Ramucirumab as second-line treatment in Chinese patients with advanced hepatocellular carcinoma and elevated alpha-fetoprotein after sorafenib (REACH-2 China): A randomised, multicentre, double-blind study

Guoliang Shao,[a,1] Yuxian Bai,[b,1] Xianglin Yuan,[c,1] Xiaomin Chen,[d] Shanzhi Gu,[e] Kangsheng Gu,[f] Chunhong Hu,[g] Houjie Liang,[h] Yabing Guo,[i] Jufeng Wang,[j] Chia-Jui Yen,[k] Victor Ho-Fun Lee,[l] Chunxiao Wang,[m] Ryan C. Widau,[m] Wanli Zhang,[n] Junjun Liu,[n] Qiang Zhang,[n] and Shukui Qin [o]*

[a]Department of Radiology, Zhejiang Cancer Hospital, Hangzhou, China
[b]Department of Gastrointestinal Oncology, Harbin Medical University Cancer Hospital, Harbin, China
[c]Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[d]Department of Intervention Therapy, Guangdong Provincial People's Hospital, Guangzhou, China
[e]Department of Interventional Radiology, Hunan Cancer Hospital, Changsha, China
[f]Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, China
[g]Department of Oncology, The Second Xiangya Hospital of Central South University, Changsha, China
[h]Department of Oncology and Southwest Cancer Centre, Southwest Hospital, Army Medical University, Chongqing, China
[i]Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China
[j]Department of Oncology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China
[k]Department of Oncology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[l]Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[m]Eli Lilly and Company, Indianapolis, USA
[n]Eli Lilly and Company, Shanghai, China
[o]Cancer Centre of Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing, China

Summary

Background In the global REACH-2 study, ramucirumab significantly improved overall survival (OS) compared with placebo in patients with advanced hepatocellular carcinoma (HCC) and elevated alpha-fetoprotein (AFP). REACH-2 China study aimed to evaluate the efficacy and safety of ramucirumab in Chinese patients with advanced HCC (NCT02435433).

Methods REACH-2 China was a randomised, double-blind, placebo-controlled, phase 3 study done at 31 centres in China between Sep 16, 2015, and March 15, 2021. Patients with advanced HCC and AFP ≥400 ng/mL after first-line sorafenib were randomly assigned (2:1) to receive ramucirumab 8 mg/kg intravenously or placebo Q2W, until disease progression or unacceptable toxicity. The primary endpoint was OS. Efficacy was assessed per intention-to-treat, and safety in patients who received any treatment.

Findings Of 104 Chinese patients enrolled (44 in the global study and 60 in the China extension study), 70 received ramucirumab and 34 received placebo. Median OS was 9·1 months in the ramucirumab group and 6·2 months in the placebo group (HR = 0·854 [95% CI: 0·536, 1·359]). The most common grade 3 or worse treatment-emergent adverse event were hypertension (5 [7·1%] of 70 patients in the ramucirumab group vs 1 [2.9%] of 34 in the placebo group), pneumonia (5 [7·1%] vs 1 [2·9%]), and hyponatraemia (4 [5·7%] vs 0 [0%]).

Interpretation Ramucirumab demonstrated clinically meaningful improvement in OS compared to placebo for Chinese patients with advanced HCC and elevated AFP, although lacking statistical superiority. Ramucirumab was well tolerated, with a manageable safety profile. The results are consistent with those of the global REACH-2 study, supporting a favourable risk-benefit profile for ramucirumab in this population.

eClinicalMedicine 2022;54: 101679
Published online xxx
https://doi.org/10.1016/j.eclinm.2022.101679

*Corresponding author at: Cancer Centre of Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing 210002, China.
E-mail address: qinsk@csco.org.cn (S. Qin).

Some results of this study were previously presented as an abstract/poster at the Annual Meeting of Chinese Society of Clinical Oncology on Sep 25-29th, 2021.

[1] Co-first authors.

Funding Eli Lilly and Company, USA.

Keywords: Ramucirumab; Second-line therapy; Advanced hepatocellular carcinoma; Phase 3 study; China

Research in context

Evidence before this study

We searched PubMed and presentations at major oncology congresses with the search terms "hepatocellular carcinoma", "advanced hepatocellular carcinoma", "AFP", "targeted therapy", "phase 3", "trials", "clinical trials", and "VEGFR-2", for articles or abstracts published in English up to Jan 1, 2022, that reported primary results of clinical trials assessing systemic targeted treatment in patients with advanced hepatocellular carcinoma (HCC). REACH-2 (NCT02435433) is a randomized, double-blind, placebo-controlled, phase 3 study demonstrating improved survival with ramucirumab in patients with advanced HCC and elevated AFP after sorafenib. To account for the potential ethnic/geographical variation in treatment outcomes, this study was designed to evaluate the efficacy and safety of ramucirumab in Chinese patients from REACH-2.

Added value of this study

The efficacy data and safety profile of ramucirumab in this REACH-2 China study, demonstrate a favourable risk-benefit profile, consistent with the global REACH-2 study. REACH-2 China study provides evidence that ramucirumab might be an effective treatment option for Chinese patients with advanced HCC and elevated AFP after previous sorafenib treatment.

Implications of all the available evidence

The use of ramucirumab as second-line treatment might be an option for Chinese patients with advanced HCC and elevated AFP. Directions for future exploration include a broader patient population, assessment of ramucirumab in other lines of therapy, as well as novel combinations.

Introduction

Hepatocellular carcinoma (HCC) (about 75–85% of primary liver cancer) is the sixth most common malignancy and the third leading cause of cancer-related mortality worldwide.[1] HCC is particularly prevalent in Asia, especially in China, which accounts for 45·3% of the global incidence, largely associated with chronic hepatitis B virus (HBV) infection.[2,3] China also accounts for 47·1% of all liver cancer-related deaths, with an estimated 391 152 deaths in 2020.[2,3] Most patients present with advanced stage disease due to asymptomatic features in the early stages with fast progression and the 5-year survival rate is 3%.[4]

HCC is characterised by high vascularity, and its development and progression are all closely related to angiogenesis. Anti-angiogenic therapies have demonstrated significant improvements in clinical outcomes and approved to treat patients with advanced HCC over the last decade.[5–8] Ramucirumab is a humanised monoclonal antibody that specifically binds to the extracellular domain of VEGFR-2 with high affinity and inhibits the signal transduction leading to angiogenesis.[9] In the global, randomised, placebo-controlled, double-blind, phase 3 REACH-2 study (data cut-off, March 15, 2018; N = 292), ramucirumab improved survival compared with placebo in patients with advanced HCC and elevated alpha-fetoprotein (AFP) who had previously received sorafenib,[10] confirmed the results from the REACH trial in which survival benefit was noted in a prespecified subgroup of patients with baseline AFP ≥ 400 ng/mL.[11] REACH-2 is the first positive Phase 3 HCC trial in a biomarker-selected population known for poor prognosis,[10] which led to the approval of ramucirumab as second-line treatment for patients with HCC and elevated AFP in the USA, Europe, and other regions. In the global REACH-2 study, only 44 patients were recruited from China, this sample size was not sufficient to demonstrate the consistency of treatment effects in Chinese population with global results.[10] To satisfy China's regulatory requirement, an extension study of REACH-2 was conducted to assess ramucirumab in additional patients from mainland China.

