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

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Summary

Background Patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations have poor prognosis. We aimed to establish the efficacy of ramucirumab in patients with advanced hepatocellular carcinoma and α-fetoprotein concentrations of 400 ng/mL or higher.

Methods REACH-2 was a randomised, double-blind, placebo-controlled, phase 3 trial done at 92 hospitals, clinics, and medical centres in 20 countries. Eligible patients were aged 18 years or older and had histologically or cytologically confirmed hepatocellular carcinoma, or diagnosed cirrhosis and hepatocellular carcinoma, Barcelona Clinic Liver Cancer stage B or C disease, Child-Pugh class A liver disease, Eastern Cooperative Oncology Group (ECOG) performance statuses of 0 or 1, α-fetoprotein concentrations of 400 ng/mL or greater, and had previously received first-line sorafenib. Participants were randomly assigned (2:1) via an interactive web response system with a computer-generated random sequence to 8 mg/kg intravenous ramucirumab every 2 weeks or placebo. All patients received best supportive care. The primary endpoint was overall survival. Secondary endpoints were progression-free survival, proportion of patients achieving an objective response, time to radiographic progression, safety, time to deterioration in scores on the Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8 (FHSI-8), and time to deterioration in ECOG performance status. We also pooled individual patient data from REACH-2 with data from REACH (NCT01140347) for patients with α-fetoprotein concentrations of 400 ng/mL or greater. Efficacy analyses were by intention to treat, whereas safety analyses were done in all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT02435433.

Findings Between July 26, 2015, and Aug 30, 2017, 292 patients were randomly assigned, 197 to the ramucirumab group and 95 to the placebo group. At a median follow-up of 7·6 months (IQR 4·0–12·5), median overall survival (8·5 months [95% CI 7·0–10·6] *vs* 7·3 months [5·4–9·1]; hazard ratio [HR] 0·710 [95% CI 0·531–0·949]; p=0·0199) and progression-free survival (2·8 months [2·8–4·1] *vs* 1·6 months [1·5–2·7]; 0·452 [0·339–0·603]; p<0·0001) were significantly improved in the ramucirumab group compared with the placebo group. The proportion of patients with an objective response did not differ significantly between groups (nine [5%] of 197 *vs* one [1%] of 95; p=0·1697). Median time to deterioration in FHSI-8 total scores (3·7 months [95% CI 2·8–4·4] *vs* 2·8 months [1·6–2·9]; HR 0·799 [95% CI 0·545–1·171]; p=0·238) and ECOG performance statuses (HR 1·082 [95% CI 0·639–1·832]; p=0·77) did not differ between groups. Grade 3 or worse treatment-emergent adverse events that occurred in at least 5% of patients in either group were hypertension (25 [13%] in the ramucirumab group vs five [5%] in the placebo group), hyponatraemia (11 [6%] *vs* 0) and increased aspartate aminotransferase (six [3%] *vs* five [5%]). Serious adverse events of any grade and cause occurred in 68 (35%) patients in the ramucirumab group and 28 (29%) patients in the placebo group. Three patients in the ramucirumab group died from treatment-emergent adverse events that were judged to be related to study treatment (one had acute kidney injury, one had hepatorenal syndrome, and one had renal failure).

Interpretation REACH-2 met its primary endpoint, showing improved overall survival for ramucirumab compared with placebo in patients with hepatocellular carcinoma and α-fetoprotein concentrations of at least 400 ng/mL who had previously received sorafenib. Ramucirumab was well tolerated, with a manageable safety profile. To our knowledge, REACH-2 is the first positive phase 3 trial done in a biomarker-selected patient population with hepatocellular carcinoma.

Funding Eli Lilly.

Research in context

Evidence before this study

Before REACH-2 trial enrolment began, we searched PubMed, the abstracts of major oncology congresses (specifically the American Society of Clinical Oncology and European Society for Medical Oncology congresses), and ClinicalTrials.gov with the search terms "hepatocellular carcinoma", "advanced hepatocellular carcinoma", "AFP", "targeted therapy", "phase 3", "trials", "clinical trials", and "VEGFR-2" for preclinical reports and clinical trials published in English up to Jan 1, 2015. This search showed that sorafenib was the first drug with efficacy in advanced, metastatic hepatocellular carcinoma in the first-line setting and the only globally approved drug when REACH-2 was designed. Several other drugs have not been associated with survival benefits in clinical trials in patients with hepatocellular carcinoma, including some trials in which investigators attempted to use biomarker results to guide treatment. Patients with hepatocellular carcinoma with increased α-fetoprotein concentrations have poor prognosis, and overexpression of α-fetoprotein has been associated with a distinct subtype of hepatocellular carcinoma that has a potentially distinct biology. We identified few studies of α-fetoprotein in relation to specific systemic treatment in advanced hepatocellular carcinoma. The randomised REACH study investigated ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma after first-line sorafenib. Although the study did not meet its primary endpoint of overall survival, ramucirumab was well tolerated, and a subgroup analysis suggested an increasing effect of ramucirumab on overall survival with increasing concentrations of baseline α-fetoprotein that was meaningful in patients with baseline α-fetoprotein of at least 400 ng/mL. This finding was the basis of the hypothesis for REACH-2.

Added value of this study

To our knowledge, REACH-2 is the first phase 3, randomised, placebo-controlled trial done in patients with hepatocellular carcinoma who were enrolled on the basis of a biomarker (ie, α-fetoprotein concentrations ≥400 ng/mL). Overall survival was significantly improved in patients with α-fetoprotein concentrations of at least 400 ng/mL who received second-line ramucirumab than in those who received placebo after previous first-line sorafenib. Treatment with ramucirumab was well tolerated, with a clinically acceptable safety profile. The positive results of REACH-2 support VEGFR2 as a therapeutic target in hepatocellular carcinoma. Our results also provide further clinical evidence that hepatocellular carcinoma that is associated with increased α-fetoprotein concentrations could be a subtype of disease that requires a different treatment strategy.

Implications of all the available evidence

Ramucirumab is a treatment option for patients with hepatocellular carcinoma and increased α-fetoprotein concentrations after previous sorafenib treatment. In future, thoughtful consideration of previous treatment, the toxicity profiles of the available options, and applicable biomarker results should be used to guide treatment decisions for patients with hepatocellular carcinoma. Directions for future exploration include assessment of ramucirumab in other lines of therapy, as well as novel combinations.

Introduction

Hepatocellular carcinoma is the most common primary hepatic malignancy and the third most common cause of cancer-related death worldwide.[1] Many factors are clinically applicable in assessments of the prognosis of patients with hepatocellular carcinoma, including stage, performance status, severity of underlying liver disease, histopathology, and α-fetoprotein concentration.[2–6]

Sorafenib was the first drug to show improved median overall survival in patients with hepatocellular carcinoma.[7,8] Since the approval of sorafenib, only three other drugs—the first-line treatment lenvatinib and the second-line treatments regorafenib and cabozantinib—have shown clinical benefits in phase 3 clinical trials.[9–11] All three drugs are oral multikinase inhibitors. In a phase 2 trial of tivantinib as second-line therapy,[12] investigators selected patients with high MET-expression hepatocellular carcinoma, but there was no improvement in overall survival.

In hepatocellular carcinoma, an α-fetoprotein concentration higher than 400 ng/mL has been consistently associated with poor prognosis in several treatment settings,[13,14] and is an included parameter in several prognostic scoring systems.[2,3,15] α-fetoprotein is a continuous variable, and a worse prognosis is associated with concentrations of α-fetoprotein higher than 400 ng/mL.[16–18] VEGF and VEGFR2-mediated signalling have important roles in angiogenesis and tumour growth, including in hepatocellular carcinoma.[19,20] Increased α-fetoprotein concentrations has been associated with increased VEGFR expression and increased angiogenesis in hepatocellular carcinoma.[21–23] After sorafenib therapy, roughly half of patients have α-fetoprotein concentrations of 400 ng/mL or greater, and effective and well tolerated treatments are needed in this population.[18,24]

Ramucirumab is a human IgG1 monoclonal antibody that inhibits ligand activation of VEGFR2, and showed initial anti-tumour activity in a phase 2 study of advanced first-line hepatocellular carcinoma.[19,20] REACH was a global, randomised, double-blind, placebo-controlled, phase 3 study[18] of the efficacy and safety of ramucirumab monotherapy after first-line sorafenib in 565 patients with advanced hepatocellular carcinoma. Ramucirumab did not significantly improve overall survival compared with placebo in the intention-to-treat population (hazard ratio [HR] 0·87 [95% CI 0·72–1·05]; p=0·14). However,

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See Online for appendix

a clinically meaningful and significant improvement in overall survival was noted in the ramucirumab group compared with the placebo group in the prespecified subpopulation (n=250) of patients with baseline α-fetoprotein concentrations of 400 ng/mL or greater (median overall survival 7·8 months (95% CI 5·8–9·3) *vs* 4·2 months (3·7–4·8; HR 0·674 [95% CI 0·508–0·895]; p=0·006).[18] We aimed to investigate the efficacy and safety of ramucirumab monotherapy in patients with hepatocellular carcinoma and baseline α-fetoprotein concentration of 400 ng/mL or greater after intolerance to, or progression during, previous sorafenib therapy.

