

## Reply to comments

### Dear Editors and Reviewers:

Thank you for your consideration for our manuscript. We have carefully revised our manuscript according to the reviewers' comments. The revised parts were indicated with red color in the revised manuscript. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Reviewer #1: Zeng et al. reviewed "Advances in postoperative adjuvant therapy for primary liver cancer".

1. In abstract section, How was immune checkpoint inhibitors (ICI)?

**Reply:** Thank you for your comments. We have modified "adjuvant systemic therapy (e.g., molecular targeted agents)" to "adjuvant systemic therapy (e.g., molecular targeted agents and immunotherapy)" in abstract section. Please see the page 3 line 60 in the revised manuscript.

2. In Introduction section, "HCC often occurs in the setting of chronic liver disease with or without cirrhosis, and the most common etiologies are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol intake, and aflatoxin exposure." How was NASH?

**Reply:** Thank you for your advice. We have added the content of NASH as "Growing evidence suggests that nonalcoholic fatty liver disease (NAFLD) especially nonalcoholic steatohepatitis [NASH]-related cirrhosis is associated with the development of HCC and represents an increasingly common risk factor for HCC in Western countries[3-6]". Please see the page 4 line 87-90 in the revised manuscript.

Reviewer #2:

1. GLOBOCAN data should be updated to reveal the most recent statistics in 2021.

**Reply:** Thank you for your comments. We have updated GLOBOCAN data to the latest statistics like "Primary liver cancer (PLC) is one of the most common malignancies worldwide. According to the Global Cancer Data (GLOBOCAN) 2020, the annual number of new cases of liver cancer reached 905,677 worldwide, ranking 7th in malignant tumors, whereas the annual number of deaths

caused by PLC was 830,180, ranking 2nd in malignant tumors[1]. Approximately 50% of the cases of global liver cancer occur in China, and data released by the National Cancer Center in 2021 showed that liver cancer has become the 4th most common malignant tumor in China, and its mortality rate ranks 2nd, with a ratio of incidence to mortality rates reaching 1:0.8[2]” to page 4, line 76-82.

2. Nearly 25% of all HCCs harbour mutations including TERT, TP53 and CTNNB1, with the translational potential for clinical impact. Although they have remained undruggable for a long time, I believe these should be discussed, if not mentioned in the review.

**Reply:** Thank you for your advice. We have added the discussion associated with mutations including TERT, TP53 and CTNNB1 in Conclusion section as “The most frequently mutated genes of HCC patients were TP53, TERT, and CTNNB1, which mainly lead to the occurrence and development of HCC[146-148]. Many of these abnormalities may be pharmacologically tractable. However, biomarker-matched trials are still limited in this disease, and many of the genomic alterations in HCC remain challenging to target.”. Please see the page 19 line 573-577 in the revised manuscript.

3. RCTs and meta-analyses based on RCTs exploring the efficacy of adjuvant interferon therapy for HCC should also be included.

**Reply:** Thank you for your comments. We have added the studies (updates) on Interferon, Vitamin K2 analog and retinoids, as well as heparanase inhibitor PI-88 in postoperative HCC. In details as follows: Please see the page 17 to 18, line 515-556 in the revised manuscript.

4. Include studies (updates) on Vitamin K2 analog and retinoids, as well as heparanase inhibitor PI-88 in postoperative HCC.

**Reply:** Thank you for your comments. We have added the studies (updates) on Interferon, Vitamin K2 analog and retinoids, as well as heparanase inhibitor PI-88 in postoperative HCC. In details as follows: Please see the page 17 to 18, line 515-556 in the revised manuscript.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.