

Dear Science Editor Ruo-Yu Ma and reviewers,

We thank you for your critical review of our manuscript entitled “Change in arterial tumor perfusion is an early biomarker of lenvatinib efficacy in patients with unresectable hepatocellular carcinoma.”

We greatly appreciate the very constructive comments and valuable suggestions, which have been incorporated into our revisions to produce what we believe is a significantly improved and extensively revised manuscript.

Please see the attached files for our point-by-point responses to the comments from the reviewers. We have denoted our revisions by underlining to facilitate re-review. We appreciate the constructive comments provided by the reviewers.

Sincerely yours,
Hidekatsu Kuroda, M.D

Our responses to the comments from the reviewers are as follows:

RESPONSES TO THE REVIEWER 03502244

Comment #1: Well written manuscript. Needs English proof reading.

Response: We thank the reviewer for the valuable suggestion. According to your suggestion, we have received proofreading again, and have attached the updated language certificate.

RESPONSES TO THE REVIEWER 02451459

Comment #1: It would also be good to compare and contrast the magnitude of arterial tumor perfusion changes with previous studies on sorafenib. The results would further justify the efficacy of lenvatinib in comparison, and provides stronger evidence that this is indeed a suitable biomarker for efficacy.

Response: We fully agree with this comment. According to your suggestion, we have added a comparison between our study on lenvatinib and previous studies on sorafenib in the DISCUSSION section (page 10, line 10~).

Comment #2: Why is Day 7 selected as the duration for monitoring? Were there prior studies that examined other duration as well? This information would help to ascertain if the conditions for monitoring has been optimized.

Response: We thank the reviewer for the valuable suggestion. We selected Day 7 for monitoring as it was used in previous studies on sorafenib. The paper by Sugimoto et al. (2012) clearly indicated that the ratio between the CEUS parameter values at baseline and Day 7 was significantly different in responders and non-responders to sorafenib therapy. We have added the reason that we set Day 7 as the duration for monitoring in the METHODS section (page 7, line 33~).

Comment #3: Between patients with steady disease and progressive disease, were there any differences in terms of the arterial tumor perfusion parameters? This information would be helpful to determine the biomarker is robust enough to provide a good read-out of a graded response.

Response: Thank you for these appropriate comments. There were no significant differences between patients with stable and progressive disease in any TIC parameters. We have added this in the RESULTS section (page 9, line 19~).

RESPONSES TO THE REVIEWER 02998194

Comment #1: The need for credible biomarkers is well-known and with your study you fulfill this aim. Your study is a comprehensive study that demonstrate a biomarker for a promising novel treatment for HCC.

Response: We thank the reviewer for the careful reading my manuscript and fruitful suggestions.