PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Durvalumab with or without tremelimumab combined with particle therapy for advanced hepatocellular carcinoma with macrovascular invasion: protocol for the DEPARTURE phase Ib trial
AUTHORS	Ogasawara, Sadahisa; Koroki, Keisuke; Makishima, Hirokazu; Wakatsuki, Masaru; Takahashi, Asahi; Yumita, Sae; Nakagawa, Miyuki; Ishino, Takamasa; Ogawa, Keita; Fujiwara, Kisako; Iwanaga, Terunao; Sakuma, Takafumi; Fujita, Naoto; Kojima, Ryuta; Kanzaki, Hiroaki; Kobayashi, Kazufumi; Kiyono, Soichiro; Nakamura, Masato; Kanogawa, Naoya; Saito, Tomoko; Kondo, Takayuki; Nakagawa, Ryo; Nakamoto, Shingo; Muroyama, Ryosuke; Chiba, Tetsuhiro; Ozawa, Yoshihito; Kawasaki, Yohei; Kurokawa, Tomoya; Hanaoka, Hideki; Tsuji, Hiroshi; Kato, Naoya

VERSION 1 – REVIEW

REVIEWER	Seufferlein, Thomas Universitat Ulm, Department of Internal Medicine I
REVIEW RETURNED	03-Jan-2022

GENERAL COMMENTS	This is a straight forward, well designed and interesting phase Ib trial in advanced HCC with MVI using a combination of immune checkpoint inhibitors and particle therapy. The trial is well described and I have only two minor comments: While Figure 3 clearly shows that the trial will only move to cohort B in case of no DLT or only 1/6 in cohort A this is less clearly described in the respective text. A slight modification of the wording could improve clarity. I was suprised to learn that the authors obviously postulate a synergistic effect of ICI and CIRT only on intra- and extrahepatic metastasis (Figure 2). Is there a reason to believe that the ICIs might not also work on the primary tumor itself when the tumor has undergone CIRT? The neoantigens generated by CIRT are likley to be present in the primary tumor as well and could lead to a more active immune response. This idea could also be part of the reason why there are sequential biopsies planned. The authors may consider to slightly adapt Figure 2.

REVIEWER	Roudi, Raheleh Iran University of Medical Sciences
REVIEW RETURNED	31-Jan-2022

GENERAL COMMENTS	The authors should add the novelty of their study using the relevant and recent publications in liver cancer immunotherapy such as Navid Sobhani, et al - 2021

REVIEWER	Charalampakis, Nikolaos Metaxa Cancer Hospital of Piraeus, Medical Oncology Department
REVIEW RETURNED	31-Jan-2022

GENERAL COMMENTS	The authors of this paper are conducting a phase Ib trial exploring the use of immunotherapy combined with particle therapy for advanced HCC with macrovascular invasion. There are predominantly positive aspects in this paper. Strengths This paper investigates a very interesting topic. Immunotherapy and particle radiotherapy have shown promising results with encouraging outcomes. However, strong prospective data with the combination are still lacking. Thus, this trial provides a useful attempt to draw some conclusions on effectiveness so that more evidence is gathered for such a novel therapeutic modality. Moreover, the methodology and design of the protocol is sound. Weaknesses Apart from the strong points, the protocol does not have any significant drawbacks. We should appraise the authors for designing and conducting such an interesting protocol for this difficult cohort of patients with HCC and macrovascular invasion.

REVIEWER	Huang, Jee-Fu Kaohsiung Medical University Chung Ho Memorial Hospital
REVIEW RETURNED	01-Feb-2022

GENERAL COMMENTS	The study protocol was well-written one addressing the pressing need of potential therapeutic exploration for those patients with advanced HCC and MVI. The study design and the flowchart were clearly defined and depicted. The outcome measurements were sufficiently listed. The major point of dose-limiting toxicities was clear. The anticipated results will provide informative data in the direction. Two points need clarification. 1. Exclusion criteria 9: "Patients coinfected with hepatitis B and C viruses or with hepatitis B and D viruses" The rationale and the reason could be explained. 2. The sample size estimation could be addressed more for clarification.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. While Figure 3 clearly shows that the trial will only move to cohort B in case of no DLT or only 1/6 in cohort A this is less clearly described in the respective text. A slight modification of the wording could improve clarity.

Thank you for your comment. We have clarified the description of the conditions for transition to cohort B (Page 11, Lines 20–25).

2. I was suprised to learn that the authors obviously postulate a synergistic effect of ICI and CIRT only on intra- and extrahepatic metastasis (Figure 2). Is there a reason to believe that the ICIs might not also work on the primary tumor itself when the tumor has undergone CIRT? The neoantigens generated by CIRT are likley to be present in the primary tumor as well and could lead to a more active immune response. This idea could also be part of the reason why there are sequential biopsies planned. The authors may consider to slightly adapt Figure 2.

We agree with your comment and revised Figure 1 accordingly.

Reviewer 2

1. The authors should add the novelty of their study using the relevant and recent publications in liver cancer immunotherapy such as Navid Sobhani, et al - 2021Editor's review.

Thank you for your pertinent comment. We have added references to emphasize the novelty of this study (Page 7, Lines 15–17).

Reviewer 3

1. Strengths
This paper investigates a very interesting topic. Immunotherapy and particle radiotherapy have shown promising results with encouraging outcomes. However, strong prospective data with the combination are still lacking. Thus, this trial provides a useful attempt to draw some conclusions on effectiveness so that more evidence is gathered for such a novel therapeutic modality. Moreover, the methodology and design of the protocol is sound.
Weaknesses
Apart from the strong points, the protocol does not have any significant drawbacks. We should appraise the authors for designing and conducting such an interesting protocol for this difficult cohort of patients with HCC and macrovascular invasion.

We thank you for your encouraging comments. We will continue our efforts in making this trial a success.

Reviewer 4
1. Exclusion criteria 9: "Patients coinfected with hepatitis B and C viruses or with hepatitis B and D viruses" The rationale and the reason could be explained.

In the HIMALAYA trial (NCT03298451), which compared durvalumab plus tremelimumab and sorafenib in patients with hepatocellular carcinoma, patients coinfected with hepatitis B and C viruses or with hepatitis B and D viruses were excluded from the trial. Thus, we defined these criteria following the inclusion and exclusion criteria of the HIMALAYA trial.

2. The sample size estimation could be addressed more for clarification.

We determined the sample size based on the feasibility within the study period (Page 12, Lines 24–25).

VERSION 2 – REVIEW

REVIEWER	Seufferlein, Thomas Universitat Ulm, Department of Internal Medicine I
REVIEW RETURNED	13-Mar-2022

GENERAL COMMENTS	The authors have substantially improved their mansucript including the addition of novel references and provide now a very concise study protocol of their planned phase Ib trial. I have no further comments or criticisms.

REVIEWER	Huang, Jee-Fu Kaohsiung Medical University Chung Ho Memorial Hospital
REVIEW RETURNED	11-Mar-2022

GENERAL COMMENTS	The Authors have sufficiently responded to the points raised.