HCC is known to be a heterogeneous tumour, ethnic/geographical variation is seen in the prevalence, disease aetiology, clinical features, treatment practice, and responses,[12] thus it is especially important to evaluate and report the treatment for HCC patients from the region of greatest prevalence. This REACH-2 China study aimed to evaluate the efficacy and safety of ramucirumab in Chinese patients with advanced HCC who were enrolled in the global REACH-2 study and China extension study (data cut-off, March 15, 2021) and to determine consistency with the benefit observed in the global population of REACH-2. We also conducted an integrated analysis by pooling individual-level patient

data to investigate the efficacy and safety of ramucirumab in a larger population of Chinese patients from REACH-2 and REACH (AFP ≥400 mg/mL).

Methods

Study design and participants

REACH-2 (NCT02435433) is a randomised, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of ramucirumab in patients with advanced HCC and elevated AFP after sorafenib; and the results from the global REACH-2 study have been previously published with the full protocol.[10] In addition to the global study, REACH-2 included a China extension study which enrolled additional patients to support regulatory approval in China, since the required number of Chinese patients was not achieved in the global REACH-2 study. The REACH-2 China extension study was conducted under the same protocol and only enrolled patients from mainland China after global enrollment was completed. This REACH-2 China study was designed to assess the efficacy and safety of ramucirumab in Chinese patients enrolled from mainland China, Hong Kong, and Taiwan either in the global REACH-2 study or China extension study (data cut-off, March 15, 2021), and to determine consistency with the benefit observed in the global population of REACH-2.

Eligible patients were aged ≥18 years, had histopathologically or cytologically confirmed HCC (or a diagnosis of cirrhosis and HCC with classical imaging characteristics), Child-Pugh class A liver disease, Barcelona Clinic Liver Cancer (BCLC) stage B or C disease, at least one measurable lesion as per the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) and adequate organ function, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, serum AFP concentrations ≥400 ng/mL. Patients had received prior sorafenib therapy and discontinued treatment at least 14 days before randomization due to intolerance or disease progression. Patients with chronic viral hepatitis were eligible, irrespective of viral load. For the China extension study, patients had to have Chinese ancestry and residence in mainland China.

Key exclusion criteria included history or current hepatic encephalopathy, previous liver transplantation, hepatic locoregional therapy following sorafenib or within 28 days prior to randomization, oesophageal or gastric varices requiring immediate intervention (patients with evidence of portal hypertension [including splenomegaly] or history of variceal bleeding must have had endoscopic evaluation), and uncontrolled arterial hypertension.

The study was reviewed and approved by the Institutional Review Boards or Ethics Committee of each participating centre and was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice Guidelines, and applicable local regulations. Written informed consent was obtained from all patients before any study-specific procedures were performed.

Randomisation and masking

Eligible patients were randomised in a 2:1 ratio utilizing an interactive web response system (IWRS) to receive either ramucirumab or placebo and stratified by macrovascular invasion (yes vs no), and ECOG performance status (0 vs 1). Patients, investigators, and the sponsor were masked to treatment assignment. Ramucirumab was visibly indistinguishable from placebo.

Procedures

Patients received intravenous ramucirumab (8 mg/kg) or placebo every 14 days until disease progression (assessed radiologically or clinically; if the patient experienced a treatment benefit, at the discretion of the investigator, study treatment may continue beyond radiographic progression until clinical progression), unacceptable toxicity, or withdrawal of consent. All patients received the best supportive care, as determined by the investigator, including the use of concomitant drugs.

Tumour assessments were done using CT with contrast or MRI by investigators according to RECIST version 1.1 at baseline, every 6 weeks during the first 6 months of treatment, and every 9 weeks thereafter until disease progression or death. Patient-reported outcomes were assessed at baseline, then every 6 weeks during treatment, and at the beginning of short-term follow-up, using the Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8 (FHSI-8) and the EuroQol 5-Dimension-5 Level Questionnaire (EQ-5D-5L).[13,14] Physician-reported ECOG performance status was assessed at baseline, each cycle, and the short-term follow-up visit.

Safety assessments included adverse events, laboratory abnormalities, and vital signs. Safety data were collected continuously throughout the study. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 23.1; clinical laboratory toxicity and adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Outcomes

The primary endpoint was OS (time from randomisation to death from any cause). Secondary endpoints were PFS (time from randomisation to radiographic progression or death), time to radiographic progression (TTP, time from randomisation to first documented disease progression), objective response rate (ORR, the proportion of patients who achieved the best overall

response [BOR] of complete or partial response), safety, time to deterioration (TTD) in FHSI-8 total score (time from randomisation to the first clinically meaningful ≥3 points decrease from baseline),[15] EQ-5D-5L index score (time from randomisation to the first clinically meaningful ≥0.058 point decrease from baseline),[16] and ECOG PS (time from randomisation to recording of performance status of 2 or higher).

Statistical analysis

In the global REACH-2 study, a sample size of approximately 279 patients (targeting 221 deaths) was planned to provide 80% power to detect an HR of 0·67 favouring ramucirumab over placebo, using a log-rank test at a one-sided significance level of 0·025 for OS.[10] The sample size for the Chinese population was determined to demonstrate consistency with the global results, rather than statistical significance for differences in efficacy between treatments. A total enrollment of approximately 105 patients from China was planned to provide at least 80% probability of retaining at least 50% of the assumed effect size within the global population, which was estimated using simulation based on Method 1 from PMDA Guidance[17] with effect size defined as -log (HR), and in line with the regulatory requirements of the China authority for the approval of new drugs. If fewer than 105 Chinese patients were enrolled after the global REACH-2 study reached its planned total sample size, additional patients from China could be randomised to the 2 treatment arms (also in a 2:1 ratio) during a China extension study. No multiplicity adjustment, alpha allocation or formal hypothesis testing was performed, as this China study was not powered for inferential statistical analysis given the relatively small sample size.

The same statistical analysis methods were used for this REACH-2 China study as for the global study.[10] All Chinese patients who were randomised to study treatment were evaluable for efficacy. Safety-evaluable patients included those who received ≥1 dose of the study drug. Survival functions for OS, PFS, TTP, and TTD for FHSI-8, EQ-5D, and ECOG PS were estimated using the Kaplan-Meier method. Hazard ratio (HR) and 95% confidence interval (CI) were estimated using the Cox proportional hazard regression model. Different from the Cox model used for the global study, which was stratified by the randomization factors, an unstratified Cox model was adopted for the China study in consideration of the relatively small sample size. The proportional hazard assumption was checked and confirmed through visual inspection of the estimated survival curves. Subgroup analyses for OS and PFS based on baseline characteristics were conducted using the Cox model. Sensitivity analyses for OS included per-protocol population analysis, stratified analysis based on IWRS and case report form strata, and analysis based on baseline AFP level as measured in a central laboratory (Covance Central Laboratories; Indianapolis, IN, USA). Additional sensitivity analyses were done to explore the effect of post-discontinuation systemic therapy (PDT) and potential baseline imbalances in AFP level on OS, where an unstratified Cox model that included baseline AFP (log_{10}-transformed) as a covariate was utilized. ORR was reported with two-sided 95% CIs using the Clopper-Pearson method for each treatment group. Patient flow through the trial, baseline characteristics, and AEs were summarised by descriptive statistics.

