Dear Gong:

Thank you for giving us the opportunity to revise our manuscript " Adjuvant sorafenib in hepatocellular carcinoma: a cautionary comment of STORM trial" (26921). We appreciate the reviewer's comments, to which we respond point-by-point below. We have indicated all changes.

Best wishes,

Jian-Hong Zhong

Reviewer Comments to the Author:

Reviewer: 1

Nice editorial, clear and convincing.One orphographic error: "trialinvolving" - page 4, line 3 at the bottom

Response: We thank the reviewer. We have revised this word.

Reviewer: 2

In this manuscript, Zhong JH et al. described sorafenib therapy as adjuvant treatment in hepatocellular carcinoma patients. There are several problems to be corrected.1. Please rewrite the Author contributions. Authors wrote that “Zhong JH and Du XK designed the study” and “Zhong JH, Wang YY, Gong WF, Ma L, Xiang BD, and Li LQ analyzed the data”. This manuscript is not an original article. These expressions are regarded to be incorrect. Where is the analyzed data in this article?

Response: We rewrote this content.

2. The context from the 2nd to 3rd paragraphs would not be so good. In the 2nd paragraph, authors introduced a trial in which sorafenib was administrated after surgery. The next paragraph, they were to demonstrate the opposite results of other trials. However, they described here the trial in which sorafenib was used as adjuvant after TACE, which disturbed the context. Instead, discussing the results of STORM here would lead to the better understanding by readers. In addition, thinking of adjuvant therapy after surgery, STORM trial is very important one. Therefore, the name of Phase III trial “STORM” should be added in the main body.

Response: We thank the reviewer. We have rewrote these paragraphs.

Reviewer: 3

This editorial entitled “Adjuvant sorafenib in hepatocellular carcinoma: do we go right?” was well written and interesting in its field although the conclusion might be a bit exaggerated. The authors want to assess questions about the value of sorafenib for patients with hepatocellular carcinoma after surgery. Here some comments: 1. Up till now the only tumor-directed palliative option for HCC is sorafenib, an oral multi kinase inhibitor. The title made indicates that we need to review again the use of sorafenib. In this case, the discussion about any other option replacing sorafenib should be also included in the text, otherwise the title should be adjusted accordingly.

Response: We have added a paragraph at the last of this editorial.

2. There are some parameters to assess whether a drug has a good efficacy in treatment response, such as survival, time to progression, disease free survival, adverse reaction, risk of recurrence, efficacy against metastasis, etc. It would be better if author summarizes from all the references and clinical trials based on those parameters and therefore the efficacy of sorafenib can be assess more objective both in positive and negative results.

Response: All these results were summarized in Table 1.

3. It is best to provide all the clinical trials or study in one table mentioning its positive or negative result.

Response: Table 1.

4. The author mentioned in page 5 that sorafenib may worsen outcomes in certain patients. However it was not suitable with the reference provided (ref 3) in which a study by Bruix J (J Hepatol. 2012;57:821-9) mentioned that from their exploratory subgroup analyses showed that sorafenib consistently improved median OS and DCR compared with placebo in patients with advanced HCC, irrespective of disease etiology, baseline tumor burden, performance status, tumor stage, and prior therapy. And from reference 9, although the conclusion made stating that sorafenib is not an effective intervention in the adjuvant setting for HCC, we can see inside the article that the disease progression by sorafenib is better than placebo (recurrence for sorafenib /placebo : 170/279).

Response: Actually, in the trial of STORM, significantly more recurrence-free survival events occurred in the placebo group (270/558) than in the sorafenib

group (194/556, p<0.001) after median follow up of only 8.5 months. In fact, median recurrence-free survival was slightly longer in the placebo group according to the independent radiological assessment (33.7 vs. 33.3 months; p=0.26).

5. In the last paragraph, both clinical trials NCT00908752, NCT01009801 were terminated, therefore it is not wise to make conclusion based on these study.
Response: We have rechecked these two trials. And we revised the sentence as: in this sense, some ongoing trials of adjuvant anti-angiogenic agents for solid cancers (e.g. NCT00908752, NCT01009801) are already terminated