

RESPONSE TO REVIEWERS:

We wish to express our appreciation to the Reviewers for their insightful comments, which have helped us to significantly improve the paper.

Reviewer 1's comment 1:

The authors showed the median cumulative dose was 20,000mg. Does the cumulative dose have difference between the two groups (the intervention group and non-intervention group)? If the patients in the intervention group take the higher dose which may induce more severe AEs than non-intervention group, they may get the better OS just because of the higher dosage.

Response:

We thank the Reviewer for this pertinent comment. According to the Reviewer's comments, we evaluated the median cumulative doses in the intervention and non-intervention groups, which were 32,200 and 17,400 mg, respectively, showing a significant difference ($P = 0.047$). Intervention by pharmacists prolonged the TTF and improved adherence, involving the MPR and cumulative dose, leading to an improvement in OS.

Reviewer 1's comment 2:

If possible, the authors can clarify that all patients enrolled in this study receive no other treatment in the same time because some physicians indeed choose the sorafenib therapy combined with other therapeutic strategy such like transarterial

chemoembolization or radiotherapy for the longer time to disease progression or OS.[1.2]

Response:

We thank the Reviewer for this pertinent comment. As the Reviewer noted, a study indicated that the combination of sorafenib and transcatheter arterial chemoembolization (TACE) improved the TTP. We did not combine sorafenib therapy with other treatment methods, such as TACE; monotherapy with sorafenib resulted in the acquisition of a surrogate marker that improves OS.

Reviewer 1's comment 3:

In this study, the sample size is a weak point. A meta-analysis was published this year which included 12 cohort studies with 1017 participants and found the similar conclusion, the HFSR is a beneficial indicator for HCC patients receiving sorafenib.

Response:

We thank the Reviewer for this pertinent comment. As the Reviewer noted, the sample size of our study was small, but a meta-analysis of the data obtained from 1,017 subjects, involving 12 cohort studies, showed that HFSR was a beneficial indicator that improves the prognosis. In addition, we established a double-check system consisting of primary outpatient care by pharmacists specializing in cancer treatment and secondary outpatient care by physicians. As a result, an improvement in adherence was achieved, and maximum therapeutic effects on HCC were obtained, suggesting that MKI-associated HFSR is a surrogate marker for OS even when the sample size is small.

Thank you again for your comments on our manuscript. We trust that the revised manuscript is now suitable for publication.