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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
Position: Associate Editor
Academic degree: MD, PhD
Professional title: Professor
Reviewer's Country/Territory: Japan
Author's Country/Territory: China

Manuscript submission date: 2022-09-18

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2022-11-07 10:21

Reviewer performed review: 2022-11-10 15:01

Review time: 3 Days and 4 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

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 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,

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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.

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Reviewer's code: 06490930
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: China

Manuscript submission date: 2022-09-18

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-01-19 02:01

Reviewer performed review: 2023-01-31 14:30

Review time: 12 Days and 12 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

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

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patients in this study showed regression of the radiation field target lesion! It is hoped that the author can further improve the summary of radiotherapy combined with immunotherapy in the treatment of advanced liver cancer

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06492155
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: China
Author's Country/Territory: China

Manuscript submission date: 2022-09-18
Reviewer chosen by: Dong-Mei Wang
Reviewer accepted review: 2023-01-19 06:41
Reviewer performed review: 2023-02-06 09:05
Review time: 18 Days and 2 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
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statements	Conflicts-of-Interest: [ ] Yes [Y] No

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 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.