Effect of ramucirumab on ALBI grade in patients with advanced HCC: Results from REACH and REACH-2

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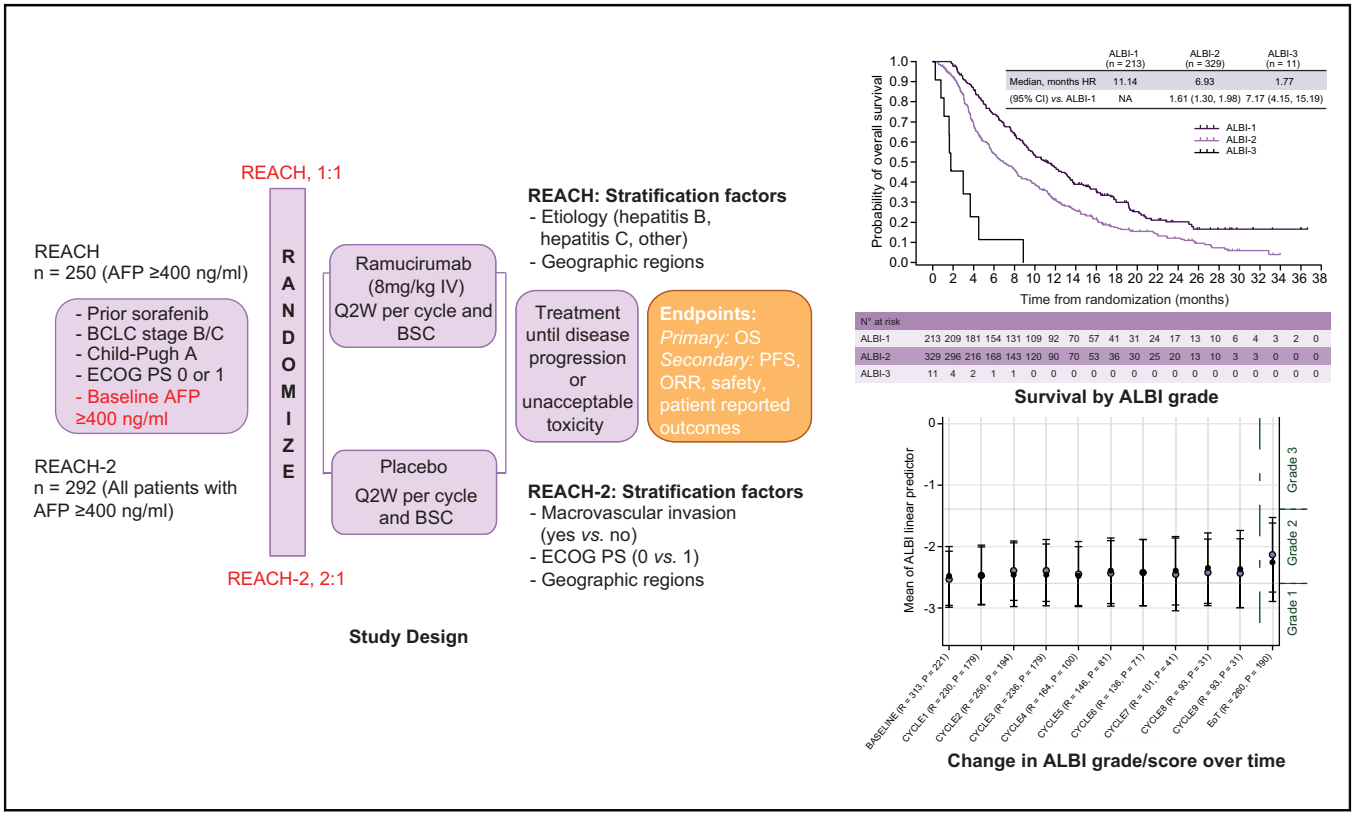
Graphical abstract



Highlights

- In patients with HCC, the severity of coexisting liver dysfunction is usually categorised using the Child-Pugh system.
- We demonstrate that the simpler albumin–bilirubin (ALBI) nomogram can be used for pre-treatment prognostication and on-treatment assessment.
- Ramucirumab did not negatively impact on liver function compared to placebo in patients with advanced HCC and elevated AFP.

Lay summary

Hepatocellular carcinoma is the third leading cause of cancer-related death worldwide. Prognosis is affected by many clinical factors including liver function both before and during anticancer treatment. Here we have used a validated approach to assess liver function using 2 laboratory parameters, serum albumin and bilirubin (ALBI), both before and during treatment with ramucirumab in 2 phase III placebo-controlled studies. We confirm the practicality of using this more simplistic approach in assessing liver function prior to

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- Liver-specific adverse events were reported more frequently in patients with more severe liver disfunction at baseline.
- Ramucirumab provided a survival benefit irrespective of baseline liver function in patients with advanced HCC and elevated AFP.

and during anticancer therapy, and demonstrate ramucirumab did not impair liver function when compared with placebo.

Research article

JHEP|Reports

Effect of ramucirumab on ALBI grade in patients with advanced HCC: Results from REACH and REACH-2

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Background & Aims: The albumin–bilirubin (ALBI) grade/score is derived from a validated nomogram to objectively assess prognosis and liver function in patients with hepatocellular carcinoma (HCC). In this *post hoc* analysis, we assessed prognosis in terms of survival by baseline ALBI grade and monitored liver function during treatment with ramucirumab or placebo using the ALBI score in patients with advanced HCC.

Methods: Patients with advanced HCC, Child-Pugh class A with prior sorafenib treatment were randomised in REACH trials to receive ramucirumab 8 mg/kg or placebo every 2 weeks. Data were analysed by trial and as a meta-analysis of individual patient-level data (pooled population) from REACH (alpha-fetoprotein ≥400 ng/ml) and REACH-2. Patients from REACH with Child-Pugh class B were analysed as a separate cohort. The ALBI grades and scores were calculated at baseline and before each treatment cycle.

Results: Baseline characteristics by ALBI grade were balanced between treatment arms among patients in the pooled population (ALBI-1, n = 231; ALBI-2, n = 296; ALBI-3, n = 7). Baseline ALBI grade was prognostic for overall survival (OS; ALBI grade 2 *vs.* 1; hazard ratio [HR]: 1.38 [1.13–1.69]), after adjusting for other significant prognostic factors. Mean ALBI scores remained stable in both treatment arms compared with baseline and were unaffected by baseline ALBI grade, macrovascular invasion, tumour response, geographical region, or prior locoregional therapy. Baseline ALBI grades 2 and 3 were associated with increased incidence of liver-specific adverse events and discontinuation rates in both treatments. Ramucirumab improved OS in patients with baseline ALBI grade 1 (HR 0.605 [0.445–0.824]) and ALBI grade 2 (HR 0.814 [0.630–1.051]).

Conclusions: Compared with placebo, ramucirumab did not negatively impact liver function and improved survival irrespective of baseline ALBI grade.

