Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study

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Summary

Background Immunotherapy with immune checkpoint inhibitors combined with an anti-angiogenic tyrosine-kinase inhibitor (TKI) has been shown to improve overall survival versus anti-angiogenic therapy alone in advanced solid tumours, but not in hepatocellular carcinoma. Therefore, a clinical study was conducted to compare the efficacy and safety of the anti-PD-1 antibody camrelizumab plus the VEGFR2-targeted TKI rivoceranib (also known as apatinib) versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma.

Methods This randomised, open-label, international phase 3 trial (CARES-310) was done at 95 study sites across 13 countries and regions worldwide. Patients with unresectable or metastatic hepatocellular carcinoma who had not previously received any systemic treatment were randomly assigned (1:1) to receive either camrelizumab 200 mg intravenously every 2 weeks plus rivoceranib 250 mg orally once daily or sorafenib 400 mg orally twice daily. Randomisation was done via a centralised interactive response system. The primary endpoints were progression-free survival, as assessed by the blinded independent review committee per Response Evaluation Criteria in Solid Tumours version 1.1, and overall survival in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of the study drugs. We report the findings from the prespecified primary analysis for progression-free survival and interim analysis for overall survival. This study is registered with ClinicalTrials.gov (NCT03764293).

Findings Between June 28, 2019, and March 24, 2021, 543 patients were randomly assigned to the camrelizumab–rivoceranib (n=272) or sorafenib (n=271) group. At the primary analysis for progression-free survival (May 10, 2021), median follow-up was 7·8 months (IQR 4·1–10·6). Median progression-free survival was significantly improved with camrelizumab–rivoceranib versus sorafenib (5·6 months [95% CI 5·5–6·3] *vs* 3·7 months [2·8–3·7]; hazard ratio [HR] 0·52 [95% CI 0·41–0·65]; one-sided p<0·0001). At the interim analysis for overall survival (Feb 8, 2022), median follow-up was 14·5 months (IQR 9·1–18·7). Median overall survival was significantly extended with camrelizumab–rivoceranib versus sorafenib (22·1 months [95% CI 19·1–27·2] *vs* 15·2 months [13·0–18·5]; HR 0·62 [95% CI 0·49–0·80]; one-sided p<0·0001). The most common grade 3 or 4 treatment-related adverse events were hypertension (102 [38%] of 272 patients in the camrelizumab–rivoceranib group *vs* 40 [15%] of 269 patients in the sorafenib group), palmar-plantar erythrodysaesthesia syndrome (33 [12%] *vs* 41 [15%]), increased aspartate aminotransferase (45 [17%] *vs* 14 [5%]), and increased alanine aminotransferase (35 [13%] *vs* eight [3%]). Treatment-related serious adverse events were reported in 66 (24%) patients in the camrelizumab–rivoceranib group and 16 (6%) in the sorafenib group. Treatment-related death occurred in two patients: one patient in the camrelizumab–rivoceranib group (ie, multiple organ dysfunction syndrome) and one patient in the sorafenib group (ie, respiratory failure and circulatory collapse).

Interpretation Camrelizumab plus rivoceranib showed a statistically significant and clinically meaningful benefit in progression-free survival and overall survival compared with sorafenib for patients with unresectable hepatocellular carcinoma, presenting as a new and effective first-line treatment option for this population.

Funding Jiangsu Hengrui Pharmaceuticals and Elevar Therapeutics.

Introduction

Primary liver cancer is a major health burden globally, ranking sixth in incidence and third in mortality among all cancers.[1] Hepatocellular carcinoma constitutes about 75–85% of primary liver cancer cases.[2] About 72% of hepatocellular carcinomas are diagnosed in Asia, with hepatitis B virus infection as the most common risk factor.[2] The multitargeted tyrosine-kinase inhibitors

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Research in context

Evidence before this study

We searched PubMed for clinical trials published in English between Jan 1, 2017, and Nov 30, 2022, using the terms "PD-1" OR "PD-L1" OR "pembrolizumab" OR "nivolumab" OR "atezolizumab" OR "durvalumab" OR "avelumab" AND "hepatocellular carcinoma", as well as abstract records of the American Society of Clinical Oncology, European Society of Medical Oncology, and American Association for Cancer Research using the same search terms. We identified six randomised phase 3 superiority studies of unresectable hepatocellular carcinoma in the first-line setting, including four assessing immunotherapy with anti-angiogenic therapy (IMbrave150 on atezolizumab plus bevacizumab, ORIENT-32 on sintilimab plus IBI305 [a bevacizumab biosimilar], COSMIC-312 on atezolizumab plus cabozantinib, and LEAP-002 on pembrolizumab plus lenvatinib), one assessing dual immunotherapy (HIMALAYA on tremelimumab plus durvalumab) and one assessing single-agent immunotherapy (CheckMate 459 on nivolumab). Significant benefits in progression-free survival and overall survival were found with atezolizumab–bevacizumab and sintilimab-IBI305 compared with sorafenib as first-line treatment for unresectable hepatocellular carcinoma. Progression-free survival, but not overall survival, was significantly improved with atezolizumab–cabozantinib versus sorafenib. Neither progression-free survival nor overall survival were significantly extended with pembrolizumab–lenvatinib versus lenvatinib alone. The primary endpoint of overall survival was met in HIMALAYA, but not in CheckMate 459 with sorafenib as the control group.

Added value of this study

This phase 3 study on camrelizumab plus rivoceranib is the first to report significant progression-free survival and overall survival benefits with the combination of an anti-PD-1 antibody and an orally administered, small-molecule, anti-angiogenic agent over sorafenib as first-line treatment for unresectable hepatocellular carcinoma. To our knowledge, the median overall survival of 22·1 months in the camrelizumab–rivoceranib group was the longest one observed for any systemic treatment in global phase 3 trials in unresectable hepatocellular carcinoma. Survival benefits with camrelizumab–rivoceranib were generally consistent across clinically relevant subgroups. In addition, safety was manageable with no new safety signals identified.

Implications of all the available evidence

Camrelizumab plus rivoceranib showed a positive benefit-to-risk profile versus sorafenib and presents as a new first-line treatment option for unresectable hepatocellular carcinoma. The incorporation of an orally administered, anti-angiogenic tyrosine-kinase inhibitor in the immune-combination regimen could provide clinicians with more flexibility in treatment selection in practice.

(TKIs) sorafenib and lenvatinib were established as the standard first-line treatment for unresectable hepatocellular carcinoma on the basis of the SHARP, SHARP-Asia-Pacific, and REFLECT trials; they showed a modest improvement in median overall survival against placebo.[3–5] Over the past 5 years, immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 pathway have emerged as new treatment options for advanced hepatocellular carcinoma.[6–9] Nevertheless, only a small subset of patients with hepatocellular carcinoma derive a response to ICI monotherapy,[6–9] and no survival gain over sorafenib was observed in the first-line setting.[8]

On the basis of the concept that anti-angiogenic therapy can ameliorate an immunosuppressive tumour microenvironment[10] and, thereby, potentiate tumour response to immunotherapy, a few phase 3 trials have assessed an ICI with anti-angiogenic agent as first-line therapy for unresectable hepatocellular carcinoma, including the global IMbrave150, COSMIC-312, and LEAP-002 trials[11–14] and the ORIENT-32 trial from China.[15] However, mixed results were reported for combination therapies when compared with sorafenib or lenvatinib monotherapies, with significant improvement in overall survival reached only with an ICI in combination with anti-VEGF antibody, but not with multitargeted TKI.[16] Oral TKIs are of interest due to their convenient route of administration, improved flexibility with dosing (ie, shorter half-life), and the potential to spare screening gastroduodenoscopy (which is required for bevacizumab in treating hepatocellular carcinoma).[11] Alternatively, the dual immunotherapy of tremelimumab plus durvalumab also showed improved overall survival versus sorafenib in the phase 3 HIMALAYA trial.[17] However, with a median overall survival of less than 2 years for all systemic treatments in phase 3 trials in unresectable hepatocellular carcinoma, there remains an unmet medical need for additional effective first-line regimens.[11–15,17]

Camrelizumab is a humanised IgG4 monoclonal antibody with high affinity for PD-1.[18] Rivoceranib (also known as apatinib) is a small-molecule, highly selective VEGFR2-targeted TKI that exerts anti-tumour effects by inhibiting tumour cell proliferation and neovascularisation and by counteracting the immunosuppressive effects of the tumour microenvironment.[19] Camrelizumab and rivoceranib have each shown efficacy and safety in advanced hepatocellular carcinoma and have been approved as monotherapy in the second-line setting in China.[9,20] In a phase 1 study in pre-treated hepatocellular carcinoma and gastric or gastro-oesophageal junction cancer, camrelizumab plus rivoceranib showed encouraging anti-tumour activity and acceptable tolerability, with the recommended phase 2 dose established as camrelizumab 200 mg every 2 weeks plus rivoceranib 250 mg once daily.[21] In a

subsequent phase 2 trial in advanced hepatocellular carcinoma, camrelizumab plus rivoceranib as second-line therapy showed improved clinical efficacy compared with historical data of camrelizumab or rivoceranib monotherapy.[22] Additionally, the combination as first-line treatment led to an objective response rate (ORR) of 34·3% (95% CI 23·3–46·6), a median progression-free survival of 5·7 months (95% CI 5·4–7·4), and an 18-month overall survival rate of 58·1% (45·4–68·9).[22] In this study, we assessed the efficacy and safety of camrelizumab plus rivoceranib versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma.