REACH (NCT01140347) and REACH-2 were phase 3 trials with similar protocol procedures, efficacy assessments, and treatment regimens,[10,11] Chinese patients from the REACH-2 and REACH (AFP≥400 ng/mL) were pooled and analysed to achieve a more precise estimation of the treatment effect in a larger patient population. All pooled analyses were done at the level of individual patient data, and the prespecified endpoints included OS, PFS, ORR, and safety. Subgroup analyses for OS based on aetiology were conducted to explore the association between disease aetiology and survival outcomes in Chinese patients with HCC. Similar methods from REACH-2 were applied to the pooled data. Cox proportional hazard model was used to estimate HR, with the treatment arm as a single covariate and stratified by study (REACH vs REACH-2) to control for any potential inter-study differences, including study design, baseline characteristics, post-discontinuation treatment, data collection, and study operation. SAS version 9.4 was used for statistical analysis.

Role of the funding source

The study sponsor, Eli Lilly and Company, was involved in the study design, data collection, analysis, interpretation, and the writing of this report. All authors had full access to all trial data, vouch for the integrity of the data, and had final responsibility for the decision to submit the manuscript for publication.

Results

Of 165 patients screened at 31 sites in China, 104 eligible patients (global study, N = 44; China extension study, N = 60) were randomised to ramucirumab (N = 70) or placebo (N = 34) between Sep 16, 2015, and March 15, 2021. All randomised Chinese patients received study treatment and thus constituted both the intent-to-treat and safety populations (see patient flow diagram, Figure 1). At the data cut-off on March 15, 2021, 1 (1·4%) patient in the ramucirumab group was still receiving study treatment; the median duration of follow-up was 7·5 months (IQR 3·8-13·5).

Baseline characteristics were generally balanced between the treatment groups (Table 1), with the

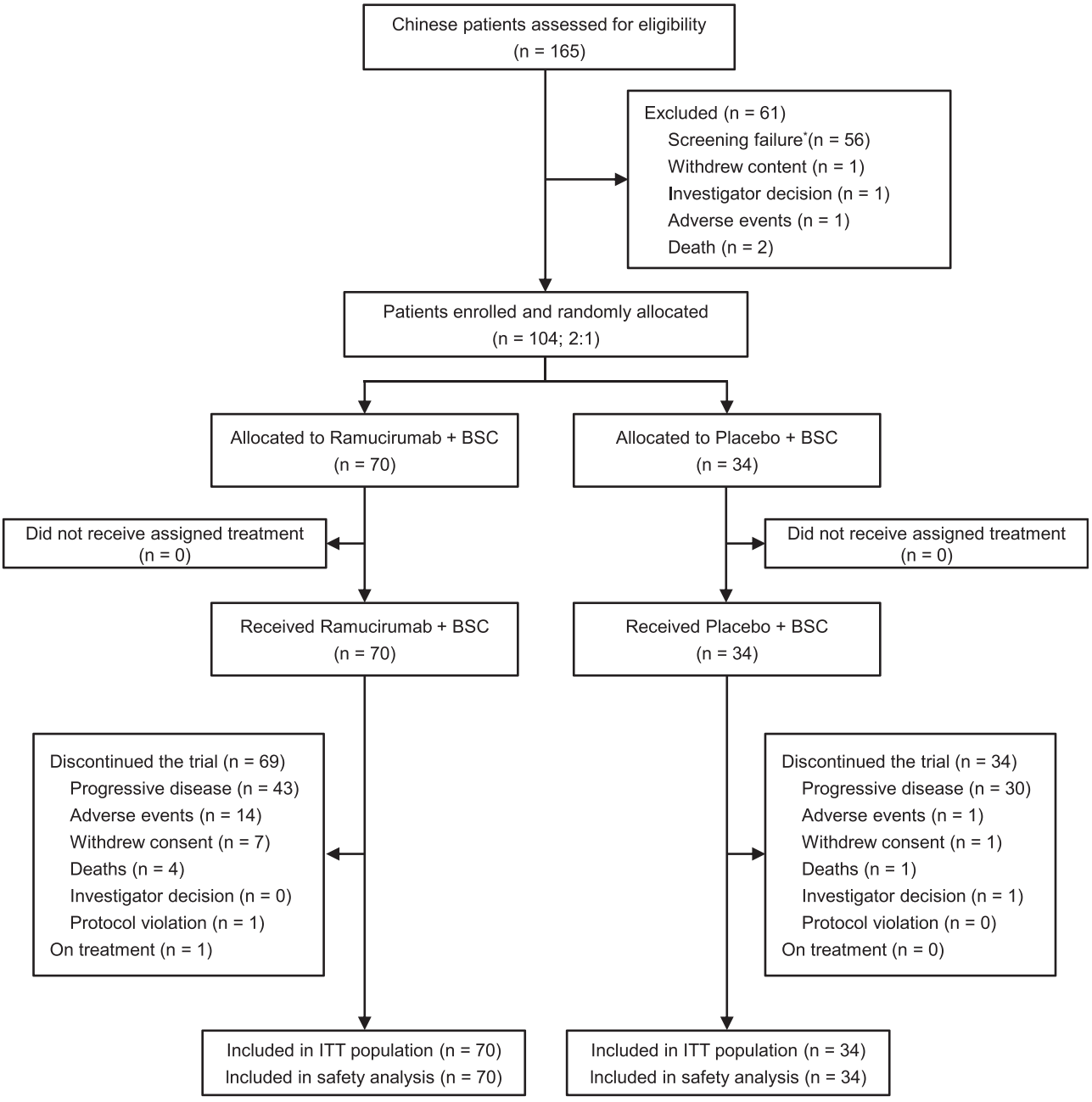

Figure 1. Patient flow diagram.
*Patients did not meet inclusion or exclusion criteria.

following exceptions: the proportion of patients with age ≥65 and Child-Pugh score A-5 was higher, the proportion of male patients, the proportion of patients who had received prior transarterial chemoembolization, and the median baseline AFP level was lower in the ramucirumab group than in the placebo group.

After disease progression or the end of study treatment, the percentage of patients who received at least one subsequent line of PDT was relatively lower in the ramucirumab group compared with the placebo group (44·3% vs 52·9%). The most commonly used PDT in both groups included targeted small molecular therapy (24·3% vs 35·3%), and immunotherapy (20·0% vs 20·6%) (Supplementary Table 1).

