Ramucirumab for Patients with Intermediate-Stage Hepatocellular Carcinoma and Elevated Alpha-Fetoprotein: Pooled Results from Two Phase 3 Studies (REACH and REACH-2)

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Keywords

Ramucirumab · Barcelona clinic liver cancer stage · α -fetoprotein

Abstract

Background: Intermediate-stage hepatocellular carcinoma (HCC), as defined by Barcelona Clinic Liver Cancer (BCLC) stage B, is heterogeneous in terms of liver function and tumor burden. REACH and REACH-2 investigated ramucirumab in patients with HCC after prior sorafenib, with REACH-2 enrolling only patients with baseline α -fetoprotein (AFP)

≥ 400 ng/mL. An exploratory analysis of outcomes by BCLC stage was performed. **Methods:** A pooled meta-analysis of independent patient data (stratified by study) from REACH (AFP ≥ 400 ng/mL) and REACH-2 was performed. All patients had Child-Pugh A, Eastern Cooperative Oncology Group performance status 0–1, prior sorafenib treatment, and either HCC BCLC stage B (refractory/not amenable to locoregional therapy) or BCLC stage C. Patients were randomized to ramucirumab 8 mg/kg or placebo every 2 weeks. Median overall survival (OS) and progression-free survival were estimated by the Kaplan-Meier method. Treatment effects in BCLC stage B and C were evaluated by Cox proportional-hazards

model; prognosis of BCLC staging for OS was evaluated by multivariate Cox proportional-hazards model. Tumor responses were evaluated according to Response Evaluation in Solid Tumors v1.1. Liver function was assessed with albumin-bilirubin score. **Results:** Baseline characteristics were generally balanced between treatment arms in each BCLC stage. BCLC staging trended as an independent prognostic factor for OS (B vs. C; hazard ratio [HR] 0.756 [95% CI 0.546–1.046]). Consistent treatment benefit was observed for ramucirumab versus placebo across BCLC stages. Median OS for ramucirumab versus placebo was 13.7 versus 8.2 months; HR (95%): 0.43 (0.23–0.83) and 7.7 versus 4.8 months; HR (95%): 0.72 (0.59–0.89) for BCLC stage B and C, respectively. Adverse events (AEs) were consistent with observations from both studies; hypertension was the most frequent grade ≥ 3 AE. Liver function was preserved throughout the study and similar between treatment arms in both BCLC stages. **Conclusions:** Ramucirumab provided a better survival benefit irrespective of BCLC stage and was well tolerated without compromising liver function during treatment.

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Background

The Barcelona Clinic Liver Cancer (BCLC) staging system categorizes patients into 4 main prognostic groups (stages A, B, C, and D) based on tumor burden, severity of liver disease, and Eastern Cooperative Oncology Group performance status (ECOG PS) [1–3]. Intermediate-stage hepatocellular carcinoma (HCC) is classified as BCLC stage B and is a heterogeneous disease in terms of liver function and tumor burden [4, 5]. BCLC stage B includes all patients having a Child-Pugh score of A or B with an ECOG PS 0, who also have a single nodule >5 cm, or multiple nodules >3 in number, or at least one of these >3 cm, without macrovascular invasion and extrahepatic spread [6]. Transarterial chemoembolization (TACE) is the recommended first-line treatment in most clinical practice guidelines with over half of all patients with intermediate-stage HCC treated with this procedure [7–9]. Due to population heterogeneity, however, the treatment benefits observed with TACE have been variable with a high rate of tumor recurrence. There is a wide gap between clinical practice guidelines and applied clinical practice with regards to intermediate HCC [10–12]. Recently, lenvatinib has been shown to benefit patients with intermediate HCC when compared with TACE in the unresectable setting [5]. While intermediate HCC patients may initially be treated with locoregional therapies, nearly all patients

experience disease progression and require systemic therapy [13]. Actually, evidence of TACE efficacy was established by meta-analysis of several randomized controlled trials comparing TACE with no therapy (best supportive care) when systemic therapy was virtually not existing [14]. In other words, there is no evidence that TACE or systemic therapy is better in intermediate-stage HCC with high tumor burden.

A number of systemic treatments are currently being investigated and/or are approved for the treatment of HCC [15]. Tyrosine kinase inhibitors (e.g., sorafenib, lenvatinib, regorafenib, and cabozantinib) have shown positive survival benefits for patients with intermediate and advanced HCC [16–20]. Checkpoint inhibitors such as atezolizumab (in combination with bevacizumab), nivolumab, and pembrolizumab have also shown efficacy in these patient populations [21–24]. Recently, an antiangiogenic agent, ramucirumab, has demonstrated improved overall survival (OS) in patients with advanced HCC and elevated α -fetoprotein (AFP) [25–27].