Methods

Study design and participants

REACH-2 was a randomised, double-blind, placebo-controlled, phase 3 study done at 92 hospitals, clinics, and medical centres in 20 countries (appendix pp 2–9). Eligible patients had a diagnosis of hepatocellular carcinoma based on either histopathological or cytological findings or, in the absence of histological confirmation, a diagnosis of cirrhosis and hepatocellular carcinoma with classical imaging characteristics (at least a three-phase liver protocol by CT or MRI and a lesion that showed arterial hyperenhancement and could wash out in the venous phase). Eligible patients also had Barcelona Clinic Liver Cancer (BCLC) stage B or C disease that was refractory or not amenable to locoregional therapy, Child-Pugh class A liver disease, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, serum α-fetoprotein concentrations of 400 ng/mL or higher (as measured by a local laboratory), adequate haematological and biochemical parameters, and were aged 18 years or older. Sorafenib was the only previous systemic treatment for hepatocellular carcinoma that was allowed, and it had to have been discontinued at least 14 days before randomisation because of intolerance or disease progression. Eligible patients also had at least one measurable lesion as per the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) and adequate organ function. Patients were excluded if they had hepatic locoregional therapy after sorafenib, major surgery in the 28 days before randomisation, a history of or current hepatic encephalopathy, previous liver transplantation, oesophageal or gastric varices requiring endoscopic treatment, and uncontrolled arterial hypertension. We also excluded patients with clinically meaningful ascites (ie, worse than grade 1 on the US National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE; version 4.0]) resulting from cirrhosis. Patients who had been on a stable medical regimen (for ≥3 months) to manage ascites were eligible if no evidence of ascites that would require further intervention was apparent during clinical examination. A full list of inclusion and exclusion criteria is in the protocol (appendix pp 57–61).

REACH-2 complied with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable local regulations. Ethics committees at all participating centres approved the protocol, and all patients provided written informed consent. An independent data monitoring committee regularly assessed unblinded safety data at each safety interim analysis (appendix p 10).

Randomisation and masking

Investigators enrolled patients, who were subsequently randomly allocated (2:1) to treatment with ramucirumab or placebo via an interactive web-response system with a computer-generated random sequence. Randomisation was stratified by geographical region (region 1 [Americas, Europe, Australia, Israel] *vs* region 2 [Asia, excluding Japan] *vs* region 3 [Japan]), macrovascular invasion (yes *vs* no), and ECOG performance status (0 *vs* 1). Because the previous REACH trial showed a potential benefit of ramucirumab in patients with increased baseline α-fetoprotein concentrations who received first-line sorafenib, we used a 2:1 randomisation ratio to allocate a smaller percentage of patients to placebo. 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 for 1 h every 14 days until disease progression, unacceptable toxicity, or withdrawal of consent. All patients received best supportive care, as determined by the investigator, including use of concomitant drugs. Tumours were assessed by CT or MRI at baseline, every 6 weeks during the first 6 months of treatment, and every 9 weeks thereafter. All response assessments were done locally by investigators according to RECIST (version 1.1).[25]

Safety data were collected continuously. Local laboratory assessments were done at baseline, before each treatment cycle, and 30 days after treatment discontinuation, and were graded according to CTCAE (version 4.0). Dose modifications were permitted for non-life-threatening grade 3 clinical adverse events that were considered to be at least possibly related to study treatment. Treatment was generally discontinued for grade 4 clinical adverse events. Further details about permitted dose modifications are in the appendix (pp 72–76).

Adverse events and drug exposure were summarised. Adverse events were graded according to the CTCAE (version 4.0) and were judged by investigators to be related or unrelated to study treatment. Two safety interim analyses were done when approximately 50 and 150 patients had received three cycles of study treatment, died, or discontinued study treatment. Thereafter, safety reviews were done twice a year by the independent data monitoring committee. Patient-reported outcomes were assessed with the Functional Assessment of Cancer

Therapy Hepatobiliary Symptom Index 8 (FHSI-8) at baseline, then every 6 weeks, and at treatment discontinuation. The FHSI-8 is a self-administered questionnaire with specific focus on the most frequent and concerning symptoms that patients with hepatobiliary malignancies tend to have.[26] The eight symptoms assessed by the instrument are lack of energy, nausea, pain, weight loss, back pain, fatigue, jaundice, and stomach pain or discomfort. Compliance with FHSI-8 was estimated as the proportion of completed FHSI-8 assessments relative to expected assessments at baseline and every 6 weeks (appendix p 20). Physician-reported ECOG performance status was assessed each cycle.

Outcomes

The primary endpoint was overall survival, which was defined as time from randomisation to death from any cause. Secondary endpoints were investigator-assessed progression-free survival, which was defined as time from randomisation to radiographic progression or death, time from randomisation to radiographic progression, the proportion of patients who achieved an objective response, patient-reported disease-related symptoms (assessed with FHSI-8), time to deterioration of FHSI-8 score, time to deterioration in ECOG performance status, and safety. Time to deterioration of FHSI-8 score was the time from randomisation to the first clinically meaningful deterioration (≥3 points) in total FHSI-8 scores. Time to deterioration in performance status was defined as the time from randomisation to recording of a performance status of 2 or higher. Pharmacokinetic and immunogenicity results, and data for health-related quality of life will be reported separately.

Statistical analysis

Assuming a true HR of 0·67 and median overall survival of 4·5 months in the placebo group and 6·7 months in the ramucirumab group, the study was designed to have 80% statistical power to detect 221 events (deaths) in 279 patients at a one-sided significance level of 0·025. An interim analysis of efficacy that necessitated a large study population of 399 patients had been planned, but was removed after a protocol amendment (April 24, 2017) to consolidate to a single final overall survival analysis, at which the planned study size, power, and HR assumption were reduced to those detailed. This decrease in HR assumption remained sufficient to observe a treatment effect consistent with the results noted in REACH and enabled earlier completion of the study. The decision was made by the principal investigator, the members of the steering committee, and the study sponsor. The rationale for these amendments, including changes to sample size, is described in the protocol (appendix pp 127–28). Data cutoff for the REACH-2 analysis was March 15, 2018.

We assessed all efficacy outcomes in the intention-to-treat population. We applied a gatekeeping testing strategy in the order overall survival, progression-free survival, time to radiographic progression, time to deterioration of FHSI-8 scores, and time to deterioration of ECOG performance status. All main efficacy analyses were stratified by the randomisation stratification factors. We estimated survival curves and medians with 95% CIs by the Kaplan-Meier method, and HRs were estimated with a stratified Cox regression model. For the primary analysis, we compared overall survival between treatment groups with a stratified log-rank test. We used the same approach to assess progression-free survival and time to radiographic progression. We examined and tested the proportional hazards assumption in the Cox model using the Kolmogorov-type supremum test. The proportion of patients with objective responses is presented with a two-sided 95% CI and compared between groups with the exact Cochran-Mantel-Haenszel test. All safety analyses were done in the safety population, which was defined as all patients who received any quantity of ramucirumab or placebo.