There were 59 deaths in the ramucirumab group and 26 deaths in the placebo group, with a primary cause of

Variable	Ramucirumab + BSC *N* = 70	Placebo + BSC *N* = 34
Age, years		
Median (range)	57 (24–80)	55 (31–76)
<65	55 (78·6)	30 (88·2)
≥65	15 (21·4)	4 (11·8)
Sex		
Male	55 (78·6)	31 (91·2)
Female	15 (21·4)	3 (8·8)
ECOG PS		
0	35 (50·0)	17 (50·0)
1	35 (50·0)	17 (50·0)
Child-Pugh score		
A5	55 (78·6)	23 (67·6)
A6	15 (21·4)	11 (32·4)
Barcelona Clinic Liver Cancer stage		
Stage B	10 (14·3)	2 (5·9)
Stage C	60 (85·7)	32 (94·1)
Aetiology of HCC		
Hepatitis B	55 (78·6)	26 (76·5)
Hepatitis C	10 (14·3)	4 (11·8)
Significant Alcohol Use	2 (2·9)	0
Primary Biliary Cirrhosis	0	1 (2·9)
Cryptogenic Cirrhosis	7 (10·0)	1 (2·9)
Other	3 (4·3)	2 (5·9)
MVI present	24 (34·3)	13 (38·2)
EHS present	50 (71·4)	27 (79·4)
MVI and/or EHS present	56 (80·0)	31 (91·2)
Duration of prior sorafenib therapy		
<5 months	41 (58·6)	20 (58·8)
≥5 months	29 (41·4)	14 (41·2)
Median (IQR), months	3·9 (1·8, 8·2)	3·4 (1·8, 9·2)
Reason for discontinuation of sorafenib		
Progressive disease	60 (85·7)	30 (88·2)
Intolerance	9 (12·9)	4 (11·8)
Time from last sorafenib treatment to randomisation		
<1 months	36 (51·4)	20 (58·8)
≥1 months	34 (48·6)	14 (41·2)
Median α-fetoprotein (IQR), ng/mL	4109·5 (1331·0, 28447·8)	5459·2 (1588·5, 32869·0)
Prior locoregional therapy	49 (70·0)	27 (79·4)
Transarterial chemoembolization	41 (58·6)	24 (70·6)

***Table 1*: Patient characteristics (Chinese patients from REACH-2).**
Data are n (%) unless otherwise indicated.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; IQR, interquartile range; MVI, macrovascular invasion.

death due to disease progression (57 patients in the ramucirumab group and 26 in the placebo group). Median OS was 9·1 months [95% CI 6·6-11·3] in the ramucirumab group and 6·2 months [4·4-10·7] in the placebo group (unstratified HR 0·854 [95% CI 0·536-1·359]; Figure 2). Most subgroups analysed for OS showed a benefit with ramucirumab compared with placebo, without a statistically significant difference (Supplementary Figure 1). Sensitivity analyses of the OS data provided similar results after adjusting for baseline AFP level, censoring users of PDT, using stratified modelling and per-protocol set (Figure 3 and Supplementary Table 2).

Median PFS was 2·8 months [95% CI 2·0-3·8] in the ramucirumab group and 1·5 months [1·4-2·8] in the placebo group (unstratified HR 0·488 [95% CI 0·304-0·785]; Figure 2). All subgroup analyses favoured treatment with ramucirumab (Supplementary Figure 2).

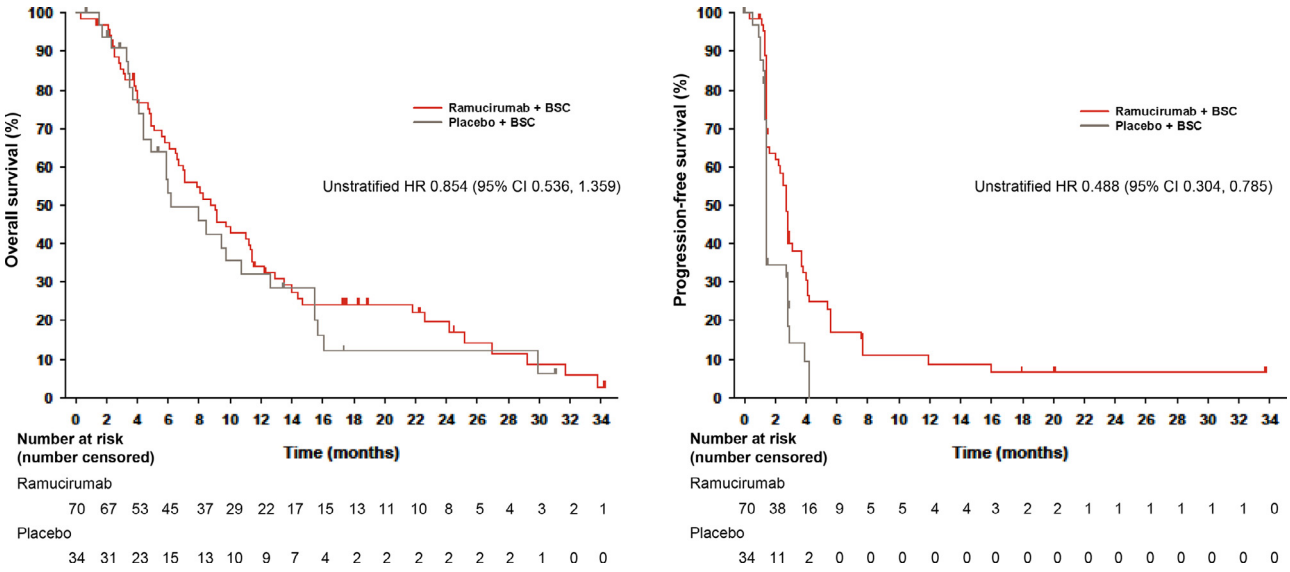

Figure 2. Kaplan–Meier plots of overall survival and progression-free survival (Chinese patients from REACH-2).
Note: Hazard ratio was estimated by an unstratified Cox proportional model with treatment group as a single covariate.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Median TTP was 2·8 months (95% CI 1·5-3·8) in the ramucirumab group and 1·5 months (1·4-2·8) in the placebo group (unstratified HR 0·488 [95% CI 0·274-0·733]). Three (4·3%, 95% CI 0·9·0) of 70 patients in the ramucirumab group had an objective response, with no responders in the placebo group. The proportion of patients with disease control was 50·0% [95% CI 38·3-61·7] in the ramucirumab group and 32·4% [16·6-48·1] in the placebo group.

