PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in treating hepatocellular carcinoma with portal vein tumor thrombus: A study protocol
AUTHORS	Wang, Kang; Yu, Hong-Ming; Xiang, Yan-Jun; Cheng, Yu-Qiang; Ni, Qian-Zhi; Guo, Wei-Xing; Shi, Jie; Feng, Shuang; Zhai, Jian; Cheng, Shu-Qun

VERSION 1 – REVIEW

REVIEWER	Xu, Xiao Hangzhou First People's Hospital, Zhejiang University School of Medicine
REVIEW RETURNED	11-Jun-2022

GENERAL COMMENTS	This is a promising multi-center phase II clinical trial. The authors aim to investigate the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in treating HCC patients with PVTT. The results of this clinical trail may provide a new therapeutic regimen for HCC patients with PVTT and further improve the efficacy and prognosis of these patients. There are several comments: 1. This study investigate the efficacy and safety of radiotherapy combined with immunotherapy in treating HCC patients with PVTT. What is the specific type of radiotherapy used in this study? Is it SBRT? 2. As you mentioned in the treatment plan, The treatment will continue until disease progression occurs. While, the CheckMate 459 clinical trial (PMID: 34914889) investigated the treatment effect of nivolumab compared with sorafenib advanced HCC. This study challenged the conventional treatment strategy of stopping treatment after tumor progression, and found that patients who continue to receive treatment after tumor progression can achieve superior overall survival than patients who stop treatment when progression occurs. It suggested that progress in imaging does not necessarily mean treatment failure. Whether such a positive treatment strategy is worth taking in HCC patients with PVTT who have very poor prognosis, and whether it can improve the prognosis of these patients? 3. In the treatment plan, atezolizumab plus bevacizumab will be given at 3±1 d after the initiation of radiotherapy. At present, there are three forms of radiotherapy combined with immunotherapy in clinical practice: sequential therapy (radiotherapy followed by immunotherapy), induction therapy (concurrent radiotherapy after several cycles of immunotherapy) and concurrent therapy (concurrent radiotherapy and immunotherapy at initiation).

	However, the optimal sequencing of radiotherapy and immunotherapy is yet to be definitively described. What is your consideration for choosing concurrent therapy in this study? 4. In this study, the rate of surgical conversions is one of the secondary endpoints. As you mentioned in this part, the resectability criteria include successful down-staging of the tumor. What is the definition of successful down-staging? In fact, most advanced HCC patients are accompanied by cirrhosis and decompensation of liver function. A recent study (PMID: 34456082) reported that type 1 or 2 PVTT patients with preoperative AFP ≤ 100 ng/mL who underwent liver transplantation could have satisfactory OS similar to that of patients within the milan criteria. What is your opinion about the surgical treatment after successful down-staging?

REVIEWER	Zheng, Shusen First Affiliated Hospital, School of Medicine, Zhejiang University, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery
REVIEW RETURNED	09-Jul-2022

GENERAL COMMENTS	1.It is mentioned that the DCRs, PFSs, TTPs and DORs will be calculated in accordance with the RECIST version 1.1, modified RECIST (mRECIST), and immune-modified RECIST (imRECIST), respectively. Whether the different efficacy evaluation criteria will lead to statistic error in secondary endpoints. 2.The research design is quite comprehensive and feasible to serve for further research. However, as the author said, the size of patients enrolled is small. Whether the scale of patients enrolled could be appropriately expanded to further increase the accuracy.