We did pre-planned subgroup and sensitivity analyses. Subgroups defined before database lock were sex, age group (<65 years *vs* ≥65 years), race (Asian *vs* white *vs* other), geographical region (region 1 *vs* region 2 *vs* region 3), cause of hepatocellular carcinoma (hepatitis B virus *vs* hepatitis C virus *vs* other), presence of extrahepatic metastases (yes *vs* no), presence of macrovascular invasion (yes *vs* no), BCLC score (B *vs* C), baseline ECOG performance status (0 *vs* 1), previous locoregional therapy (yes *vs* no), and reason for discontinuation of sorafenib (progressive disease *vs* intolerance). For analyses within each subgroup, we used the Kaplan-Meier method for estimation of medians for all time-to-event endpoints, the unstratified log-rank test for comparisons of treatment effect, an unstratified Cox regression model for estimations of HRs, and Wald tests for subgroup-by-treatment interactions. Pre-planned sensitivity analyses for overall survival included a per-protocol population analysis, an unstratified analysis, a stratified analysis based on case report form strata, an analysis based on baseline α-fetoprotein concentrations as measured in a central laboratory (Covance Central Laboratories; Indianapolis, IN, USA), and analyses in which potential prognostic factors were adjusted for with multivariate Cox regression analyses.

We did additional post-hoc sensitivity analyses to address the specific effect of post-discontinuation therapy and potential baseline imbalances in α-fetoprotein concentrations on overall survival. HRs and p values for treatment effect were based on a stratified Cox model that included baseline α-fetoprotein (log_{10}-transformed) as a covariate. We did a post-hoc analysis of patients with baseline ascites to investigate incidence of adverse events.

Because both REACH[18] and REACH-2 were global trials of the same treatment regimen and had similar study eligibility and protocol procedures, we did a pooled individual patient data analysis before database

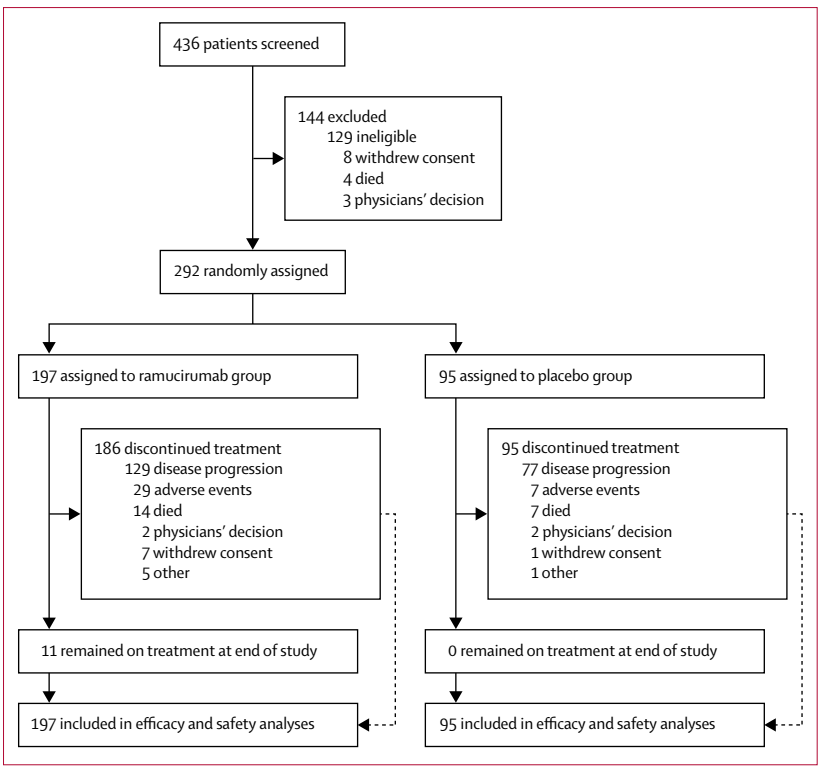


Figure 1: **Trial profile**
All randomly assigned patients received treatment.

lock and unblinding of REACH-2 to assess the pooled population of patients in each study with α-fetoprotein concentrations of 400 ng/mL or greater. Pooling of patient-level data provided a substantially larger patient population, which enabled more precise estimation of the treatment effect and greater statistical power for subgroup analyses. All pooled efficacy analyses were done at the level of individual patient data, stratified by study, and prespecified before REACH-2 database lock. Prespecified endpoints in the individual patient data analysis included overall survival, progression-free survival, objective response, time to radiographic progression, and time to deterioration of FHSI-8 scores and ECOG performance status. We used similar methods for the pooled analysis that we used for the other prespecified endpoints of REACH-2. Pooled safety analyses were also done at the level of individual patient data (and coded with the Medical Dictionary for Regulatory Activities [version 20.1]), and prespecified before REACH-2 database lock.

We assessed the heterogeneity of treatment effects between the two studies with a Cox regression model including a treatment-by-study interaction term, and with the Cochran's Q test and I^2 statistic. We further assessed the effect of potential heterogeneity between the two studies by a random-effects frailty model, in which we estimated the treatment effect after adjustment for the study as a random effect. We analysed all data using SAS (version 9.2 or higher). REACH-2 is registered with ClinicalTrials.gov, number NCT02435433.

Role of the funding source

The study funder had roles in study design of REACH and REACH-2, and was involved in data collection, analysis, and interpretation, and writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between July 26, 2015, and Aug 30, 2017, 436 patients were screened and 292 were enrolled and randomly assigned, 197 to the ramucirumab group and 95 to the placebo group (figure 1). Data cutoff for the REACH-2 analysis was March 15, 2018, by which time 281 patients were off treatment, and 11 patients in the ramucirumab group were still receiving therapy. 206 (71%) of 292 had disease progression, and 221 (76%) had died. Median duration of follow-up for overall survival was 7·6 months (IQR 4·0–12·5).

Median duration of previous sorafenib therapy was 4·1 months in both groups, and 50 (17%) patients discontinued sorafenib because of intolerance (table 1; appendix p 11). Time from disease progression while on sorafenib to randomisation was similar in the ramucirumab (1·2 months [IQR 0·7–2·6]; n=166) and placebo (1·1 months [0·7–2·0]; n=76) groups. Baseline characteristics were generally well balanced between groups (table 1). Baseline α-fetoprotein concentration was the only factor with a potential imbalance between groups (2741 ng/mL [IQR 1178–11861] in the placebo group *vs* 3920 ng/mL [1175–20000] in the ramucirumab group), which was probably due to chance. The distribution of baseline α-fetoprotein concentration in both groups is shown in the appendix (p 32).

Median overall survival was significantly improved in the ramucirumab group compared with the placebo group (8·5 months [95% CI 7·0–10·6] *vs* 7·3 months [5·4–9·1]; HR 0·710 [95% CI 0·531–0·949]; p=0·0199; figure 2). Kaplan-Meier plots of overall survival estimated improved outcomes with ramucirumab compared with placebo starting approximately in the third month of treatment, with differences between the two groups increasing with time (figure 2A). We noted no significant deviation from the proportional hazards assumption (p=0·306). The treatment effect for the overall survival sensitivity analyses was consistent with that for the primary overall analysis (appendix p 12). ECOG performance status, presence of macrovascular invasion, and baseline α-fetoprotein were significantly prognostic for overall survival in multivariate Cox analyses (data not shown).

Most subgroup analysed for overall survival showed a benefit with ramucirumab compared with placebo (figure 2B). Post-discontinuation systemic therapies for

