Reference: Manuscript Number: 38197

Title of the Manuscript: Targeted Therapy or Immunotherapy? Optimal Treatment in HCC

1. Reviewer ID#: 03003338

Comments to Authors:

1. The authors should modify the outline and the structure to make the content to corresponding to the title. 2. The authors should check the manuscript carefully to avoid repeated appearance of same data in different parts in the text. For example, the second paragraph on page 4 was seemed to be copied to be the second paragraph on page 8. 3. The numbers from the same reference differed in different parts of the text by mistake? For example, the numbers in the last paragraph on page 6 were completely different with those in the second paragraph on page 10. However, both of them refer to Ref12. 4. The Conclusion part. The authors should rewrite the session and be careful with grammatic problems. 5. The whole article should be typed carefully to leave space between words.

Classification: Grade D (Fair)

Language Evaluation: Grade B: minor language polishing

Conclusion: Major revision

Response: Thank you for your review

1.1. We have changed the outline to corresponding to the title of targeted therapy and immunotherapy. (Please see the yellow highlights).

1.2. The data for nivolumab as first line and second line were from the same reference, but they were from different patient population. Nivolumab as a first

line treatment in HCC (page 4) was evaluated in 56 sorafenib naïve patients, but nivolumab as a second line treatment (page 8) was evaluated in 214 HCC patients. The most common AEs and grade 3/4 AEs were the same, but I already deleted the AEs on nivolumab as a first line treatment.

1.3. The reference for PD-L1 as a biomarker has the same reference in nivolumab study (ref # 12). Only for the RR data in PD-L1.

1.4. No change in conclusion section. We already proofread the entire article and have edited the grammatical error including were (in AEs sections). Please see the yellow highlights.

1.5. The whole article has been typed carefully.

2. Reviewer ID#: 02445408

Targeted Therapy or Immunotherapy? Optimal Treatment in HCC Contratto M et al. Targeted Therapy or Immunotherapy? Optimal Treatment in HCC Name of Journal: World Journal of Gastrointestinal Oncology Manuscript Type: MINIREVIEWS

1. - The overall structure of the manuscript: it contains title, abstract, key words, core tips, introduction, main body, conclusions and references. Methods is absent. Title reflects the major topics and content of the study. Abstract reflects importance of the work, it background but lack of method

Response: Method: This minireview summarizes potential treatments in HCC based on clinical trials that have been published in manuscript or abstract format from 1994 – 2018.

2. - The scientific question proposed:
   Hepatocellular carcinoma is a lethal disease associated to B or C Hepatitisand Hepatic cirrhosis (alcoholic or not). Patients with advanced hepatocellular carcinoma often have a poor prognosis and limited treatment options following prior systemic therapy.
   Immunotherapy offers systemic treatment options in first and second line treatment. Having in count that sorafenib is a tyrosine kinase inhibitor that has been approved by FDA for the first line treatment of HCC due to the achieved improvement in median overall survival authors described the characteristic of the drugs and the principal trials that led to this achievement. They also described drugs that are considered potential first and second line systemic treatment options in HCC that have been studied in different protocols and the rationale for this proposal.
   Response: Agreed
   3.- Authors made a revision of the last trials in the referred disease. It is a complex disease that needs a

comprehensive approach. Theyproposed the optimal sequencing of treatment and the potential biomarkers that may predict benefits according to the therapy

Response: Agreed

4. Authors cited main actual research to support the information presented. In the main body of the work they made the discussion according to the results of each investigation, which significantly give information to the potential lectors.The diagram of the potential sequencing treatment options in HCC is explicative.

Response: Agreed

5.- The discussion is in the main body of the work not in a discussion section, but I believe that brings enough information to the lector according to the state of art in the treatment of HCC

Response: Agreed

6. Conclusions are clearly presented. They provided encouraging for further investigation.

Response: Agreed

7. References are according to the actual research in the field of HCC investigation.

Response: Agreed

8. The manuscript present consideration of a very important cancer problem today

Response: Agreed

9. The manuscript is original

Response: Agreed

10. There is no indication of academic misconduct

Response: Agreed

11. The manuscript presents the addition of tumor biomarkers that might be used in order to predict response to treatment

Response: Agreed

12. Title reflects the major topics and content of the study.

Response: Agreed

13. Yes, I think so

Response: Agreed

14. Yes, I think so Conclusions: Hepatocellular carcinoma is one of the principal causes of cancer death all over the world, it is a necessity to find the more effective and safe systemic therapy to treat this cancer. Authors presents promise for improvement of therapeutic options in HCC. Weakness: the absent of the description of the method Authors work referred to a very sensitive problem, with the description of the state of the art in the

investigation field, then I think that I it will be important for the medical practice of medical community If authors delineate the method of the article it should be published

Response: Agreed. We have added the method in abstract and some information in conclusion. Thank you

Comments to Authors: It is a good work Need only a minor revision

Classification: Grade C (Good)

Language Evaluation: Grade B: minor language polishing

Conclusion: Minor revision

Response: Thank you very much, reviewer.

