PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol of Notable-HCC: A phase Ib study of neoadjuvant tislelizumab with stereotactic body radiotherapy in patients with resectable hepatocellular carcinoma
AUTHORS	Zhang, Bo; Yue, Jinbo; Shi, Xuetao; Cui, Kai; Li, Lei; Zhang, Chengsheng; Sun, Pengfei; Zhong, Jingtao; Li, Zhongchao; Zhao, Lei

VERSION 1 – REVIEW

REVIEWER	Marron, Thomas Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute
REVIEW RETURNED	15-Mar-2022

GENERAL COMMENTS	You need a thorough grammatical evaluation of the intro and the discussion. The discussion is good, but a bit scatterbrained, and the references are dated, as is the context (emerging trials, and FDA approvals). The endpoints should be better clarified. It seems you have three primary endpoints? and the evaluation of response is not clear, typically this would be pathologically, but seems in the discussion/methods you are using RECIST based on imaging? please clarify.

REVIEWER	Abrams, Ross Hadassah Medical Center, Oncology
REVIEW RETURNED	29-May-2022

GENERAL COMMENTS	This protocol needs a statistical section in the methods. I have taken the liberty of adding a potential goal I have made some suggestions to improve the use of the English language - hopefully without altering meaning. The authors Should Not assume that no additional edits regarding English language usage are required.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Dr. Thomas Marron, Icahn School of Medicine at Mount Sinai Comments to the Author: You need a thorough grammatical evaluation of the intro and the discussion.
Response:
we understand that the linguistic barrier can be a problem for non-English native authors. Before we re-submit the manuscript, we sent the revised manuscript to the professional English editing service. we believe the linguistic issue of the manuscript has got significant improvement.

The discussion is good, but a bit scatterbrained,
Response:
We went through the full text of the “discussion”, and feel the paragraph of “different sequence of RT and ICI” is about the technical details, and is not closely related to the other issues in the “discussion”, so we delete this paragraph, trying to make the “discussion” more clear and compact.
……and the references are dated, as is the context (emerging trials, and FDA approvals).
Response:
According to the reviewer’s requirement, we updated some important but relatively dated references. When we first submitted the manuscript, the ref. 13 (neoadjuvant application of nivolumab alone or nivolumab plus ipilimumab in HCC) has not been published, and it was reported as an abstract in ASCO conference. Later it was published in Lancet Gastroenterol Hepatol in March. And in the same issue of Lancet Gastroenterol Hepatol, another neoadjuvant ICI (cemiplimab, anti PD-1) trial in HCC was also published. We cite both of them in the revised manuscript.
We also updated the references about the rationale of combining radiotherapy with immune checkpoint blockade (ref. 17-20).
The endpoints should be better clarified. It seems you have three primary endpoints? and the evaluation of response is not clear, typically this would be pathologically, but seems in the discussion/methods you are using RECIST based on imaging? please clarify. Response:
As described in the section of “Outcome measures and endpoints”, We have four primary endpoints:
1. Delay to surgery: the number of patients experiencing a surgery delay over 6 weeks or later
2. ORR after neoadjuvant SBRT+tislelizumab and before the surgery, according to the RECIST v1.1/ mRECIST criteria
3. Pathologic response rate on evaluation of the resected specimen: pCR, pPR and MPR
4. Determination of safety and tolerability of the sequential SBRT/tislelizumab: incidence of Treatment-Emergent Adverse Events
Just as what the reviewer has pointed out, if available, pathological evaluation of tumour response is always the best choice. Indeed, it is much more accurate than imagining evaluation. I don’t find relevant results in HCC, but after the neoadjuvant chemo-radiation therapy of rectal cancer, 5% to 53% of patients with clinical CR (defined by DRE, endoscopic examination and MRI) still have viable tumor cells, while 8.3 to 16.6% of patients who did not fulfill the criteria of clinical CR reached pCR at pathological examination of the resected specimen [1-4].
The reason why we still set imaging evaluation of tumour response as another primary endpoint is here: In neoadjuvant scenario, specimen underwent pre-operative I/O + RT will be resected, so we will have an opportunity to compare the imaging tumour evaluation result to the pathological result, and validate the accuracy of imaging evaluation of tumour response after I/O+RT.
Reviewer: 2 [See attachment.]Prof. Ross Abrams, Hadassah Medical CenterComments to the Author:This protocol needs a statistical section in the methods.
Response:
Revised according the reviewer’s requirement. We add a ‘Statistical analysis” section after the “Outcome measures and endpoints” section.
I have taken the liberty of adding a potential goal
Response:
We appreciate this valuable suggestion. Indeed, the underlining rationale of this trial is: whether combination of neoadjuvant RT and ICIs can bring additional survival benefit to HCC patients.
I have made some suggestions to improve the use of the English language - hopefully without altering meaning. The authors Should Not assume that no additional edits regarding English language usage are required.Response:
We really appreciate the extra linguistic editing of our manuscript, and we also acknowledge that the linguistic barrier can be problematic for non-English native authors. Before we re-submit the manuscript, we sent the revised manuscript to the professional English editing service. we believe the linguistic issue of the manuscript has got significant improvement.

Reviewer: 1 Competing interests of Reviewer: I run a very similar clinical trial. Response:
Then we believe Dr. Marron's expertise will be really helpful to our ongoing clinical trial. Effective adjuvant/neoadjuvant therapy is still an unmet need in the clinical practice of HCC, we believe RT+ICIs warrant further exploration. We are happy to learn that more centers are doing the similar work, and we hope that together we can bring more evidence to address this issue.
Reviewer: 2 Competing interests of Reviewer: none
Response: None

Reference

[1] Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg, 2004, 240(4):711–717
[2] Dalton RSJ, Velineni R, Osborne ME, et al. A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? Colorectal Dis, 2012, 14(5):567–571.
[3] Habr-Gama A. Assessment and management of the complete clinical response of rectal cancer to chemoradiotherapy. Colorectal Dis, 2006, 8(Suppl 3):21–24.
[4] Maggiori L, Bretagnol F, Aslam MI, et al. Does pathologic response of rectal cancer influence postoperative morbidity after neoadjuvant radiochemotherapy and total mesorectal excision? Surgery, 2014,155(3):468–475.