PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Adoptive immunotherapy with natural killer cells from peripheral blood CD34+ stem cells to prevent hepatocellular carcinoma recurrence after curative hepatectomy: A study protocol for an open-label, single-arm phase I study
AUTHORS	Ohira, Masahiro; Kobayashi, Tsuyoshi; Tanaka, Yuka; Imaoka, Yuki; Sato, Koki; Imaoka, Koki; Nakano, Ryosuke; Doskali, Marlen; Piao, Jinlian; Nakamura, Mayuna; Yoshida, Tetsumi; Ichinohe, Tatsuo; Kawano, Reo; Yoshimura, Kenichi; Ueda, Keiko; Tamura, Natsuko; Hirata, Taizo; Imamura, Michio; Aikata, Hiroshi; Tanimine, Naoki; Kuroda, Shintaro; Tahara, Hiroyuki; Ide, Kentaro; Ohdan, Hideki

VERSION 1 – REVIEW

REVIEWER	Roudi, Raheleh Iran University of Medical Sciences
REVIEW RETURNED	20-Jun-2022

GENERAL COMMENTS	Now, there are a panel of therapeutic option in HCC and the authors must be clarify the rational behind the selection of this treatment using the relevant and recent publications in HCC such as Navid Sobhani, et al - 2021

REVIEWER	Sun, Hui Fudan University, Department of Liver Surgery and Transplantation
REVIEW RETURNED	19-Jul-2022

GENERAL COMMENTS	The authors plan to investigate the efficacy of CD34+ NK cells on tumor recurrence after resection of hepatocellular carcinoma (HCC). The idea is interesting, and may be worthwhile to explore. Some concerns 1. The most important issue is ethical issue related with adjuvant therapy. Several pivotal trials are ongoing and probably a number of them will announce results in the second half of this year, followed by approval as a standard of care if the result is positive. If there is no ethical issue, patient recruitment may be a problem when a later phase trial is conducting. So it may be better to plan a multi-center trial to facilitate a faster trial before the standard of care in adjuvant therapy is changed. 2. the primary endpoint is safety, do you have setup an expectation/objective for a “stop” sign for toxicities associated with this treatment.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1

Query. Now, there are a panel of therapeutic option in HCC and the authors must be clarify the rational behind the selection of this treatment using the relevant and recent publications in HCC such as Navid Sobhani, et al – 2021

Reply:
Thank you for your valuable comments. As reviewer #1 pointed out, novel immune checkpoint inhibitor therapies for recurrent and advanced HCC have been substantial and reported to have good results (Navid Sobhani, et al 2021). However, no standard adjuvant therapy after hepatectomy has yet been established with proven efficacy in preventing recurrence. We believe that this point is the rationale for this study. We have added these sentences in the Introduction section (see page 4 lines 4-5).

Response to Reviewer #2
Query 1. The most important issue is ethical issue related with adjuvant therapy. Several pivotal trials are ongoing and probably a number of them will announce results in the second half of this year, followed by approval as a standard of care if the result is positive. If there is no ethical issue, patient recruitment may be a problem when a later phase trial is conducting. So it may be better to plan a multi-center trial to facilitate a faster trial before the standard of care in adjuvant therapy is changed.

Reply:
Thank you for your important comment. As the reviewer points out, there are many clinical trials on adjuvant therapies, and we plan to plan a multicenter phase II trial as soon as possible to expedite the trial.

Query 2. 2. the primary endpoint is safety, do you have setup an expectation/objective for a “stop” sign for toxicities associated with this treatment.

Reply:
Our protocol specifies that a clinical trial will be terminated as follows; 1. Significant information regarding the quality, safety, or efficacy of the cellular conditioning is obtained. 2. When it is deemed difficult to conduct the clinical research due to delays in case enrollment, frequent protocol deviations, or other reasons. 3. When it is determined that there is a problem with the safety of the protocol treatment based on the evaluation by the Committee for Regenerative Medicine. 4. If, as a result of the evaluation of relevant information obtained from sources other than this clinical research, such as papers and conference presentations, it is determined that there is a problem with the safety of the protocol treatment, or that the continuation of the clinical research is no longer meaningful. We have added these sentences in the Methods and Analysis section (see page 10 line 17- page 11 line 6).