Peer Review File

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Reviewer A

Title
Could change the title to: “Addition of transarterial chemoembolization improves outcome of tyrosine kinase and immune checkpoint inhibitors regime in patients with unresectable hepatocellular carcinoma” Or “Addition of transarterial chemoembolization to tyrosine kinase and immune checkpoint inhibitors therapies improves survival of patients with unresectable hepatocellular carcinoma”
Response: Thank you so much. We have changed the title to “Addition of transarterial chemoembolization improves outcome of tyrosine kinase and immune checkpoint inhibitors regime in patients with unresectable hepatocellular carcinoma” following your kind suggestion. (See Page 1, line 3-5)

What is the implication and what should change now? Should be rewritten.
Response: Thank you. We have added the following to this column: “Addition of TACE improves outcome of TKI plus ICI regime in patients with unresectable HCC, and has an acceptable safety profile.” (See Page 2, line 44-47)

Abstract Background: please omit “retrospective”
Response: Thank you. “retrospective” has been deleted. (See Page 2, line 52)

Conclusions: “TKI plus ICI” should be change to “TKI plus ICI regime” Replace “without TACE” with “alone”
Response: Thank you. The Conclusions part has been revised according to your comments. (See Page 2, line 70)

Introduction Page 3, lines 93-94: please move this statement to method section “In this study, we divided patients into two groups 94 according to whether they underwent TACE during treatment with TKI plus ICI.” This is a method context.
Response: Thank you. We have removed the sentence: “we divided patients into two groups according to whether they underwent TACE during treatment with TKI plus ICI.” (See Page 4, line 105)

Methods Please add a subtitle to describe and cite which guideline was used to determine the complications and grade of complications.
Response: Thank you. We have clarified the basis for the safety assessment in this study and have added a subtitle. (See Page 7, line 208-212)

Study design

Please change the “Study design” to “Study design and population” Some material from the result section has to be moved to here, please check below.
Response: Thank you for your kind suggestions. We have changed “Study design” to “Study design and population”. (See Page 4, line 110)

Statistical analyses/Para1 Please omit “Para1”
Response: Thank you. “Para1” has been deleted. (See Page 7, line 221)

Results Patient characteristics Please move page 6, lines 199-201 and page 7, lines 202-204 to method section. Page 7, line 213: please omit “By the cutoff date (1 November 2021),” Page 7, lines 213-216: please move this to method section, subtitle study population.
Response: Thank you. We have modified the section on patient characteristics according to your pertinent suggestions. (See Page 4, line 129-134; See Page 8, line 247; See Page 7, line 214-219)

TACE combined with TKI and ICI in high risk and non high-risk cohorts Page 8, lines 243-245: Please move the definition of high-risk patients to method section. This is not a result contexr.
Response: Thank you. High-risk patients have been defined in the Introduction section, so we replaced this definition with a brief description in the Results section. (See Page 9, line 273-274)

Discussion Page 9, line 279-280: please omit the first statement. Rely on the main finding without making conclusion.
Response: Thank you. The first sentence statement in the discussion section has been adjusted in accordance with your valuable suggestions. (See Page 10, line 306-307)

Conclusions Page 11, line 344: please replace “but not TACE” with “alone” Page 11, lines 345-346: Please revise “Moreover, the addition of TACE to a TKI and ICI appears to be safe and tolerable.” As “Moreover, adding TACE to TKI and ICI regime was safe and did not result in additional complication.” Page 11, line 346-347: please omit “Further prospective randomized clinical trials are needed to validate these findings.”
Response: Thank you very much. We have revised the conclusion section according to your pertinent suggestions. (See Page 11, line 367-369)

Reviewer B

General comments: Well-written manuscript. The authors need to explain why some patients received TACE and the other 49 patients did not? This is a very important question that has to be thoroughly explained, since it can result in bias in the results.
Response: We totally understand the reviewer’s concern. This is a retrospective study based on a large medical center, and there will be no prespecified intervention before patient treatment as in a prospective study. In addition, systemic therapy with or without TACE is recommended

by the China National Logging Corporation (CNLC) guidelines and thus is used by different treatment groups in the real world.