Keywords: ALBI; Liver function; Prognosis; Safety; Survival; Tumour response.
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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.[1] Prognosis in patients with HCC is affected by many clinical factors including disease stage, Eastern Cooperative Oncology Group performance status (ECOG PS), histopathology, serum alpha-fetoprotein (AFP) levels, and liver function.[2–6] In addition, most patients with HCC have associated chronic liver diseases and have poorer prognosis compared with HCC patients without chronic liver diseases.[7,8]

The Child-Pugh score, a scoring system used to measure the severity of chronic liver disease, is determined by 2 clinical and 3 laboratory measures (serum albumin, total bilirubin, ascites, prothrombin ratio, and hepatic encephalopathy).[9,10] Despite having limitations including the highly subjective evaluation of ascites and encephalopathy, the Child-Pugh score has been widely used for liver function assessment and may impact treatment effect in patients with HCC.[9,11,12] The albumin–bilirubin (ALBI) grade is a novel and validated nomogram of liver function assessment in patients with HCC. It is based solely on serum albumin and bilirubin and therefore excludes evaluation of the subjective variables and confounding factors (ascites and encephalopathy) to categorise patients into 3 prognostic risk categories.[12] Recent evidence suggests ALBI grading/scoring at baseline[13,14] and at the end of therapy[15] can predict prognosis in HCC patients. In addition to the prognostic utility, ALBI scoring/grading may be helpful in providing a detailed evaluation of hepatic function during study treatment in patients with advanced HCC.[16,17]

Vascular endothelial growth factor (VEGF) receptors (VEGFRs) 1 and 2 and their ligands are important mediators of tumour angiogenesis and contribute to the pathogenesis and progression of HCC.[18–20] Several antiangiogenic multikinase inhibitors, which also target the VEGF/VEGFR axis, have demonstrated clinical benefits in the phase III setting in HCC, including the first-line treatments sorafenib and lenvatinib and second-line treatments regorafenib and cabozantinib.[21–24] Owing to drug design and the ability to target multiple pathways, multikinase inhibitors have many overlapping toxicities, including liver decompensation requiring dose modifications or discontinuation.[25–28] Ramucirumab is an IgG1 monoclonal antibody that binds to the extracellular domain of VEGFR2 and has demonstrated clinical activity and safety as a monotherapy in patients with advanced HCC and elevated AFP from the phase III REACH and REACH-2 studies.[29,30] In this *post-hoc* analysis of patients with advanced HCC and elevated AFP from the phase III REACH and REACH-2 studies, we assessed prognosis in terms of survival by baseline ALBI grade and monitored liver function during treatment with ramucirumab (or placebo) by serial analyses of the ALBI score.

Patients and methods

Study design and patients

REACH (NCT01140347) and REACH-2 (NCT02435433) were randomised, double-blind, placebo controlled, phase III studies, whose design and patient eligibility were previously reported.[29,30] Briefly, adult patients with advanced HCC, BCLC stage B or C disease that was refractory or not amenable to locoregional therapy, Child-Pugh class A liver disease (score <7), ECOG PS 0 or 1, adequate hematological and biochemical parameters, and prior treatment with sorafenib were eligible.[29,30] The intent-to-treat (ITT) and safety populations of REACH comprised only patients with Child-Pugh class A disease. An exploratory cohort of patients with Child-Pugh class B (B7 or B8) liver disease in REACH were analysed separately, and detailed analyses have been previously published.[9] REACH did not restrict enrolment based on baseline AFP, whereas REACH-2 restricted enrolment to patients with baseline serum AFP concentrations of ≥400 ng/ml. In REACH, randomisation was stratified by geographical region and aetiology of liver disease (hepatitis B, hepatitis C, or other aetiologies).[29] In REACH-2, randomisation was stratified by macrovascular invasion (MVI), geographical region, and ECOG PS.[30] Eligible patients were randomised in REACH (1:1) and REACH-2 (2:1) to receive ramucirumab (8 mg/kg, i.v.) or placebo every 14 days (once every 2 weeks) until radiographic or clinical progression of disease, unacceptable toxicity, or withdrawal of consent. All patients received best supportive care.

REACH and REACH-2 complied with the Declaration of Helsinki, the International Conference on Harmonization 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.

Endpoints

Overall survival (OS) was defined as the time from randomisation to death from any cause, and progression-free survival was defined as the time from randomisation to radiographic progression or death. Best overall response (BOR) to treatment was assessed per RECIST version 1. Safety was assessed and adverse events (AEs) were graded per CTCAE version 4.0 throughout the study and for 30 days after treatment discontinuation. Laboratory monitoring, including serum albumin and bilirubin levels, were measured within 14 days prior to randomisation and before each cycle (every 14 days).

Liver function was assessed with the ALBI score and ALBI grade, which were defined by the ALBI linear predictor.[12] ALBI linear predictor = ($\log_{10}$bilirubin×0.66) + (albumin×−0.085), where bilirubin is in μmol/L and albumin in g/L, for ALBI score calculation. Patients were categorised into the ALBI grades by applying cut-off to the linear predictor: grade 1: ≤−2.60; grade 2: >−2.60 and ≤−1.39; and grade 3: >−1.39,[12] where a higher ALBI grade indicated worsening liver function. Child-Pugh score was collected at baseline as per the HCC practice guidelines,[10] before administration of the study treatment. No post-baseline assessment of Child-Pugh score occurred in REACH or REACH-2.

Statistical analysis

In this *post-hoc* analysis, efficacy and safety populations from REACH, REACH-2, and a meta-analysis of individual patient-level data (pooled population) from REACH (AFP ≥400 ng/ml) and REACH-2 were analysed. The pooling of patient-level data provided a substantially larger patient population, enabling a more precise estimation of the treatment effect in subgroup analyses. All pooled efficacy analyses were done at the level of individual patient data, stratified by study.[30] Limited analyses were performed on the exploratory cohort of patients from REACH with Child-Pugh class B liver disease.

Demographics and safety/tolerability data were presented for the pooled population using descriptive statistics: mean ± standard deviation, median (inter-quartile range [IQR]), numbers, and percentages. Survival (median OS in months and 95% CI) was estimated for each ALBI grade and Child-Pugh score groups using the Kaplan-Meier method, and hazard ratios (HR) between ALBI grades, and treatment arms were estimated using Cox models. Survival was determined in ITT populations of REACH (AFP all comers), REACH-2 ITT population, and the pooled population from REACH (AFP ≥400 ng/ml) and REACH-2 ITT. Multivariate Cox proportional hazards models evaluated impact of baseline ALBI grade on OS (adjusted for treatment, and for statistically significant baseline factors: baseline ECOG PS, AFP, and MVI). In the pooled population, the agreement between the ALBI grade and Child-Pugh score was assessed using Cohen's simple kappa coefficient,[31] and the performance of each system on

discriminating the OS of patients was evaluated using Harrell's C index.[32,33]

Results

Demographics and baseline characteristics by baseline ALBI grade

This exploratory analysis included a total 857 patients with advanced HCC, ECOG PS 0 or 1, prior treatment with sorafenib, and Child-Pugh class A from the ITT populations of REACH (n = 565 [ramucirumab, n = 283; placebo, n = 282]) and REACH-2 (n = 292 [ramucirumab, n = 197; placebo, n = 95]).[29,30] The focused population for this report comprises of pooled individual patient-level data from the REACH (AFP ≥400 ng/ml) and REACH-2 (n = 534, pooled population),[29,30] as ramucirumab has market authorisation for the treatment of HCC in patients who have an AFP ≥400 ng/ml. Of the 534 patients in the pooled population with Child-Pugh class A and available baseline ALBI grade, 231 patients had a baseline ALBI grade 1 (ramucirumab = 136, placebo = 95), 296 had baseline ALBI grade 2 (ramucirumab = 176, placebo = 120), and 7 had baseline ALBI grade 3 (ramucirumab = 1, placebo = 6). Baseline demographic and disease characteristics by ALBI grade were generally balanced between the treatment arms (Table 1).

