

## ANSWERING REVIEWERS



April 5, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9601-review-certificated with figures.docx and 9601-review-certificated.docx).

**Title:** Indicators of sorafenib efficacy in patients with advanced hepatocellular carcinoma

**Author:** Masayoshi Yada, Akihide Masumoto, Kenta Motomura, Hirotaka Tajiri, Yusuke Morita, Hideo Suzuki, Takeshi Senju and Toshimasa Koyanagi

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 9601

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 reviewers. Moreover, the revised manuscript has been polished and certificated by AmEditor Inc. according to the suggestion of your science editor.
  - (1) According to language polishing, the title of the manuscript was changed to "Indicators of sorafenib efficacy in patients with advanced hepatocellular carcinoma".
  - (2) As the results of language polishing by the company, we changed the title of sections of **RESULTS**, which were listed below.
    - i. We changed the 1<sup>st</sup> section, "*Characteristics of patients and adverse events*" to "*Characteristics of patients and treatment outcomes*".
    - ii. The 2<sup>nd</sup> section, "*Overall survival and time to progression*" was incorporated into the 1<sup>st</sup> section "*Characteristics of patients and treatment outcomes*".
    - iii. We added the new 2<sup>nd</sup> section "*Factors contributing to OS*".
    - iv. We changed the 3<sup>rd</sup> section "*The relationship of time to progression with contributory factors*" to "*Factors contributing to TTP*".
    - v. We made the new 4<sup>th</sup> section "*Comparison of clinical factors by location of major HCC*".

- (3) According to the reviewer 2860818's comment and the reviewer 742216's comment (Major point I), we added the 2nd clause to the 2nd sentence of *Characteristics of patients and treatment outcomes*: "At the beginning of treatment, patient liver function was designated as Child-Pugh grade A (CP-A) ( $n = 30$ ) or B (CP-B) ( $n = 16$ ). The major sites of HCC were intrahepatic ( $n = 28$ ) or extrahepatic ( $n = 18$ ), and etiologies were described as from hepatitis C virus ( $n = 26$ ), hepatitis B virus ( $n = 9$ ), or other ( $n = 11$ )."
- (4) According to the reviewer 2860818's comment, we added Figure 2 and the 1st paragraph of *Factors contributing to OS* and the 1st paragraph of *Factors contributing TTP*: "Results show that the median OS did not correlate with the etiology of HCC (Figure 2A)." and "The etiology of HCC was not associated with the median TTP (Figure 2B)". Accordingly, we changed Figure 2A-B, C-F and Figure 3 to new Figure 3A-B, D-G and Figure 4.
- (5) According to the reviewer 742216's comment (Major point I), we added a column of the size of the largest tumor to Table 2 and the 2nd paragraph line 3 of *Factors contributing to OS*: "Furthermore, the median OS of patients with  $T_{max} < 5$  was significantly longer than those with  $T_{max} > 5$  (496 vs. 245 d;  $P < 0.01$ ), and a multivariate analysis indicated that tumors  $>5$  cm significantly affected OS ( $P < 0.01$ ) (Table 2)." We further analyzed the relationship of TTP with the size of the largest tumor, and added a column of the size of the largest tumor to Table 3 and new Figure 3C, and the 3rd sentence of *Factors contributing to TTP*: "Tumor size was not associated with TTP, with no significant difference between patients with  $T_{max} < 5$  and  $T_{max} > 5$  (112 vs. 98 d) (Figure 3C, Table 3)."
- (6) According to the reviewer 742216's comment (Major point II), we added Table 4 and the 4th section of results "*Comparison of clinical factors by location of major HCC*": "Clinical factors were compared between patients with intrahepatic and extrahepatic major HCC (Table 4). The median diameter of the largest tumor was significantly larger in patients with intrahepatic major HCC compared to those with extrahepatic major HCC ( $P < 0.01$ ). Portal invasion of HCC was also more frequently observed in patients with intrahepatic major HCC ( $P < 0.01$ ). However, patient age or sorafenib dose were not correlated with location of major HCC." We further discussed in the 2nd paragraph line 10 of discussion: "Moreover, patients with intrahepatic major HCC had larger intrahepatic tumors and more frequent portal invasion than those with extrahepatic major HCC. As a result, hepatic arterial blood flow may have been increased, attenuating the efficacy of sorafenib."

(7) Answer for the reviewer 742216's comment (Minor point i):

Sorafenib is the recommended first-line treatment of patients with BCLC stage C HCC, and therefore, we excluded 24 patients with BCLC stage B and D. Additionally, we excluded 10 patients receiving sorafenib less than 30 days.

(8) Answering for the reviewer 742216's comment (Minor point ii), we described that patients with intrahepatic major HCC had the largest tumor intrahepatically.

(9) According to the reviewer 742216's comment (Minor point iii), we cited the literatures of Zugazagoitia J et al. [ref 16, PMID 22875650] and Llovet JM et al. [ref 17, PMID 9862851] and added the 1st paragraph line 5 of **DISCUSSION**: "Multivariate analysis showed that the size of the largest tumor was the only factor that correlated significantly with OS, though CP-A was associated with a prolonged OS according to a univariate analysis. Hepatic function affects OS<sup>[16]</sup>, consistent with untreated or nonsurgical HCC<sup>[17]</sup>."

We were unable to cite previous papers which had reported the presence of extra-hepatic HCC to be a good prognostic parameter of the sorafenib treatment. That is why we consider that this is new finding in our paper.

(10) We changed format of tables to 3-line table format.

3. References and typesetting were corrected

Thank you very much for your kind consideration for publication in the *World Journal of Gastroenterology*.

Sincerely yours,



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