

Reviewer #1:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: as suggested in the attached file, we urgently invite you to more systematically write this review/product monograph

1. Suggested correction: Registered tyrosine Kinase inhibitors targetting vascular endothelial growth factor reduce angiogenesis.

R: Thank you for your kind suggestion. we have modified the summary in the revised manuscript(25-26)

2. 16 pages of review is not brief.

R: Thank you for your kind suggestion. we have deleted it in the revised manuscript. (9)

3. This is considerably shorter than the placebo treated arm in the trial by Llovet et al. NEJM 2018. Update is suggested.

R: Thank you for your kind suggestion. Because most of the use of apatinib is in the Asia-Pacific region such as China, I do cite the the trial by Llovet et al. as well as the experimental results of the placebo treated arm of Sorafenib in the Asia-Pacific region.(38-39)

4. Please include reference

R: Thank you for your kind suggestion, we have already found a certain reference in the "Guidelines Insights: Hepatobiliary Cancers, Version 2.2019".(41.42)

5. Relation to results of other studies (e.g. Llovet NEJM 2008)

R: Thank you for your kind suggestion. The purpose of this phase II clinical trial is to explore the efficacy and safety of different doses of apatinib. The results are not very relevant to the studies of Llovet, and the results are that there is no difference in the efficacy of different doses (750mg and 850mg).(149-152)

6. Please include reference

R: Thank you for your kind suggestion. We have already found a certain reference in the studies of Lankhorst, S., et al. and Touyz, R.M. et al. which are listed below.(219-221)

7. There are no studies supporting this claim.

R: Thank you for your kind suggestion. We have already found a certain reference on this opinion in the studies of Shigeta, K., et al. which is listed below.(269-273)

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Well written manuscript but some minor comments: -Brief description of the parthenogenesis of HCC is needed - Barcelona clinical staging (BCLS) is better to be included with lines of treatment of HCC to define the actual place and role of the drug

1. Please delete this; no established data to support this!

R: Thank you for your kind suggestion. We have changed the title into "Apatinib as an alternative therapy for advanced hepatocellular carcinoma" .(1)

2. We thus want to see IC50 values here and comparison to other VEGFR inhibitors such as tivozanib

R: Thank you for your kind suggestion. We have added the IC50 values in the manuscript. (81-83)

3. Too much detail; this is a clinical drug monography

R: Thank you for your kind suggestion. We have deleted the redundant content. (88-90)

4. Thus not significant?

R: Thank you for your kind suggestion. The purpose of this phase II clinical trial is to explore the efficacy and safety of different doses of apatinib. The results are not very relevant to the studies of Llovet, and the results are that there is no difference in the efficacy of different doses (750mg and 850mg). (149-152)

5. What is the difference between adverse reactions and adverse effects; this paragraph is inconsistent

R: Thank you for your kind suggestion. We have changed all the "adverse reactions" into "adverse effects". (255-257)