A greater proportion of patients with ALBI grade 1 had ECOG PS 0, Child-Pugh score 5, and hepatitis B than patients with baseline ALBI grade 2. Median baseline AFP and the proportion of patients with MVI were lower in patients with ALBI grade 1. Limited comparisons of the baseline ALBI grade 3 group were made with baseline ALBI grade 1 and 2 owing to the small sample size of the baseline ALBI grade 3 group (n = 7; Table 1). Table S1 presents demographics and baseline characteristics by baseline Child-Pugh score.

In the independent cohort of 77 patients with Child-Pugh class B disease from REACH, 4 patients had ALBI grade 1 at baseline (ramucirumab = 2, placebo = 2), 47 had baseline ALBI grade 2 (ramucirumab = 27, placebo = 20), and 26 had baseline ALBI grade 3 (ramucirumab = 11, placebo = 15). Baseline characteristics among these patients were balanced between treatment arms, as has been previously described.[9]

Treatment duration

The median duration of treatment in patients in the pooled population with baseline ALBI grade 1 were 12.07 weeks (IQR 6.57–32) weeks for ramucirumab and 6.14 weeks (IQR 6–12) for placebo (Table S2). In ALBI grade 2 patients, the median duration of treatment was 8 weeks (IQR 6–17.71) for ramucirumab and 7.86 weeks (IQR 5.86–12.21) for placebo. Median relative dose intensities were at least 98% for both treatment arms in all patients, irrespective of the baseline ALBI grade (Table S2).

OS by ALBI grade or Child-Pugh score

The prognostic utility of the baseline ALBI grade and Child-Pugh scoring systems were assessed at baseline in the REACH, REACH-2, and pooled population. Visual inspection of the resulting OS Kaplan-Meier curves showed good discrimination between baseline ALBI grades (Fig. 1) and Child-Pugh scores (Fig. S1) in all populations. Results were consistent in the pooled population, with similarly worse prognosis of ALBI grade 2 compared with ALBI grade 1 (HR 1.50 [95% CI 1.23–1.83], Fig. 1C), and Child-Pugh score 6 compared with Child-Pugh score 5 (HR 1.57 [95% CI 1.29–1.90], Fig. S1C). Baseline ALBI grade remained prognostic for OS (HR 1.38 [95% CI 1.128, 1.691]), after adjusting for other baseline prognostic factors (MVI, AFP, ECOG PS, and treatment; Table S3). The kappa coefficient of 0.472 (95% CI 0.403, 0.540) indicated a moderate agreement between the ALBI grading and Child-Pugh scoring. Harrell's C index scores for ALBI grade (0.583 [95% CI 0.557, 0.608]) and Child-Pugh score (0.564 [95% CI 0.538, 0.589]) confirmed the 2 systems had similar discriminatory power to predict OS.

Results were consistent in the separate cohort of patients in REACH with Child-Pugh class B, with similarly worse prognosis of ALBI grade 3 compared with ALBI grade 1 (1.42 [95% CI 0.49–4.17]) and ALBI grade 2 compared with ALBI grade 1 (1.15 [0.41–3.25]; Fig. S2). Additional detailed analyses of this cohort have been previously published.[9]

Effect of study treatment on mean ALBI score

During the course of study treatment, the mean ALBI score remained stable in both treatment arms (Fig. 2). Compared with baseline, an incremental increase in the mean ALBI score was noted in both ramucirumab and placebo arms at end of treatment in the REACH and REACH-2 populations (Fig. 2A and B). In the pooled population, this incremental increase in ALBI score from baseline to end of treatment was similar in ramucirumab-treated (from −2.5 ± 0.46 to −2.1 ± 0.61) and placebo-treated (from −2.5 ± 0.48 to −2.3 ± 0.64) patients and did not translate into a worsening of the ALBI grade in either arm (Table 2, Fig. 2C).

Consistent results were observed when patients were grouped by baseline ALBI grade (Fig. S3), MVI (Fig. S4), geographic region (Fig. S5), and prior transarterial chemoembolisation (Fig. S6). No differences were noted in mean ALBI score between treatment arms.

Results were consistent in the separate cohort of patients with Child-Pugh class B; the mean ALBI score remained stable in both treatment arms and an incremental increase in the mean ALBI score was noted at end of treatment compared with baseline in both treatment arms (Fig. S7). No differences were noted in mean ALBI score between treatment arms.

Effect of tumour response on mean ALBI score

REACH and REACH-2 allowed treatment to continue beyond radiographic progression until clinical progression. In the pooled population, rates of complete response (CR), partial response (PR), and stable disease (SD) with ramucirumab treatment (n = 316) were 0.3%, 5.1%, and 50.9%, respectively. In placebo-treated patients (n = 226), the rates of PR and SD were 0.9% and 36.3%, with no patient achieving CR. The rate of progressive disease (PD) was 35.8% with ramucirumab and 51.8% with placebo.

To determine the association between BOR and mean ALBI score during treatment, we grouped 488 evaluable patients by CR, PR, or SD (ramucirumab = 175, placebo = 83) and compared mean results with patients with BOR of PD (ramucirumab = 113, placebo = 117). In patients with CR, PR, and SD, no differences were observed in mean ALBI score from baseline to end of treatment between the ramucirumab and placebo arms in the pooled population (Fig. 3). Consistently, no differences in mean ALBI score over time were noted between ramucirumab and placebo arms at baseline, cycles 1–4, and end of treatment for patients with BOR of PD. The number of patients treated beyond radiographic progression became exceedingly small beyond cycle 4 in patients with BOR of PD. The results beyond cycle-4 were less interpretable as a result of high standard deviation.

Table 1. Demographics and baseline characteristics by baseline ALBI grade – pooled population.