REACH (Clinicaltrials.gov Identifier NCT01140347) and REACH-2 (Clinicaltrials.gov Identifier NCT02435433) were randomized, placebo-controlled, phase 3, clinical trials that investigated ramucirumab (IgG1 vascular endothelial growth factor receptor 2 antagonist) in patients with HCC who progressed on or were intolerant to sorafenib [25, 26]. REACH-2 only enrolled patients with baseline AFP levels ≥ 400 ng/mL [25]. In both clinical trials, patients with BCLC stage C disease or BCLC stage B disease not amenable or refractory to locoregional therapy were included [25, 26]. Treatment with ramucirumab provided survival benefits in REACH-2 and in those patients with a baseline AFP ≥ 400 ng/mL in REACH [25, 26]. Here, we show the results of an exploratory analysis conducted to investigate the efficacy and safety of ramucirumab in advanced HCC patients with elevated AFP from REACH-2 and REACH by BCLC stage.

Materials and Methods

REACH and REACH-2 were randomized, placebo-controlled, double-blind, multicenter, phase 3 trials (Fig. 1). Patients either received intravenous ramucirumab (8 mg/kg) or placebo every 2 weeks (REACH randomized 1:1; REACH-2 randomized 2:1), plus best supportive care, until disease progression, unacceptable toxicity, or death [25, 26]. An individual patient data meta-analysis was performed on REACH-2 patients [25] and REACH patients with AFP ≥ 400 ng/mL [21] to investigate the efficacy and safety of ramucirumab in advanced HCC patients by BCLC stage: pooled results were stratified by study. Pooling the patient-level data increased the patient population and allowed for a more precise es-

Fig. 1. REACH and REACH-2 clinical study designs. AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; i.v., intravenous; N, number of participants; ORR, objective response rate; PFS, progression-free survival; Q2W, every 2 weeks. ClinicalTrials.gov identifier: REACH: NCT01140347, REACH-2: NCT02435433.

timination of treatment effect in subgroup analyses. Outcomes of patients in the pooled population were reported by baseline BCLC stage B or C. BCLC staging for this analysis was derived based on individual patient data entered in the electronic case report form prior to the start of second-line therapy.

Both OS and progression-free survival (PFS) were assessed using the Kaplan-Meier method, and hazard ratios (HRs) were assessed by univariate and multivariate Cox proportional-hazards models accounting for covariates of treatment, BCLC stage, and baseline AFP. Objective response rate, disease control rate, and safety were reported by BCLC stage. All response assessments were done locally by investigators according to Response Evaluation in Solid Tumors version 1.1 and adverse events (AEs) were graded according to the Common Terminology Criteria for AEs version 4.0. Laboratory monitoring, including serum albumin and bilirubin levels, were measured within 14 days prior to randomization and before administration of study drug at each cycle (every 14 days) per the protocol [25, 26]. The albumin-bilirubin (ALBI) grade was used as an assessment of overall liver function [28, 29]. The ALBI linear predictor, ALBI score, was determined using the following formula: $\text{ALBI linear predictor} = (\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$, where bilirubin is in $\mu\text{mol/L}$ and albumin in g/L . Patients were categorized into the ALBI grades by applying cutoff to the linear predictor: grade 1: ≤ -2.60 ; grade 2: > -2.60 to ≤ -1.39 ; and grade 3: > -1.39 [28, 29].

Results

Data from 52 patients (ramucirumab, N = 30 and placebo, N = 22) with BCLC stage B disease and data from 490 patients (ramucirumab N = 286; placebo N = 204) with BCLC stage C disease were analyzed (Table 1). Baseline patient and disease characteristics were generally well-balanced across treatment arms. Region 3 (Japan) had a higher percentage of patients with BCLC stage B, while patients with BCLC stage C were more common in Region 2 (Asia excluding Japan). Additionally, patients with BCLC stage C had higher median levels of AFP (ramucirumab arm: 4,472 ng/mL and placebo arm: 4,375 ng/mL) than patients with BCLC stage B disease (ramucirumab arm: 1,817 ng/mL and placebo arm: 2,958 ng/mL). In the overall study population, more than half of all patients with BCLC stage B or BCLC stage C disease had undergone TACE prior to systemic treatment.