2.1. We have added the method in abstract: This minireview summarizes potential treatments in HCC based on clinical trials that have been published in manuscript or abstract format from 1994 – 2018.

2.2. Agreed

2.3. Agreed

2.4. Agreed

2.5. Agreed

2.6. Agreed

2.7. Agreed

2.8. Agreed

2.9. Agreed

2.10. Agreed

2.11. Agreed

2.12. Agreed

2.13. Agreed

2.14. We have added some information in conclusion.

3. Reviewer ID#: 01851506

Comments to Authors:

In this review Contratto and Wu reviewed the optimal treatment in hepatocellular carcinoma (HCC) with the tyrosine kinase inhibitors or monoclonal antibodies against the immune checkpoint inhibitors such as Programmed Death (PD)-1/PD-ligand(L)1. Furthermore, they discussed the biomarkers relevant to maximize the response of HCC treatment such as alpha-feto protein (AFP) and PD-L1, with ramucirumab (anti-VEGFR2 monoclonal antibody) and with anti-PD-L1 monoclonal antibody, respectively. Also they discussed the future direction biomarkers such as neoantigen, tumor mutational burden, and interferon gamma for HCC treatment. The review is concise but comprehensive, and easy to follow. However, there are some concerns about the accuracy of the description. (1) In page 7, Pembrolizumab is an immunotherapy that inhibits PD-1. Given Pembrolizumab is anti-PD-L1 monoclonal antibody that inhibits PD-1 - PD-L1 interaction, the above description is not accurate. (2) In page 9, In a phase II dose expansion cohort study of nivolumab in HCC patients either progessed or intolerant of sorafenib, RR was 32% versus 17.2% in patients with PD ≥ 1% and PD-L1 < 1%, respectively[12]. The reviewer wonders which the authors discuss here, PD-1 or PD-L1? The reviewer guesses that the authors want to compare the percentage of PD-L1 between progressed HCC patients and those intolerant of sorafenib. Should comparison between "PD ≥ 1% and PD-L1 < 1%" be correct, the authors need to explain more.

Classification: Grade B (Very good)

Language Evaluation: Grade B: minor language polishing

Conclusion: Minor revision

Response: Thank you for your review

3.1. Regarding the pembrolizumab, it is an anti-PD-1 antibody as you can find the mechanism of action in reference #16.

3.2. For phase II dose expansion cohort study of nivolumab in HCC patients who progressed or intolerant to sorafenib, this study has been published and presented that HCC patients with PD-L1 ≥ 1% had higher RR compared to HCC patient with PD-L1 < 1% regardless of whether the patients progressed or intolerant to sorafenib. I have corrected the right value for RR (26% versus 19%).

4. Reviewer ID#: 02994003

Comments to Authors:

The manuscript is well written. It was better if authors added more one diagrammatic figure and one or more table

Classification: Grade B (Very good)

Language Evaluation: Grade A: priority publishing

Conclusion: Accept

Response: Thank you for your review.

5. Reviewer ID#: 00502973

Comments to Authors:

In this manuscript, the authors briefly reviewed the current status of HCC treatment by small molecular targeted medication and mAb therapy and proposed a potential roadmap of HCC treatment. This is relevant to the scope of the Journal and interesting. Some concerns existed and need to be addressed. 1. The English can be refined. 2. In the Neoantigen section, the author stated "it produces neoantigen signature that contains four amino acid strings of peptides." Please provide the sequence of this four amino acid string. 3. In the Nivolumab section, what is HBC? 4. In the section of "Potential first line systemic treatment options in HCC", "In the randomized phase III (REFLECT) study of lenvatinib vs sorafenib in first line treatment of unresectable HCC in 954 patients (1:1) with Child Pugh Class A." is an incomplete sentence.

Classification: Grade C (Good)

Language Evaluation: Grade B: minor language polishing

Conclusion: Minor revision

Response: Thank you for your review.

5.1. It has been refined.

5.2. The four amino acid string was provided in the supplementary appendix of Reference # 20 (Figure 3A, figure 3B, table S6 and S7).

5.3. It should be HBV. I have corrected it. Thank you.

5.4. I have completed the sentence, please see the yellow highlights.