Methods

Study design

This randomised, open-label, international phase 3 trial (CARES-310) was done globally at 95 study centres across 13 countries and regions (appendix p 4). The study protocol (appendix pp 28–228) and amendments were reviewed and approved by local or central institutional review boards or ethics committees. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki, the guidelines of Good Clinical Practice, and local regulatory requirements. All patients provided written informed consent. An independent data monitoring committee was established to monitor safety regularly and to review efficacy from all preplanned analyses.

Patients

Eligible patients were aged 18 years or older with histopathologically or cytologically confirmed hepatocellular carcinoma; had Barcelona Clinic Liver Cancer stage B or C disease, which was not amenable to or had progressed after surgical or locoregional therapy; and had not previously received any systemic therapy. Other key inclusion criteria were at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), Child-Pugh class A liver function, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of 12 weeks or more, and adequate organ function. Patients with hepatitis B virus infection, who had a viral load of hepatitis B virus DNA lower than 500 IU/mL or less than 2500 copies per mL, and patients testing positive for hepatitis C virus RNA who had hepatic function meeting the eligibility criteria could also be enrolled if they agreed to receive antiviral therapy per local standard of care throughout the study. Key exclusion criteria included hepatocholangiocarcinoma, sarcomatoid hepatocellular carcinoma, mixed cell carcinoma, and lamellar cell carcinoma; patients with a history (ie, within 6 months before study treatment) of gastrointestinal bleeding or at high risk of gastrointestinal bleeding (eg, severe oesophagogastric varices, locally active peptic ulcer, and persistent faecal occult blood); uncontrolled hypertension; CNS metastases; metastatic disease involving main airway or blood vessels (eg, vena cava invasion or complete occlusion of the main trunk of the portal vein, defined as the part between the union of the splenic and superior mesenteric veins and the first bifurcation into the left and right vein—patients with partial occlusion of the main trunk or complete occlusion of a branch portal vein were eligible); and active or history of autoimmune disease. The full eligibility criteria are provided in the protocol in the appendix (pp 106–10). Participants self-reported their sex assigned at birth as male or female.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive either camrelizumab–rivoceranib or sorafenib. The randomisation was stratified by the presence of macrovascular invasion or extrahepatic metastasis (yes *vs* no), geographical region (Asia [ie, mainland China, Hong Kong, Taiwan, and South Korea] *vs* non-Asia [ie, Belgium, Italy, Germany, Poland, Russia, Spain, Türkiye, Ukraine, and the USA]), and baseline alpha-fetoprotein concentration (<400 ng/mL *vs* ≥400 ng/mL). Investigators registered patients by means of a centralised interactive response technology system with a random block size of four or six. The randomisation sequence was generated by an independent third party. The study was open-label and treatment administered to patients was unmasked.

Procedures

Patients received camrelizumab 200 mg intravenously every 2 weeks plus rivoceranib 250 mg orally once daily or sorafenib 400 mg orally twice daily. Treatment continued in 28-day cycles until unacceptable toxicity, withdrawal of informed consent, disease progression confirmed by the blinded independent review committee (BIRC) per RECIST 1.1 (unless criteria for treatment beyond disease progression were met), or investigator's decision. Patients could continue to receive camrelizumab (alone or with rivoceranib) or sorafenib beyond progression if there was evidence of clinical benefit and treatment tolerability as determined by the investigator. Patients who temporarily or permanently discontinued camrelizumab or rivoceranib due to treatment-related adverse events (TRAEs) were allowed to continue to receive a single agent of the combination regimen. Dose reduction was permitted for rivoceranib and sorafenib, but not for camrelizumab. Details regarding dose modifications are available in the appendix (pp 118–26).

Tumour radiological examination was done using enhanced CT or MRI at baseline, every 8 weeks for the first 48 weeks, and every 12 weeks thereafter. Multiphase liver imaging covering the arterial and portal venous phases was required. RECIST 1.1 (assessed by the BIRC and investigator), modified RECIST (assessed by the BIRC), and immune-modified RECIST (assessed by the investigator) were used for evaluation of tumour response. Complete and partial responses were required to be confirmed with a subsequent scan at 4 weeks or at the next scheduled assessment timepoint after the initial

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See Online for appendix

documentation. During follow-up, survival data were collected every 3 months. Safety was regularly monitored until 90 days after the last dose of camrelizumab or 30 days after the last dose of rivoceranib or sorafenib. Adverse events were graded by the investigators according to the Common Terminology Criteria for Adverse Events, version 4.0.3. Details on laboratory evaluation, patient-reported outcomes, and PD-L1 testing are provided in the appendix (p 2).

Outcomes

The dual primary endpoints were progression-free survival (ie, time from randomisation to the first radiographic progression or death) as assessed by the BIRC per RECIST 1.1 and overall survival (ie, time from randomisation to death from any cause). Secondary endpoints were progression-free survival as assessed by the investigator per RECIST 1.1 and by the BIRC per modified RECIST; ORR (ie, proportion of patients with complete or partial response as best overall response), disease control rate (ie, proportion of patients with complete or partial response or stable disease lasting for ≥8 weeks), duration of response (ie, time from the first record of objective response to the first radiographic progression or death), and time to progression (ie, time from randomisation to first radiographic progression), each as assessed by the BIRC and investigator per RECIST 1.1 and by the BIRC per modified RECIST; pharmacokinetics of camrelizumab and rivoceranib and immunogenicity of camrelizumab; and safety. Results of pharmacokinetics and immunogenicity will be reported elsewhere. Key exploratory endpoints included correlation of PD-L1 expression with efficacy and time to first deterioration (ie, a decrease of ≥10 points from baseline) in global health status, physical functioning, and role functioning on the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30).

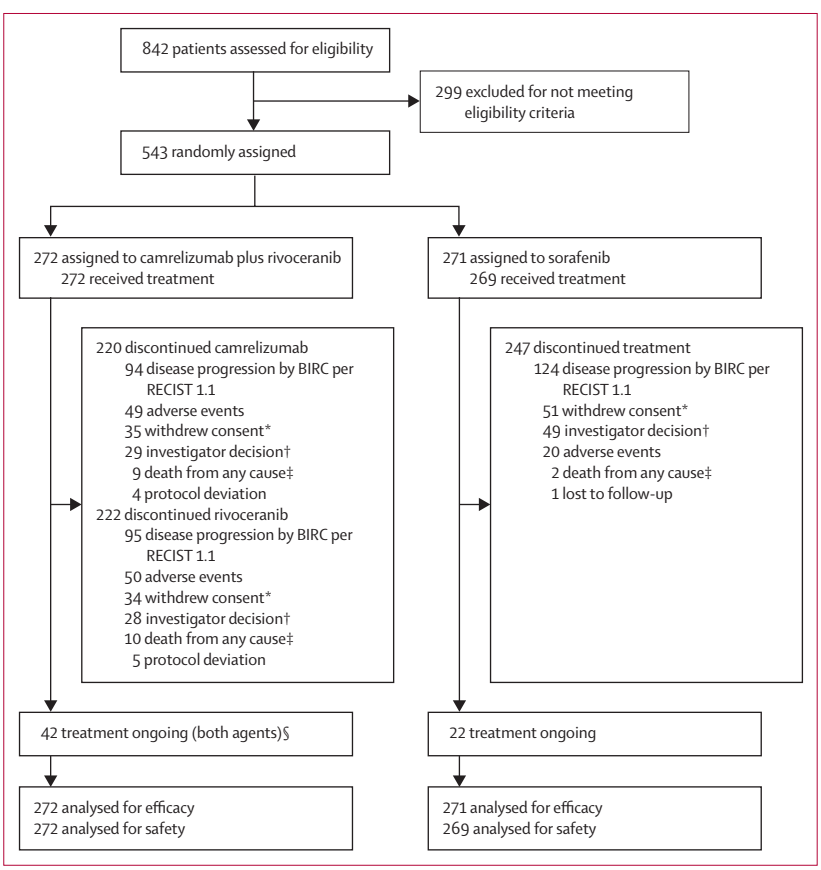


Figure 1: **Trial profile at the interim analysis of overall survival**
Per protocol, treatment beyond progression was allowed if there was evidence of clinical benefit per investigator. 40 (15%) patients in the camrelizumab–rivoceranib group and 23 (9%) in the sorafenib group were treated beyond RECIST 1.1-defined disease progression as assessed by the BIRC. Two patients in the sorafenib group did not receive treatment due to withdrawal of consent. BIRC=blinded independent review committee. RECIST=Response Evaluation Criteria in Solid Tumors. *Most patients who discontinued study treatment due to withdrawal of consent (ie, 17 patients for camrelizumab, 19 patients for rivoceranib, and 25 patients for sorafenib) had already developed progressive disease as assessed by the investigator before they discontinued the study treatment. †Most patients who discontinued study treatment due to investigator decision (ie, 19 patients for camrelizumab, 18 patients for rivoceranib, and 41 patients for sorafenib) had already developed progressive disease as assessed by the investigator before they discontinued the study treatment. ‡In the combination camrelizumab–rivoceranib therapy group, seven deaths were attributed to disease progression and three to adverse events per investigator—one death was deemed to be treatment related. In the sorafenib group, both deaths were attributed to adverse events per investigator—one death was deemed to be treatment related. §18 patients were on single agent camrelizumab (n=10) or rivoceranib (n=8).