	Ramucirumab group (n=197)	Placebo group (n=95)
Median age (IQR), years	64 (58–73)	64 (56–71)
Sex		
Female	43 (22%)	16 (17%)
Male	154 (78%)	79 (83%)
Race (self-reported)		
Asian	102 (52%)	45 (47%)
White	60 (30%)	31 (33%)
Other	1 (1%)	2 (2%)
Missing*	34 (17%)	17 (18%)
ECOG performance status		
0	113 (57%)	55 (58%)
1	84 (43%)	40 (42%)
Geographical region		
Region 1 (Americas, Europe, Australia, Israel)	101 (51%)	50 (53%)
Region 2 (Asia, excluding Japan)	55 (28%)	27 (28%)
Region 3 (Japan)	41 (21%)	18 (19%)
Child-Pugh score		
A (5 points)	123 (62%)	54 (57%)
A (6 points)	74 (38%)	41 (43%)
Barcelona Clinic Liver Cancer stage		
Stage C	163 (83%)	75 (79%)
Stage B	34 (17%)	20 (21%)
Median α-fetoprotein (IQR), ng/mL	3920 (1175–20 000)	2741 (1178 –11 681)
Macrovascular invasion present	70 (36%)	33 (35%)
Extrahepatic spread present	141 (72%)	70 (74%)
Median duration of disease† (IQR), months	20·1 (9·8–38·2)	17·6 (8·4–36·9)
Cause of hepatocellular carcinoma‡		
Hepatitis B virus	71 (36%)	36 (38%)
Hepatitis C virus	48 (24%)	28 (29%)
Substantial alcohol use	48 (24%)	21 (22%)
Steatohepatitis (non-alcoholic steatohepatitis, fatty liver)	19 (10%)	4 (4%)
Cryptogenic cirrhosis	12 (6%)	4 (4%)
Primary biliary cirrhosis	2 (1%)	2 (2%)
Hepatitis non-A, non-B, non-C virus	2 (1%)	1 (1%)
Hepatitis A virus	0	1 (1%)
Haemachromatosis	1 (1%)	0
Other§	12 (6%)	3 (3%)
(Continued from previous column)		
Initial pathological diagnostic method		
Histopathology	100 (51%)	55 (58%)
Cytology	2 (1%)	0
Imaging	95 (48%)	40 (42%)
Duration of previous sorafenib therapy¶		
<5 months	110 (56%)	57 (60%)
≥5 months	87 (44%)	38 (40%)
Median (IQR), months	4·1 (2·3–8·4)	4·1 (2·8–7·2)
Reason for discontinuation of sorafenib		
Progressive disease	166 (84%)	76 (80%)
Intolerance	31 (16%)	19 (20%)
Time from last sorafenib treatment to randomisation		
<1 month	102 (52%)	54 (57%)
≥1 month	95 (48%)	41 (43%)
Previous therapy||		
Surgery	87 (44%)	39 (41%)
Radiotherapy	36 (18%)	19 (20%)
Ascites		
None	185 (94%)	88 (93%)
Mild	12 (6%)	7 (7%)

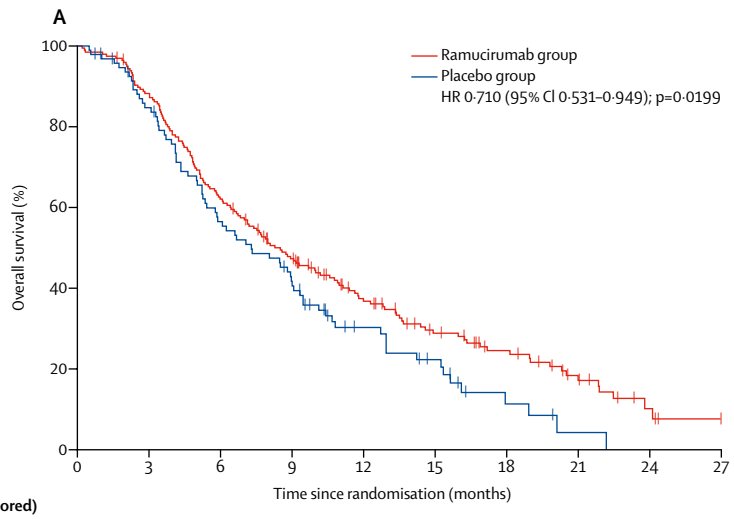
Data are n (%), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. *Race not recorded in France because of local regulations. †Time from initial diagnosis randomisation. ‡Causes were diagnosed before study entry; patients could have more than one cause of disease. §Cause was unknown in 11 of 15 patients. ¶A 5-month cutoff was also used in REACH,[18] and was the approximate median duration of sorafenib use in SHARP.[7] ||A detailed summary of previous therapies is in the appendix; all patients had received previous sorafenib. ||Defined by Child-Pugh assessment; no ascites of grade 2 or higher (per the Common Terminology Criteria for Adverse Events) were reported.

Table 1: **Demographic and baseline characteristics**

REACH-2 were generally balanced between groups (appendix p 13). Although there were some differences in the use of individual drugs, sensitivity analyses showed that the difference in overall survival was still significant between groups, after censoring for post-discontinuation systemic therapies (appendix p 14).

In view of the potential imbalance in baseline α-fetoprotein concentrations that could have favoured longer-than-expected survival in the control group, we did additional post-hoc analyses. A Cox regression analysis showed that α-fetoprotein remained a strong negative prognostic factor for overall survival, even beyond the α-fetoprotein threshold of 400 ng/mL (appendix p 14). In an analysis adjusted for baseline α-fetoprotein concentration, median overall survival was significantly longer in the ramucirumab group than the placebo group (appendix p 33).

Median progression-free survival was significantly longer in the ramucirumab group than the placebo group (2·8 months [95% CI 2·8–4·1] *vs* 1·6 months [1·5–2·7]; HR 0·452 [95% CI 0·339–0·603]; p<0·0001; figure 3A), with no deviation from the proportional hazards assumption (p=0·218). All subgroup analyses favoured treatment with ramucirumab, except for that in female patients, which included only 16 patients in the placebo group (figure 3B). Median time to radiographic progression was 3·0 months (95% CI 2·8–4·2) in the ramucirumab group and 1·6 months (1·5–2·7) in the



B

	Ramucirumab group (n/N)	Placebo group (n/N)	HR (95% CI)
Sex			
Male	115/154	63/79	0·696 (0·509–0·952)
Female	32/43	11/16	1·206 (0·591–2·459)
Age group (years)			
<65	78/102	36/49	0·848 (0·568–1·267)
≥65	69/95	38/46	0·641 (0·429–0·957)
Race			
Asian	79/102	34/45	0·754 (0·502–1·132)
White	43/60	25/31	0·855 (0·520–1·406)
Other	25/35	15/19	0·602 (0·312–1·164)
Geographical region			
Region 1	72/101	40/50	0·749 (0·506–1·108)
Region 2	41/55	21/27	0·834 (0·491–1·416)
Region 3	34/41	13/18	0·650 (0·338–1·250)
Cause of liver disease			
Hepatitis B virus	52/71	26/36	0·838 (0·522–1·347)
Hepatitis C virus	33/43	20/24	0·762 (0·435–1·334)
Other	55/74	21/24	0·633 (0·379–1·057)
Presence of extra-hepatic metastases			
Yes	108/141	55/70	0·702 (0·505–0·976)
No	39/56	19/25	0·844 (0·483–1·475)
Presence of macrovascular invasion			
Yes	59/70	27/33	0·971 (0·614–1·534)
No	88/127	47/62	0·604 (0·420–0·871)
BCLC score			
B	23/34	15/20	0·690 (0·353–1·346)
C	124/163	59/75	0·745 (0·545–1·019)
Baseline ECOG performance status			
1	64/84	33/40	0·768 (0·501–1·177)
0	83/113	41/55	0·711 (0·486–1·041)
Previous locoregional therapy			
Yes	98/127	44/59	0·823 (0·573–1·183)
No	49/70	30/36	0·648 (0·411–1·023)
Reason for discontinuation of sorafenib			
Progressive disease	125/166	60/76	0·763 (0·559–1·041)
Intolerance	22/31	14/19	0·633 (0·318–1·260)
Overall	**147/197**	**74/95**	**0·744 (0·561–0·988)**

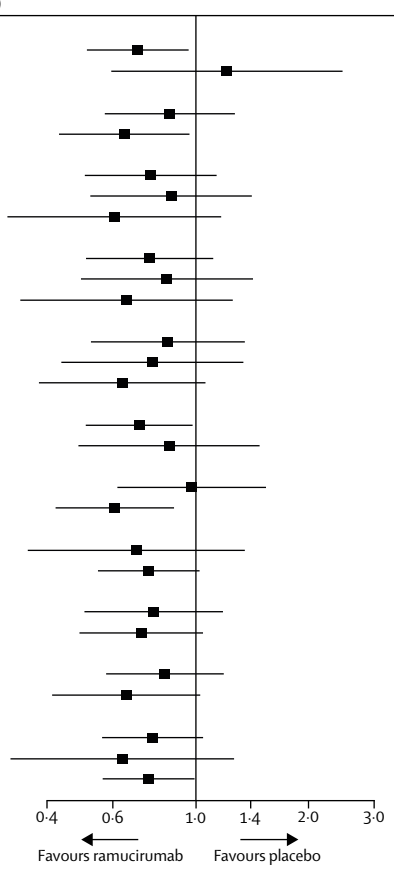


Figure 2: **Overall survival**
Kaplan-Meier curves (A) and subgroup analyses (B) per treatment group in the intention-to-treat population. The two-sided p value in (A) was log-rank stratified by geographical region, macrovascular invasion, and ECOG performance status at baseline. Region 1 includes the Americas, Europe, Israel, and Australia, region 2 includes Asia (excluding Japan), and region 3 is Japan. HR=hazard ratio. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group.