Completion rates of the FHSI-8 and EQ-5D-5L were similar and acceptable between the treatment groups, with rates of ≥97·1% at baseline, ≥82·4% at baseline plus post-baseline, and ≥65·7% at end of treatment (Supplementary Table 3). Median TTD of FHSI-8 score

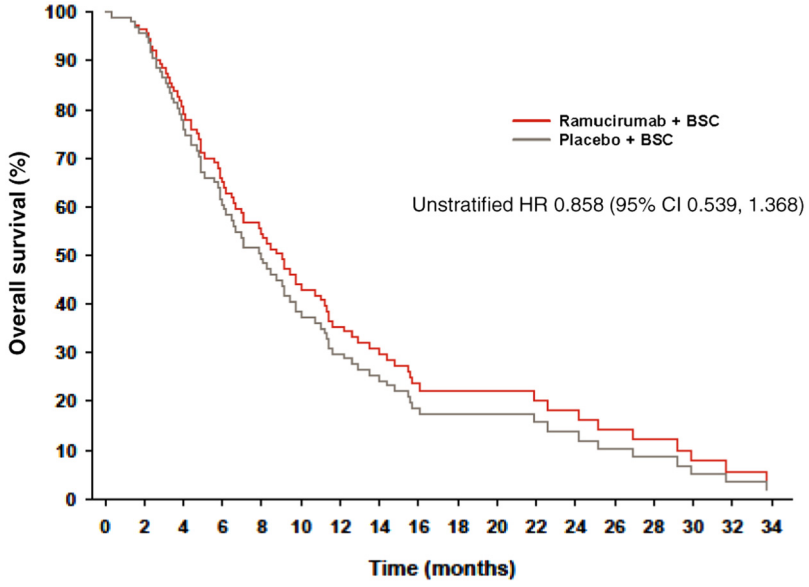

Figure 3. Estimated survival plot of overall survival adjusting for baseline AFP (Chinese patients from REACH-2).
Note: Hazard ratio was estimated by an unstratified Cox proportional model with treatment group as a single covariate.
Abbreviations: CI, confidence interval; HR, hazard ratio.

was 4·2 months [95% CI 1·6-NA] in the ramucirumab group versus 2·9 months [1·5-4·2] in the placebo group (unstratified HR 0·731 [95% CI 0·385-1·387]). Median TTD of EQ-5D-5L index score was 5·6 months [2·8-NA] in the ramucirumab group versus 2·9 months [95% CI 2·6-NA] in the placebo group (unstratified HR 0·809 [95% CI 0·377-1·736]). The unstratified HR for TTD of ECOG performance status was 0·402 (95% CI 0·099-1·632), while the number of events was limited (8/104) and insufficient for a meaningful interpretation of the result. Further details of patient-focused results will be published elsewhere.

Median duration of treatment was 9·6 weeks (IQR 5·9-15·9) in the ramucirumab group and 6·1 weeks (5·7-12·0) in the placebo group. Median relative dose intensity of ramucirumab was similar to that of placebo (98·1 % [IQR 92·6-101·2] vs 99·7% [96·1-100·3]). Dose reductions because of adverse events occurred in 4 (5·7%; anaemia [1 patient], neutrophil count decreased [1 patient], proteinuria [3 patients]) of 70 patients in the ramucirumab group, and none occurred in the placebo group. Treatment discontinuation due to TEAEs occurred in 16 (22·9%) patients in the ramucirumab group vs 1 (2·9%) in the placebo group (Supplementary Table 4).

The incidence of TEAEs was similar between groups (69 [98·6%] patients in the ramucirumab group and 29 [85·3%] in the placebo group). The most frequently reported TEAEs of any grade in the ramucirumab group were thrombocytopenia (24 [34·3%]), proteinuria (22 [31·4%]), hypoalbuminaemia (20 [28·6%]), aspartate aminotransferase increased (17 [24·3%]), abdominal pain (16 [22·99%]), and oedema peripheral (15 [21·4%]), most of which were grade 1-2 (Table 2). Grade 3 or 4 TEAEs were observed in 32 (45·7%) patients in the ramucirumab group and 10 (29·4%) in the placebo group. None of grade 3 or worse TEAEs was noted that occurred at a difference in frequency of 5% or more in patients allocated ramucirumab compared with placebo (Table 2). Findings from the analysis of laboratory data did not reveal any new or increased safety concerns (data not shown).

Serious adverse events (SAEs) were reported in 19 (27·1%) patients in the ramucirumab group and 9 (26·5%) in the placebo group, whereas treatment-related events were reported in 7 (10·0%) and 1 (2·9%) patient, respectively. Deaths for any reason, either on therapy or within 30 days of treatment discontinuation occurred in 9 (12·9%) patients in the ramucirumab group and 4 (11·8%) in the placebo group. Two (2·9%) patients in the ramucirumab group (both from pneumonia) died on treatment due to adverse events, whereas both were judged to be unrelated to study treatment by the investigator. No patients in the placebo group died on treatment because of adverse events.

Common treatment-emergent adverse events of special interest (AESI) of any grade that were more frequent in the ramucirumab group than in the placebo group were liver injury or failure, bleeding or haemorrhage, proteinuria, hypertension, and infusion-related reactions (Table 3). Incidences of grade 3 or worse AESI were low in both groups.

We pooled the individual patient data for Chinese patients from REACH-2 and REACH (AFP ≥400 mg/mL). The combined population comprised 155 patients, with 98 patients in the ramucirumab group and 57 in the placebo group. Baseline characteristics of the pooled Chinese patients were broadly similar to those of Chinese patients from REACH-2 (Table 1 and Supplementary Table 5). However, median baseline AFP concentrations, the proportion of patients with macrovascular invasion present, and duration of prior sorafenib therapy <5 months were higher in the pooled Chinese patients than in Chinese patients from REACH-2 (Table 1 and Supplementary Table 5). Baseline characteristics were balanced between the ramucirumab vs placebo group in the pooled Chinese patients, except for the higher proportion of patients with age ≥65, the lower proportion of patients with macrovascular invasion present, and the lower median level of AFP noted in the ramucirumab group (Supplementary Table 5).

Within the pooled Chinese patients, the median OS was 7·1 months [95% CI 5·8-9·7] in the ramucirumab group and 4·7 months [3·7-6·2] in the placebo group, with a stratified HR of 0·735 [95% CI 0·512-1·055] (Figure 4). HBV infection is the most frequent aetiologic factor in Chinese patients with HCC and was balanced between ramucirumab and placebo groups (78 [79·6%] vs 44 [77·2%]). Post-hoc analyses showed that the median OS for ramucirumab vs placebo was 6·9 vs 4·4 months [HR 0.673, 95% CI 0.443-1.020] in HBV-related HCC patients, and 8·5 vs 5·9 months (HR 0.844, 95% CI 0.379-1.879) in non-HBV HCC patients. No significant difference was detected in treatment effect in OS by the aetiology subgroup (OS interaction *p*-value =0.31). Improvements in PFS (2·6 months [95% CI 1·5-2·8] vs 1·5 [1·4-1·5]; stratified HR 0·666 [95% CI 0·459-0·967]; Figure 4), ORR (3·1% [95% CI 0·0-6·5] vs 0%), and DCR (44·9% [95% CI 35·1-54·7] vs 29·8% [17·9-41·7]) were also observed. These findings were consistent with the those in REACH-2 study.