Characteristic	ALBI grade 1 (n = 231)		ALBI grade 2 (n = 296)		ALBI grade 3* (n = 7)	
	Ram + BSC (n = 136)	Placebo + BSC (n = 95)	Ram + BSC (n = 176)	Placebo + BSC (n = 120)	Ram + BSC (n = 1)	Placebo + BSC (n = 6)
Males	103 (75.7)	78 (82.1)	140 (79.5)	102 (85)	1 (100)	5 (83.3)
Age (years), median (min–max)	62 (30–88)	59 (26–85)	65 (39–86)	63.5 (31–83)	54 (54–54)	65.5 (56–72)
ECOG PS (0)	87 (64)	57 (60)	84 (47.7)	56 (46.7)	1 (100)	3 (50)
Geographic region						
Region 1 (Americas, Europe, Israel and Australia)	54 (39.7)	43 (45.3)	99 (56.3)	59 (49.2)	0	4 (66.7)
Region 2 (Asia, excluding Japan)	53 (39)	37 (38.9)	46 (26.1)	38 (31.7)	0	0
Region 3 (Japan)	29 (21.3)	15 (15.8)	31 (17.6)	23 (19.2)	1 (100)	2 (42.9)
Discontinuation of sorafenib owing to HCC progression	115 (84.6)	77 (81.1)	156 (88.6)	111 (92.5)	1 (100)	5 (83.3)
Duration of prior sorafenib, median months (min–max)	3.71 (0.46–44.42)	3.98 (0.49–31.9)	3.63 (0.39–56.31)	4.35 (0.49–36.5)	1.41 (1.41–1.41)	2.96 (1.74–26.45)
CP score†						
A – 5	121 (89)	84 (88.4)	66 (37.5)	49 (40.8)	0	0
A – 6	15 (11)	11 (11.6)	107 (60.8)	71 (59.2)	0	4 (66.7)
B – 7+8	0	0	3 (1.7)	0	1 (100)	2 (33.3)
Baseline BCLC stage, C	115 (84.6)	83 (87.4)	153 (86.9)	103 (85.8)	1 (100)	6 (100)
Extrahepatic spread (present)	102 (75)	73 (76.8)	120 (68.2)	90 (75)	1 (100)	4 (66.7)
MVI (present)	40 (29.4)	27 (28.4)	71 (40.3)	46 (38.3)	1 (100)	1 (16.7)
Aetiology						
Hepatitis B	68 (50)	48 (50.5)	54 (30.7)	49 (40.8)	0	2 (33.3)
Hepatitis C	23 (16.9)	15 (15.8)	60 (34.1)	38 (31.7)	0	3 (50)
Significant alcohol use	21 (15.4)	15 (15.8)	48 (27.3)	25 (20.8)	1 (100)	2 (50)
Baseline AFP (ng/ml), median (IQR)	3,859 (1,185.5–17,694)	2,656 (1,170–13,530)	4,299.5 (1,246.95–26,910)	5,336.45 (1,397–29,017.35)	38,628 (38,628–38,628)	15,322.49 (2,559–44,170)
No. of prior TACE, n (%)						
0	56 (41.2)	47 (49.5)	80 (45.5)	49 (40.8)	0 (0)	4 (66.7)
1	76 (55.9)	45 (47.4)	90 (51.1)	70 (58.3)	1 (100)	1 (16.7)
≥2	4 (2.9)	3 (3.2)	6 (3.4)	1 (0.8)	0 (0)	1 (16.7)

All data are presented as n (%), unless specified. Note: 5 patients from REACH-2 and 3 patients from REACH (n = 8) with baseline ALBI measurement were not analysed because of missing baseline lab values.
AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CP, Child-Pugh; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IQR, inter-quartile range; MVI, macrovascular invasion; Ram, ramucirumab; TACE, transarterial chemoembolisation.
* Interactive voice response system/IWRS data, entered by the investigator at the time of enrolment, indicated that all patients in the ITT population had CP class A liver function; however, based on data from the case report forms, 6 patients in the subgroup of patients with AFP ≥400 ng/ml were determined to have liver function of CP class B rather than CP class A. There were no ALBI-3 or CP-7+8 patients in REACH-2.
† Used for determining Cohen's kappa coefficient and Harrell's C index scores.

Safety and tolerability by baseline ALBI score

Patients with a higher ALBI grade at baseline had increased incidence of liver-specific AEs of special interest (AESIs) in both treatment arms in the pooled population. No liver AESI of grade 3 or worse was recorded that showed a difference in frequency of 5% or more in patients allocated to ramucirumab compared with placebo (Table 3). In patients with any grade of AE, a higher ALBI grade at baseline was also associated with increased incidence of treatment discontinuation due to AEs in both treatment arms. AEs leading to discontinuation of study treatment were more frequently reported in patients allocated to ramucirumab compared with placebo (ALBI grade 1: 13.2% *vs.* 4.2%; ALBI grade 2: 18.2% *vs.* 12.5%). Proteinuria (2.9% *vs.* 0%) was the most common AE leading to discontinuation in the ALBI grade 1 group, whereas hepatic encephalopathy (1.7% *vs.* 0%) and oesophageal varices haemorrhage (1.7% *vs.* 3.3%) were the most common AEs leading to discontinuation in the ALBI grade 2 group (Table 4).

Ramucirumab treatment effect by baseline ALBI grade

Ramucirumab-treated patients had longer median OS compared with placebo in patients with baseline ALBI grade 1 (11.4 months *vs.* 6.60 months, HR 0.605; 95% CI 0.445–0.824), (Fig. 4A) and baseline ALBI grade 2 (5.75 months *vs.* 4.21 months, HR 0.814; 95% CI 0.630–1.051; Fig. 4B) in the pooled population. Improvement in OS appeared to be numerically greater for patients with baseline ALBI grade 1 than those with baseline ALBI grade 2; however, there was no statistically significant difference in OS improvement between ALBI grades (OS interaction *p* value = 0.1808).

Ramucirumab improved OS when compared with placebo in patients with baseline Child-Pugh score 5 (10.6 months *vs.* 6.4 months, HR 0.646; 95% CI 0.499–0.836) and baseline Child-Pugh score 6 (6.1 months *vs.* 4.1 months, HR 0.719; 95% CI 0.531–0.974). Improvement in OS was greater for patients with baseline Child-Pugh score 5 than in patients with baseline Child-Pugh score 6 (Fig. S8). Consistent with OS results, ramucirumab improved the progression-free survival compared with placebo in patients with baseline ALBI grade 1 (2.83 months *vs.* 1.45 months, HR 0.425 [95% CI 0.315–0.575]) and grade 2 (2.60 months *vs.* 2.00 months, HR 0.730 [95% CI 0.563–0.946]).