The study ended on 1 Nov 2021. Why did the authors stop collecting data almost 2 years ago? In other words, why is there a 2 year delay in reporting this data?
Response: Thank you for your rigorous comment. This study was ended on 1 Nov 2021, data collation and paper writing were completed last year. Unfortunately, delays in the presentation of these data resulted from a rough submission process. Even so, we do not think this affects the conclusions of the study, since the efficacy end point was met in more than 65% of the patients, making the statistical results robust. Since the posterior line treatment of HCC patients is complex and diverse, extending the follow-up time will also lead to statistical bias. Therefore, it is necessary to design a more rigorous prospective clinical trial to reduce various biases as much as possible, which is our future research direction.

Were the patients treated with both TKI and ICI?
Response: Thank you for pointing this out. All patients in this study were treated with both TKI and ICI, and both treatments were administered simultaneously.

Method: Page 5 line 162: “post TACE and every 1-2 months”. Is this correct? The patients were being followed and scanned every 1-2 months? That is too close follow up and is not the standard. Please explain if this is correct and if yes, why were the patients being followed this closely?
Response: Thank you for pointing this out. All patients were assessed for tumor response by abdominal contrast-enhanced computed tomography (CT) or magnetic resonance (MR) imaging before each TACE and TKI plus ICI treatment. If the patient's disease is effectively controlled, follow-up is extended to every 3 months until data cutoff, death, or loss of follow-up. Our previous statement was not clear and we have corrected it. (See Page 6, line 181-184)

Page 5 line 164: Why did the authors use both RECIST and mRECIST to evaluate the response?
Response: Thank you. RECIST 1.1 has been validated and provides more conservative estimates of response rates than mRECIST. The assessment of RECIST 1.1 also allows comparison of response data with pivotal studies in patients with HCC, such as the Imbrave150 and KEYNOTE-240 trial. mRECIST has not been prospectively validated or evaluated in immuno-oncology therapy (1). However, traditional criteria, such as RECIST 1.1, which are based on tumor diameter reduction, underestimate the efficacy and do not predict survival in HCC patients treated with TACE (2). Therefore, the mRECIST has been developed to measure the reduction in viable tumor burden, which is considered to be more preferred for the evaluation of tumors treated with TACE. In this study, TACE and immunotherapy may co-exist in the treatment of HCC patients, the use of one evaluation criteria may only partially reflect the tumor response rate. Therefore, we used two recognized versions of mRECIST and RECIST1.1 to avoid evaluation bias as much as possible. (1) El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. The Lancet 2017;389(10088):2492-2502. (2) Ronot M, Bouattour M, Wassermann J, et al. Alternative

response criteria (Choi, European association for the study of the liver, and modified Response Evaluation Criteria in Solid Tumors [RECIST]) versus RECIST 1.1 in patients with advanced hepatocellular carcinoma treated with sorafenib. Oncologist 2014;19:394–402.

Discussion: Line 295: Authors mention: “but in our opinion it is clinically important”. The authors need to provide evidence and reference not opinion. Please either delete or revise.
Response: Thank you. The above inappropriate description has been removed. (See Page 10, line 320)

Reviewer C

1. Change the title from "may" to "could."
Response: Thank you. We have revised the title of the article according to the comments of reviewer A, and the current title is “Addition of transarterial chemoembolization improves outcome of tyrosine kinase and immune checkpoint inhibitors regime in patients with unresectable hepatocellular carcinoma”. I wonder if you think this adjustment is appropriate. (See Page 1, line 3-5)