REVIEWER	Hasegawa, Kiyoshi The University of Tokyo Graduate School of Medicine Faculty of Medicine, Hepato-Biliary-Pancreatic Surgery Division
REVIEW RETURNED	13-Jul-2022

GENERAL COMMENTS	The authors described a study protocol to investigate the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in treating hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT). The study design is an open-label, multi-center, single-arm phase II clinical trial aims. Patient s with unresectable HCC with PVTT confirmed by imaging findings are eligible for the study, and 42 cases are planned for enrollment. Radiotherapy is first given at 40 Gy/20f/26d to PVTT, followed by CT evaluation and dose escalation to 54-56 Gy/27-28f with adjustment of the irradiated site. Atezolizumab plus bevacizumab is started within 2-3 days after the start of radiotherapy and continued until there is an unsustainable adverse event or disease progression. The primary endpoint is objective response rate, and secondary endpoints include overall survival, disease control rate, progression free survival, time to progression and duration of response. This is an interesting and clinically important study to focus on the combination of radiotherapy and immunotherapy plus targeted therapy against HCC with PVTT. I have minor comments and questions for this study.

	1. Eligibility criteria include “6) not suitable for radical surgical treatment”. It would be better to clarify the criteria for unresectability. 2. Who will evaluate ORR? Is it the central judgment or the physician in charge? 3. In statistical methods, the authors assumed an ORR of 47% to calculate the required number of evaluable patients. What is the basis for the “47%”? Please provide a citation if you have a source.

REVIEWER	Stiller, Charles National Cancer Registration and Analysis Service
REVIEW RETURNED	11-Aug-2022

GENERAL COMMENTS	This paper presents the protocol for an open label, single arm, phase II trial of radiotherapy combined with atezolizumab plus bevacizumab in treatment of hepatocellular carcinoma with portal vein tumour thrombosis. The protocol is well-designed and generally well-specified, but the paper could be improved by attention to the following points. Introduction, sentence 2. Should “prevalence” be “annual incidence”? Please specify whether it is crude or age-standardised. Introduction, paragraph 2, final sentence. “On the contrary, eastern countries …”, but only reference 13, from Korea, is cited. If Korea is not in fact the only country to adopt these strategies, then there should be a small number of other references from other countries, such as China and Japan. Methods and analysis - eligibility criteria. I may have misunderstood, but inclusion criterion 13 appears to me to be irrelevant if inclusion criterion 7 is satisfied. Methods and analysis - treatment plan, paragraph 3. Could you indicate whether there are any objective criteria for deciding, in any particular case of severe toxicity, whether the action taken should be (i) delayed administration only, (ii) reduced dose only, or (iii) delayed administration and reduced dose? Will the action taken be decided by the clinical team, or by the patient, or by clinical team and patient in consultation? Methods and analysis - monitoring. Is there any stopping rule for the trial in the event of widespread toxicity or early evidence of lack of efficacy?

VERSION 1 – AUTHOR RESPONSE

POINT-BY-POINT RESPONSES TO THE COMMENTS OF REVIWER #1

Comment 1: This study investigate the efficacy and safety of radiotherapy combined with immunotherapy in treating HCC patients with PVTT. What is the specific type of radiotherapy used in this study? Is it SBRT?

Response: We thank the Reviewer for the comment. Indeed, Intensity-modulated radiotherapy (IMRT) was conducted in this trial, which was clarified in the manuscript.

Comment 2: As you mentioned in the treatment plan, The treatment will continue until disease progression occurs. While, the CheckMate 459 clinical trial (PMID: 34914889) investigated the treatment effect of nivolumab compared with sorafenib advanced HCC. This study challenged the conventional treatment strategy of stopping treatment after tumor progression, and found that patients who continue to receive treatment after tumor progression can achieve superior overall survival than patients who stop treatment when progression occurs. It suggested that progress in imaging does not necessarily mean treatment failure. Whether such a positive treatment strategy is worth taking in HCC patients with PVTT who have very poor prognosis, and whether it can improve the prognosis of these patients?

Response: We thank the Reviewer for this comment that improve the quality of our manuscript. We fear that we have not been clear, probably in part due to the translation. The treatment was discontinued when there was no additional clinical benefit, as judged by the investigator (based on imaging, biochemical indicators, and clinical status of the patient). Then, the patient received the guideline-recommended second-line therapy. This was clarified in the revised manuscript accordingly.

