Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 80135

Title: Immunotherapy for advanced or recurrent hepatocellular carcinoma

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03699961

SPECIFIC COMMENTS TO AUTHORS

Title: Immunotherapy for advanced or recurrent hepatocellular carcinoma Ying-zhe Luo, Hong Zhu. 1) General Comments In this review manuscript, the authors well summarized the current knowledge of immunotherapy for advanced hepatocellular carcinoma. Although the description is consistent with the content of referenced reports, the referenced results may be inconsistent among various reports. The authors should thoroughly discuss about the inconsistency among reports and hypothesize the reasons for the discrepancy. Furthermore, poor English hinders understanding of the content. The followings are several concerns that the authors may wish to consider: 2) Specific comments Major concerns: 1. In the paragraph of "Tremelimumab", it is described that "Compared with tremelimumab monotherapy, the combination of anti-CTLA-4 and anti-PD-L1 agents significantly enhanced anti-tumor efficacy and reduced the incidence of adverse events.". At the same time, in the section of "COMBINATION OF DOUBLE IMMUNE AGENTS THERAPIES", there is description that "However, the rate of adverse events was also significantly higher with the combination of nivolumab and ipilimumab than with the nivolumab monotherapy.". Because two descriptions are inconsistent in terms of the adverse events in the combination therapies using anti-PD-L1 and anti-CTLA-4 antibodies, the authors should thoroughly discuss if the

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

adverse events were significantly different among mono and combination therapies and the reasons for these inconsistent results. Minor concerns: 1. In the introduction, there is a description that the recurrence rate of early-stage HCC patients within 5 years after curative resection is approximately 70%. However, the recurrence rate is largely owing to a background liver disease. It is not reasonable to define the single recurrent rate for all patients with different types of background liver diseases. 2. In the introduction, there is a description that "Radical treatment of recurrent HCC includes repeated hepatic resection and liver transplantation; these radical treatments are complex to complete owing to the shortage of donors, small residual areas, hepatic dysfunction, and multiple metastases.". What do the authors mean by "small residual areas"? 3. Poor English should be polished.

Reply to reviewer: We are very grateful to your reviewing our paper so carefully. In view of the referenced results may be inconsistent among various reports, we modify and discuss this part. In response to your valuable suggestions, I would like to give the following answers:

Major concerns:

1. Reply: In the paragraph " tremelimumab ", it was incorrect to draw the conclusion that "the combination of anti-CTLA-4 and anti-PD-L1 drugs can significantly enhance anti-tumor efficacy and reduce the incidence of adverse events compared with tremelimumab monotherapy", and we have corrected this part. In fact, whether it's a combination of tremelimumab and durvalumab or a combination of nivolumab and ipilimumab, The trials have shown that the combination can only enhance anti-tumor efficacy, not reduce the incidence of adverse events.
   Meanwhile, compared with the combination of the T300+D (tremelimumab 300 mg plus durvalumab 1,500 mg [one dose each during the first cycle] followed by durvalumab 1,500 mg once every 4 weeks), tremelimumab monotherapy (750 mg once every 4 weeks [seven doses] and then once every 12 weeks) had a higher rate of grade ≥ 3 adverse events. We considered the higher rate of grade ≥ 3 adverse events

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

associated with the cumulative dose of tremelimumab. We make the changes in the manuscript.

Minor concerns:

1. Reply: In response to the unreasonable definition of the single recurrence rate in patients with different types of background liver disease in the introduction, we modified the original sentence to " The recurrence rate in early HCC patients remains high at 5 years post curable excision ".

2. Reply: “small residual areas” refers to “small residual areas of liver after HCC resection”, We have corrected the inaccuracy of the description of this part.

3. As for our poor English, we have invited native-English speakers to polish and correct this manuscript.

Finally, thanks again for pointing out the problems in our manuscript.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 80135

Title: Immunotherapy for advanced or recurrent hepatocellular carcinoma

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06490930

SPECIFIC COMMENTS TO AUTHORS

Cancer has entered the era of immunotherapy. In the treatment of liver cancer, a series of immune checkpoint inhibitors have made phased progress, but the results are still controversial. At the same time, the application space of radiotherapy in liver cancer is becoming more and more extensive. Previous basic studies have shown that radiotherapy can not only enhance the phagocytosis of dendritic cells and macrophages on injured tumor cells, but also promote antigen presentation and activation of tumor-specific T cells, thus playing a role in sensitizing immunotherapy. On the other hand, immunotherapy can induce vascular normalization through T cell-dependent pathway, improve the hypoxic microenvironment in tumor, and enhance the effect of radiotherapy. On the other hand, immunotherapy can enhance the immune induction effect of radiotherapy and increase the incidence of distant effect.The study, CA 209-678, from the team at the National Cancer Centre Singapore (NCCS) and Singapore Central Hospital (SGH), just published in The Lancet Gastroenterology & Hepatology, Y90 (Yttrium-90) radiation embolization combined with nabuliumab in the treatment of advanced hepatocellular carcinoma is not only safe and well tolerated, but 81% of the patients in this study showed regression of the radiation field target lesion! It is hoped

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

that the author can further improve the summary of radiotherapy combined with immunotherapy in the treatment of advanced liver cancer.

Reply to reviewer： Thanks for your decision and constructive comments on my manuscript. According to your suggestions, we have supplemented the contents of the part of "COMBINATION OF IMMUNE AGENTS AND LOCOREGIONAL THERAPIES", including the data and analysis from the CA 209-678 study and mechanism of interaction between radiotherapy and immunotherapy.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 80135

Title: Immunotherapy for advanced or recurrent hepatocellular carcinoma

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06492155

SPECIFIC COMMENTS TO AUTHORS

This review summarized several immunotherapies including ICI, CAR-T, and vaccines for HCC. While in recent years, a number of articles reviewed the advances in immunotherapy for HCC have been published, this review is not innovative enough. Anyway, this article concluded the undergoing clinical trials well and the clinical data quoted were rich. As a reviewer, I agree with what is stated in this review. Some points could still be amended, and I am only responsible for the comments mentioned below. Points: 1. In the parts of "SINGLE IMMUNE AGENT THERAPY" and "COMBINATION OF IMMUNE AGENTS AND ANTIANGIOGENNIC DRUG THERAPIES", the mechanism of some drugs were described but some were not. Although some ICIs drugs could be found in the picture, the subsequent antiangiogenic drugs are rarely described. These could be described in a few words or pictures to refine the content. 2. The table contents should be distributed more evenly. The existing tables could be merged, and the CAR-T and tumor vaccines could be organized into tables to reduce the list of trials in the text. 3. Overall, the immunotherapies mentioned in the text were not comprehensive. More treatments will enrich the article such as adoptive cell therapies besides CAR-T therapy. 4. The picture was not sufficient. It would be better if it could

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

summarize which available therapies are in this review. 5. Some Trial identifier in the table has hyperlinks (NCT03006926, NCT03713593), the format needs to be uniform.

Reply to reviewer：Thanks very much for your valuable comments on my manuscript. In response to your valuable suggestions, I would like to give the following answers:

1. We improved the description of anti-angiogenic drug mechanisms in the manuscript.

2. Your suggestions on the form are very reasonable. We will modify the form as required after communicating with the magazine.

3. We have supplemented the immunotherapy in the manuscript, including adoptive cell transfer.

4. According to your comments, we have added pictures to summarize the treatment methods in this review.

5. We have hyperlinked all the trail identifier in the manuscript.