2. Include patients' characteristic information, such as tumor stage, in the abstract.
Response: Thank you. We have taken your suggestion and added important information about patient characteristics to the results section of the abstract. “Data from patients with unresectable HCC who received TKI plus ICI treatment between July 2017 and April 2020 were collected. The median intrahepatic tumor size was 8.7 cm (interquartile range, 5.9-12.4 cm). At data cut-off, …”. (See Page 2, line 59-61)

3. Provide the results of the "TACTICS-L trial" (https://doi.org/10.1159/000531377) in the introduction.
Response: Thank you. We have presented the ORR-related study results of the TACTICS-L trial and cited this abstract in the introduction section. (See Page 3, line 97-99)

4. Summarize previous published literatures on the combination therapy of TACE plus TKI/ICI, such as the CHANCE001, instead of stating that it "remains unclear."
Response: Thank you. Descriptions of relevant inaccuracies have been amended to the following. To date, “CHANCE001” and other few studies have reported the efficacy of TACE combined with TKI and ICI in the treatment of unresectable HCC. However, the contribution of TACE to the combination of TKI and ICI remains unclear. (See Page 3, line 101-104)

5. Clarify if Child B refers to Child-Pugh Score 7 in the Methods section.
Response: Thank you. This study collected HCC cases with Child-Pugh class A or B7-9 liver disease, which we clarified in the Methods section. (See Page 4, line 121)

6. Provide detailed information about the "missing follow-up data" in line 111, including the follow-up period.

Response: Thank you. In this study, follow-up data were obtained from patient follow-up phone calls, outpatient periodic review and readmission case data. If complete follow-up data were not obtained through these methods, patients were excluded from this study. Access to follow-up data has been added on page 4, line 118-120.

7. Provide detailed information about Lobaplatin, as it is not a commonly used drug for TACE globally.
Response: Thank you for pointing this out. Lobaplatin is a third-generation anti-tumor drug with good water solubility, strong anti-tumor activity, no cross-resistance with other platinum, and low toxicity. It is one of the commonly used agents for TACE treatment of HCC in Asian population. Wang et al. found that lobaplatin has better efficiency in the aspects of patient's mean survival time and therapeutic response in TACE (1). A study by Lu et al. reported that Lobaplatin-based chemoembolization may elicit effective tumor response for recurrent HCCs and improve the overall survival of patients with unresectable HCC recurrence following orthotopic liver transplantation (2). More recently, lobaplatin has also been selected as a TACE agent in some studies (3, 4). (1) Wang N, Lv Y, Xu A, et al. Application of lobaplatin in trans-catheter arterial chemoembolization for primary hepatic carcinoma. Asian Pac. J. Cancer Prev 2014;15(2):647–650. (2) Zhou B, Shan H, Zhu K, et al. Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. J. Vasc. Interv. Radiol 2010;21(3):333–338. (3) He M, Li Q, Shen J, et al. Predictive factors for the benefit of triple-drug transarterial chemoembolization for patients with unresectable hepatocellular carcinoma. Cancer Med 2019;8(9):4200-4213. (4) Li Q, He M, Chen H, et al. Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin Versus Transarterial Chemoembolization for Large Hepatocellular Carcinoma: A Randomized Phase III Trial. J Clin Oncol 2022;40(2):150-160.

8. Explain your TACE technique of using a 5:1 ratio mixture and if there are any preclinical or clinical studies supporting this approach, as the CIRSE standard guideline recommends a 1:2-1:3 ratio.
Response: Thank you. Lobaplatin was mixed with lipiodol at a ratio of 1:2 or 1:3. Sorry for our mistake in description, which has been corrected. (See Page 5, line 154)

9. Provide the number of patients who received each TKI and ICI in the discussion session.
Response: Thank you. The type of combination of TKI and ICI used in this study and the corresponding number of patients are detailed in the table below. We consider that the addition of this information is necessary, but it would be more appropriate to put it in the results section as supplementary material. (See Page 8, line 247)

