First, restrictive eligibility criteria of this trial might not adequately reflect the overall patient population, despite the authors mentioning that their criteria were relatively less stringent among phase 3 trials. The study mainly included stage C patients with class A score, resulting in more opportunities for them to receive second-line therapies or later therapies. Consequently, this inclusion might have influenced the extended overall survival seen in both the combination and sorafenib groups than in other global trials. In clinical practice, however, many patients with stage C hepatocellular carcinoma have poor performance status and therefore do not have the chance to receive effective treatment. To address this issue, we suggest adopting a more patient-centric trial or real-world study design with broader enrolment criteria to ensure a more representative study population.

Second, there are concerns relating to the high proportion of patients with hepatitis B virus (HBV). The overall survival benefits observed in the combination group, particularly in the HBV-infected subgroup, have also been observed in the COSMIC-312[2] and HIMALAYA[3] studies (appendix). Notably, the immune subsets between viral and non-viral etiological hepatocellular carcinoma are entirely different[4]. In-depth analysis has revealed that the microenvironment of HBV-related hepatocellular carcinoma is more immunosuppressive and enriched with PD-1 positive regulatory T cells and CD8 positive resident memory T cells.[5] Therefore, understanding the immune features specific to virus-related hepatocellular carcinoma is crucial for identifying patients with advanced hepatocellular carcinoma who could benefit from tyrosine-kinase inhibitor (TKI)-based immunotherapy doublets. We further summarise the synergistic effects of TKIs and PD-1 inhibitors in patients with HBV-related hepatocellular carcinoma (appendix), which will aid in designing rational combinatory immunotherapy approaches tailored to each cause.

See **Online** for appendix

Just as the philosophy of Wan Fa Gui Zong in the ancient Chinese book *Tao Te Ching* suggests, everything changes in form, but the essence remains unchanged. For hepatocellular carcinoma with a complex heterogeneity and immune microenvironment, the inner essence might lie in the cause of the disease. Therefore, foreseeable future clinical trials should be designed based on the regional characteristics of different hepatocellular carcinoma populations, rather than relying solely on subgroup analysis in multicentre clinical trials.

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*Heming Li, Jinshan Yan, *Tao Han*
than1984@sina.com

Department of Medical Oncology, the First Hospital of China Medical University, Shenyang 110001, China (HL, JY, TH)

1 Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. *Lancet* 2023; **402:** 1133–46.
2 Kelley RK, Rimassa L, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2022; **23:** 995–1008.
3 Chan L, Kudo M, Sangro B, et al. 714P Impact of viral aetiology in the phase III HIMALAYA study of tremelimumab (T) plus durvalumab (D) in unresectable hepatocellular carcinoma (uHCC). *Ann Oncol* 2022; **33:** S869–70.
4 Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol* 2022; **19:** 151–72.
5 Lim CJ, Lee YH, Pan L, et al. Multidimensional analyses reveal distinct immune microenvironment in hepatitis B virus-related hepatocellular carcinoma. *Gut* 2019; **68:** 916–27.

We read with interest the excellent trial study by Shukui Qin and colleagues[1] whereby camrelizumab plus rivoceranib was reported as a new and effective first-line treatment option for patients with unresectable hepatocellular carcinoma. However, regarding the design of this valuable study, we have identified several concerns.

First, a phase 2 trial[2] focusing on camrelizumab monotherapy in patients with advanced hepatocellular carcinoma did not show different efficacy rates on objective response for the group receiving camrelizumab every 2 weeks or for disease control rate for the group receiving camrelizumab every 3 weeks. The authors chose a regimen of 2-week cycles that might increase the frequency and dosage of camrelizumab intravenously, subsequently contributing to the frequent occurrence of adverse events and short-term drug resistance.

Second, most participants enrolled in this study were patients from mainland China, who exhibit different characteristics than patients from high-income countries, such as hepatitis B virus infection, genetic mutations,[3] and use of traditional Chinese medicine treatments.[4] These characteristics largely influence the immune microenvironment of patients, thereby affecting the efficacy of immunotherapy and leading to different prognosis of patients from high-income countries.

Third, camrelizumab monotherapy[2] in advanced hepatocellular carcinoma found 13 (7%) of 199 patients had hyperprogression at the first response evaluation compared with the baseline, which is a high-risk immune-related adverse event. Patients also needed another potentially effective salvage therapy immediately;[2] however, this important immune-related adverse event was missing in the report.

Despite these pitfalls, the study by Qin and colleagues[1] provides new first-line treatment strategies for patients with unresectable hepatocellular carcinoma. However, we need more rigorous evidence to validate this result.

We declare no competing interests.

*Jun-Ke Wang, *Rui Liao*
liaorui99@163.com

Department of Hepatobiliary Surgery, the People's Hospital of Yubei District of Chongqing City, Chongqing, China (J-KW); Department of Hepatobiliary Surgery, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China (RL)

1 Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. *Lancet* 2023; **402:** 1133–46.