Statistical analysis

The study was designed to enrol approximately 510 patients (appendix p 2). One progression-free survival analysis was planned at the occurrence of 332 progression-free survival events, and two overall survival analyses (one interim and a final) were planned at the occurrence of 251 (70% of 359 total expected) deaths and 359 deaths, respectively. The overall type 1 error was controlled at a one-sided α level of 0·025, with an initial α level of 0·005 for progression-free survival and 0·020 for overall survival, with an α-reallocation approach (appendix p 3). The interim and final analyses of the overall survival were controlled through α allocation using the Lan-DeMets O'Brien-Fleming spending function. A nominal α penalty of 0·00001 (independent of the Lan-DeMets O'Brien-Fleming) was planned for an administrative analysis (not formal) of overall survival with less than 251 deaths at the progression-free survival analysis. ORR as assessed by the BIRC per RECIST 1.1 was planned to be sequentially tested at a one-sided α level of 0·025 when both primary endpoints were statistically significant. The actual primary analysis for progression-free survival was performed at the occurrence of 339 progression-free survival events, with the corresponding significance boundary of 0·005. The interim analysis for overall survival was performed at the occurrence of 262 (73% of 359 total expected) deaths, with the corresponding significance boundary of 0·0087. In this Article, we report the findings from the prespecified primary analysis for progression-free survival and interim analysis for overall survival.

Efficacy was analysed in the intention-to-treat population, comprising all randomised patients. Safety

	Camrelizumab–rivoceranib (n=272)	Sorafenib (n=271)
Age, years	58 (48–66)	56 (47–64)
<65	191 (70%)	210 (77%)
≥65	81 (30%)	61 (23%)
Sex		
Male	227 (83%)	230 (85%)
Female	45 (17%)	41 (15%)
Geographical region		
Asia*	225 (83%)	224 (83%)
Non-Asia†	47 (17%)	47 (17%)
Race		
Asian	226 (83%)	224 (83%)
White	44 (16%)	46 (17%)
Black or African American	1 (<1%)	0
Other	1 (<1%)	1 (<1%)
Ethnicity		
Hispanic or Latinx	4 (1%)	2 (<1%)
Eastern Cooperative Oncology Group performance status		
0	120 (44%)	116 (43%)
1	152 (56%)	155 (57%)
Alpha-fetoprotein		
<400 ng/mL	176 (65%)	171 (63%)
≥400 ng/mL	96 (35%)	100 (37%)
Barcelona Clinic Liver Cancer stage		
Stage B	38 (14%)	40 (15%)
Stage C	234 (86%)	231 (85%)
Child-Pugh score		
Class A (5 points)	236 (87%)	230 (85%)
Class A (6 points)	36 (13%)	41 (15%)
Albumin–bilirubin grade		
1	153 (56%)	165 (61%)
2	117 (43%)	106 (39%)
3	2 (<1%)	0
(Table 1 continues in next column)		

	Camrelizumab–rivoceranib (n=272)	Sorafenib (n=271)
(Continued from previous column)		
Macrovascular invasion, extrahepatic metastasis, or both	200 (74%)	200 (74%)
Macrovascular invasion‡	40 (15%)	52 (19%)
Extrahepatic metastasis	175 (64%)	180 (66%)
Aetiology§		
Hepatitis B virus	208 (76%)	197 (73%)
Hepatitis C virus	22 (8%)	29 (11%)
Non-viral¶	42 (15%)	45 (17%)
Previous local therapy for hepatocellular carcinoma	161 (59%)	150 (55%)
PD-L1 expression		
TPS <1%	220 (81%)	212 (78%)
TPS ≥1%	32 (12%)	39 (14%)
CPS <1	190 (70%)	180 (66%)
CPS ≥1	62 (23%)	71 (26%)
Unknown	20 (7%)	20 (7%)

Data are median (IQR) or n (%). CPS=combined positive score. TPS=tumour proportion score. *Includes mainland China, Hong Kong, Taiwan, and South Korea. †Includes Belgium, Italy, Germany, Poland, Russia, Spain, Türkiye, Ukraine, and the USA. ‡Patients with invasion of—or tumour thrombus in—the main trunk of the portal vein (partial occlusion only), contralateral portal vein branch, or both, were included. §Main underlying cause of hepatocellular carcinoma per investigator. ¶Includes non-alcoholic fatty liver disease, alcohol cirrhosis, aflatoxin exposure, and other non-hepatitis B virus and non-hepatitis C virus causes (known or unknown).

Table 1: **Baseline characteristics**

was analysed in patients who received at least one dose of study medication. Median progression-free survival, overall survival, time to progression, and duration of response were estimated using the Kaplan-Meier method, and the associated 95% CIs were estimated using the Brookmeyer-Crowley method. Progression-free survival and overall survival were compared between groups using a log-rank test stratified by the randomisation stratification factors. HRs and the corresponding 95% CIs were estimated using a stratified Cox proportional hazard model. The proportional hazards assumption for progression-free survival and overall survival was evaluated and supported by visual inspection of log-log plots (ie, Schoenfeld residuals; appendix p 22). Survival rates at prespecified landmark timepoints were estimated by the Kaplan-Meier method, and the corresponding 95% CIs were calculated using the normal approximation. Hazard ratios (HRs) and 95% CIs for progression-free survival (per RECIST 1.1 by the BIRC) and overall survival in prespecified and post-hoc subgroups were estimated using an unstratified Cox proportional hazard model. ORR and disease control rate (per RECIST 1.1 by the BIRC) were compared using the Cochran-Mantel-Haenszel test stratified by randomisation stratification factors, and the absolute differences between groups were calculated. 95% CIs for the rates were estimated using the Clopper-Pearson method and 95% CIs for difference in rates were estimated using the normal approximation. Prespecified subgroup analysis for ORR were also performed. Prespecified time to deterioration in health-related quality-of-life outcomes were analysed using the same method as for other time-to-event endpoints; changes from baseline in health-related quality-of-life outcomes were analysed using the Mixed Model for Repeated Measures. All statistical analyses were done using SAS (version 9.4).

The trial is registered with ClinicalTrials.gov (NCT03764293).

Role of the funding source

The study was sponsored by Jiangsu Hengrui Pharmaceuticals and was co-funded by Elevar Therapeutics. Jiangsu Hengrui Pharmaceuticals collaborated with academic authors regarding the study design, data

collection, data analysis, data interpretation, and writing of the report.

Results

Between June 28, 2019, and March 24, 2021, 842 patients were assessed for eligibility and 543 were enrolled and randomly assigned to either the camrelizumab–rivoceranib group (n=272) or the sorafenib group (n=271). All 543 patients were included in the efficacy analysis and 541 treated patients (two patients in the sorafenib group did not receive any study medication) were included in the safety analysis (figure 1). The patient baseline characteristics are shown in table 1. Overall, 36% patients had an alpha-fetoprotein concentration of 400 ng/mL or more, 75% had hepatitis B virus aetiology, and 74% had macrovascular invasion, extrahepatic metastasis, or both (table 1).

As of the data cutoff for the primary analysis of progression-free survival (May 10, 2021), the median follow-up was 7·8 months (IQR 4·1–10·6). 158 (58%) of 272 patients in the camrelizumab–rivoceranib group and 181 (67%) of 271 in the sorafenib group had disease progression as assessed by the BIRC per RECIST 1.1 or had died. Progression-free survival was significantly improved in the camrelizumab–rivoceranib group compared with the sorafenib group (median 5·6 months [95% CI 5·5–6·3] *vs* 3·7 months [95% CI 2·8–3·7]; HR 0·52 [95% CI 0·41–0·65]; one-sided p<0·0001; figure 2A). Results of progression-free survival per modified RECIST by the BIRC and per RECIST 1.1 by investigator were consistent with the primary analysis (appendix p 5). Exploratory analysis of progression-free survival per immune-modified RECIST by investigator are shown in the appendix (p 6). Overall survival was not formally tested with 153 deaths recorded at this cutoff point, because it was less than the number required for simultaneous testing.

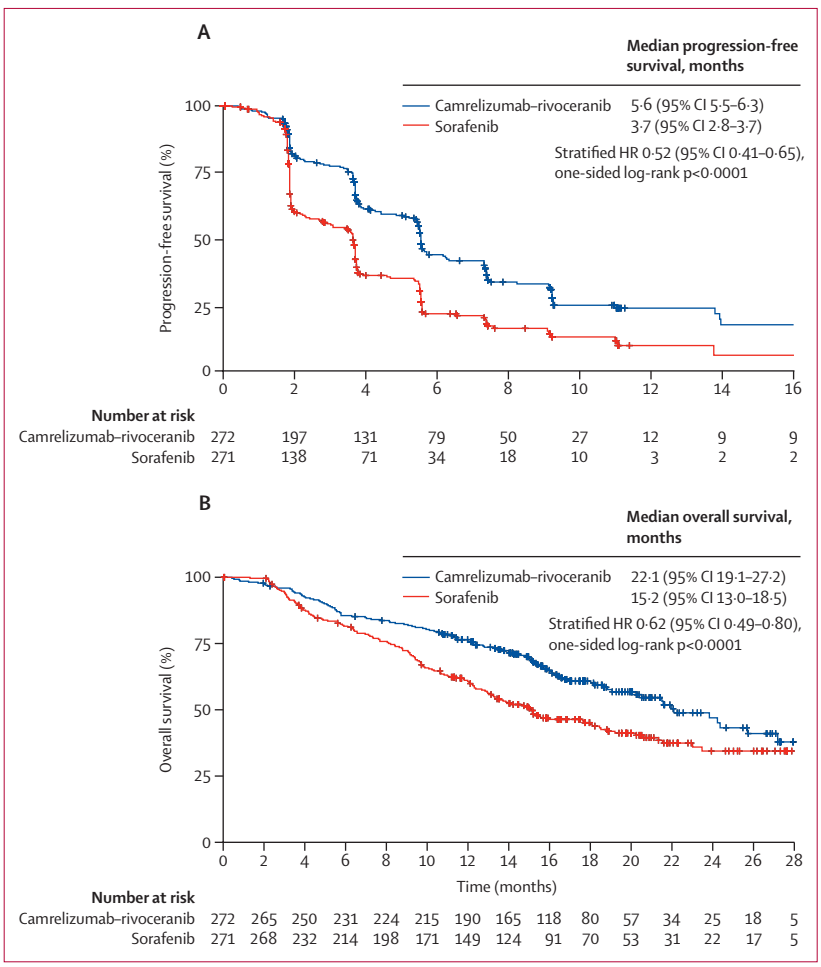


Figure 2: **Kaplan-Meier plot of progression-free survival at the primary analysis of progression-free survival and overall survival at the interim analysis of overall survival**