To investigate what factors were significantly associated with survival, univariate and multivariate analyses of OS adjusted for baseline BCLC stage were performed. BCLC

Table 1. Baseline demographics and disease characteristics

<i>n</i> (%) except where indicated	BCLC stage B		BCLC stage C	
	ramucirumab, <i>N</i> = 30	placebo, <i>N</i> = 22	ramucirumab, <i>N</i> = 286	placebo, <i>N</i> = 204
Gender, male	27 (90)	19 (86)	219 (77)	170 (83)
Age, years, median	65	65	63	62
ECOG PS 0	30 (100)	22 (100)	143 (50)	96 (47)
Geographical region				
Region 1 (Americas, Europe, Australia, Israel)	14 (47)	12 (55)	140 (49)	96 (47)
Region 2 (Asia excluding Japan)	3 (10)	2 (9)	98 (34)	76 (37)
Region 3 (Japan)	13 (43)	8 (36)	48 (17)	32 (16)
Child-pugh score A-5	22 (73)	12 (55)	168 (59)	123 (60)
Prior TACE	22 (73)	11 (50)	157 (55)	112 (55)
Number of prior TACE				
0	8 (27)	11 (50)	129 (45)	92 (45)
1–2	13 (43)	7 (32)	123 (43)	85 (42)
≥3	9 (30)	4 (18)	34 (12)	27 (13)
Progression on sorafenib	27 (90)	19 (86)	247 (86)	179 (88)
Macrovascular invasion present	0	0	113 (40)	77 (38)
Extrahepatic spread present	0	0	226 (79)	171 (84)
Median duration of prior sorafenib, months	4.8	5.2	3.6	3.9
Median AFP (IQR), ng/mL	1,817 (1,000–6,425)	2,958 (1,591–12,317)	4,472 (1,283–24,494)	4,375 (1,174–23,120)
ALBI grade				
1	15 (50)	9 (41)	121 (42)	86 (42)
2	15 (50)	13 (59)	161 (56)	107 (53)
3	0	0	1 (0.3)	6 (3)
Etiology of liver disease				
Hepatitis B virus	12 (40)	6 (27)	112 (39)	96 (47)
Hepatitis C virus	10 (33)	10 (46)	73 (26)	46 (23)
Significant alcohol use	4 (13)	4 (18)	67 (23)	39 (19)
Steatohepatitis	2 (7)	1 (5)	24 (8)	10 (5)
Other	6 (20)	3 (14)	37 (13)	27 (13)

AFP, α -fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; TACE, transarterial chemoembolization.

stage was prognostic for OS in the univariate analysis (stage B vs. stage C; HR 0.68, 95% CI 0.49–0.94; *p* value 0.02). When we adjusted for treatment and baseline AFP in the multivariate analysis, it did not reach statistical significance (stage B vs. stage C; HR 0.76, 95% CI 0.55–1.05; *p* value 0.0917) (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000516605).

Ramucirumab provided a benefit to OS and PFS irrespective of BCLC stage (Fig. 2a, b). No significant difference in treatment effect by BCLC subgroup was detected (OS interaction *p* value = 0.273; PFS interaction *p* value = 0.432), indicating a comparable benefit with ramucirumab in patients with BCLC stage B and C disease. For BCLC stage B, the median OS for the ramucirumab arm versus placebo was 13.7 versus 8.2 months (HR 0.43, 95% CI

0.23–0.83) and the median PFS was 4.2 versus 2.8 months (HR 0.33, 95% CI 0.17–0.64). For BCLC stage C, the median OS for the ramucirumab arm versus placebo was 7.7 versus 4.8 months (HR 0.72, 95% CI 0.59–0.89) and the median PFS was 2.8 versus 1.5 months (HR 0.60, 95% CI 0.49–0.74).

Differences in post-discontinuation therapies (PDTs) (online suppl. Table 2) and AFP (Table 1) were noted in BCLC stage B; however, the OS benefit persisted after adjusting for AFP levels (online suppl. Fig. 1) and PDTs (online suppl. Fig. 2). A higher proportion of intermediate-stage patients in the ramucirumab arm experienced an objective response (*n* = 5, 17%) and disease control (*n* = 24, 80%) than patients with advanced-stage disease (4% and 54%, respectively) (Table 2).