Discussion

ALBI grading is based solely on serum bilirubin and albumin levels and is a simpler prognostic scoring system when compared with the Child-Pugh score criteria as it eliminates the

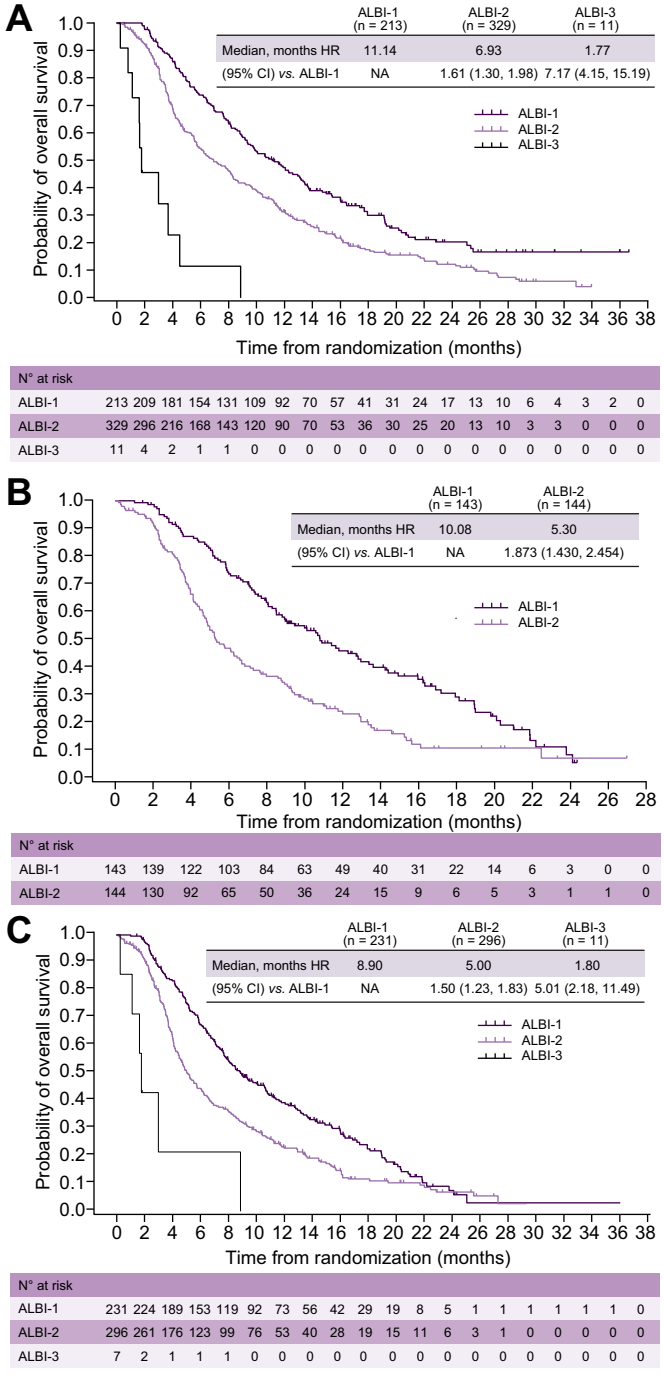

Fig. 1. OS by baseline ALBI grade in (A) REACH, (B) REACH-2, and (C) pooled population. OS presented for combined treatment arm – ramucirumab and placebo. Six patients with CP class B were inadvertently enrolled in REACH ITT. AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALBI-1, ALBI-2 and ALBI-3: ALBI grades 1, 2, and 3; HR, hazard ratio; OS, overall survival; Ram, ramucirumab.

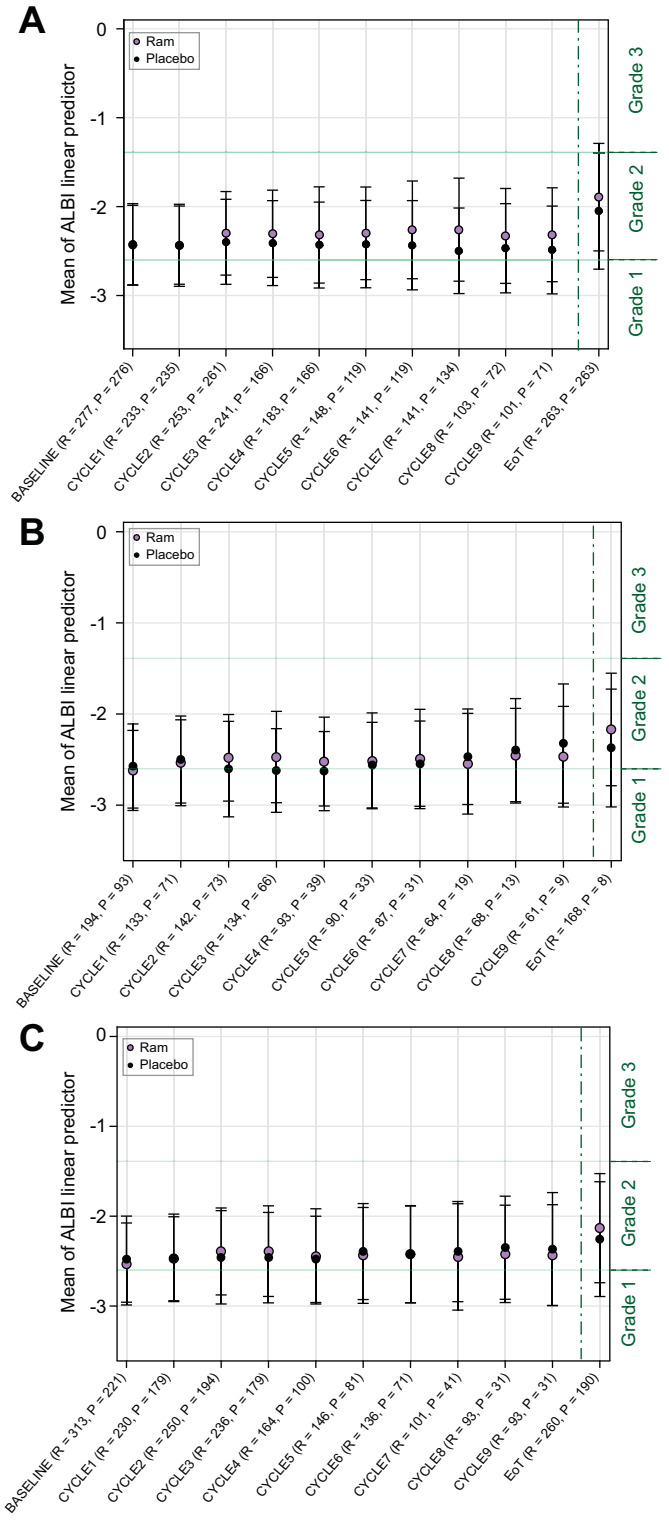

Fig. 2. ALBI over time in (A) REACH, (B) REACH-2, and (C) pooled population. AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; P, placebo; Ram, ramucirumab.

evaluation of the subjective factors of ascites and encephalopathy.[12] The ALBI nomogram has also been useful in further prognostically stratifying patients within each BCLC stage[34] and Child-Pugh class of HCC.[13,17,35] This exploratory analysis of the REACH and REACH-2 studies[29,30] provides significant evidence supporting the use of ALBI grading for prognosticating survival in the second-line setting and also for monitoring liver function during systemic therapy. To the best of our knowledge, this is the most comprehensive analysis of the relationship between ALBI grade and score with prognosis, treatment effect, and monitoring

Table 2. Mean change in ALBI score from baseline to end of treatment – pooled population.