Median duration of therapy and relative dose intensity was similar in the pooled Chinese patients and in Chinese patients from REACH-2 (Supplementary Table 4). Common TEAEs, SAEs, and AESI occurred at similar incidence and severity in the pooled Chinese patients and Chinese patients from REACH-2 (Tables 2 and 3). None of grade 3 or worse TEAEs was noted that occurred at a difference in frequency of 5% or more in patients allocated ramucirumab compared with placebo (Table 2). No new safety signals were identified.

	Chinese patients from REACH-2				Pooled Chinese patients from REACH-2 and REACH (AFP≥400 ng/mL)			
	Ramucirumab + BSC *N* = 70		Placebo + BSC *N* = 34		Ramucirumab + BSC *N* = 98		Placebo + BSC *N* = 56	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5
TEAE, n (%)	69 (98·6)	36 (51·4)	29 (85·3)	10 (29·4)	95 (96·9)	46 (46·9)	50 (89·3)	25 (44·6)
Platelet count decreased	22 (31·4)	3 (4·3)	0	0	22 (22·4)	3 (3·1)	0	0
Proteinuria	22 (31·4)	2 (2·9)	0	0	28 (28·6)	2 (2·0)	4 (7·1)	0
Aspartate aminotransferase increased	17 (24·3)	4 (5·7)	9 (26·5)	2 (5·9)	23 (23·5)	7 (7·1)	15 (26·8)	8 (14·3)
Hypoalbuminaemia	16 (22·9)	0	6 (17·6)	0	21 (21·4)	0	9 (16·1)	0
Oedema peripheral	15 (21·4)	0	2 (5·9)	0	24 (24·5)	0	6 (10·7)	0
Blood bilirubin increased	14 (20·0)	3 (4·3)	6 (17·6)	2 (5·9)	17 (17·3)	5 (5·1)	13 (23·2)	7 (12·5)
Hypertension	13 (18·6)	5 (7·1)	3 (8·8)	1 (2·9)	16 (16·3)	6 (6·1)	5 (8·9)	1 (1·8)
Alanine aminotransferase increased	12 (17·1)	0	7 (20·6)	4 (11·8)	12 (12·2)	0	9 (16·1)	5 (8·9)
Anaemia	12 (17·1)	3 (4·3)	2 (5·9)	0	14 (14·3)	4 (4·1)	4 (7·1)	0
Abdominal pain	11 (15·7)	1 (1·4)	3 (8·8)	1 (2·9)	13 (13·3)	1 (1·0)	6 (10·7)	1 (1·8)
Cough	9 (12·9)	0	5 (14·7)	0	15 (15·3)	0	8 (14·3)	0
Neutrophil count decreased	9 (12·9)	1 (1·4)	3 (8·8)	0	9 (9·2)	1 (1·0)	3 (5·4)	0
Abdominal distension	8 (11·4)	0	2 (5·9)	0	14 (14·3)	0	10 (17·9)	2 (3·6)
Ascites	8 (11·4)	1 (1·4)	2 (5·9)	0	13 (13·3)	1 (1·0)	7 (12·5)	2 (3·6)
Decreased appetite	8 (11·4)	0	7 (20·6)	0	12 (12·2)	0	14 (25·0)	0
Fatigue	8 (11·4)	0	2 (5·9)	0	13 (13·3)	0	4 (7·1)	1 (1·8)
Pneumonia	8 (11·4)	5 (7·1)	1 (2·9)	1 (2·9)	8 (8·2)	5 (5·1)	1 (1·8)	1 (1·8)
Pyrexia	7 (10·0)	0	4 (11·8)	0	11 (11·2)	0	7 (12·5)	0
Vomiting	7 (10·0)	1 (1·4)	4 (11·8)	0	9 (9·2)	1 (1·0)	8 (14·3)	0
White blood cell count decreased	7 (10·0)	0	2 (5·9)	0	7 (7·1)	0	2 (3·6)	0

***Table 2*: Treatment-emergent adverse events occurring in at least 10% of patients in the ramucirumab group, irrespective of causality.**
Data are n (%).

	Chinese patients from REACH-2				Pooled Chinese patients from REACH-2 and REACH (AFP≥400 ng/mL)			
	Ramucirumab + BSC *N* = 70		Placebo + BSC *N* = 34		Ramucirumab + BSC *N* = 98		Placebo + BSC *N* = 56	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Liver injury	39 (55·7)	10 (14·3)	17 (50·0)	7 (20·6)	50 (51·0)	14 (14·3)	29 (51·8)	17 (30·4)
Hepatic encephalopathy	0	0	1 (2·9)	0	0	0	1 (1·8)	0
Bleeding/haemorrhage events	18 (25·7)	6 (8·6)	2 (5·9)	0	22 (22·4)	6 (6·1)	10 (17·9)	5 (8·9)
Gastrointestinal haemorrhage events	8 (11·4)	4 (5·7)	1 (2·9)	0	10 (10·2)	4 (4·1)	6 (10·7)	4 (7·1)
Proteinuria	23 (32·9)	2 (2·9)	0	0	29 (29·6)	2 (2·0)	4 (7·1)	0
Hypertension	14 (20·0)	5 (7·1)	3 (8·8)	1 (2·9)	17 (17·3)	6 (6·1)	5 (8·9)	1 (1·8)
Infusion-related reaction[a]	7 (10·0)	0	1 (2·9)	0	9 (9·2)	0	2 (3·6)	0
Venous thromboembolic events	0	0	0	0	0	0	1 (1·8)	1 (1·8)
Congestive heart failure	0	0	1 (2·9)	1 (2·9)	0	0	1 (1·8)	1 (1·8)
Arterial thromboembolic events	0	0	0	0	0	0	1 (1·8)	1 (1·8)
Fistula	0	0	0	0	0	0	0	0
Gastrointestinal perforation	0	0	1 (2·9)	1 (2·9)	0	0	1 (1·8)	1 (1·8)
Healing complication	1 (1·4)	0	0	0	1 (1·0)	0	0	0
Posterior reversible encephalopathy syndrome	0	0	0	0	0	0	0	0

***Table 3*: Treatment-emergent adverse events of special interest.**

Data are n (%).

[a] Occurring within 24 h of infusion.