Fig. 2. OS (a) and PFS (b) by baseline BCLC stage. Kaplan-Meier analysis for OS and PFS shown by treatment arm (ramucirumab [red] vs. placebo [grey]) for pooled REACH and REACH-2 patients by BCLC stage; BCLC B (N = 52) and BCLC C (N = 487). A Wald test of treatment-by-subgroup interaction from stratified Cox model was used, stratified by study identification. BCLC, Barcelona Clinic Liver Cancer (staging categories); CI, confidence interval; HR, hazard ratio; N, number of patients in intent-to-treat population; OS, overall survival; PFS, progression-free survival.

Compared with baseline values, an incremental increase in the mean ALBI score was noted in both ramucirumab- and placebo-treated patients at the end of study treatment (Fig. 3). This incremental increase was similar in both treatment arms and BCLC stages and was not sig-

nificant enough for a worsening of the ALBI grade. Treatment-emergent AEs (TEAEs) were consistent with those found in the intent-to-treat population of REACH and REACH-2. Hypertension was the most frequent grade ≥ 3 TEAE (Table 3) and no new safety signals were detected.

Table 2. Best overall response (RECIST v 1.1) by baseline BCLC stage

<i>n</i> (%)	BCLC stage B		BCLC stage C	
	ramucirumab, <i>N</i> = 30	placebo, <i>N</i> = 22	ramucirumab, <i>N</i> = 286	placebo, <i>N</i> = 204
ORR	5 (17)	1 (5)	12 (4)	1 (1)
DCR	24 (80)	13 (59)	154 (54)	71 (35)

All response assessments were done locally by investigators according to RECIST (version 1.1). BCLC, Barcelona Liver Cancer Clinic; RECIST, Response Evaluation in Solid Tumors; ORR, objective response rate; DCR, disease control rate.

Fig. 3. Effect of study treatment on ALBI score/grade by baseline BCLC stage. ALBI linear predictor was used as a measure of liver function over the course of the treatment cycle. The numbers of patients in each group at baseline were RAM BCLC B (*N* = 30, red); PL BCLC B (*N* = 22, grey); RAM BCLC C (*N* = 283, blue); and PL BCLC C (*N* = 199, green). Patients were categorized into the ALBI grades using cut-offs: Grade 1: ≤ -2.60 ; Grade 2: > -2.60 to ≤ -1.39 ; and Grade 3: > -1.39 . ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer (staging categories); BS, baseline; C 1–9, cycle 1–9; EOT, end of treatment; PL, placebo; RAM, ramucirumab.

Discussion

In this exploratory, post-hoc analysis, we investigated the efficacy and safety of ramucirumab by BCLC stage in patients from REACH (AFP ≥ 400 ng/mL) and REACH-2. We found that ramucirumab demonstrated improved survival outcomes over placebo for patients with intermediate and advanced-stage HCC. The survival benefit of ramucirumab versus placebo observed in patients with BCLC stage B was numerically greater than in those with BCLC stage C (median delta of +5.5 vs. +2.9 months). This benefit in OS remained after accounting for differences in baseline AFP levels and PDT. The baseline median AFP levels of the BCLC stage C patients were much higher than those of the BCLC stage B patients, consistent with other studies that have demonstrated that AFP levels are known to correlate with HCC subclasses and elevated levels are associated with poor survival outcomes [30].

The higher percentage of patients in the ramucirumab arm with BCLC stage B versus BCLC stage C who received PDT (40% vs. 29%, respectively) may suggest that earlier introduction of molecularly targeted drugs, including ramucirumab, at the intermediate stage may lead to increased opportunities for PDT and longer survival [5, 31].

The BCLC staging system is well-known for establishing treatment strategies and potential prognoses associated with each of the 4 main stages [2]. In our study, BCLC stage was prognostic for OS in the univariate analysis (stage B vs. stage C; HR 0.68, 95% CI 0.49–0.94) but did not reach significance when we adjusted for treatment and baseline AFP in the multivariate analysis (stage B vs. stage C; HR 0.76, 95% CI 0.55–1.05). The smaller population size of patients with BCLC stage B disease from our pooled population likely contributed to the lack of statistical significance.