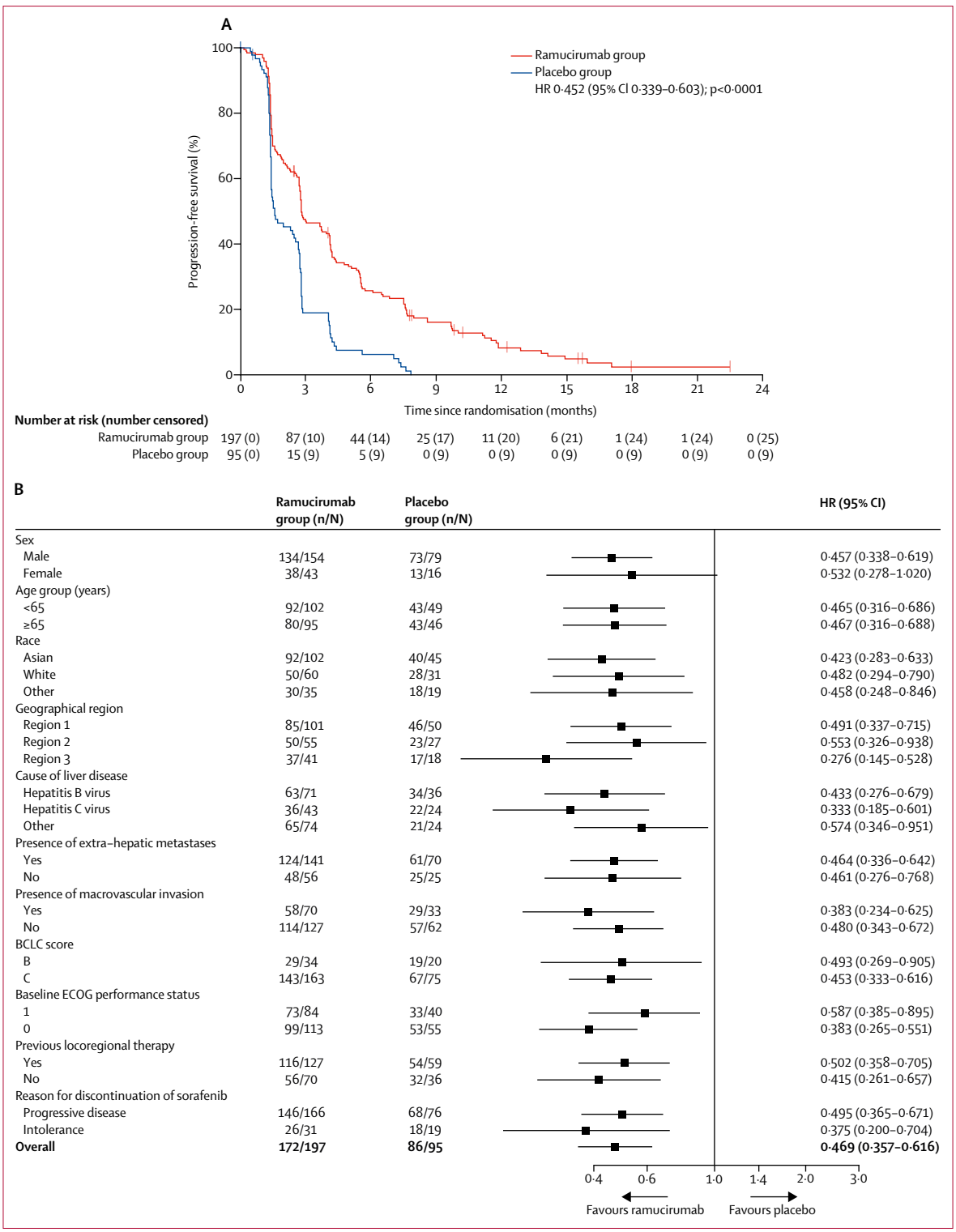


Figure 3: **Progression-free survival**
Kaplan-Meier curves (A) and subgroup analyses (B) per treatment group in the intention-to-treat population. The HR in (A) was stratified by geographical region, macrovascular invasion, and ECOG performance status at baseline, and the two-sided p value was log-rank stratified for comparison with placebo. Region 1 includes the Americas, Europe, Israel, and Australia, region 2 includes Asia (excluding Japan), and region 3 is Japan. HR=hazard ratio. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group.

	Ramucirumab group (any cause; n=197)				Placebo group (any cause; n=95)				Ramucirumab group (treatment-related; n=197)				Placebo group (treatment-related; n=95)			
	Grades 1–2	Grade 3	Grade 4*	Grade 5*	Grades 1–2	Grade 3	Grade 4*	Grade 5*	Grades 1–2	Grade 3	Grade 4*	Grade 5*	Grades 1–2	Grade 3	Grade 4*	Grade 5*
Treatment-emergent adverse events in ≥10% patients (either group)																
Fatigue	47 (24%)	7 (4%)	NA	NA	13 (14%)	3 (3%)	NA	NA	26 (13%)	2 (1%)	NA	NA	5 (5%)	0	NA	NA
Peripheral oedema	47 (24%)	3 (2%)	0	0	13 (14%)	0	0	0	13 (7%)	2 (1%)	0	0	5 (5%)	0	0	0
Decreased appetite	43 (22%)	3 (2%)	0	0	18 (19%)	1 (1%)	0	0	21 (11%)	0	0	0	4 (4%)	0	0	0
Abdominal pain	36 (18%)	3 (2%)	NA	NA	10 (11%)	2 (2%)	NA	NA	6 (3%)	1 (1%)	NA	NA	3 (3%)	0	NA	NA
Nausea	37 (19%)	0	NA	NA	11 (12%)	0	NA	NA	23 (12%)	0	NA	NA	2 (2%)	0	NA	NA
Diarrhoea	32 (16%)	0	0	0	13 (14%)	1 (1%)	0	0	13 (7%)	0	0	0	4 (4%)	1 (1%)	0	0
Headache	28 (14%)	0	NA	NA	4 (4%)	1 (1%)	NA	NA	9 (5%)	0	NA	NA	0	0	NA	NA
Constipation	26 (13%)	1 (1%)	0	0	18 (19%)	1 (1%)	0	0	2 (1%)	1 (1%)	0	0	3 (3%)	0	0	0
Insomnia	21 (11%)	0	NA	NA	5 (5%)	1 (1%)	NA	NA	1 (1%)	0	NA	NA	0	0	NA	NA
Pyrexia	20 (10%)	0	0	0	3 (3%)	0	0	0	2 (1%)	0	0	0	1 (1%)	0	0	0
Vomiting	20 (10%)	0	0	0	7 (7%)	0	0	0	5 (3%)	0	0	0	1 (1%)	0	0	0
Treatment-emergent adverse events of special interest																
Bleeding or haemorrhage events	38 (19%)	9 (5%)	1 (1%)	0	9 (9%)	2 (2%)	1 (1%)	0	20 (10%)	1 (1%)	0	0	4 (4%)	0	1 (1%)	0
Epistaxis†	26 (13%)	1 (1%)	0	0	3 (3%)	0	0	0	14 (7%)	0	0	0	2 (2%)	0	0	0
Gastrointestinal haemorrhage events	5 (3%)	7 (4%)	0	0	3 (3%)	2 (2%)	0	0	0	1 (1%)	0	0	0	0	0	0
Hepatic haemorrhage events	0	0	1 (1%)	0	0	0	0	0	0	0	0	0	0	0	0	0
Pulmonary haemorrhage events	3 (2%)	1 (1%)	0	0	1 (1%)	0	0	0	0	0	0	0	0	0	0	0
Hypertension	24 (12%)	25 (13%)	0	0	7 (7%)	5 (5%)	0	0	17 (9%)	15 (8%)	0	0	4 (4%)	2 (2%)	0	0
Proteinuria	36 (18%)	4 (2%)	0	0	4 (4%)	0	0	0	23 (12%)	4 (2%)	0	0	3 (3%)	0	0	0
Arterial thromboembolic events	2 (1%)	0	1 (1%)	2 (1%)	0	0	0	1 (1%)	2 (1%)	0	1 (1%)	1 (1%)	0	0	0	0
Venous thromboembolic events	2 (1%)	0	0	0	1 (1%)	1 (1%)	0	0	1 (1%)	0	0	0	1 (1%)	0	0	0
Gastrointestinal perforation	0	2 (1%)	0	0	0	2 (2%)	0	0	0	1 (1%)	0	0	0	0	0	0
Congestive heart failure	0	0	0	1 (1%)	0	1 (1%)	0	0	0	0	0	0	0	0	0	0
Fistula	1 (1%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Liver injury or failure	42 (21%)	28 (14%)	4 (2%)	4 (2%)	13 (14%)	14 (15%)	1 (1%)	0	11 (6%)	3 (2%)	0	3 (2%)	2 (2%)	0	0	0
Ascites†	27 (14%)	7 (4%)	0	1 (1%)	5 (5%)	2 (2%)	0	0	3 (2%)	1 (1%)	0	0	1 (1%)	0	0	0
Hepatic encephalopathy†	2 (1%)	5 (3%)	1 (1%)	0	0	0	0	0	1 (1%)	1 (1%)	0	0	0	0	0	0
Infusion-related reactions ‡	17 (9%)	0	0	0	3 (3%)	0	0	0	13 (7%)	0	0	0	2 (2%)	0	0	0