(A) Kaplan-Meier curve of progression-free survival as assessed by the blinded independent review committee according to Response Evaluation Criteria in Solid Tumors 1.1. (B) Kaplan-Meier curve of overall survival. HR=hazard ratio.

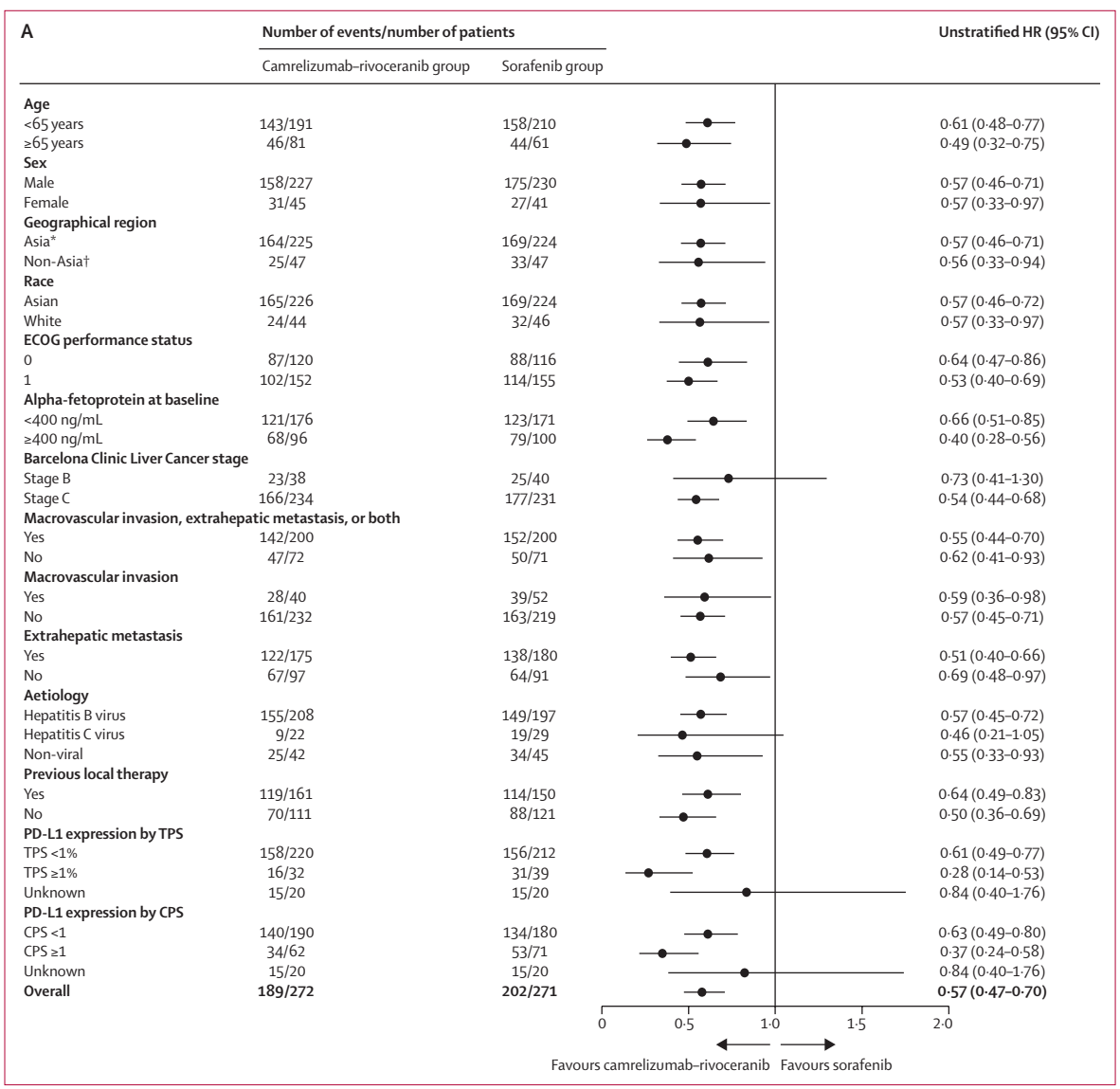
As of the data cutoff for the interim analysis of overall survival (Feb 8, 2022), the median follow-up was 14·5 months (IQR 9·1–18·7). 42 (15%) of 272 patients in the camrelizumab–rivoceranib group and 22 (8%) of 271 in the sorafenib group remained on study treatment (figure 1). 72 (26%) patients in the camrelizumab–rivoceranib group and 100 (37%) in the sorafenib group discontinued at least one agent due to withdrawal of consent or investigator decision. Among them, 42 (15%) in the camrelizumab–rivoceranib group and 66 (25%) in the sorafenib group discontinued at least one agent after investigator-assessed disease progression (figure 1, appendix p 7). Subsequent systemic anticancer therapy was administered to 90 (33%) patients in the camrelizumab–rivoceranib group and 130 (48%) in the sorafenib group after end of study treatment (appendix pp 8–9). The most common post-study treatment was targeted therapy (81 [30%] patients in the camrelizumab–rivoceranib group and 107 [40%] patients in the sorafenib group), followed by immunotherapy (40 [15%] in the camrelizumab–rivoceranib group and 90 [33%] in the sorafenib group).

At the data cutoff, 111 (41%) patients in the camrelizumab–rivoceranib group and 151 (56%) patients in the sorafenib group had died. Overall survival was significantly extended with camrelizumab–rivoceranib versus sorafenib (HR 0·62, 95% CI 0·49–0·80; one-sided p<0·0001; figure 2B). Median overall survival was 22·1 months (95% CI 19·1–27·2) in the camrelizumab–rivoceranib group versus 15·2 months (13·0–18·5) in the sorafenib group (figure 2B). The overall survival rate was 76·5% (95% CI 71·0–81·1) in the camrelizumab–rivoceranib group versus 60·8% (54·6–66·4) in the sorafenib group at 12 months, and 60·9% (54·2–66·9) in the camrelizumab–rivoceranib group versus 45·2% (38·8–51·4) in the sorafenib group at 18 months (figure 2B). Overall survival was more favourable with camrelizumab–rivoceranib compared with sorafenib in most predefined subgroups (figure 3B).

Post-hoc analysis showed that overall survival consistently favoured combination treatment in patients with albumin–bilirubin grade 1 (HR 0·72, 95% CI 0·51–1·01) and in patients with albumin–bilirubin grade 2 (HR 0·49, 95% CI 0·35–0·71) at baseline (appendix p 23).

As of Feb 8, 2022, 189 (69%) patients in the camrelizumab–rivoceranib group and 202 (75%) patients in the sorafenib group had disease progression based on the BIRC assessment per RECIST 1.1 or had died. At the updated analysis, median progression-free survival was 5·6 months (95% CI 5·5–7·4) in the camrelizumab–rivoceranib group versus 3·7 months (3·1–3·7) in the sorafenib group (HR 0·54, 95% CI 0·44–0·67). The progression-free survival rate was 48·2% (95% CI 41·9–54·3) in the camrelizumab–rivoceranib group versus 25·3% (19·8–31·1) in the sorafenib group at 6 months and 29·8% (24·1–35·8) in the camrelizumab–rivoceranib group versus 12·4% (8·3–17·3) in the sorafenib group at 12 months. Across all predefined and post-hoc subgroups, HR for progression-free survival consistently favoured camrelizumab–rivoceranib over sorafenib (figure 3A, appendix p 23).