Patient population	Time/grade	Ram	Placebo	Total
Overall		n = 313	n = 221	N = 534
ALBI linear predictor, (mean ± SD)	Baseline	−2.5 ± 0.46	−2.5 ± 0.48	−2.5 ± 0.47
	EoT	−2.1 ± 0.61	−2.3 ± 0.64	−2.2 ± 0.62
Grade at EoT, n (%; 95% CI)	1	70 (22.4; 17.9–27.4)	62 (28.1; 22.2–34.5)	132 (24.7; 21.1–28.6)
	2	157 (50.2; 44.5–55.8)	108 (48.9; 42.1–55.7)	265 (49.6; 45.3–54.0)
	3	33 (10.5; 7.4–14.5)	20 (9.0; 5.6–13.6)	53 (9.9; 7.5–12.8)
Baseline ALBI grade 1		n = 136	n = 95	n = 231
ALBI linear predictor (mean ± SD)	Baseline	−3.0 ± 0.24	−2.9 ± 0.23	−2.9 ± 0.23
	EoT	−2.5 ± 0.45	−2.6 ± 0.51	−2.6 ± 0.48
Grade at EoT, n (%)	1	61 (44.9; 36.5–53.6)	54 (56.8; 46.3–67.0)	115 (49.8; 43.2–56.4)
	2	58 (42.6; 34.2–51.4)	32 (33.7; 24.3–44.1)	90 (39.0; 32.6–45.6)
	3	1 (0.7; 0.0–4.0)	4 (4.2; 1.2–10.4)	5 (2.2; 0.7–5.0)
Baseline ALBI grade 2		n = 176	n = 120	n = 296
ALBI linear predictor (mean ± SD)	Baseline	−2.2 ± 0.28	−2.2 ± 0.27	−2.2 ± 0.28
	EoT	−1.8 ± 0.50	−2.0 ± 0.51	−1.9 ± 0.51
Grade at EoT, n (%)	1	9 (5.1; 2.4–9.5)	8 (6.7; 2.9–12.7)	17 (5.7; 3.4–9.0)
	2	99 (56.3; 48.6–63.7)	76 (63.3; 54.1–71.9)	175 (59.1; 53.3–64.8)
	3	31 (17.6; 12.3–24.1)	13 (10.8; 5.9–17.8)	44 (14.9; 11.0–19.4)
Baseline ALBI grade 3		n = 1	n = 6	n = 7
ALBI linear predictor (mean ± SD)	Baseline	−1.3	−1.3 ± 0.06	−1.3 ± 0.06
	EoT	−1.2	−0.6 ± 0.39	−0.8 ± 0.42
Grade at EoT, n (%)	1	0 (0.0; 0.0–97.5)	0 (0.0; 0.0–45.9)	0 (0.0; 0.0–41.0)
	2	0 (0.0; 0.0–97.5)	0 (0.0; 0.0–45.9)	0 (0.0; 0.0–41.0)
	3	1 (100.0; 2.5–100.0)	3 (50.0; 11.8–88.2)	4 (57.1; 18.4–01.1)

ALBI, albumin–bilirubin; EoT, end of treatment; Ram, ramucirumab.

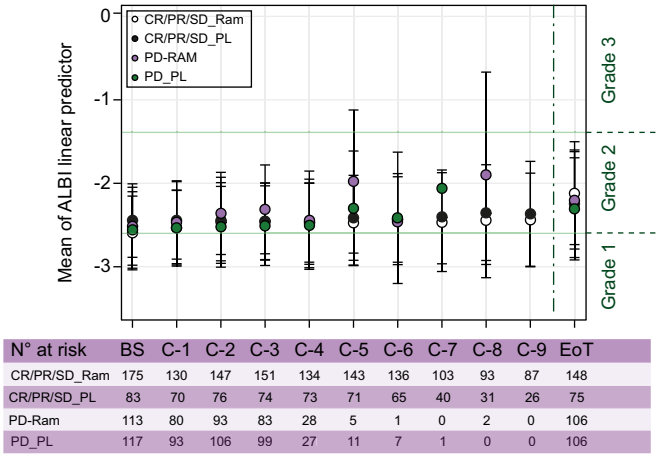

Fig. 3. ALBI over time by BOR – pooled population. ALBI, albumin–bilirubin; BOR, best overall response; BS, Baseline; C-1–C-9, cycle 1–cycle 9; CR, complete response; EoT, end of treatment; PD, progressive disease; PL, placebo; PR, partial response; Ram, ramucirumab; SD, stable disease.

of liver function during treatment of patients with advanced HCC in the randomised phase III setting.

ALBI grading has been used as a prognostic indicator for survival in HCC after curative therapies,[36] ablation or embolisation,[37,38] and systemic treatment.[13,15,34,39–41] In the advanced disease setting, patients with HCC with baseline ALBI grade 1 experienced longer survival outcomes compared with patients with HCC with grade 2 (or higher) after treatment with sorafenib,[13,15,34,40] lenvatinib,[42] cabozantinib,[43] and nivolumab.[14] A similar and consistent observation was observed in our dataset of randomised second-line patients with HCC when analysed by baseline ALBI grade and also by Child-Pugh score. Patients treated with ramucirumab had longer progression-free survival and OS compared with patients receiving placebo, irrespective of baseline ALBI grade. A similar observation was reported in patients treated with cabozantinib from *post-hoc* analysis of the phase III CELESTIAL study.[43] Survival outcomes from REACH, REACH-2, and CELESTIAL suggest patients with baseline ALBI grade 1 derive more benefit from systemic therapy than patients with ALBI grade 2. This larger magnitude of survival benefit for patients with ALBI grade 1 at baseline underscores the need for randomised clinical trials examining systemic therapy, *vs.* locoregional therapy earlier, while the liver function is still preserved.

Progression of HCC negatively affects liver function in several ways such as by increased tumour volume, worsening/emerging vascular invasion, and progression of liver fibrosis.[44] The deterioration in liver function limits the treatment opportunities and causes worsening of prognosis in patients with HCC.[45] In the present study, an incremental increase in mean ALBI score from baseline to end of treatment was observed in both ramucirumab- and placebo-treated patients, and did not translate into a worsening of the ALBI grade, and likely represents progression of disease. No meaningful/significant changes in the ALBI score/grade were seen on treatment before progression in patients with Child-Pugh class A or B liver disease, supporting low liver toxicity in patients treated with ramucirumab. Additional analyses suggested the magnitude of change in ALBI score during study treatment was independent of a patient's baseline ALBI grade, baseline MVI, tumour response, geographical region, or prior locoregional therapy. Although the patient populations of REACH and REACH-2 were notably different from a cohort of Child-Pugh class B patients in CheckMate-040, a tumour response-dependent change in both ALBI score and grade were noted in nivolumab-treated patients that was not observed in our dataset. In CheckMate-040, patients with best overall response of CR/PR maintained a stable ALBI score and grade during treatment, but the majority of patients with SD/PD had a worsening of both ALBI scores and grade based on maximum

Table 3. Grade ≥3 liver AESIs by baseline ALBI grade – pooled population.

