

20 Dec 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: HCC Targeted therapy for WJG 13-12-21 final.doc).

Title: Development of Systemic Therapy for Hepatocellular Carcinoma at 2013: Updates and Insights

Author: Stephen L. Chan, Winnie Yeo

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6592

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:

i. BRISK-FL: it should be mentioned that this was a non-inferiority design and that the goal of non-inferiority for brivanib was not reached (leading to the discontinuation of the brivanib-program)

Reply: The revised manuscript has included this point. (page 5 and 6)

ii. page 10 HDAC: please check the description of the mechanism of action: seems to be a mistake (less condensed-inactivation of gene transcription?)

Reply: Thank you for the proofread. It has been amended accordingly (page 10).

iii. page 13, first sentence: does not make sense, please check (patient population?)

Reply: The typo has been amended accordingly (page 13)

iv. Combination treatments: it is not correct that the study by Melanie Thomas in the end yielded impressive result. The JCO publication was only an interim analysis, the final publication was much less impressive (Kaseb et al., *Oncology* 2012; 82: 67; please present this as well/instead). So it is not surprising to see another study (ref. 57) showing much less impressive results.

Reply: The point is well taken and the manuscript has been amended accordingly to give a more comprehensive picture to readers (page 13 and 14).

v. chemotherapy, page 14: it should be noted that the EACH study did not include a control arm (sorafenib or at least placebo), so it only proved that it was less toxic than the comparator regimen. So far, no chemotherapy regimen was ever able to show a survival advantage in any stage of HCC. Unfortunately, the anti-tumor activity seems to be offset by the hepatotoxicity.

Reply: Thank you for the comments. The statement on chemotherapy has been amended accordingly

(page 14).

vi. page 16, TACE-combinations: it is incorrect that the SPACE trial did not yield a significantly positive effect in the TTRP, since the predefined p-value for the one-sided log-rank test was set at 0.15; so the trial is a positive trial from a statistical point of view. It is however true that nobody is impressed by the results. Please also rephrase page 16, since the results were not "negative" but certainly "discouraging" or "unimpressive".

Reply: The wording on description of SPACE trial has been amended.

vii. page 17: the description of the BCLC stage C is inaccurate, please improve -staging systems: references 72 and 74 are the same manuscript and this is of extremely poor quality (reasons are given in commentary in J Hepatol 2012; 56: 488) and misleading: this manuscript should never be cited or used as an argument for a staging system. It is very important to distinguish between "prognostic systems" (not the primary intention of BCLC but also useful to some extent) and "treatment staging systems" like BCLC

Reply: The perception of reviewer on staging system is well taken. We understood the area on staging system for HCC is still highly controversial. We have amended the point in the revised manuscript to address the point of reviewer. However, we still consider the reference by Huitzil-Melendez FD et al. to be worthwhile for citing in the manuscript.

viii. page 18: a comment on selection tools for selection patients for TACE (e. g. ART-score, Hepatology 2013) might be reasonable here -references: please check for current citation;

Reply: This reference has been added as suggested.

ix. A manuscript published in 2011 (e. g. ref. 57) can be cited with the full reference, not only with the DOI.

Reply: This reference has been updated.

Reviewer 2:

i. references should be updated and should be changed to the correct form (for example, sometimes "J Clin Oncol", but sometimes "Journal of Clinical Oncology"). The reference number in the Table 1 might be wrong and should be corrected (Ref 83-85 are not included in the reference section).

Reply: The references have been updated according to the style of journal. The references in the table 1 has also been amended.

3 References and typesetting were corrected

Yours sincerely,

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