Given that results for both primary endpoints were statistically significant, ORR as assessed by the BIRC per RECIST 1.1 was sequentially tested. 69 (25%) of 272 (95% CI 20–31) patients in the camrelizumab–rivoceranib group and 16 (6%) of 271 (3–9) in the sorafenib group had a confirmed objective response (difference 19% [95% CI 14–25]; one-sided p<0·0001), which was significantly higher for the patients in the camrelizumab–rivoceranib group. The benefits in ORR were generally consistent across predefined



(Figure 3 continues on next page)

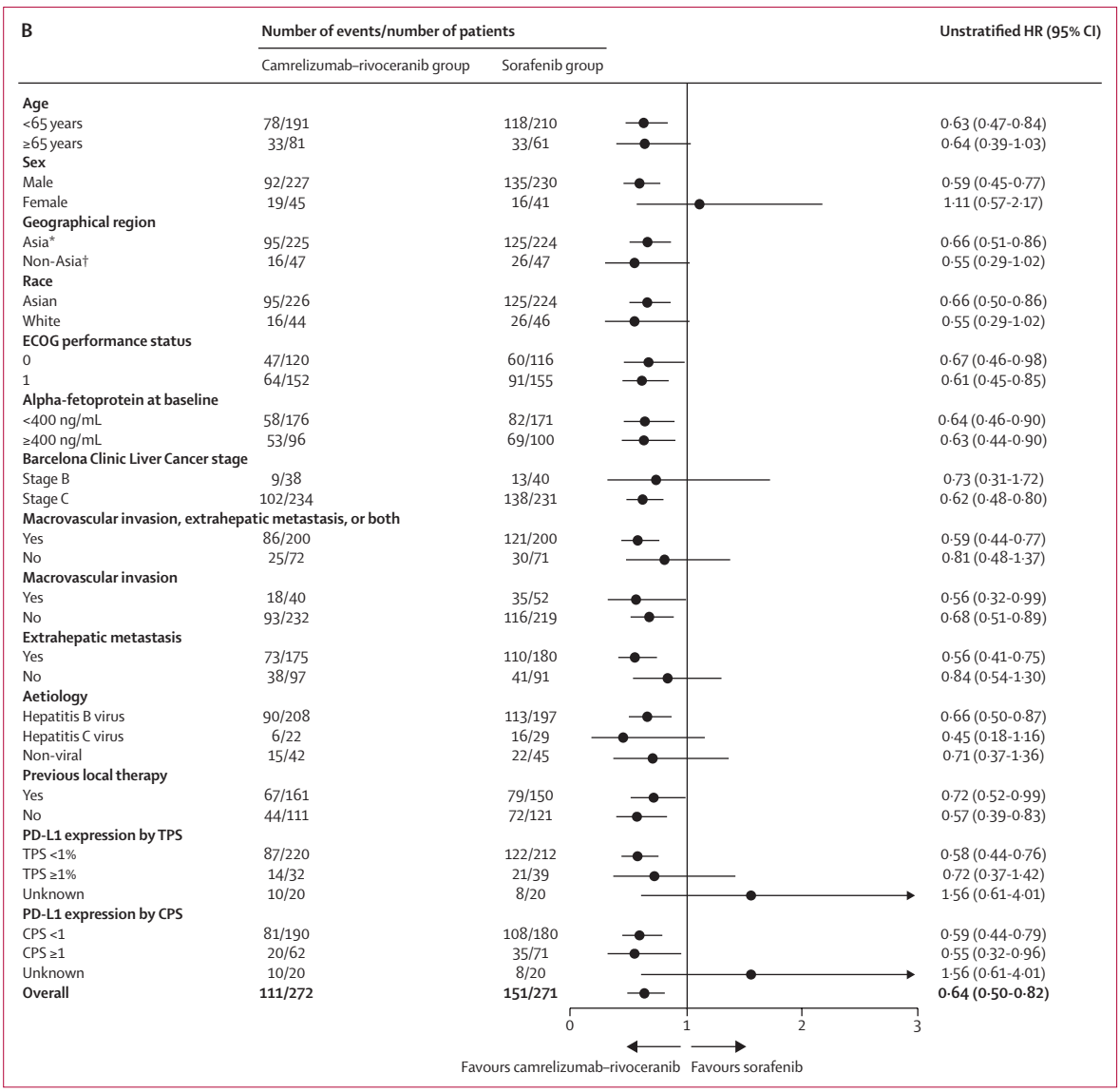


Figure 3: **Progression-free survival and overall survival in prespecified subgroups at the interim analysis of overall survival**
(A) Forest plot of progression-free survival as assessed by the blinded independent review committee according to RECIST 1.1. (B) Forest plot of overall survival. Subgroups with a sample size of less than ten patients in either treatment group are not shown. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. TPS=tumour proportion score. *Includes mainland China, Hong Kong, Taiwan, and South Korea. †Includes Belgium, Italy, Germany, Poland, Russia, Spain, Türkiye, Ukraine, and the USA.

subgroups (appendix p 24). In responders, the median duration of response was 14·8 months (95% CI 8·4–not reached [NR]) with camrelizumab–rivoceranib and 9·2 months (5·3–NR) with sorafenib (data not mature), and the median time to response was 1·9 months (IQR 1·9–3·7) with camrelizumab–rivoceranib and 3·7 months (1·9–4·7) with sorafenib. The disease control rate was 78% (95% CI 73–83) in the camrelizumab–rivoceranib group and 54% (48–60) in the sorafenib group (difference 24% [95% CI 17–32]). Tumour response according to modified RECIST by the BIRC and RECIST 1.1 by investigator was consistent with findings according to RECIST 1.1 by the BIRC (appendix p 10). In patients with a target lesion diameter value after baseline, reduction of any magnitude in the sum of diameter in the target lesion was seen in 182 (73%) of 250 patients in the camrelizumab–rivoceranib group and in 84 (36%) of 236 patients in the sorafenib group as assessed by the BIRC per RECIST 1.1. Additionally, reduction of 30% or more in the sum of diameter in the target lesion was seen in 88 (35%) of 250 patients in the camrelizumab–rivoceranib group and in 21 (9%) of 236 patients in the sorafenib group (appendix p 25).

As of Feb 8, 2022, the median time to deterioration in global health status was 11·2 months (95% CI 7·6–NR) in the camrelizumab–rivoceranib group and NR (95% CI

7·4–NR) in the sorafenib group (HR 1·02, 95% CI 0·77–1·36). The median time to deterioration in physical function was not reached in both groups, with no significant difference in risk of deterioration observed with camrelizumab–rivoceranib (HR 0·78, 95% CI 0·58–1·06). The median time to deterioration in role functioning was not reached (95% CI 11·5–NR) in the camrelizumab–rivoceranib group and was 10·1 months (95% CI 7·6–NR) in the sorafenib group (HR 0·88, 95% CI 0·66–1·18; appendix pp 11, 26). Results on changes from baseline in the scores in functioning and symptom domains on EORTC QLQ-C30 and EORTC QLQ-HCC18 scales up to week 57 are provided in the appendix (p 12). A favourable trend in the camrelizumab–rivoceranib group over the sorafenib group was seen in all functioning and most symptom domains (appendix p 12).

As of Feb 8, 2022, the median duration of treatment was 6·9 months (IQR 3·6–13·4) for camrelizumab, 6·5 months (3·4–11·9) for rivoceranib, and 3·8 months (1·9–7·4) for sorafenib. Overall, 271 (99%) of 272 treated patients in the camrelizumab–rivoceranib group and 265 (99%) of 269 in the sorafenib group had at least one adverse event. 238 (88%) patients in the camrelizumab–rivoceranib group and 182 (68%) patients in the sorafenib group had grade 3 or higher events (appendix pp 13–14). The time-at-risk exposure-adjusted incidence of adverse events was 261 per 100 person-months

	Camrelizumab–rivoceranib (n=272)				Sorafenib (n=269)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-related adverse event	45 (17%)	193 (71%)	26 (10%)	1 (<1%)	128 (48%)	128 (48%)	12 (4%)	1 (<1%)
Hypertension	87 (32%)	100 (37%)	2 (1%)	0	76 (28%)	40 (15%)	0	0
Aspartate aminotransferase increased	102 (38%)	42 (15%)	3 (1%)	0	85 (32%)	14 (5%)	0	0
Proteinuria	118 (43%)	16 (6%)	0	0	67 (25%)	5 (2%)	0	0
Alanine aminotransferase increased	92 (34%)	34 (13%)	1 (<1%)	0	72 (27%)	8 (3%)	0	0
Platelet count decreased	94 (35%)	28 (10%)	4 (1%)	0	85 (32%)	4 (1%)	0	0
Blood bilirubin increased	92 (34%)	24 (9%)	0	0	71 (26%)	4 (1%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	69 (25%)	33 (12%)	0	0	122 (45%)	41 (15%)	0	0
Diarrhoea	77 (28%)	6 (2%)	0	0	91 (34%)	14 (5%)	0	0
Reactive cutaneous capillary endothelial proliferation	72 (26%)	7 (3%)	0	0	0	0	0	0
Neutrophil count decreased	57 (21%)	14 (5%)	2 (1%)	0	24 (9%)	1 (<1%)	2 (1%)	0
White blood cell count decreased	66 (24%)	7 (3%)	0	0	35 (13%)	3 (1%)	0	0
Gamma-glutamyltransferase increased	39 (14%)	25 (9%)	2 (1%)	0	29 (11%)	15 (6%)	5 (2%)	0
Hypothyroidism	58 (21%)	0	0	0	16 (6%)	0	0	0
Fatigue	46 (17%)	7 (3%)	0	0	20 (7%)	1 (<1%)	0	0
Blood alkaline phosphatase increased	44 (16%)	3 (1%)	0	0	30 (11%)	3 (1%)	0	0
Conjugated blood bilirubin increased	34 (13%)	10 (4%)	2 (1%)	0	28 (10%)	6 (2%)	2 (1%)	0
Rash	40 (15%)	5 (2%)	0	0	47 (17%)	3 (1%)	0	0
Anaemia	41 (15%)	4 (1%)	0	0	19 (7%)	2 (1%)	0	0
Decreased appetite	39 (14%)	3 (1%)	0	0	31 (12%)	3 (1%)	0	0
Unconjugated blood bilirubin increased	33 (12%)	2 (1%)	0	0	20 (7%)	1 (<1%)	0	0
Hypoalbuminaemia	34 (13%)	0	0	0	21 (8%)	0	0	0
Weight decreased	28 (10%)	4 (1%)	0	0	33 (12%)	6 (2%)	0	0
Asthenia	29 (11%)	3 (1%)	0	0	15 (6%)	0	0	0
Haematuria	31 (11%)	0	0	0	12 (4%)	0	0	0
Nausea	31 (11%)	0	0	0	14 (5%)	0	0	0
Headache	28 (10%)	2 (1%)	0	0	4 (1%)	1 (<1%)	0	0
Blood lactate dehydrogenase increased	26 (10%)	1 (<1%)	0	0	29 (11%)	0	0	0
Lymphocyte count decreased	18 (7%)	8 (3%)	0	0	14 (5%)	3 (1%)	0	0
Amylase increased	15 (6%)	9 (3%)	1 (<1%)	0	6 (2%)	0	1 (<1%)	0
Hyponatraemia	13 (5%)	8 (3%)	0	0	8 (3%)	1 (<1%)	0	0
Lipase increased	7 (3%)	7 (3%)	6 (2%)	0	6 (2%)	4 (1%)	1 (<1%)	0
Hypophosphataemia	17 (6%)	2 (1%)	0	0	27 (10%)	12 (4%)	0	0
Upper gastrointestinal haemorrhage	2 (1%)	6 (2%)	0	0	0	0	0	0
Alopecia	4 (1%)	0	0	0	52 (19%)	0	0	0

