Point-by-point response to the reviewers:

Reviwer#1 (**Reviewer's code:** 00006459)

Thank you for your valuable comments.

1. Reviewer's comment:
    1. *The author comment about weight-based dosing is commended; I encourage addition of any further evidence that can be cited that would support this conclusion.*
    2. *It is necessary to add information and commentary about adverse events / side effects that were associated with the new medicines.*
    3. *Please add reference numbers to each table so that there is clarity regarding the publication or publications that the presented data is derived from.*
    4. *I prefer that in each figure legend there be clarity regarding the publication or publications that the data referred to is derived from.*
    5. *The paragraph that extends over pages 17 and 18 could be reconsidered to provide greater clarity, please. I would not use the word "extremely" here.*
    6. *Page 18 para 2: rephrase "This will increases .."*
    7. *Page 20: I suggest even more caution in comments on data that , as is mentioned, is from n=21 and n=26 patients.*

Author's response:

1. I added one reference, which support the weight-based dosing in the revised manuscript (page 8, line 15).

2. I added information and commentary about adverse events/side effects that were associated with the new medicines.

   Lenvatinib: page 9, line 2-8

   Regorafenib: page 10, line 4-7

   Cabozantinib: page 13, line 13-15

   Ramucirumab: page 14, line 15-19

   Nivolumab: page 20, line 7-9

   Pembrolizumab: page 21, line 1-4

3. Reference numbers were added to each table 1-8.
4. Reference numbers were added to each Fig 1-5.
5. As suggested, sentences were corrected for clarity and the term "extremely" was deleted.
6. As suggested, it was rephrased as follows; This high tumor response obtained in many patients will increase
7. As suggested, the sentence was added as follows; However, again we have to be cautious on the results derived from small numbers of patients in phase 1/2 trial similar to atezolizumab/bevacizumab combination trial.

Reviwer#2 (**Reviewer's code:** 00503516)

Thank you for your valuable comments.

Reviewer' s comments:

1. *By looking at table 1, it does not seem that Lenvatinib has been used in clinical trials*

1-8.

2. *It is necessary to more extensively describe the data reported in figure 4.*
3. *In figure 5, it is necessary to specify the time measure unit (weeks? Months?)*

Author's response:

1. Reviewer's comment is correct. Sentences were corrected for the clarity of this statement (page 5-6 in the revised manuscript) as follows; Although eight clinical trials with various agents/modalities comparing with sorafenib conducted in the last decade has shown negative outcomes, the results of the REFLECT trial with use of lenvatinib met its primary endpoint of non-inferiority of prolonging OS compared with sorafenib.
2. As suggested, more detailed explanation was added to legend of Fig 4 as follows; such as immunosuppressive cells (tumor associated macrophage, regulatory T cells and myeloid-derived suppressor T cells) or tumor suppressive cytokines (IL10 or TGF-β). Lenvatinib also suppress the co-inhibitory checkpoint inhibitor, TIM 3 and increase the co-stimulatory molecules, CD137, OX40 or ICOS.
3. As suggested "months" was added in Fig 5.

Reviwer#3 (**Reviewer's code:** 03538879)

Thank you for your valuable comments.

Reviewer's comments:

1. *The enhanced efficacy of combination therapies rely on the identification of serum or tissue biomarkers that would allow a better patient selection for individual treatments. So, can you comment on that about the biomarker identification for*

HCC treatments ?As we know, with the best suitable biomarkers we selected may decide the patients who are fit for one or combination therapy.

2. *What's your opinion on the ongoing CheckMate-459, Everyone is eagerly awaiting the results. Is it will be a huge change if the results are positive?*

Author's response:

1. Reviewer's comment was well taken. However, although extensive research on finding biomarker that predicts the response to monotherapy or combination immunotherapy, unfortunately no promising biomarker was found so far. We need to keep trying to find out such biomarkers. This statement was added in the revised manuscript as follows; Biomarker that predicts response to immunotherapy or combination immunotherapy is still an unmet need in immunotherapy of HCC and extensive effort to identify such biomarkers is warranted.
2. I agree everyone is awaiting the results of CheckMate-459. However, we need to wait some time for the results. If the trial is positive, 1st option among the 1st line agents becomes undoubtedly should be nivolumab since its durable long-lasting response in responders. Following sentences were added in the revised manuscript; If this study is positive, 1st option among 1st line agents will undoubtedly become nivolumab because of its durable long-lasting response in responders.

Reviwer#3 (**Reviewer's code:** 00069630)

Thank you for your valuable comments.