Financial support
The authors received no financial support to produce this manuscript.

Conflict of interest
The author declares no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure form for further details.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.05.035

References
[1] Chuah S, Lee J, Song Y, Kim HD, Wasser M, Kaya NA, et al. Uncoupling immune trajectories of response and adverse events from anti-PD-1 immunotherapy in hepatocellular carcinoma. J Hepatol 2022 Sep;77(3):683–694.
[2] Ahern E, Solomon BJ, Hui R, Pavlakis N, O'Byrne K, Hughes BGM. Neo-adjuvant immunotherapy for non-small cell lung cancer: right drugs, right patient, right time? J ImmunoTherapy Cancer 2021;9(6):e002248.
[3] Agostinetto E, Losurdo A, Nader-Marta G, Santoro A, Punie K, Barroso R, et al. Progress and pitfalls in the use of immunotherapy for patients with triple negative breast cancer. Expert Opin Investig Drugs 2022;9:1–25.
[4] Colin P, Delattre M, Minini P, Micallef S. An escalation for bivariate binary endpoints controlling the risk of overtoxicity (EBE-CRO): managing efficacy and toxicity in early oncology clinical trials. J Biopharm Stat 2017;27(6):1054–1072.
[5] Kittelson JM, Spyropoulos AC, Halperin JL, Kessler CM, Schulman S, Steg G, et al. Balancing risk and benefit in venous thromboembolism trials: concept for a bivariate endpoint trial design and analytic approach. J Thromb Haemost 2013;11(8):1443–1448.

Qian Zhou*
Department of Medical Statistics, Clinical Trials Unit, The First Affiliated Hospital of Sun Yat-sen University, 58 Zhong Shan Er Road, Guangzhou, China, 510080
*Corresponding author. Address: Department of Medical Statistics, Clinical Trials Unit, The First Affiliated Hospital of Sun Yat-sen University, 58 Zhong Shan Er Road, Guangzhou, China, 510080. Tel./fax: +86-20-87755766-8649,.
E-mail address: zhouq49@mail.sysu.edu.cn

Reply to: "Challenges and issues in bivariate endpoints in study designs of translational medicine"

To the Editor:

We thank Zhou[1] for their interest and comments on our work.[2] Zhou commented that the two binary endpoints of efficacy and safety should be analyzed separately or reorganized into four groups. Indeed, the relationship between response and toxicity to immunotherapy is widely recognised, which we also acknowledged by citing the clinical trials of CheckMate040 and IMBRAVE150, where immune related adverse events (irAEs) increased in tandem with greater objective response rates (ORRs) in combination immunotherapy.[3,4] There were also other analyses that correlated irAEs with clinical benefits of immune checkpoint blockade (ICB), both in HCC and other cancer types.[5,6] With this in mind, we did explore the interaction between response and toxicity to treatment. Firstly, our multivariate analyses showed that the incidence of irAEs was a significant factor relating to progression-free survival, as would be expected (Table S8).[2] We also split our cohorts into the four different groups to verify that our biomarkers were not confounded by the interaction between response and toxicity (Figs S2C and S3B).[2] Due to the small sample size in some of the groupings, we have elected instead to conduct our main analysis on response and toxicity separately, while still acknowledging their potential co-dependence.

The author further commented on combination therapy, where we have only included patients receiving monotherapy and the limited sample size of each group in our *in vivo* mouse studies. We would like to highlight that the objective of our study was to analyse patients undergoing anti-PD1 monotherapy in order to discover potential combination therapies that would improve response rates while not increasing the incidence of irAEs. As such, we do not yet have an adequate patient cohort to act as a control for 'combined immunotherapies which have been proven to be positive in randomized clinical trials'. In fact, we are planning to conduct the first-in human trials using combination immunotherapy of anti-PD-1+anti-TNFR2, where we will be able to assess the patient data in the near future. Rather, in this current study, we validated the response and toxicity of the combination immunotherapy in our pre-clinical HCC mouse model, based upon our discovery in the HCC patient cohort treated with anti-PD-1 ICB. Hence, our study focused on discovery and pre-clinical validation, not clinical validation. The deeper mechanistic insights into the involvement of T cells and antigen-presentation cells in clinical response to ICB is another highlight of our study. Despite the small sample sizes, the strong data we observed provided sufficient proof-of-concept for an anti-PD1+anti-TNFR2 combination immunotherapy, which could encourage larger scale animal experiments and clinical trials in HCC.