Data are n (%). Treatment-related adverse events of grade 1–2 occurring in at least 10% of patients or of grade 3–5 occurring in at least 2% of patients in either group are reported.

Table 2: **Treatment-related adverse events in the safety analysis set at the interim analysis for overall survival**

in the camrelizumab–rivoceranib group and 320 per 100 person-months in the sorafenib group (appendix p 15). The adjusted rate of grade 3 or higher events was 29 per 100 person-months for the camrelizumab–rivoceranib group and 20 per 100 person-months for the sorafenib group (appendix p 15).

TRAEs occurred in 265 (97%) of 272 patients in the camrelizumab–rivoceranib group and 249 (93%) of 269 in the sorafenib group. Of these TRAEs, grade 3 or higher events occurred in 220 (81%) patients in the camrelizumab–rivoceranib group and 141 (52%) patients in the sorafenib group. The most common grade 3 or 4 TRAEs were hypertension, palmar-plantar erythrodysaesthesia syndrome, increased aspartate aminotransferase, and increased alanine aminotransferase (table 2). TRAEs led to discontinuation of any study medication in 66 (24%) patients in the camrelizumab–rivoceranib group and 12 (4%) in the sorafenib group (appendix p 16); ten (4%) patients discontinued both study medications in the camrelizumab–rivoceranib group. Dose reduction due to TRAEs was required by 128 (47%) patients in the camrelizumab–rivoceranib group and 87 (32%) in the sorafenib group. Treatment-related serious adverse events were reported for 66 (24%) patients in the camrelizumab–rivoceranib group and 16 (6%) in the sorafenib group. The most common serious adverse events in the camrelizumab–rivoceranib group included increased aspartate aminotransferase (nine [3%] patients), increased blood bilirubin (eight [3%]), upper gastrointestinal haemorrhage (eight [3%]), and increased alanine aminotransferase (seven [3%]; appendix p 17). Treatment-related deaths occurred in one patient each in the camrelizumab–rivoceranib group (multiple organ dysfunction syndrome) and sorafenib group (respiratory failure and circulatory collapse).

Immune-related adverse events of any grade as assessed by the investigator occurred in 154 (57%) of 272 patients in the camrelizumab–rivoceranib group. Of these immune-related adverse events, grade 3 or higher events occurred in 45 (17%) patients (appendix p 18). The most common immune-related adverse events of any grade were reactive cutaneous capillary endothelial proliferation (79 [29%] patients) and hypothyroidism (35 [13%]; appendix p 18). The most common events of grade 3 or 4 were increased aspartate aminotransferase (ten [4%] patients) and increased alanine aminotransferase (nine [3%]). 44 (16%) patients in the camrelizumab–rivoceranib group required systemically administered corticosteroids for the management of immune-related adverse events. TRAEs of special interest for camrelizumab and rivoceranib are provided in the appendix (p 19). Overall, grade 3 or higher hepatotoxicity (a medical category composed of grouped terms) was reported in 90 (33%) patients in the camrelizumab–rivoceranib group and 32 (12%) in the sorafenib group. The most frequent clinical diagnosis-related grade 3 or higher events in the camrelizumab–rivoceranib group were immune-mediated hepatitis (five patients [2%]), hepatic encephalopathy (four [1%]), and autoimmune hepatitis (four [1%]). Post-hoc analysis showed that mean albumin–bilirubin score was stable over the treatment period in both groups (appendix p 27). Across frequently reported medical categories (with an incidence ≥10%), 25–70% of events for camrelizumab (appendix p 20) and 40–81% of events for rivoceranib (appendix p 21) resolved in the combination therapy group by data cutoff.

Discussion

This is the first phase 3 study to report significant benefits in both progression-free survival and overall survival with the combination of an anti-PD-1/PD-L1 antibody and an orally administered, small-molecule TKI over standard TKI for unresectable hepatocellular carcinoma in the first-line setting. The dual primary endpoints were met with camrelizumab–rivoceranib, showing an improvement of 6·9 months in median overall survival and 1·9 months in median progression-free survival (per RECIST 1.1 by the BIRC), and a corresponding reduction in risk of death by 38% and of progression or death by 48% compared with the sorafenib group. The survival benefits with the combination therapy were supported by a significantly higher response rate and more durable response, as well as a higher rate of disease control than that seen in the sorafenib group.

To our knowledge, the median overall survival of 22·1 months in the camrelizumab–rivoceranib group was the longest one observed for any systemic treatment in phase 3 trials in unresectable hepatocellular carcinoma,[8,11,13–15,17] and supported the findings from the phase 2 trial of this combination.[22] The overall survival in the sorafenib group was in line with contemporary global trials in hepatocellular carcinoma,[8,11,13,17] but longer than those reported in the earlier SHARP and REFLECT trials.[3,4] Notably, a high proportion of patients in both the camrelizumab–rivoceranib (33%) and sorafenib (48%) groups received subsequent systemic treatments. Additionally, patients with viral aetiology were required to receive adequate antiviral treatment for both hepatitis B virus and hepatitis C virus infections throughout the study period per the recommendation of American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines. Strict viral control is reportedly associated with improved survival outcomes in patients with hepatocellular carcinoma.[23–25] The extended overall survival in the sorafenib group compared with that seen in the SHARP[3] and REFLECT[4] trials might reflect the evolution in practice patterns for treating hepatocellular carcinoma with the availability of newly approved second-line or later therapy and the improvement in supportive care for the underlying liver disease. Alternatively, despite a high rate of post-study treatment administration in the sorafenib group, separation of Kaplan-Meier curves of overall survival

sustained in favour of camrelizumab–rivoceranib at 12 months and 18 months, strongly supporting long-term clinical benefits with the combination therapy in the first-line setting.

For other global phase 3 studies evaluating first-line immunotherapy with anti-angiogenic therapy for unresectable hepatocellular carcinoma,[11–14] superior progression-free survival (6·8 *vs* 4·3 months; HR 0·59 [95% CI 0·47–0·76]) and overall survival (19·2 *vs* 13·4 months; HR 0·66 [95% CI 0·52–0·85]) were observed with atezolizumab–bevacizumab in IMbrave150,[11,12] whereas only progression-free survival (6·8 *vs* 4·2 months; HR 0·63 [95% CI 0·44–0·91]) but not overall survival (interim analysis, 15·4 *vs* 15·5 months; HR 0·90 [95% CI 0·69–1·18]) was significantly improved with atezolizumab–cabozantinib in COSMIC-312 with sorafenib as the comparator.[13] No significant improvement in progression-free survival (8·2 *vs* 8·1 months; HR 0·83 [0·71–0·98]) or overall survival (21·2 *vs* 19·0 months; HR 0·84 [95% CI 0·71–1·00]) was found with pembrolizumab–lenvatinib versus lenvatinib alone in the LEAP-002 trial.[14] Apart from the different combination therapy regimens, the factors that could contribute to the various outcomes across these studies included the inherent differences in study setting, comparator (lenvatinib *vs* sorafenib, although non-inferiority has been previously established[4]), eligibility criteria, and patient characteristics. Our study used relatively less stringent eligibility criteria among phase 3 trials of unresectable hepatocellular carcinoma and included patients with main trunk portal vein thrombosis (partial occlusion only; excluded in LEAP-002) and had no mandatory requirement on gastroduodenoscopy before study entry (required in LEAP-002 and IMbrave150).[11,14] Of note, in the HIMALAYA trial of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma, there was also no requirement on screening gastroduodenoscopy, but any main trunk portal vein thrombosis was excluded. At baseline, a higher proportion of patients had poor prognostic factors (including an ECOG performance status of 1, Barcelona Clinic Liver Cancer stage C, and extrahepatic metastasis) and hepatitis B virus-related hepatocellular carcinoma than patients enrolled in contemporary trials of hepatocellular carcinoma.[11,13,14,17] Although findings from other randomised trials[12–14] and meta-analysis[26] suggest that hepatocellular carcinoma of non-viral aetiology (eg, non-alcoholic fatty liver disease) might derive less survival benefits from immunotherapy than hepatocellular carcinoma of viral aetiology, our study revealed generally consistent progression-free survival and overall survival benefits across clinically relevant subgroups with the combination therapy. Favourable survival outcomes were also seen for dual immunotherapy in patients with non-viral hepatocellular carcinoma in the HIMALAYA trial, similar to the ICI-TKI combination in our study.[17] However, all subgroup findings are hypothesis-generating, and comprehensive evaluation of the efficacy in patients with viral versus non-viral aetiology is beyond the scope of this study. Given the potentially differential characteristics of anticancer immunity in viral and non-viral hepatocellular carcinoma,[27] further research is needed to clarify the role of aetiology on the effect of immune-combination therapy in treating hepatocellular carcinoma. Similarly, progression-free survival and overall survival benefits with camrelizumab–rivoceranib were persistent across Asian and non-Asian subgroups, which was supported by the consistent benefits seen across different hepatocellular carcinoma aetiology and the universal availability of multitargeted TKIs (eg, sorafenib, lenvatinib and regorafenib) and anti-PD-1/PD-L1 ICIs across the regions during the study period. In this study, survival outcomes were consistently more favourable with the combination therapy versus sorafenib regardless of baseline albumin–bilirubin grade. Additional analysis of albumin–bilirubin will be reported in a subsequent publication.