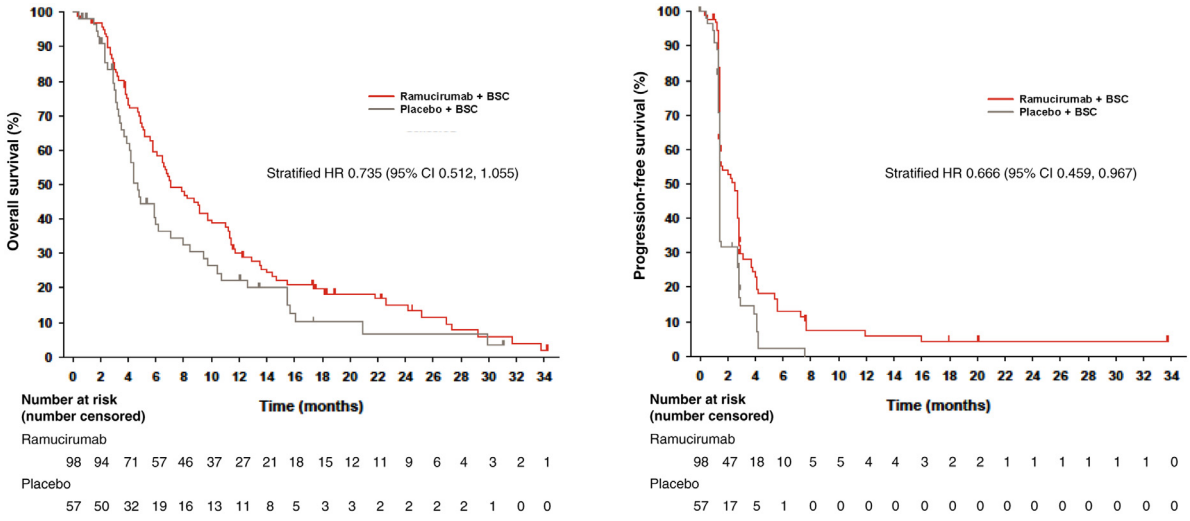

Figure 4. Kaplan–Meier plots of overall survival and progression-free survival (Pooled Chinese patients from REACH-2 and REACH with AFP≥400 ng/mL).

Note: Hazard ratio was estimated by a Cox proportional model with treatment group as a single covariate, stratified by study (REACH vs REACH-2).

Abbreviations: CI, confidence interval; HR, hazard ratio.

Discussion

The global REACH-2 study demonstrated a statistically significant and clinically meaningful improvement in OS with ramucirumab in patients with advanced HCC and baseline AFP ≥400 ng/mL after prior sorafenib therapy.[10] REACH-2 China study, as a regional study of REACH-2, showed clinically meaningful improvements in median OS with a prolongation of 2.9-month with ramucirumab in the Chinese patients, although there was no statistically significant difference between treatments. Ramucirumab was well-tolerated in the Chinese patients with an acceptable safety profile. Efficacy and safety data in this study demonstrated consistency with the results of the global REACH-2 study.

The clinical benefits were observed even though more of the Chinese patients had HBV infection (77·9 vs·36·6%), age <65 (81·7 vs 51·7%), and poor prognostic factors including ECOG PS 1 (50·0 vs 42·5%), BCLC Stage C disease (88·5 vs 81·5%), and higher AFP level (median AFP 4211·2 vs 3394·0 ng/mL), than the global population in REACH-2.[10] The differences in baseline prognostic patterns between the patient populations has been noted previously,[18] and some were expected and related to ethnic/geographical variances such as HBV incidence. The shorter median OS in the placebo group among Chinese patients compared to the global population (median OS 6·2 vs 7·3 months) may be associated with differences in baseline characteristics.

The overall prognosis and treatment effect was comparable in Chinese patients and the global REACH-2 population in terms of median OS (Chinese patients, 9·1 months [ramucirumab] vs 6·2 months [placebo], HR 0·854 [95% CI 0·536-1·359]; global population, 8·5 months vs 7·3 months, HR 0·710 [95% CI 0·531-0·949]), and in line with the pooled Chinese patients from REACH-2 and REACH with AFP ≥400 ng/mL (7·1 vs 4·7 months, HR 0·735 [95% CI 0·512-1·055]). High AFP concentrations (≥400 ng/mL) are associated with aggressive disease and were identified to be one of the strongest prognostic factors in HCC,[10,11,19] as well as a predictive biomarker for ramucirumab survival benefit.[20] In this study, all Chinese patients had high AFP levels at baseline, while even higher median values were observed in the placebo group in comparison to the ramucirumab group (5459·2 vs 4109·5 ng/mL), potentially favouring a longer survival with ramucirumab. Sensitivity analysis adjusted the effect of AFP levels on prognosis and yielded a very similar HR to the primary analysis, suggesting a consistent ramucirumab treatment benefit compared with placebo. Survival outcomes may differ by HCC disease aetiology,[21] and the post-hoc analysis showed that HCC patients with HBV had a worse prognosis than non-HBV patients. Although a lower HR of 0.673 for OS was observed in HBV-positive patients as compared with HR of 0.844 in non-HBV patients, there is no significant differential treatment effect between HBV and non-HBV subgroups. PDT may contributed to the magnitude of treatment effects.[10] A sensitivity analysis of OS censoring for the use of PDT showed decreased HR (0·746 [95% CI 0·380-1·464]), which suggesting that patients in the ramucirumab group were deriving more OS benefit than patients in the placebo group after considering the effects of PDT.

In the present analysis, the observed HR for PFS in Chinese patients was 0·488 (95% CI 0·304-0·785). PFS is suggested as a surrogate of OS in the clinical trials of advanced HCC treated with molecular targeted therapy since patients who died due to liver cirrhosis could confound the potential benefits of the investigational drug, with a threshold of HR ≤0·6 for PFS being suggestive of improvement in OS.[22] The marked improvement in PFS reflect the clinically meaningful improvement in OS in Chinese patients, which was consistent with those in the global population in REACH-2.[10]

Overall, the safety profile of ramucirumab in Chinese patients was consistent with that observed in the global population in REACH-2,[10] and generally in line with the known safety profiles for single-agent ramucirumab and the underlying disease, with no unexpected safety events reported. Most of the differences in TEAEs and AESI between the ramucirumab and placebo group in the Chinese patients were related to low-grade (grade 1-2) events, which were manageable. Hypertension, hyponatraemia, and aspartate aminotransferase increase were the only grade ≥3 TEAE that occurred in at least 5% of patients in the ramucirumab group, which was also noted in the global population in REACH-2.[10] Liver injury/liver failure and bleeding/haemorrhage events are of particular concern in patients with HCC. The incidence of liver injury/liver failure in the Chinese patients was higher than in the global population of REACH-2 (53·8% vs 36·3%), while similar between the ramucirumab and placebo groups (55·7% vs 50·0%). As expected, given the underlying liver disease in the Chinese population, most hepatic events were laboratory abnormalities, which were manageable without drug discontinuation or adjustment. Notably, hepatic encephalopathy occurred in 1 placebo recipient but not in the ramucirumab recipient. The incidence of bleeding/haemorrhage in the ramucirumab group in Chinese patients was similar to the global population in REACH-2.[10] Gastrointestinal haemorrhage, a common and life-threatening complication in patients with HCC, was observed in 8 Chinese patients (11·4%) in the ramucirumab group (grade ≥3 events in 4 patients [5·7%]) and in 1 patient (2·9%) in the placebo group.

This study had certain limitations. The REACH-2 China study was not designed nor powered to detect a statistical difference in OS. Nonetheless, the estimated HR in this study is similar to that in the global study, suggesting that there is also OS benefit with ramucirumab as a second-line treatment in Chinese patients with advanced HCC. Although the findings broadly resembled those from the REACH-2 global study, this study evaluated the benefit of ramucirumab in a high-risk HCC population with varying underlying aetiologic factors, distinct clinical features, and different treatment practices; and confirmed that the treatment effect of ramucirumab is consistent across ethnicities and geographies.