Table 3. TEAEs by baseline BCLC stage

TEAEs in ≥15% patients in ramucirumab arm, <i>n</i> (%)	BCLC stage B				BCLC stage C			
	ramucirumab, <i>N</i> = 30		placebo, <i>N</i> = 22		ramucirumab, <i>N</i> = 286		placebo, <i>N</i> = 201	
	any grade	grade ≥3	any grade	grade ≥3	any grade	grade ≥3	any grade	grade ≥3
Patients with ≥1 TEAE	29 (97)	19 (63)	20 (91)	9 (41)	277 (97)	162 (57)	186 (93)	107 (53)
Peripheral edema	15 (50)	0 (0)	6 (27)	0 (0)	77 (27)	3 (1)	32 (16)	0 (0)
Ascites	9 (30)	2 (7)	2 (9)	2 (9)	57 (20)	13 (5)	31 (15)	7 (4)
Decreased appetite	9 (30)	0 (0)	5 (23)	0 (0)	61 (21)	4 (1)	41 (20)	1 (1)
Proteinuria	8 (27)	1 (3)	2 (9)	0 (0)	48 (17)	3 (1)	10 (5)	0 (0)
Diarrhea	7 (23)	0 (0)	4 (18)	0 (0)	51 (18)	1 (0)	22 (11)	1 (1)
Fatigue	7 (23)	0 (0)	3 (14)	0 (0)	69 (24)	8 (3)	36 (18)	6 (3)
Hypertension	7 (23)	5 (17)	4 (18)	1 (5)	59 (21)	33 (12)	16 (8)	7 (4)
Increased blood bilirubin	6 (20)	2 (7)	1 (5)	0 (0)	25 (9)	8 (3)	23 (11)	17 (9)
Headache	6 (20)	0 (0)	0 (0)	0 (0)	47 (16)	1 (0)	14 (7)	1 (1)
Abdominal pain	5 (17)	0 (0)	3 (14)	0 (0)	56 (20)	5 (2)	38 (19)	9 (5)
Arthralgia	5 (17)	0 (0)	0 (0)	0 (0)	9 (3)	2 (1)	7 (4)	0 (0)
Asthenia	5 (17)	1 (3)	0 (0)	0 (0)	32 (11)	8 (3)	14 (7)	1 (1)
Hypoalbuminemia	5 (17)	0 (0)	2 (9)	1 (5)	31 (11)	2 (1)	9 (5)	0 (0)
Nasopharyngitis	5 (17)	0 (0)	2 (9)	0 (0)	10 (4)	0 (0)	7 (4)	0 (0)
Nausea	5 (17)	0 (0)	0 (0)	0 (0)	57 (20)	0 (0)	36 (18)	0 (0)
Pruritus	5 (17)	0 (0)	0 (0)	0 (0)	22 (8)	0 (0)	17 (9)	1 (1)
Pyrexia	5 (17)	0 (0)	1 (5)	0 (0)	35 (12)	0 (0)	13 (7)	0 (0)

AEs were graded according to the CTCAE (version 4.0). AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

No new safety signals were detected during this analysis when compared with the intent-to-treat population, with hypertension being the most prevalent grade ≥3 TEAE. Liver toxicity was minimal in both treatment arms. Mean ALBI score measured at baseline through the end of treatment, demonstrated baseline liver function was preserved throughout the study and was similar in each treatment arm for patients with BCLC stage B and C disease. Although an incremental increase in the mean ALBI score was noted in both ramucirumab and placebo treatment arms at the end of study treatment, it was not significant enough to increase the ALBI grade and likely represented the negative effects of disease progression.

Our study supports the second-line use of ramucirumab in the treatment of patients with HCC, AFP ≥400 ng/mL, and either BCLC stage B who are refractory or not eligible for TACE, or BCLC stage C disease. Guidelines based on the BCLC staging system for intermediate or advanced HCC recommend TACE or systemic therapy for unresectable disease [8, 12, 32, 33]. However, intermediate-stage HCC is a heterogeneous disease in terms of liver function and tumor burden and not all patients with intermediate-stage disease will benefit from TACE [3, 32, 34, 35]. Due to this heterogeneity and the wide range of

benefits observed from TACE, several groups have proposed subclassification systems for intermediate-stage HCC that allocate additional treatment options by subclass [32, 36–38]. While there have been attempts to prospectively or retrospectively validate some of these subclassification systems, none of them have gained worldwide consensus.

In our overall study population, just over half of all patients with BCLC stage B or C disease had undergone TACE prior to systemic treatment, with 14% of those patients undergoing the procedure 3 or more times. Repeated TACE utilization increases the risk for complications and has been shown to result in liver ischemia/necrosis, leading to a faster deterioration of liver function [5, 8, 33, 39–44]. Additional investigation is needed to fully discern the most appropriate treatment options in the unresectable and second-line setting that will best benefit patients with intermediate-stage HCC. For patients with intermediate-stage or advanced HCC who were unsuitable for TACE, systemic therapy with sorafenib has been the preferred option; however, lenvatinib has demonstrated noninferiority to sorafenib in the unresectable setting and may now represent an additional option. Additionally, treatment with lenvatinib recently demonstrated

a survival benefit and preserved liver function when compared with TACE in patients with unresectable, intermediate-stage HCC with high tumor burden [5, 31].