Data are n (%). The table shows treatment-emergent adverse events occurring in at least 10% of patients at grades 1–2 or of special interest at any grade, according to either preferred terms defined by the Medical Dictionary for Regulatory Activities (version 20·1) or consolidated categories.A table showing treatment-emergent adverse events occurring at grades 1–2 in at least 10% of patients in either treatment group, or at grades 3–5 in one or more patients in either treatment group, is in the appendix (pp 17–19). There were 16 grade 5 treatment-emergent adverse events in the ramucirumab group (two cases of pneumonia, and one each of ascites, splenic infarction, acute myocardial failure, myocardial infarction, generalised oedema, multiple organ dysfunction syndrome, hepatorenal syndrome, acute hepatic failure, sepsis, ruptured liver carcinoma, tumour rupture, cerebral ischaemia, acute kidney injury, and renal failure). Four grade 5 treatment-emergent adverse events were recorded in the placebo group (one case each of myocardial infarction, pneumonia, respiratory tract infection, and lung disorder). NA=not applicable. *Fields marked NA are those for which the Common Terminology Criteria for Adverse Events do not define the grade and no events were reported. †Preferred term. ‡Occurring within 24 h of infusion.

Table 2: **Treatment-emergent adverse events**

placebo group (HR 0·427 [95% CI 0·313–0·582]; p<0·0001). The proportion of patients with an objective response did not differ between groups (nine [5%] *vs* one [1%]; p=0·1697; appendix p 15). The proportion of patients with disease control (ie, an objective response or stable disease) was significantly higher in the ramucirumab group than in the placebo group (118 [59·9%; 95% CI 53·1–66·7] of 197 *vs* 37 [38·9%; 95% CI 29·1–48·8] of 95; p=0·0006; appendix p 15).

Median duration of therapy was 12 weeks (IQR 6–28) in the ramucirumab group and 8 weeks (6–13) in the placebo group, and the median relative dose intensity was 98% or higher in both groups (appendix p 16). Treatment discontinuation because of any adverse events (35 [18%] of 197 *vs* 10 [11%] of 95) or because of treatment-related adverse events (21 [11%] *vs* three [3%]) occurred more often in the ramucirumab group than in the placebo group (appendix p 16). Dose reductions (nine [5%] *vs* two [2%]), delays (12 [6%] *vs* three [3%]), and omissions (57 [29%] *vs* ten [11%]) because of adverse events of any causality were more common in the ramucirumab group than in the placebo group. Supportive care included use of concomitant drugs for 195 (99%) patients in the ramucirumab group and 91 (96%) patients in the placebo group. The proportion of patients receiving best supportive care and specific types of best supportive care seemed similar across treatment groups (data not shown).

The most frequently reported treatment-emergent adverse events of any grade in the ramucirumab group were fatigue (54 [27%]), peripheral oedema (50 [25%]), hypertension (49 [25%]) and decreased appetite (46 [23%]), most of which were grade 1–2 (table 2). Hypertension and hyponatraemia were the only grade 3 or worse treatment-emergent adverse events that were noted in 5% or more of patients and at higher frequencies in the ramucirumab group than in the placebo group, whereas increased aspartate aminotransferase concentrations were noted in five [5%] patients in the placebo group and six [3%] in the ramucirumab group (table 2; appendix pp 17–19).

Serious adverse events of any grade and cause were recorded in 68 (35%) participants in the ramucirumab group and 28 (29%) in the placebo group, whereas treatment-related adverse events of any grade were recorded in 21 (11%) and five (5%) patients, respectively. Treatment-related serious adverse events that occurred in the ramucirumab group but not in the placebo group were dyspnoea and hepatic encephalopathy, both of which occurred in two (1%) patients. Treatment-related serious adverse events in the placebo group were deep-vein thrombosis, haemorrhage, infusion-related reaction, ruptured liver carcinoma, appendicitis, and septic shock, all of which occurred in one (1%) patient (appendicitis and septic shock occurred in the same patient).

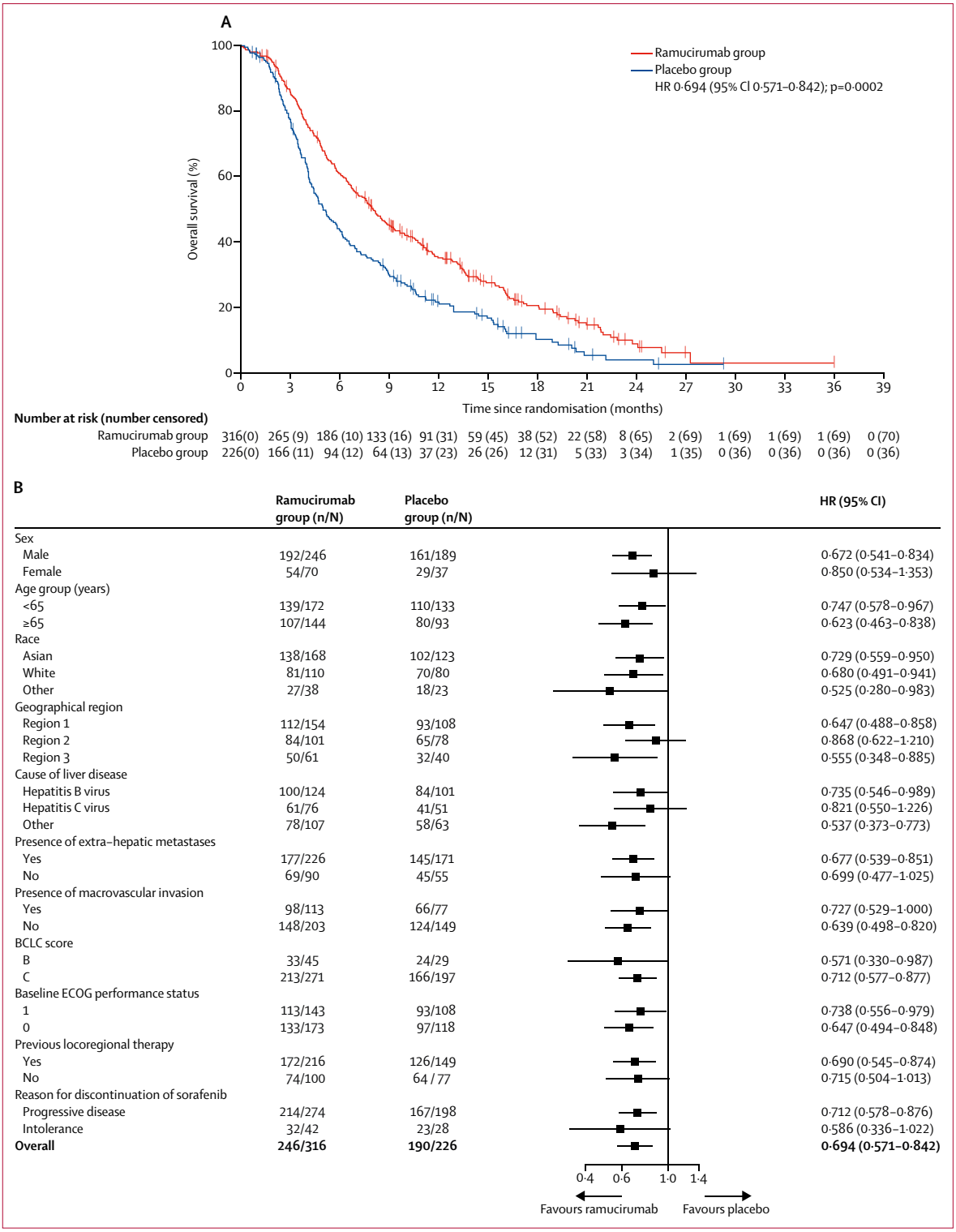
Common adverse events of special interest (as prespecified by protocol [appendix pp 84–88]) of any grade that were more frequent in the ramucirumab group than in the placebo group were hypertension, liver injury or failure, proteinuria, infusion-related reactions, and bleeding or haemorrhage (table 2). The frequency of other any-grade and high-grade adverse events of special interest was similar between the two groups (table 2). No meaningful difference between treatment groups was noted in the incidence of adverse events of special interest by cycle (data not shown). A post-hoc analysis of the 19 patients with baseline ascites showed no increased risk of clinically important adverse events of special interest, including events related to underlying liver disease (data not shown).