10. Compare the evaluation criteria of mRECIST and RECICL, as TACTIC and TACTICS-L demonstrated the advantages of TACE using RECICL.
Response: Thank you for pointing this out. In the RECICL evaluation criteria, Lipiodol retention area in the nodule after 1 month following TACE was regarded as necrosis. Particularly, new intrahepatic lesions were not regarded as ‘progressive disease’, as they are indicative of the natural tumor biology of HCC and do not imply treatment failure or moving

to the next line of treatment. We support the future use of RECICL for the evaluation of tumor response to TACE. But compared with RECICL, mRECIST may be more widely used in the evaluation of TACE related therapy. Moreover, in our study, not all patients underwent TACE treatment, the patients in one cohort were treated only with a combination of TKI and ICI, they were not eligible for the RECICL evaluation.

11. Discuss the issue of the selection of evaluation criteria
Response: Thank you. RECIST 1.1 has been validated and provides more conservative estimates of response rates than mRECIST. It also allows comparison of response data with pivotal studies in patients with HCC, such as the Imbrave150 and KEYNOTE-240 trial. mRECIST has not been prospectively validated or evaluated in immuno-oncology therapy (1). However, traditional criteria like RECIST 1.1, which are based on tumor diameter reduction, underestimate the efficacy and do not predict survival in HCC patients treated with TACE (2). Therefore, the mRECIST has been developed to measure the reduction in viable tumor burden, which is considered to be more preferred for the evaluation of tumors treated with TACE. In this study, TACE and immunotherapy may co-exist in the treatment of HCC patients, the use of one evaluation criteria may only partially reflect the tumor response rate. Therefore, we used two recognized versions of mRECIST and RECIST1.1 to avoid evaluation bias as much as possible. We have added additional explanations to the double-criteria evaluation of this study in the Methods section. (See Page 6, line 186-196) (1) El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. The Lancet 2017;389(10088):2492-2502. (2) Ronot M, Bouattour M, Wassermann J, et al. Alternative response criteria (Choi, European association for the study of the liver, and modified Response Evaluation Criteria in Solid Tumors [RECIST]) versus RECIST 1.1 in patients with advanced hepatocellular carcinoma treated with sorafenib. Oncologist 2014;19:394–402.

Reviewer D

1. Table S1: Please use another column to indicate the data of non-TACE group.

Supplementary material

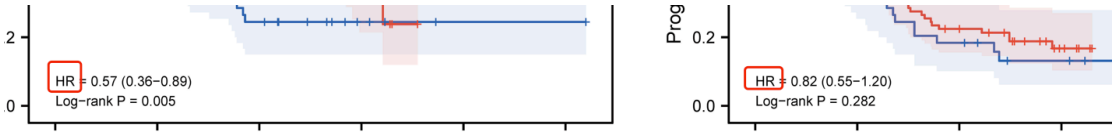
Table S1. Collocation selection of systemic combination therapy at baseline

TACE group, non-TACE group	Sorafenib	Lenvatinib
Nivolumab	14 (14.3), 5 (10.2)	7 (7.1), 1 (2.0)
Pembrolizumab	4 (4.1), 2 (4.1)	14 (14.3), 4 (8.2)
Camrelizumab	40 (40.8), 30 (61.2)	19 (19.4), 7 (14.3)

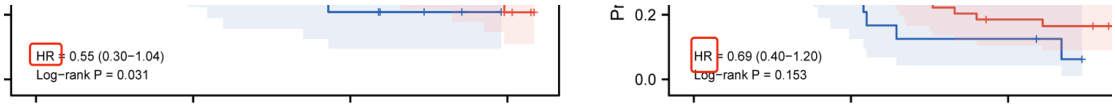
Except where indicated, data are numbers of patients, with percentages in parentheses.

Response: Thank you very much for providing us with a reference template. We have revised Table S1 according to your suggestions.

2. Figure 2: Please revise them to “HR (95% CI)” and resend us updated figure.



3. Figures 4-5: Please revise them to “HR (95% CI)” and resend us updated figures.



Response: We have updated the figure according to your suggestion.