At the time REACH-2 was conducted, sorafenib was the only approved first-line treatment for advanced HCC. The treatment landscape has changed dramatically in recent years, atezolizumab and bevacizumab have become the new standard of care for advanced HCC.[23,24] Other clinical trials exploring the combination of immunotherapy with anti-VEGF therapy for the treatment of HCC are currently in explored.[25] Recognizing the rapidly evolving treatment landscape, a global open-label expansion cohort of the REACH-2 study was initiated to address the data gap that exists on the efficacy and safety of ramucirumab in patients who received first-line systemic therapy other than sorafenib; the efficacy (median OS 8·7 months [95% CI 4·6-12·2]) and safety profile of ramucirumab following a non-sorafenib-based systemic therapy were consistent with that observed in patients who received prior sorafenib in the REACH-2 study.[26] Available data indicate that ramucirumab is an important second-line treatment option for patients with AFP ≥400 ng/mL. Further clinical and real-world data for a broader patient population and regimens would be useful in determining the role of ramucirumab used in the second-line treatment of HCC.

In conclusion, this REACH-2 China study demonstrated clinically meaningful improvement in OS for ramucirumab compared with placebo in Chinese patients with advanced HCC and elevated AFP after sorafenib, even though no statistical significance was observed. Ramucirumab was well tolerated, with a manageable safety profile. The efficacy data and the safety profile in the Chinese patients were generally consistent with the findings in the global REACH-2 study and provide evidence suggesting that ramucirumab might be a promising treatment option for Chinese patients with advanced HCC and elevated AFP in the second line setting.

Contributors

RW, QZ, and SKQ designed the study. GLS, YXB, XLY, XMC, SZG, KSG, CHH, HJL, YBG, JFW, CJY, HFL, and SKQ gathered the data. CXW and WLZ analysed and verified the underlying data. GLS, YXB, XLY, CXW, RW, WLZ, JJL, QZ and SKQ interpreted the data. JJL wrote the manuscript. All authors reviewed and approved the final version. All authors had full access to all the data in the study, vouch for the integrity of the data, and had final responsibility for the decision to submit for publication.

Data sharing statement

Lilly provides access to all individual participant data collected during the trial, after anonymisation, except for pharmacokinetic or genetic data. Data are available for request 6 months after the indication studied have been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been

approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Editor note

The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

Declaration of interests

VL reports grant from AstraZeneca, consulting fees from AQUILAB, and personal fees from Amgen, AstraZeneca, Boston Scientific, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Takeda; and has served on advisory boards for Amgen, AstraZeneca, Merck Sharp & Dohme, Pfizer, Takeda. CXW, RW, WLZ, JJL, and QZ are employees of, shareholders in, Eli Lilly. All other authors declare no competing interests.

Acknowledgements

This study was funded by Eli Lilly and Company. Li Zhou from Eli Lilly and Company contributed to the interpretation of results for patient-reported outcomes.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101679.

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(3):209–249.
2 Organization WH. GLOBOCAN 2020. Cancer fact sheets. Liver. https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf.
3 Organization WH. GLOBOCAN 2020. Population fact sheets. China. https://gco.iarc.fr/today/data/factsheets/populations/160-china-fact-sheets.pdf.
4 Institute NC. Seer. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. https://seer.cancer.gov/statfacts/html/livibd.html.
5 Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378–390.
6 Cheng A-L, Kang Y-K, 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(1):25–34.
7 Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet North Am Ed*. 2017;389(10064):56–66.
8 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(7):559–568.
9 Lu D, Shen J, Vil MD, et al. Tailoring in vitro selection for a picomolar affinity human antibody directed against vascular endothelial growth factor receptor 2 for enhanced neutralizing activity. *J Biol Chem*. 2003;278(44):43496–43507.
10 Zhu AX, Kang Y-K, Yen C-J, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(2):282–296.
11 Zhu AX, Park JO, Ryoo B-Y, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16(7):859–870.
12 Zhou J, Sun H-C, Wang Z, et al. Guidelines for diagnosis and treatment of primary liver cancer in China (2017 Edition). *Liver Cancer*. 2018;7(3):235–260.
13 Yount S, Cella D, Webster K, et al. Assessment of patient-reported clinical outcome in pancreatic and other hepatobiliary cancers: the FACT hepatobiliary symptom index. *J Pain Symptom Manage*. 2002;24(1):32–44.
14 Luo N, Liu G, Li M, Guan H, Jin X, Rand-Hendriksen K. Estimating an EQ-5D-5L value set for China. *Value Health*. 2017;20(4):662–669.
15 Steel J, Eton D, Cella D, Olek M, Carr B. Clinically meaningful changes in health-related quality of life in patients diagnosed with hepatobiliary carcinoma. *Ann Oncol*. 2006;17(2):304–312.
16 McClure NS, Al Sayah F, Xie F, Luo N, Johnson JA. Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores. *Value Health*. 2017;20(4):644–650.
17 MHLW. *Basic principles on global clinical trials*. Notification No 0928010; 2007.
18 Qin S, Ren Z, Feng Y-H, et al. Atezolizumab plus Bevacizumab versus Sorafenib in the Chinese subpopulation with unresectable hepatocellular carcinoma: phase 3 randomized, open-Label IMbrave150 Study. *Liver Cancer*. 2021;10(4):296–308.
19 Nakazawa T, Hidaka H, Takada J, et al. Early increase in α-fetoprotein for predicting unfavorable clinical outcomes in patients with advanced hepatocellular carcinoma treated with sorafenib. *Eur J Gastroenterol Hepatol*. 2013;25(6):683–689.
20 Zhu AX, Finn RS, Kang Y-K, et al. Serum alpha-fetoprotein and clinical outcomes in patients with advanced hepatocellular carcinoma treated with ramucirumab. *Br J Cancer*. 2021;124(8):1388–1397.
21 Galle PR, Kudo M, Llovet JM, et al. Ramucirumab in patients with previously treated advanced hepatocellular carcinoma: impact of liver disease aetiology. *Liver Int*. 2021;41(11):2759–2767.
22 Llovet JM, Montal R, Villanueva A. Randomized trials and endpoints in advanced HCC: role of PFS as a surrogate of survival. *J Hepatol*. 2019;70(6):1262–1277.
23 Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905.
24 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(7):977–990.
25 Foerster F, Galle PR. The current landscape of clinical trials for systemic treatment of hcc. *Cancers*. 2021;13(8):1962.
26 Finn RS, Yau T, Hsu C-H, et al. *Ramucirumab for Patients with Advanced Hepatocellular Carcinoma and Elevated A-Fetoprotein Following a Non-Sorafenib Based First-Line Therapy: Final Results from an Expansion Cohort of REACH-2*, American Society of Clinical Oncology; 2022.