2 Qin S, Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. *Lancet Oncol* 2020; **21:** 571–80.

3 Gao Q, Zhu H, Dong L, et al. Integrated proteogenomic characterization of HBV-related hepatocellular carcinoma. *Cell* 2019; **179:** 561–77.

4 Wu Y, Lin H, You X, et al. Immune checkpoint blockade in Chinese patients with hepatocellular carcinoma: characteristics and particularity. *Front Oncol* 2022; **12:** 764923.

We read with keen interest the positive results of the CARES-310 study by Shukui Qin and colleagues,[1] which compared camrelizumab plus rivoceranib to sorafenib as the first-line treatment in advanced hepatocellular carcinoma. This study is the first to show an improved overall survival using a combination regimen of an immune checkpoint inhibitor (ICI) and an oral tyrosine-kinase inhibitor (TKI) compared with TKI monotherapy.[1] Two previous studies, COSMIC-312[2] and LEAP-002,[3] which used different combinations of ICI and TKI failed to show any clinically or statistically significant improvements in overall survival. The authors noted several differences in patient characteristics and exclusion criteria between the previous studies and CARES-310,[1] including main portal vein thrombosis and the requirement on oesophagogastroduodenoscopy before treatment initiation. However, another key difference is in the aetiology of hepatocellular carcinoma. Hepatitis B virus (HBV), hepatitis C virus (HCV), and non-viral causes are known to have distinct pathophysiology in hepatocarcinogenesis, with HBV-related hepatocellular carcinoma likely to attain a more pronounced benefit from ICI than other subgroups.[4] Although the study showed similar overall survival regardless of the aetiology of hepatocellular carcinoma, one should be aware that the subgroup analysis was done in an exploratory manner. In addition, only 25·4% of the participants in the CARES-310 study had HCV or non-viral hepatocellular carcinoma compared with 51·5% in LEAP-002 and 70·7% in COSMIC-312 (appendix). Further confirmatory study to establish the overall survival benefit should be pursued in patients with HCV and non-viral hepatocellular carcinoma before any conclusions can be made regarding the overall survival benefits for this patient population.

See Online for appendix

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*Ben Ponvilawan, *Marc T Roth*
mroth@saint-lukes.org

Department of Internal Medicine, University of Missouri–Kansas City School of Medicine, Kansas City, MO, USA (BP, MTR); Department of Hematology/Oncology, St Luke's Cancer Institute, Kansas City, MO 64111, USA (MTR)

1 Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. *Lancet* 2023; **402:** 1133–46.

2 Kelley RK, Rimassa L, Cheng A-L, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2022; **23:** 995–1008.

3 Finn RS, Kudo M, Merle P, et al. LBA34 Primary results from the phase III LEAP-002 study: lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). *Ann Oncol* 2022; **33:** S1401.

4 Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol* 2022; **19:** 151–72.

Author's reply

The letters we have received in response to the CARES-310 study[1] are valuable and meaningful. We thank Heming Li and colleagues for their Correspondence. In the existing phase 3 trials of advanced hepatocellular carcinoma, reasonable inclusion and exclusion criteria should consider the patient's tolerability and safety. Currently, randomised controlled trials are still the highest level of clinical studies in evidence-based medicine, which can clarify the efficacy and safety of a drug or drug combination compared with standard treatment while minimising confounding factors and ensuring study quality. The eligibility criteria of Child-Pugh class A liver function in the CARES-310 study[1] are consistent with other global international phase 3 trials in unresectable hepatocellular carcinoma (such as IMbrave150).[2] Patients in the CARES-310 study had a more severe stage of Barcelona Clinic Liver Cancer and poorer physical performance status than in other trials, but camrelizumab plus rivoceranib still had better overall survival benefit compared with those phase 3 trials (such as IMbrave150).[2] However, we agree that conducting further real-world studies and evaluating this regimen in a broader population after obtaining results from the CARES-310 confirmatory trial[1] is necessary.

The liver is an immunoprivileged organ with resistance against immune responses. An increasing number of basic research studies suggest that the immune system is heavily involved in various causes of hepatocellular carcinoma (eg, hepatocellular carcinoma related to hepatitis B virus (HBV), hepatitis C virus (HCV), non-alcoholic steatohepatitis, and alcoholic steatohepatitis), although the immune microenvironment of different types of hepatocellular carcinoma has unique characteristics.[3] In CARES-310, patients had consistent survival benefits with camrelizumab plus rivoceranib, regardless of viral or non-viral cause. Given the heterogeneous causes of non-viral hepatocellular carcinoma, different subtypes might respond differentially to immunotherapy. Currently, aetiological considerations do not have a part in therapy decisions for hepatocellular carcinoma, without