviewers are highlighted in red.

We hope the revised manuscript is now acceptable for publishing in *World Journal of Hepatology.*

Sincerely yours,

Xueying Sun, MD, PhD

The Hepatosplenic Surgery Center

Department of General Surgery

The First Affiliated Hospital of Harbin Medical University

Harbin, China

Telephone/Fax: +86-451-53643628

E-mail: kevsun88@hotmail.com or k.sun@auckland.ac.nz