The differences between the Singapore and Korea cohorts were already explained in the description of our patient cohorts. The Singapore patient cohort was recruited from real-world clinical patients with advanced HCC undergoing anti-PD1 immunotherapy. As a result, their clinical characteristics were very heterogenous. To ensure that the immune targets we discovered were not affected by this heterogeneity, we collaborated and validated our targets with the group from Korea, who had a more controlled cohort of patients with HCC from their clinical trial (NCT03695952). The analyses

Received 27 July 2022; accepted 14 August 2022; available online 24 August 2022
https://doi.org/10.1016/j.jhep.2022.08.017

were conducted separately in each individual cohort, with Korean patients as the validation cohort, precisely as we recognized their differences. We are encouraged by the fact that despite significant differences between the two cohorts (as analyzed by Zhou[1]), the same immune targets remained robust and significant. Our multivariate analyses of these factors within each cohort also show that these clinical characteristics do not significantly confound our analyses (Table S8).[2] We hope that this will encourage other groups to expand their work beyond Asian cohorts to examine if the same immune targets can be validated in their cohorts.

Finally, the author commented on the rationale for using the word "trajectory" in our study. We used the word "trajectory" in a broad sense of the different paths the immune response can take in response or irAEs to immunotherapy, not in the narrower sense of a timepoint analysis. Response and irAEs in immunotherapy are generally understood to occur in tandem, as mentioned above. Our study uncouples these two events and shows that there are differences in the immune responses in each event. In addition, we have also conducted timepoint analysis with pre- and post-treatment samples with implications on the potential movements and modifications of these immune cells, supporting the distinct "trajectory" pathways that the cells took in response to ICB.

In conclusion, we thank the author once again for the tremendous interest and time invested in interpreting and understanding our study. We would acknowledge the limited sample sizes but remain encouraged by our data that show the potential of novel combination immunotherapy, which we are currently planning to expand to a larger scale clinical validation.

Financial support

This work was supported by the National Medical Research Council (NMRC), Singapore (ref numbers: NMRC/OFLCG/003/2018, NMRC/TCR/015-NCC/2016, NMRC/CSA-SI/0013/2017, NMRC/CSA-SI/0018/2017 and NMRC/STaR/020/2013).

Conflict of interest

All authors declared no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

S. Chuah and V. Chew drafted the letter and D. Tai edited and approved the final version.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.08.017.

References

Author names in bold designate shared co-first authorship

[1] Zhou Q. Challenges and issues in bivariate endpoints in study designs of translational medicine. J Hepatol 2022;77:1726–1727.
[2] Chuah S, Lee J, Song Y, Kim HD, Wasser M, Kaya NA, et al. Uncoupling immune trajectories of response and adverse events from anti-PD-1 immunotherapy in hepatocellular carcinoma. J Hepatol 2022;77:683–694.
[3] Yau T, Kang Y-K, Kim T-Y, El-Khoueiry AB, Santoro A, Sangro B, et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040. J Clin Oncol 2019;37. 4012-4012.
[4] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894–1905.
[5] Xu S, Lai R, Zhao Q, Zhao P, Zhao R, Guo Z. Correlation between immune-related adverse events and prognosis in hepatocellular carcinoma patients treated with immune checkpoint inhibitors. Front Immunol 2021;12:794099.
[6] **Ye W**, **Olsson-Brown A**, Watson RA, Cheung VTF, Morgan RD, Nassiri I, et al. Checkpoint-blocker-induced autoimmunity is associated with favourable outcome in metastatic melanoma and distinct T-cell expression profiles. Br J Cancer 2021;124:1661–1669.

Samuel Chuah[1]
David Tai[2]
Valerie Chew[1,*]
[1]*Translational Immunology Institute (TII), SingHealth Duke-NUS Academic Medical Centre, Singapore 169856, Singapore*
[2]*Division of Medical Oncology, National Cancer Centre Singapore, Singapore 169610, Singapore*
[*]Corresponding author. Address: Translational Immunology Institute (TII), SingHealth Duke-NUS Academic Medical Centre, Singapore 169856, Singapore.
E-mail address: valerie.chew@duke-nus.edu.sg (V. Chew)

An individualized cirrhosis screening strategy might be more cost-effective in the general population

To the Editor:

We read with great interest the article by Labenz, Arslanow *et al.*[1] recently published in *Journal of Hepatology*. This article showed that the structured early detection of asymptomatic liver cirrhosis (SEAL) approach, involving assessment of elevated liver enzymes and calculation of the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), has the potential to increase the detection of advanced liver fibrosis and cirrhosis in the general population. This prospective study is important and timely for guiding the detection of early cirrhosis in clinical practice. After careful consideration, we put forward the following suggestions.

First, the performance of the non-invasive methods for diagnosing advanced fibrosis and cirrhosis might be affected by patient age and comorbidities. Wang *et al.* reported that the APRI showed

Keywords: Cirrhosis; Chronic liver disease; Noninvasive.
Received 29 May 2022; received in revised form 23 June 2022; accepted 24 June 2022; available online 16 July 2022
https://doi.org/10.1016/j.jhep.2022.06.035