Deaths for any reason, either on therapy or within 30 days of treatment discontinuation occurred in 39 (20%) patients in the ramucirumab group and 16 (17%) in the placebo group. Six (3%) patients in the ramucirumab group (one each from acute kidney injury, generalised oedema, hepatorenal syndrome, myocardial infarction, pneumonia, and renal failure) and three (3%) in the placebo group (one each from lung disorder, myocardial infarction, and respiratory tract infection) died on treatment because of adverse events. Three deaths in the ramucirumab group were judged to be related to study treatment: one each from acute kidney injury, hepatorenal syndrome, and renal failure.

Compliance with the FHSI-8 was 99% or higher at baseline and 67% or higher at the end of treatment and was balanced between groups (appendix p 20). Median time to deterioration of FHSI-8 scores (3·7 months [95% CI 2·8–4·4] *vs* 2·8 months [1·6–2·9]; HR 0·799 [95% CI 0·545–1·171]; p=0·238) and ECOG performance statuses (HR 1·082 [95% CI 0·639–1·832]; p=0·77) did not differ between the ramucirumab and placebo groups. However, the number of events was insufficient for meaningful statistical assessment of deterioration in ECOG performance status.

We pooled individual patient data from REACH[18] and REACH-2. The combined population comprised 542 patients with baseline α-fetoprotein concentrations of at least 400 ng/mL, 316 of whom were randomly assigned to ramucirumab and 226 of whom were randomly assigned to placebo. Baseline characteristics of patients included in the pooled analysis from both trials were broadly similar (appendix pp 21–24). However, median baseline α-fetoprotein concentrations, the proportion of patients with BCLC stage C disease, and the proportion of patients with disease caused by hepatitis B virus were lower in REACH-2 than in REACH (appendix pp 23–24).[18]

Previous therapies and baseline characteristics were balanced between the two groups in the pooled analysis (ramucirumab *vs* placebo), including median α-fetoprotein (appendix pp 21–24, 26–27). In the pooled analysis of efficacy, median overall survival was significantly improved in the ramucirumab group than the placebo group (8·1 months [95% CI 6·9–9·3] *vs*



	Ramucirumab group (n/N)	Placebo group (n/N)	HR (95% CI)
Sex			
Male	192/246	161/189	0·672 (0·541–0·834)
Female	54/70	29/37	0·850 (0·534–1·353)
Age group (years)			
<65	139/172	110/133	0·747 (0·578–0·967)
≥65	107/144	80/93	0·623 (0·463–0·838)
Race			
Asian	138/168	102/123	0·729 (0·559–0·950)
White	81/110	70/80	0·680 (0·491–0·941)
Other	27/38	18/23	0·525 (0·280–0·983)
Geographical region			
Region 1	112/154	93/108	0·647 (0·488–0·858)
Region 2	84/101	65/78	0·868 (0·622–1·210)
Region 3	50/61	32/40	0·555 (0·348–0·885)
Cause of liver disease			
Hepatitis B virus	100/124	84/101	0·735 (0·546–0·989)
Hepatitis C virus	61/76	41/51	0·821 (0·550–1·226)
Other	78/107	58/63	0·537 (0·373–0·773)
Presence of extra-hepatic metastases			
Yes	177/226	145/171	0·677 (0·539–0·851)
No	69/90	45/55	0·699 (0·477–1·025)
Presence of macrovascular invasion			
Yes	98/113	66/77	0·727 (0·529–1·000)
No	148/203	124/149	0·639 (0·498–0·820)
BCLC score			
B	33/45	24/29	0·571 (0·330–0·987)
C	213/271	166/197	0·712 (0·577–0·877)
Baseline ECOG performance status			
1	113/143	93/108	0·738 (0·556–0·979)
0	133/173	97/118	0·647 (0·494–0·848)
Previous locoregional therapy			
Yes	172/216	126/149	0·690 (0·545–0·874)
No	74/100	64 / 77	0·715 (0·504–1·013)
Reason for discontinuation of sorafenib			
Progressive disease	214/274	167/198	0·712 (0·578–0·876)
Intolerance	32/42	23/28	0·586 (0·336–1·022)
Overall	**246/316**	**190/226**	**0·694 (0·571–0·842)**

Figure 4: **Pooled analysis of overall survival in the REACH-2 and REACH trials**
Kaplan-Meier curves (A) and subgroup analyses (B) by treatment group in the pooled intention-to treat populations. The pooled population includes all patients from REACH-2, as well all patients from REACH who had baseline α-fetoprotein concentrations of 400 ng/mL. The two-sided p value was log-rank stratified by geographical region, macrovascular invasion, and ECOG performance status at baseline. Region 1 includes the Americas, Europe, Israel, and Australia, region 2 includes Asia (excluding Japan), and region 3 is Japan. HR=hazard ratio. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group.

5·0 [4·3–6·1]; HR 0·694 [95% CI 0·571–0·842; p=0·0002; figure 4). This finding was consistent with the individual HRs for overall survival in patients in both studies who had α-fetoprotein concentrations of 400 ng/mL or higher (appendix p 34). Findings for progression-free survival and the proportions of patients with objective responses or disease control in the pooled analysis were consistent with those in each study (appendix pp 28–30).

We did formal analyses to assess potential population and treatment heterogeneity between the two trials in baseline characteristics, such as the differences in baseline α-fetoprotein concentrations, BCLC stage, and cause of hepatocellular carcinoma, as noted previously (appendix pp 30, 34). There was no evidence of heterogeneity in treatment effect between the two studies (Cochran's Q test p=0·50). In the random-effect model in which study was adjusted for as a random effect, patients in the ramucirumab group had a decreased hazard of death compared with those in the placebo group (HR 0·689 [95% CI 0·568–0.835]; p=0·0002).

Median duration of therapy and relative dose intensity were similar in the pooled population and in REACH-2 (appendix p 16). Common treatment-emergent adverse events of any cause, serious adverse events, and treatment-emergent adverse events of special interest occurred at similar incidence and severity in the pooled analysis and in REACH-2 (table 2; appendix pp 17, 31). Hypertension (40 [13%] of 316 *vs* eight [4%] of 223) and hyponatraemia (16 [5%] *vs* 5 [2%]) were the most common grade 3 or worse treatment-emergent adverse events that occurred in 5% or more of patients and at a higher frequency in the ramucirumab group than in the placebo group (appendix p 31).

Discussion

The randomised, double-blind phase 3 REACH-2 trial met its primary endpoint of improved overall survival with ramucirumab compared with placebo in patients with advanced hepatocellular carcinoma and baseline α-fetoprotein concentrations of at least 400 ng/mL who had previously been treated with sorafenib. To our knowledge, REACH-2 is the first positive phase 3 study in a biomarker-selected population of patients with hepatocellular carcinoma. Treatment with ramucirumab conferred an increase in overall survival of 1·2 months with median follow-up of 7·6 months (4·0–12·5). The HR for overall survival in REACH-2 (and the HR of 0·694 [95% CI 0·571–0·842] in the pooled analysis of REACH-2 and REACH) was similar to the HRs for overall survival reported in other phase 3 trials in patients with hepatocellular carcinoma, including trials of cabozantinib (HR 0·76 [95% CI 0·63–0·92]) and regorafenib (HR 0·63 [0·50–0·79]) versus placebo, although these studies were done in different patient populations.[10,11] There was also a significant difference in the secondary endpoints of progression-free survival, time to progression, the proportion of patients with disease control, and time to deterioration in FHSI-8 scores in REACH-2. We used conventional RECIST in REACH-2 to maintain consistency with REACH, and we noted that the results for progression-free survival and radiographic response were similar in both trials.[18]

Our FHSI-8 results are especially noteworthy because similar findings were also reported in REACH,[27] and, to our knowledge, improvements in patient-reported symptoms have not been reported with any other systemic second-line therapies in hepatocellular carcinoma. Assessment of cancer-related symptoms and physical functioning in RESORCE[10] showed that scores on the Functional Assessment of Cancer Therapy—Hepatobiliary instrument were significantly worse with regorafenib than with placebo. Additional analyses are underway to assess the treatment effect of ramucirumab on time to deterioration of individual symptoms in the FHSI-8.