Comment 3: In the treatment plan, atezolizumab plus bevacizumab will be given at 3±1 d after the initiation of radiotherapy. At present, there are three forms of radiotherapy combined with immunotherapy in clinical practice: sequential therapy (radiotherapy followed by immunotherapy), induction therapy (concurrent radiotherapy after several cycles of immunotherapy) and concurrent therapy (concurrent radiotherapy and immunotherapy at initiation). However, the optimal sequencing of radiotherapy and immunotherapy is yet to be definitively described. What is your consideration for choosing concurrent therapy in this study?

Response: We thank the Reviewer for this comment. There are some studies on concurrent radiotherapy with sorafenib,[1 2] which explored the feasibility of concurrent radiotherapy and systemic therapy. Hence, the concurrent approach was chosen in this study, which was also based on the experience in our center. The introduction of previous studies on concurrent radiotherapy and sorafenib was added in the revised manuscript.

Comment 4: In this study, the rate of surgical conversions is one of the secondary endpoints. As you mentioned in this part, the resectability criteria include successful down-staging of the tumor. What is the definition of successful down-staging?

In fact, most advanced HCC patients are accompanied by cirrhosis and decompensation of liver function. A recent study (PMID: 34456082) reported that type 1 or 2 PVTT patients with preoperative AFP ≤ 100 ng/mL who underwent liver transplantation could have satisfactory OS similar to that of patients within the milan criteria. What is your opinion about the surgical treatment after successful down-staging?

Response: We thank the Reviewer for this sound comment. The definition of successful downstaging was based on the CSCO guideline, which was 1) stage Ia, Ib, and IIa, 2) IIb, if the tumor is confined to the same segment or the same side of the liver, or intraoperative radiofrequency ablation can be performed at the same time to treat the lesions outside the resection range, and 3) IIIa/b, if the tumor is confined to the hemi-liver, and it is expected that the tumor thrombus can be completely during the operation, surgical resection of the tumor and thrombectomy through the portal vein can be considered.

Actually, at our center, surgery is encouraged after successful downstaging. Postoperative adjuvant therapy is considered when needed.

POINT-BY-POINT RESPONSES TO THE COMMENTS OF REVIWER #2

Comment 1: It is mentioned that the DCRs, PFSs, TTPs and DORs will be calculated in accordance with the RECIST version 1.1, modified RECIST (mRECIST), and immune-modified RECIST (imRECIST), respectively. Whether the different efficacy evaluation criteria will lead to statistic error in secondary endpoints.

Response: We thank the Reviewer for the comment. Currently, both RECIST 1.1 and mRECIST are recommended by guidelines as the efficacy evaluation criteria for patients with HCC.[3] For patients receiving immunotherapy, the imRECIST criteria can also be used.[4] Therefore, in this study, we utilized 3 evaluation criteria and observe whether there are differences in the efficacy of the patients judged by different evaluation criteria and also provide some evidence for the selection of the optimal efficacy evaluation criteria for HCC patients treated with radiotherapy + systemic therapy.

Comment 2: The research design is quite comprehensive and feasible to serve for further research. However, as the author said, the size of patients enrolled is small. Whether the scale of patients enrolled could be appropriately expanded to further increase the accuracy.

Response: We agree with the Reviewer. Still, this study is a single-arm phase II clinical trial to explore the preliminary efficacy and safety of TA regimen combined with radiotherapy in HCC patients with PVTT. In addition, the minimum sample size calculation was also done. After the initial efficacy is verified preliminarily, it will be confirmed in a larger study.

POINT-BY-POINT RESPONSES TO THE COMMENTS OF REVIWER #3

Comment 1: Eligibility criteria include "6) not suitable for radical surgical treatment". It would be better to clarify the criteria for unresectability.