	ALBI grade 1		ALBI grade 2		ALBI grade 3	
Liver AESIs, n (%)	Ram (n = 136)	Placebo (n = 95)	Ram (n = 176)	Placebo (n = 120)	Ram (n = 1)	Placebo (n = 6)
AESI liver injury/liver failure	16 (11.8)	18 (18.9)	46 (26.1)*	39 (32.5)†	0	2 (33.3)
Ascites	4 (2.9)	3 (3.2)	11 (6.3)	6 (5.0)	0	0
ALT increased	2 (1.5)	3 (3.2)	1 (0.6)	4 (3.3)	0	1 (16.7)
AST increased	5 (3.7)	8 (8.4)	10 (5.7)	17 (14.2)	0	0
Blood bilirubin increased	0	6 (6.3)	10 (5.7)	10 (8.3)	0	1 (16.7)
GGT increased	0	3 (3.2)	1 (0.6)	4 (3.3)	0	1 (16.7)
Hepatic encephalopathy	2 (1.5)	0	7 (4)	1 (0.8)	0	0
Hepatic failure	0	4 (4.2)	3 (1.7)	1 (0.8)	0	0
Hypoalbuminaemia	0	0	2 (1.1)	1 (0.8)	0	0
Oesophageal varices haemorrhage	2 (1.5)	0	4 (2.3)	8 (6.7)	0	0
Hyperbilirubinaemia	1 (0.7)	4 (4.2)	2 (1.1)	7 (5.8)	0	1 (16.7)

All AESIs occurred in ≥2% patients by preferred term. All data are presented as n (%), unless specified.
AESI, adverse event of special interest; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; Ram, ramucirumab.
* Ramucirumab arm ALBI grade 2 *vs.* grade 1, Fischer's exact test *p* value 0.0016.
† Placebo arm ALBI grade 2 *vs.* grade 1, Fischer's exact test *p* value 0.0296.

Table 4. Discontinuation because of AEs by baseline ALBI grade – pooled population.

	ALBI grade 1		ALBI grade 2	
	Ram (n = 136)	Placebo (n = 95)	Ram (n = 176)	Placebo (n = 120)
Discontinued because of AEs in ≥2 patients by baseline ALBI	18 (13.2)	4 (4.2)	32 (18.2)	15 (12.5)
Proteinuria	4 (2.9)	0	2 (1.1)	0
Oesophageal varices haemorrhage	1 (0.7)	0	3 (1.7)	4 (3.3)
Hepatic encephalopathy	1 (0.7)	0	3 (1.7)	0
Liver carcinoma ruptured	1 (0.7)	1 (1.1)	0	1 (0.8)
Pneumonia	2 (1.5)	0	0	0
General physical health deterioration	0	0	2 (1.1)	0
Hepatorenal syndrome	0	0	2 (1.1)	0
Myocardial infarction	0	0	1 (0.6)	1 (0.8)
Portal vein thrombosis	0	0	1 (0.6)	1 (0.8)
Pulmonary embolism	0	0	1 (0.6)	1 (0.8)

All data are presented as n (%), unless specified.
AE, adverse event; ALBI, albumin–bilirubin; Ram, ramucirumab.

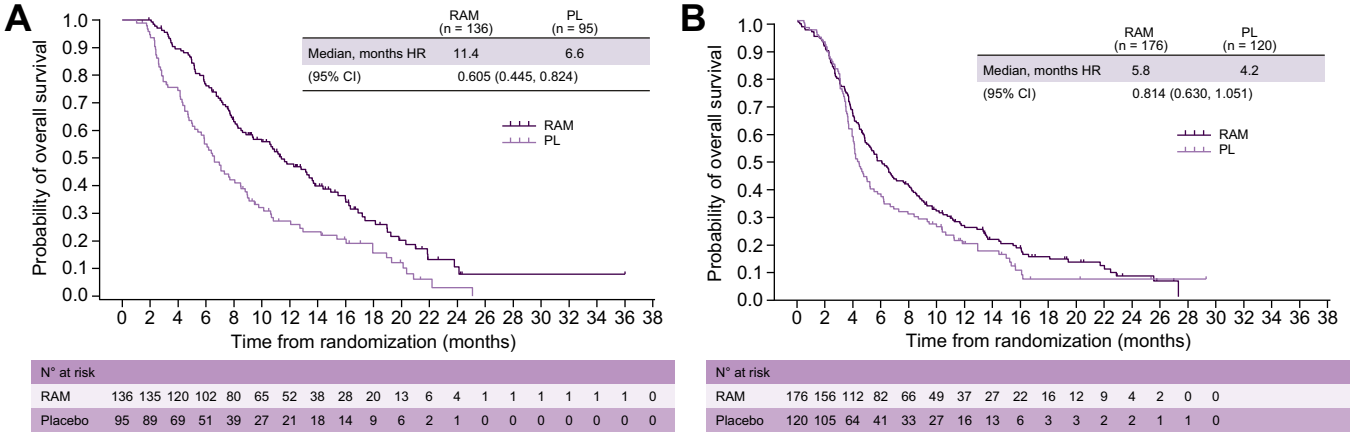

Fig. 4. Effect of ramucirumab treatment on OS by baseline ALBI grade: (A) ALBI grade 1, (B) ALBI grade 2 – pooled population. ALBI, albumin–bilirubin; ALBI-1, ALBI-2, and ALBI-3, ALBI Grades 1, 2, and 3; HR, hazard ratio; PL, placebo; RAM, ramucirumab.

post-baseline value compared with baseline.[46] Because of the lack of a control arm in the CheckMate-040 study,[46] it is difficult to determine whether these differences were influenced by the enrolled patient population and disease setting, or possibly by the frequency of laboratory measurements and radiographic assessments. Changes in ALBI score/grade during study treatment with an immune checkpoint inhibitor have not been reported in a randomised controlled trial.

A modified version of ALBI grading (mALBI) has been proposed and recently validated in Japan. The mALBI further refines

patients with ALBI grade 2 into 2 separate subgrades (grade 2a [>−2.60 to <−2.270] and 2b [>−2.270 to <−1.39]), with worsening survival noted in ALBI grade 2b when compared with ALBI grade 2a.[16,47] In a single-arm study of lenvatinib, patients with baseline modified ALBI (mALBI) grade 1 had longer OS than patients with baseline modified ALBI grade 2a or 2b.[41] A similar observation was made for patients with baseline Child-Pugh score 5 than those with baseline Child-Pugh score 6, indicating worsened prognosis with worsened modified ALBI or Child-Pugh grade.[41] The effect of regorafenib or cabozantinib on the ALBI score or grade during treatment in the RESORCE and CELESTIAL studies have not been published for comparison in a similar second-line Child-Pugh class A population to our dataset.

Safety findings based on ALBI grade from our study were in alignment with the previous safety evidence where the incidence of grade ≥3 liver related AESIs and discontinuations were lower in patients with baseline ALBI grade 1 than in patients with baseline ALBI grade 2 and 3 and treated with locoregional therapy,[37] sorafenib,[13] lenvatinib,[42] or cabozantinib,[43] A lower proportion of ramucirumab-treated patients experienced liver-related AESIs than the placebo-treated patients in the pooled population, irrespective of the ALBI grade. However, discontinuations because of AEs were more frequent in the ramucirumab-treated group than in the placebo-treated group, irrespective of the baseline ALBI grade. No detailed analysis of safety results by baseline ALBI grade from the phase III RESORCE study have been published.