Tumour objective response as evaluated by the BIRC per RECIST 1.1 was consistent with that evaluated by the BIRC per modified RECIST and by the investigator per RECIST 1.1. The magnitude of improvement in the ORR with camrelizumab–rivoceranib versus sorafenib (25% *vs* 6% per RECIST 1.1 by the BIRC) was in line with that reported for atezolizumab–bevacizumab (30% *vs* 11%) in IMbrave150[11] and compared favourably with atezolizumab–cabozantinib (11% *vs* 4%) in COSMIC-312.[13] Moreover, 78% of all patients allocated camrelizumab–rivoceranib attained disease control and 35% of patients with post-baseline assessment of the target lesion showed tumour shrinkage of 30% or more in the combination therapy group, highlighting the broad range of patients who could derive clinical benefits.

The optimal companion TKI for ICI in the treatment of unresectable hepatocellular carcinoma deserves further exploration. TKIs such as cabozantinib and lenvatinib not only show potent VEGFR2 inhibitory activity (half maximal inhibitory concentration [IC_{50}] of 0·035 nM for cabozantinib and 3 nM for lenvatinib) at protein kinase level but also strongly inhibit other subclasses of receptor tyrosine kinases (eg, MET, KIT, RET, AXL, TIE2, and FLT3) at IC_{50} values of less than 100 nM.[28,29] Rivoceranib also suppresses several receptor tyrosine kinases including RET, KIT, and C-SRC with IC_{50} values of 13 nM, 429 nM, and 530 nM, respectively, but it is a more potent and selective inhibitor against VEGFR2 with an IC_{50} of 1 nM.[30] Additionally, camrelizumab has a unique binding epitope compared with other anti-PD-1 antibodies. Camrelizumab bounds to PD-1 via its heavy chain and blocks PD-1/PD-L1 interaction via its light chain, and the glycosylation of asparagine 58 promotes the interaction of camrelizumab with PD-1, which is different with the binding of nivolumab or pembrolizumab to PD-1.[31] Taken together, we speculate that the potent and selective VEGFR2 activity of rivoceranib and the distinct binding epitope of camrelizumab might be contributing factors for the robust clinical efficacy of camrelizumab–rivoceranib.

Currently, no recognised biomarker has been established for immunotherapy-based regimens in advanced hepatocellular carcinoma. In this study, patients given camrelizumab–rivoceranib showed improved progression-free survival and ORR versus those given sorafenib across the PD-L1 positive and negative subgroups, consistent with the findings for the combination therapy in IMbrave150.[12] There appeared a trend for an increased response rate with PD-L1 enrichment in the camrelizumab–rivoceranib group, as seen in patients receiving immunotherapy-based regimens in other trials in advanced hepatocellular carcinoma.[7,8,12] Nevertheless, due to the exploratory nature of the analysis and the reported interassay heterogeneity in the detection of PD-L1 expression,[32] further research is needed to fully assess the utility of PD-L1 expression for predicting outcome to immunotherapy in hepatocellular carcinoma. Alternatively, markers of pre-existing T-cell immunity at baseline were strongly associated with clinical activity of atezolizumab plus bevacizumab in hepatocellular carcinoma and the potential of these markers also merits further investigation.[33]

The safety profile of camrelizumab–rivoceranib was generally consistent with the toxicity spectrum reported for each agent and the underlying hepatocellular carcinoma disease, with no new safety signals identified.[9,20] The most common grade 3 or 4 TRAE associated with the combination therapy was hypertension (grade 4, n=2), which occurred in approximately half of the patients who had a grade 3 or 4 event and presented as a driving event for the relatively high incidence of grade 3 or 4 TRAEs with the regimen compared with approved non-TKI containing regimens for unresectable hepatocellular carcinoma.[11,17] Hypertension was mostly manageable, and rarely resulted in treatment discontinuation. An increased incidence of hypertension was also observed in pivotal studies of other ICI-TKI combinations, which led to their approval in other tumour types.[34–36] Additionally, hepatotoxicities of grade 3 or higher, predominantly manifested as hepatic laboratory abnormalities (with scarce clinical events such as hepatic encephalopathy and ascites), were more frequent with the combination therapy versus sorafenib, which could result from the overlapping hepatoxicities of the individual agents. Despite this observation, liver function (as measured by albumin–bilirubin score) remained stable throughout the treatment period with the combination therapy. Notably, the incidence of grade 3 or 4 TRAEs in the sorafenib group in our study was higher than that reported in other global phase 3 trials in unresectable hepatocellular carcinoma (52% *vs* 32–46%).[11,13,17] Our study population consisted of patients who were potentially more vulnerable to adverse events, with an elevated proportion having an ECOG performance status of 1 and having received previous locoregional therapy at baseline. This factor might have contributed to the increased risk of overall and hepatic toxicities with both sorafenib and, in particular, camrelizumab–rivoceranib (with long-term exposure) in our study.[37] Reactive cutaneous capillary endothelial proliferation is a well characterised camrelizumab-related skin adverse event that is mostly of low grade and self-limited, as observed in this study.[9,38–41] Consistent with previous reports,[22,42] the incidence of reactive cutaneous capillary endothelial proliferation was markedly reduced with the camrelizumab–rivoceranib combination compared with camrelizumab monotherapy, implying that the development of reactive cutaneous capillary endothelial proliferation on skin might be inhibited via blockade of the VEGF/VEGFR signalling pathway.[38] Treatment-related serious adverse events were more frequent in the camrelizumab–rivoceranib group and the incidence was in line with that observed with other ICI-TKI combinations in advanced cancers (18–36%).[13,43–45] Notably, treatment duration of study medication in the camrelizumab–rivoceranib group was nearly double that in the sorafenib group and the safety follow-up period after end of treatment was also longer (up to 90 days *vs* 30 days). Thus, the safety of the combination therapy should be interpreted within this context. Most TRAEs with the camrelizumab–rivoceranib combination were adequately managed using standard supportive care, dose modification, and discontinuation of either agent as clinically appropriate, and the rate of discontinuation of all study treatments due to TRAEs was low and similar between the two groups, suggesting that most patients could tolerate the combination therapy or monotherapy after one drug withdrawal. The tolerability and overall benefit-to-risk profile of camrelizumab–rivoceranib was also supported by the preserved health-related quality of life compared with sorafenib during the treatment period. Alternatively, the generally increased rate of TRAEs and need for dose modification with ICI-TKI combinations[46] imply that physicians might require additional education and hands-on experience to optimise toxicity management for this treatment strategy. In our study, concomitant direct-acting antiviral agents were permitted for hepatitis C virus control. With infrequent use of agents with known drug–drug interaction potential with the study medications, no significant effects on overall safety outcomes were anticipated.

The study recorded a high treatment discontinuation rate due to consent withdrawal or investigator decision, mainly after investigator-assessed disease progression. With a specific reporting rule for end of treatment reason, these rates were largely attributed to the patients or physician refusing to wait for disease progression confirmation by the BIRC, or patients having clinical or radiographic progression during continuous study treatment following BIRC-assessed progression. After excluding patients who discontinued after investigator-assessed disease progression, the rate of treatment discontinuation due to consent withdrawal in the combination group (7%) and sorafenib group (10%) was in broad accordance with other phase 3 trials of hepatocellular carcinoma.[11,13,17]

A main limitation of this study was its open-label design. The use of overall survival and BIRC-assessed progression-free survival as dual primary endpoints, as well as other BIRC-assessed radiographic outcomes, could serve to limit the potential for open-label bias. Notably, a higher treatment discontinuation rate due to consent withdrawal or investigator decision was observed in the sorafenib group than in the camrelizumab–rivoceranib group. This difference was driven by the increased proportion of patients and physicians (out of ethical consideration) who refused to wait for disease progression confirmation by the BIRC in the sorafenib group after investigator-assessed progression, possibly due to faster disease deterioration or less clear clinical benefits of treatment beyond progression with sorafenib. Nevertheless, the overall rate of censoring of patients due to start of new-anticancer therapy before BICR-assessed disease progression (12 [4%] of 272 with camrelizumab–rivoceranib and 18 [7%] of 271 with sorafenib) or study withdrawal (two [1%] and one [<1%], respectively) in the primary progression-free survival analysis and censoring due to study withdrawal (six [2%] and eight [3%], respectively) in overall survival analysis was generally low and balanced between the treatment groups. Since the imbalanced treatment discontinuation rates were mostly not associated with premature or unbalanced censoring, their influence on study outcome might be low. Another limitation of this study was that most participants enrolled were in Asia (and had hepatocellular carcinoma of viral aetiology), partly due to the high prevalence of hepatocellular carcinoma in Asia and low prevalence in the non-Asia region, and because of the delayed initiation of patient enrolment in some European and North American countries resulting from the COVID-19 pandemic. Although our subgroup analysis revealed consistent clinical benefits with camrelizumab–rivoceranib across geographical region, race, and aetiology subgroups, some patient subgroups (eg, Black and Hispanic racial and ethnic groups) were of a small sample size, necessitating further investigation to substantiate the treatment effect in these populations.