Response: We thank the Reviewer for the comment. The definition of resectability based on the CSCO guideline was stated in the Endpoint, which was 1) stage Ia, Ib, and IIa, 2) IIb, if the tumor is confined to the same segment or the same side of the liver, or intraoperative radiofrequency ablation can be performed at the same time to treat the lesions outside the resection range, and 3) IIIa/b, if the tumor is confined to the hemi-liver, and it is expected that the tumor thrombus can be completely removed or removed during the operation, surgical resection of the tumor and thrombectomy through the portal vein can be considered.

Comment 2: Who will evaluate ORR? Is it the central judgment or the physician in charge?

Response: We thank the Reviewer for this fair comment. The responses will be independently evaluated by three to six experienced senior physicians who are not investigators in this study. It was clarified in the manuscript.

Comment 3: In statistical methods, the authors assumed an ORR of 47% to calculate the required number of evaluable patients. What is the basis for the "47%"? Please provide a citation if you have a source.

Response: We thank the Reviewer. Due to the lack of evidence of T+A+radiotherapy in patients with HCC and PVTT, the assumption of ORR in this study was based on the investigators' experience. It is a single-arm trial preliminarily exploring the efficacy and safety of TA regimen combined with radiotherapy in HCC patients with PVTT. The trial will provide actual ORR data that will be used for the design of a larger phase confirmatory trial.

POINT-BY-POINT RESPONSES TO THE COMMENTS OF REVIWER #4

Comment 1: Introduction, sentence 2. Should "prevalence" be "annual incidence"? Please specify whether it is crude or age-standardised.

Response: We thank the Reviewer. It was revised as suggested.

Comment 2: Introduction, paragraph 2, final sentence. "On the contrary, eastern countries …", but only reference 13, from Korea, is cited. If Korea is not in fact the only country to adopt these strategies, then there should be a small number of other references from other countries, such as China and Japan.

Response: We thank the Reviewer. We added references from other Eastern countries.[5-8]

Comment 3: Methods and analysis - eligibility criteria. I may have misunderstood, but inclusion criterion 13 appears to me to be irrelevant if inclusion criterion 7 is satisfied.

Response: We thank the Reviewer for the comment. The prior "therapy" in inclusion criterion 13 was not limited to anti-tumor therapy (as in inclusion criterion 7). Therefore, the interpretation of inclusion criteria 7 and 13 is that patients who have not received anti-tumor therapy before and the toxicity related to other treatments (non-anti-tumor therapy) must have been resolved to grade $\leq$1.

Comment 4: Methods and analysis - treatment plan, paragraph 3. Could you indicate whether there are any objective criteria for deciding, in any particular case of severe toxicity, whether the action taken should be (i) delayed administration only, (ii) reduced dose only, or (iii) delayed administration and reduced dose? Will the action taken be decided by the clinical team, or by the patient, or by clinical team and patient in consultation?

Response: We thank the Reviewer for this constructive comment. Delayed treatment or dose reduction will be determined by the clinical team, and the specific adjustment plan will be determined by the investigator based on the patient's clinical condition. As stated in the manuscript, in case of severe toxicity, the administration will be delayed and/or the dose will be reduced. If any serious adverse event (SAE) occurs during the radiotherapy, or the radiotherapy is delayed for more than 4 weeks for any reason, radiotherapy sessions will be terminated. The doses of atezolizumab and bevacizumab will be adjusted according to the drug's instructions.

Comment 4: Methods and analysis - monitoring. Is there any stopping rule for the trial in the event of widespread toxicity or early evidence of lack of efficacy?

Response: We thank the Reviewer. The stopping rules for the trial are 1) the investigators find serious safety issues, or 2) the administrative department cancels the trial. The termination of the trial can be temporary or permanent. When terminating the trial, all records will be kept for future reference. It was clarified in the manuscript.

