

## 25695 Topic Highlight

Dear Editor,

Thank you for the preliminary acceptance and for the reviewers' suggestions which help us to improve our paper. Following you will find point by point response to your comments:

1. Reviewer 00680628:

- "For easy understanding, a table form may be clear and favorable (as Table 1 and Table 2 in the manuscript; including Child-Pugh grade, vascular involvement, tumor number and size, adverse effects, overall survival, etc. ).": published studies are reported in the text, while ongoing studies are summarized in the tables. As a result, the information required (Child-Pugh grade, vascular involvement, tumor number and size, adverse effects, overall survival) were not available for ongoing studies reported in the tables (<https://clinicaltrials.gov/ct2/search/advanced>). However, they were modified including Child-Pugh grade;
- "Besides tumor aggressiveness, degree of liver dysfunction and adverse effects of drugs may contribute to overall drug benefit. Systemic chemotherapy is usually not well tolerated by patients with significant underlying hepatic dysfunction. The authors should address these factors." : on page 3 line 35 we integrate with the following: "HCC is considered a relative chemorefractory tumor..."
- "The manuscript provided many studies in ongoing clinical trials. As described in the discussion, "some of new molecules disappearing after phase I/II studies without published results". As this is a review article, drugs used in these clinical trials may be deleted because of unknown results." : In the present paper clinical trials with unknown results were just omitted both in the text and in the tables.
- "Targeting therapy in non-advanced HCC is worthy mention": on page 5 line 6 we reported an ongoing study in initial HCC "Sorafenib is also under evaluation in initial HCC in association with stereotactic radiosurgery (RTOG-1112)." Moreover, on page 14 line 29 a further comment is added: "Until now, all efforts are concentrated on advanced HCC, because transplantation, surgery and local treatments gave the best chance of cure in early HCC. However, attempts to reduce

recurrences are ongoing especially with sorafenib in association with local therapies. ”

- “Reference 1 cited is inappropriate..”: reference 1 has been substituted with a recent one.

**2. Reviewer 02936403:**

- The manuscript by Montella et al., investigate whether novel targeted drugs really impact the next future. Overall, this manuscript is clearly written and discusses most of novel drugs in HCC therapy.

Thank you for the positive comments.

**3. Reviewer 00503516**

On page 15 line 34 comments on toxicity related to bortezomib were reported.

We have tried to provide all points required to our manuscript (Topic Highlight), however, as communicated in our previous mail, we were unable to complete “Step 4. Please subject the manuscript to *CrossCheck* analysis and the final title to Google Scholar search, and store screenshot images of the results.”

We hope that you could help to get the final acceptance of the manuscript.

Thank you in advance

Liliana Montella behalf of the Authors