In conclusion, camrelizumab plus rivoceranib was associated with a statistically significant and clinically meaningful improvement in progression-free survival and overall survival compared with sorafenib and had a manageable safety profile. The overall favourable benefit-to-risk profile supports camrelizumab with rivoceranib as a new first-line treatment option for patients with unresectable hepatocellular carcinoma who have not previously received any systemic therapy.

Contributors

SQ and SLC conceived and designed this study. SQ is the global leading principal investigator for the study. SQ, SLC, A-LC, AK, and AV are steering committee members of the study. SQ, SLC, SG, YB, ZR, XLin, ZC, WJ, YJ, YG, XH, ZM, JL, YiC, JX, HR, FY, WL, YaC, YZ, AS, M-PS, MP, DM, DP, YO, IS, T-SY, A-LC, AK, and AV enrolled patients and collected the data. CC was responsible for directing statistical analysis, and all authors participated in data interpretation. The manuscript was drafted by SQ and SLC and was reviewed as well as revised by all authors. SQ, LW, and CC had full access to and verified all the data. All authors accept responsibility for the decision to submit the manuscript for publication.

Declaration of interests

SLC reports honoraria from AstraZeneca, Eisai, Merck Sharp & Dohme, Roche, and Bayer; consulting or advisory roles for AstraZeneca, Eisai, Merck Sharp & Dohme, Bristol Myers Squibb, and Roche; and research funding from Eisai and Ipsen. A-LC reports consulting or advisory roles for Merck Sharp & Dohme, Bristol Myers Squibb, Bayer Healthcare, AstraZeneca, Genentech/Roche, IPSEN Innovation, BeiGene, and EXE; speaker's bureau for Ono Pharmaceutical, Bayer Yakuhin, Novartis, Amgen Taiwan, and Chugai Pharmaceutical; expert testimony for Merck Sharp & Dohme, Ono Pharmaceutical, Eisai, and IPSEN Innovation; and participation on an advisory board for Abbisko Therapeutics. AV reports personal fees from AstraZeneca, Amgen, BeiGene, Böhringer Mannheim, Bristol Myers Squibb, BTG, Daiichi Sankyo, Eisai, Incyte, Ipsen, Merck Sharp & Dohme, PierreFabre, Roche, Servier, Sirtex, Tahio, Terumo, Jiangsu Hengrui Pharmaceuticals, GSK, and Imaging Equipment (Advanced Accelerator Applications). XLia, CC, and LW were employees of Jiangsu Hengrui Pharmaceuticals at the time of the study. All other authors declare no competing interests.

Data sharing

Individual de-identified participant data that underlie the results reported in this Article can be requested 24 months after study completion. Researchers should submit a proposal to the corresponding author outlining the reasons for requiring the data. The leading clinical site and sponsor will check whether the request is subject to any intellectual property or confidentiality obligations. A signed data access agreement with the sponsor is required before accessing shared data. The study protocol is provided in the appendix (pp 28–228).

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References

1 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71:** 209–49.

2 Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. *J Hepatol* 2020; **72:** 250–61.

3 Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359:** 378–90.

4 Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391:** 1163–73.

5 Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10:** 25–34.

6 Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol* 2020; **38:** 193–202.

7 Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; **19:** 940–52.

8 Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2022; **23:** 77–90.

9 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.

10 Huinen ZR, Huijbers EJM, van Beijnum JR, Nowak-Sliwinska P, Griffioen AW. Anti-angiogenic agents—overcoming tumour endothelial cell anergy and improving immunotherapy outcomes. *Nat Rev Clin Oncol* 2021; **18:** 527–40.

11 Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020; **382:** 1894–905.

12 Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022; **76:** 862–73.

13 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.

14 Finn RS, Kudo M, Merle P, et al. 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** (suppl 7)**:** S1401.

15 Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2–3 study. *Lancet Oncol* 2021; **22:** 977–90.

16 Fulgenzi CAM, D'Alessio A, Airoldi C, et al. Comparative efficacy of novel combination strategies for unresectable hepatocellular carcinoma: a network metanalysis of phase III trials. *Eur J Cancer* 2022; **174:** 57–67.

17 Abou-Alfa Ghassan K, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evidence* 2022; published online June 6. https://doi.org/10.1056/EVIDoa2100070.

18 Markham A, Keam SJ. Camrelizumab: first global approval. *Drugs* 2019; **79:** 1355–61.

19 Scott LJ. Apatinib: a review in advanced gastric cancer and other advanced cancers. *Drugs* 2018; **78:** 747–58.

20 Qin S, Li Q, Gu S, et al. Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol* 2021; **6:** 559–68.

21 Xu J, Zhang Y, Jia R, et al. Anti-PD-1 antibody SHR-1210 combined with apatinib for advanced hepatocellular carcinoma, gastric, or esophagogastric junction cancer: an open-label, dose escalation and expansion study. *Clin Cancer Res* 2019; **25:** 515–23.

22 Xu J, Shen J, Gu S, et al. Camrelizumab in combination with apatinib in patients with advanced hepatocellular carcinoma (RESCUE): a nonrandomized, open-label, phase II trial. *Clin Cancer Res* 2021; **27:** 1003–11.

23 Ghany MG, Morgan TR, AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. *Hepatology* 2020; **71:** 686–721.

24 Torres HA, Pundhir P, Mallet V. Hepatitis C virus infection in patients with cancer: impact on clinical trial enrollment, selection of therapy, and prognosis. *Gastroenterology* 2019; **157:** 909–16.

25 Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. *Gastroenterology* 2017; **152:** 1297–309.

26 Pfister D, Núñez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. *Nature* 2021; **592:** 450–56.

27 Pinter M, Pinato DJ, Ramadori P, Heikenwalder M. NASH and hepatocellular carcinoma: immunology and immunotherapy. *Clin Cancer Res* 2023; **29:** 513–20.

28 Tohyama O, Matsui J, Kodama K, et al. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. *J Thyroid Res* 2014; **2014:** 638747.

29 Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther* 2011; **10:** 2298–308.

30 Tian S, Quan H, Xie C, et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. *Cancer Sci* 2011; **102:** 1374–80.

31 Liu K, Tan S, Jin W, et al. N-glycosylation of PD-1 promotes binding of camrelizumab. *EMBO Rep* 2020; **21:** e51444.

32 Pinato DJ, Mauri FA, Spina P, et al. Clinical implications of heterogeneity in PD-L1 immunohistochemical detection in hepatocellular carcinoma: the Blueprint-HCC study. *Br J Cancer* 2019; **120:** 1033–36.

33 Zhu AX, Abbas AR, de Galarreta MR, et al. Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma. *Nat Med* 2022; **28:** 1599–611.

34 Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med* 2021; **384:** 1289–300.

35 Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019; **380:** 1116–27.

36 Makker V, Colombo N, Casado Herráez A, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. *N Engl J Med* 2022; **386:** 437–48.

37 Singh H, Gong Y, Roy P, et al. FDA analysis of ECOG performance status and safety outcomes. *J Clin Oncol* 2020; **38** (suppl)**:** 12024.

38 Wang F, Qin S, Sun X, et al. Reactive cutaneous capillary endothelial proliferation in advanced hepatocellular carcinoma patients treated with camrelizumab: data derived from a multicenter phase 2 trial. *J Hematol Oncol* 2020; **13:** 47.

39 Fang W, Yang Y, Ma Y, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. *Lancet Oncol* 2018; **19:** 1338–50.

40 Yang Y, Zhou T, Chen X, et al. Efficacy, safety, and biomarker analysis of camrelizumab in previously treated recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN study). *J Immunother Cancer* 2021; **9:** e003790.

41 Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol* 2020; **21:** 832–42.

42 Zhou C, Wang Y, Zhao J, et al. Efficacy and biomarker analysis of camrelizumab in combination with apatinib in patients with advanced nonsquamous NSCLC previously treated with chemotherapy. *Clin Cancer Res* 2021; **27:** 1296–304.

43 Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. *J Clin Oncol* 2020; **38:** 2960–70.

44 Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 2019; **20:** 711–18.

45 Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2020; **21:** 1563–73.

46 Maria Fulgenzi CA, Scheiner B, Korolewicz J, et al. Efficacy and safety of frontline systemic therapy for advanced HCC: a network meta-analysis of landmark phase III trials. *JHEP Rep* 2023; **5:** 100702.