References

1. Chen SW, Lin LC, Kuo YC, et al. Phase 2 study of combined sorafenib and radiation therapy in patients with advanced hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2014;88(5):1041-7. doi: 10.1016/j.ijrobp.2014.01.017 [published Online First: 2014/03/26]
2. Rim CH, Park S, Shin IS, et al. Is the Concurrent Use of Sorafenib and External Radiotherapy Feasible for Advanced Hepatocellular Carcinoma? A Meta-Analysis. *Cancers (Basel)* 2021;13(12) doi: 10.3390/cancers13122912 [published Online First: 2021/07/03]
3. Llovet JM, Lencioni R. mRECIST for HCC: Performance and novel refinements. *J Hepatol* 2020;72(2):288-306. doi: 10.1016/j.jhep.2019.09.026 [published Online First: 2020/01/20]
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5. Yoon SM, Ryoo BY, Lee SJ, et al. Efficacy and Safety of Transarterial Chemoembolization Plus External Beam Radiotherapy vs Sorafenib in Hepatocellular Carcinoma With Macroscopic Vascular Invasion: A Randomized Clinical Trial. *JAMA Oncol* 2018;4(5):661-69. doi: 10.1001/jamaoncol.2017.5847
6. Cheng S, Yang J, Shen F, et al. Multidisciplinary management of hepatocellular carcinoma with portal vein tumor thrombus - Eastern Hepatobiliary Surgical Hospital consensus statement. *Oncotarget* 2016;7(26):40816-29. doi: 10.18632/oncotarget.8386 [published Online First: 2016/10/27]

7. Kudo M, Kawamura Y, Hasegawa K, et al. Management of Hepatocellular Carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 Update. *Liver Cancer* 2021;10(3):181-223. doi: 10.1159/000514174 [published Online First: 2021/07/10]

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VERSION 2 – REVIEW

REVIEWER	Hasegawa, Kiyoshi The University of Tokyo Graduate School of Medicine Faculty of Medicine, Hepato-Biliary-Pancreatic Surgery Division
REVIEW RETURNED	08-Sep-2022

GENERAL COMMENTS	The authors revised the manuscript almost properly to my comments. However, one minor point had better be settled. They said that the ORR to decide the required number of evaluable patients was not based on the evidence but investigators' experience, which may be a weak point of this study. On the other hand, I understand their thought that strict estimation of the required number of patients is unnecessary. Thus, I recommend the authors to describe how to and why to use 47% as the ORR in statistical methods.

REVIEWER	Stiller, Charles National Cancer Registration and Analysis Service
REVIEW RETURNED	06-Sep-2022

GENERAL COMMENTS	The authors have satisfactorily addressed all editorial and review comments in their revised manuscript.

VERSION 2 – AUTHOR RESPONSE

POINT-BY-POINT RESPONSES TO THE COMMENTS OF REVIEWER#4

Reviewer#4 has no further comments.

POINT-BY-POINT RESPONSES TO THE COMMENTS OF REVIEWER#3

Comment 1: They said that the ORR to decide the required number of evaluable patients was not based on the evidence but investigators' experience, which may be a weak point of this study. On the other hand, I understand their thought that strict estimation of the required number of patients is unnecessary. Thus, I recommend the authors to describe how to and why to use 47% as the ORR in statistical methods.

Response: We are grateful for this sound comments from reviewer#3. As we mentioned in the last response letter, the lack of evidence of T+A+radiotherapy in patients with HCC and PVTT led to the difficulty of an evidence-based estimated ORR. Instead, we searched for literatures of other systemic regimens combined with radiotherapy and found out the ORR was 61.1% in HCC patients with PVTT treated with sorafenib and IMRT in a retrospective study [1]. Hence, we assumed the treatment strategies in this study might bring an increase of 20% to the ORR from 27% in IMbrave150 study after discussion among investigators based on the experience. The description of estimated ORR was added in the Methods.

Reference

1. Abulimiti M, Li Z, Wang H, et al. Combination Intensity-Modulated Radiotherapy and Sorafenib Improves Outcomes in Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis. *J Oncol* 2021;2021:9943683. doi: 10.1155/2021/9943683