Before REACH-2, attempts to select patients with hepatocellular carcinoma, who would derive an overall survival benefit, on the basis of a biomarker have been unsuccessful.[12,28,29] By contrast with other biomarker-driven studies, a large clinical dataset from which to generate the REACH-2 hypothesis was available from REACH. Translational work before and since completion of REACH has suggested that tumours expressing α-fetoprotein could be indicative of a biologically distinct subtype of hepatocellular carcinoma associated with poor prognosis, more stem-cell-like features (such as Ep-CAM expression), increased VEGF pathway activity, and increased activity of VEGFR2-targeted antibodies in preclinical models.[21–23,30]

Although α-fetoprotein has been used as a prognostic factor for hepatocellular carcinoma for decades, and is included in prognostic scoring scales,[2,3,15] its role and biological function in the disease is still not clearly understood. Concentrations higher than 400 ng/mL have been associated with poor outcomes and aggressive tumour features, but this threshold does not have a clearly identified biological significance.[31,32] Fluctuating α-fetoprotein concentrations associated with inflammatory activity in patients with cirrhosis only are less likely to exceed concentrations of 400 ng/mL compared with patients with hepatocellular carcinoma with or without cirrhosis.[33]

Although the HR for overall survival in REACH-2 was consistent with that in REACH and the pooled analysis of the two trials, the median overall survival in the placebo group of REACH-2 of 7·3 months (95% CI 5·4–9·1) was notably long in a population with poor prognosis (ie, α-fetoprotein ≥400 ng/mL). In previous second-line trials[18,34] in patients with increased α-fetoprotein who had received sorafenib, median overall survival in the placebo group was roughly 4–6 months. REACH-2 had a small placebo group (n=95), which might have introduced variability. We assessed other factors that could have contributed to the

longer-than-expected median overall survival in the placebo group. Post-discontinuation therapy use was relatively balanced between the groups, and analyses censoring for the use of post-discontinuation therapy showed little effect on overall survival. There was no clear bias towards more indolent disease in REACH-2: median time between previous therapy and study entry was similar to that in other trials.[10] Although unknown imbalances in other prognostic factors could have existed between groups, such as a difference in patterns of progression during previous sorafenib therapy,[35] the prognostic effect of the apparent chance imbalance in baseline α-fetoprotein concentrations was identified to be the largest single factor contributing to the observation of longer-than-expected overall survival in the placebo group in our data. Post-hoc analyses of REACH-2 showed the association between α-fetoprotein concentrations and prognosis even beyond the threshold of 400 ng/mL, supporting the hypothesis that the lower baseline α-fetoprotein concentrations in the placebo group could have resulted in improved overall survival compared with the ramucirumab group. Once we considered the effect of α-fetoprotein concentrations on prognosis in adjusted analyses, the median overall survival in the placebo group of REACH-2 (6·7 months [95% CI 3·9–12·8]) was more consistent with that in placebo groups in previous trials.[10,18] Similarly, in the pooled analysis of REACH-2 and REACH, in which baseline α-fetoprotein concentrations were balanced between the two treatment groups, median overall survival was 5·0 months (95% CI 4·3–6·1) in the placebo group.

In view of these results, although other unknown imbalances could potentially have affected the result, the prognostic effect of baseline α-fetoprotein concentrations should be a consideration in future trial designs. The results of REACH-2 and REACH clearly show that further work is needed to better understand the relationships between α-fetoprotein concentrations, prognosis, and treatment efficacy.

In REACH-2, the only grade 3 or worse treatment-emergent adverse events that occurred in at least 5% of patients in the ramucirumab group were hypertension and hyponatraemia, which was also noted in the pooled population. Across the two phase 3 trials, ramucirumab was well tolerated, and had a safety profile consistent with the established safety profile for single-agent ramucirumab and the disease state of hepatocellular carcinoma.[18,20] The median treatment duration of ramucirumab was consistent with the median progression-free survival in the ramucirumab group, which suggests that ramucirumab was well tolerated. Additionally, in two phase 3 trials in patients with hepatocellular carcinoma,[27] there was a non-significant delay in deterioration of patient-reported symptoms in patients receiving second-line ramucirumab. Oral multi-kinase inhibitors that have shown improvements in overall survival (the first-line therapies sorafenib and lenvatinib and the second-line regorafenib and cabozantinib) in hepatocellular carcinoma are associated with clinically important toxicities that commonly necessitate dose reductions, delays, or discontinuations.[7–11,36,37] In RESORCE,[10] in which regorafenib was assessed as a second-line therapy in patients with hepatocellular carcinoma, patients who discontinued previous sorafenib because of intolerance—ie, those who were unable to receive 400 mg or more of sorafenib daily for at least 20 of the last 28 days of treatment—were excluded.[10] The results of REACH-2 help to address the unmet treatment needs of patients with hepatocellular carcinoma who discontinued sorafenib because of either disease progression or intolerance.

The population enrolled in REACH-2 was consistent with those enrolled in other trials of second-line treatments for hepatocellular carcinoma, and included patients from several geographical regions who represented all the major causes of hepatocellular carcinoma. REACH-2 also included some patients who were excluded from other trials in patients with hepatocellular carcinoma, including those who were intolerant to sorafenib,[10] or those who had major vessel macrovascular invasion (who were excluded from REFLECT).[9]

REACH-2 has several potential limitations related to the population of patients enrolled. Patients with severe liver cirrhosis (Child-Pugh Class B or worse) were excluded in line with guidelines[31,38] for trial exclusion because concurrent liver cirrhosis is associated with high mortality independent of cancer and patient intolerance to any significant treatment-related toxicity. Patients with baseline α-fetoprotein concentrations of less than 400 ng/mL were also excluded because of the results of REACH, and thus no further data are available for ramucirumab in this patient population. A further limitation was that REACH-2 did not include patients who received first-line systemic therapy other than sorafenib, which was the only treatment associated with an overall survival benefit when the trial was designed. However, in recognition of the fact that the therapeutic landscape is changing, an expansion cohort has been initiated to study ramucirumab in patients with hepatocellular carcinoma and baseline α-fetoprotein concentrations of at least 400 ng/mL who received first-line treatments other than sorafenib. Analysis of this expansion cohort will be detailed in a future report.

The efficacy and safety results of the pivotal REACH-2 study show that ramucirumab could be a well-tolerated second-line treatment for patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations. To our knowledge, REACH-2 is the first successful phase 3 study in a biomarker-selected patient population with advanced hepatocellular carcinoma. The safety profile also makes ramucirumab a good potential candidate for assessment in combination with other agents, including immune checkpoint inhibitors, and in previous lines of therapy.

Contributors
AXZ, RSF, PRG, and JML contributed to study design, data analysis, data interpretation, and writing of the report. Y-KK, C-JY, MP, K-MR, IO, DBS, GG, CB, TO, and MM contributed to data collection and data interpretation. EA, GB, HYL, KM, PM, BD, and J-BH contributed to data collection, data interpretation, and writing of the report. YH contributed to data analysis, data interpretation, writing of the report, and creation of the figures. PBA contributed to the literature search, study design, data analysis, data interpretation, and writing of the report. MK contributed to study design, data collection, and data interpretation. All authors reviewed and approved the submitted Article.

Declaration of interests
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Data-sharing statement
Eli Lilly provides access, after anonymisation, to all individual participant data collected during the trial, except for pharmacokinetic and genetic data. Data can be requested 6 months after the indication studied has been approved in the USA and EU or after primary publication acceptance, whichever is later. No expiration date for data requests is set once the 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, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal. Further details about submitting a data request are available online.

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