This exploratory analysis has several limitations related to the population of patients enrolled in REACH and REACH-2. The protocols restricted enrolment to patients without ascites or hepatic encephalopathy at baseline, and patients with total bilirubin <1.5 times the upper limit of institutional normal value and required resolution of all clinically significant toxic effects of prior locoregional therapy, surgery, or other anticancer therapy to grade ≤1. Patients with severe liver cirrhosis (Child-Pugh class B or worse) were excluded from the ITT populations of both studies, and only limited analyses could be performed in patients with Child-Pugh class B disease who were enrolled in REACH. Hepatic encephalopathy is an AE that is largely unique to a population with end-stage liver disease, and the patients with more severe liver dysfunction/poorer liver function are at higher risk for this event.[9] However, no difference was noted in mean ALBI score between treatment arms, but a higher incidence of hepatic encephalopathy was reported in Child-Pugh class B patients receiving ramucirumab. Although more objective, the lack of assessment of this clinically meaningful event of hepatic encephalopathy within the ALBI grade/score may be an important limitation to the overall assessment of liver function. A further limitation is REACH and REACH-2 did not include patients who received first-line systemic therapy other than sorafenib, which was the only approved first-line treatment when the trials were designed. Recent evidence suggests ALBI is still prognostic in patients treated with lenvatinib, nivolumab, and cabozantinib,[14,41,43] suggesting the usefulness of ALBI grading is independent of therapy.

Conclusions

This combined analysis of the REACH and REACH-2 trials confirmed baseline ALBI grade is useful in prognosticating patients with advanced HCC, following sorafenib. During the course of study treatment ramucirumab did not negatively alter liver function, as measured by the ALBI score and grade, when compared with placebo. The ALBI score/grade variations in both treatment arms were independent of baseline ALBI grade, baseline MVI, tumour response, geographic region, and transarterial chemoembolisation. Ramucirumab-treated patients with AFP ≥400 ng/ml had survival benefit irrespective of the baseline ALBI grade, with longer survival in patients with baseline ALBI grade 1. Given the apparently larger magnitude of survival benefit for patients with ALBI grade 1 at baseline, it is advisable to reserve second-line of therapy for patients whose liver function is still preserved.

Abbreviations

AE, adverse event; AESI, adverse event of special interest; AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BOR, best overall response; BSC, best supportive care; CP, Child-Pugh; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, inter-quartile range; ITT, intent-to-treat; MVI, macrovascular invasion; OS, overall survival; PD, progressive disease; PR, partial response; Ram, ramucirumab; SD, stable disease; TACE, transarterial chemoembolisation; VEGF, vascular endothelial growth factor; VEGFRs, vascular endothelial growth factor receptors.

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Conflicts of interest

M.K.: conflict with Daiichi Sankyo, Otsuka, Taiho, Astellas Pharma, Chugai, AbbVie, BMS, EA Pharma, Takeda, Gilead, Eisai, Ono, Bayer, MSD, BMS, and Eli Lilly and Company. P.G.: conflict with Bayer, BMS, MSD, Merck, SIRTEX, AstraZeneca, Sillajen, Eli Lilly and Company, Ipsen, Roche, and Eisai. G.B.: declares no conflicts of interest that pertain to this work. Y-K.K.: conflict with ONO, BMS, Eli Lilly and Company, Roche, Daehwa, and Taiho. C-J. Yen: declares no conflicts of interest that pertain to this work. R.S.F.: conflict with Astra Zeneca, Bayer, BMS, Eli Lilly and Company, Pfizer, Merck, Novartis, Roche/Genentech, and Eisai. J.M.L.: conflict with Bayer, Eisai Inc, BMS, IPSEN, Eli Lilly and Company, Celsion Corp, Elelixis, Merck, Glycotest, Can-Fite, Blueprint, Incyte, Navigant, Leerink Swann LLC, Midatech Ltd, Fortress Biotech Inc, and Spring Bank Pharmaceuticals. E.A.: received honoraria from IPSEN, Bayer, Terasphere, Sirtex, Sanofi, Novartis, and Servier; served as an advisor and consultant for IPSEN, Bayer, Terasphere, Sirtex, Sanofi, Novartis, and Servier; and reports receipt of research grant and funding from Eli Lilly and Company. P.M.: conflict with Bayer, Ipsen/Exelixis, BMS, Onxeo, MSD, AstraZeneca, Eisai, and Roche. S.L.C.: conflict with Eisai, Merck, and AstraZeneca. D.H.P.: conflict with Bayer, Eisai, BMS, and Sirtex. M.I.: conflict with Bayer, Bristol-Myers Squibb, Eisai, Sumitomo Dainippon, EA Pharma, Takeda Pharmaceutical, AstraZeneca, Chugai, Merck Serono, Gilead, ASLAN, Daiichi Sankyo, Novartis, Teijin Pharma, Kyowa Hakko Kirin, NanoCarrier, Shire, Yakult, Taiho, Baxalta, Nobelpharma, Otsuka, Ono, MSD, J-Pharma, Mylan, NIHON SERVIER, and Eli Lilly and Company. T.Y.: received personal fees from Eli Lilly and Eisai. A.V.: conflict with Eli Lilly and Company, EISAI, Roche, BMS, MSD, Bayer, BTG, AstraZeneca, Ipsen, Novartis; Y-H. Huang: Eisai, BMS, Merck, AstraZeneca, Bayer, Gilead, Abbvie, Roche, Eli Lilly, and IPSEN. P.B.A.: employed by Eli Lilly and Company, stocks held in Eli Lilly and Company. R.Y.: Eli Lilly Japan KK, stocks held in Eli Lilly and Company. K.S.: Eli Lilly Japan KK. C.W.: employed by Eli Lilly and Company, stocks

held in Eli Lilly and Company. R.C.W.: employed by Eli Lilly and Company, stocks held in Eli Lilly and Company. A.X.Z.: conflict with Eisai, BMS, Merck, Novartis, Sanofi, AstraZeneca, Bayer, Roche, Eli Lilly and Company, and Exelixis.

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

Authors' contributions

Substantial contributions to conception and design: M.K., P.R.G., G.B., R.S.F., J.M.L., P.B.A., R.Y., R.C.W., A.X.Z.

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Analysis and/or interpretation of data: R.S.F., A.V., P.A., C.W., M.K., P.R.G., G.B., Y.K.K., C.J.Y., E.A., P.M., S.L.C., D.H.P., M.I., T.Y., Y.H.H., P.B.A., R.Y., K.S., R.C.W., A.X.Z.

Drafting, revising, review, and approval of the final submitted report: all authors.

Data availability

Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once they 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. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhepr.2020.100215.

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Author names in bold designate shared co-first authorship

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