For patients with HCC who are intolerant to or progress on sorafenib, regorafenib [18], cabozantinib [20], and ramucirumab (for patients with AFP ≥ 400) [25] have been approved for second-line therapy based on large, randomized, phase 3 trials. The PD-1 antibody, nivolumab [21], either alone or in combination with ipilimumab [45], has been granted accelerated approval in the USA based on a phase 1/2 study, and outcomes of confirmatory trial of combination therapy are currently awaited. Another PD-1 antibody, pembrolizumab, has also been approved as a second-line treatment option after sorafenib based on a phase 1/2 study [46]. However, both nivolumab and pembrolizumab failed to show their survival benefit over comparators (sorafenib or placebo) in the phase 3 CheckMate 459 [47] and KEYNOTE-240 trials [24].

While several second-line agents are now available for patients with BCLC stage B and C disease, published reports of outcomes by BCLC stage are limited. To the best of our knowledge, no separate subgroup analyses by BCLC stage have been reported with cabozantinib in CELESTIAL [48], regorafenib in RESORCE [49], nivolumab monotherapy in CHECKMATE-040 [21], or ipilimumab + nivolumab in CHECKMATE-040 [45], nor is this data available in the primary publications. The magnitude of survival benefit was not equivalent across BCLC stage with single-agent pembrolizumab. In the KEYNOTE-240 trial, a trend in improved OS was reported in pembrolizumab-treated patients with BCLC stage C disease (HR: 0.77, 95% CI: 0.58–1.01) with less clear activity in patients with BCLC stage B disease (HR: 0.93, 95% CI: 0.51–1.68) [50]. Despite not being powered for subgroup analysis, these results in combination with REACH/REACH-2 data, suggest BCLC staging can affect efficacy outcomes for different systemic therapies and could be explored in future studies. One ongoing phase 4 study is assessing the efficacy and safety of various doses of cabozantinib in patients with HCC BCLC stage B who failed or are not eligible for TACE, or BCLC stage C who have already received 1 to 2 systemic therapies, one of which was sorafenib (CLERANCE; ClinicalTrials.gov NCT03963206). In Japan, the prospective, observational study PRISM is ongoing to explore the real-world evidence of second- or third-line treatment in BCLC B and C stage HCC patients (UMIN ID 000040488).

A limitation of this study is the considerably smaller population of BCLC B patients compared with the BCLC C patients. This was likely due to the inclusion criteria of

the REACH and REACH-2 studies that specified patients with BCLC stage C disease or BCLC stage B disease not amenable or refractory to locoregional therapy. Additionally, only patients with prior sorafenib treatment were included in the analysis. Additional studies are needed to determine the efficacy of second-line treatment with ramucirumab subsequent to first-line interventions other than sorafenib, and this is currently under investigation in an expansion cohort of the REACH-2 study (ClinicalTrials.gov Identifier NCT02435433) [51]. Acknowledging limitations of sample size, ramucirumab provided a survival benefit for patients with advanced HCC and elevated AFP (≥ 400 ng/mL) and did not alter liver function compared to placebo irrespective of BCLC stage.

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Statement of Ethics

REACH (NCT01140347) and REACH-2 (NCT02435433) both 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 centers approved the protocol, and all patients provided written informed consent [25, 26].

Conflict of Interest Statement

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Author Contributions

All the authors approved the final version of the manuscript for submission to Liver Cancer and have participated sufficiently in the work to agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Conception of the work: H. Lim, R. Yoshikawa, R. Widau, A. Zhu, M. Kudo, and R. Finn. Design of the work: H. Lim, R. Widau, A. Zhu, and M. Kudo. Acquisition of data for the work: M. Morimoto, M. Ikeda, P. Galle, H. Lim, A. Zhu, M. Kudo, and R. Finn. Analysis of data for the work: P. Galle, J. Llovet, H. Lim, K. Liang, C. Wang, P. Abada, R. Widau, and R. Finn. Interpretation of data for the work: K. Rau, M. Ikeda, C. Yen, P. Galle, J. Llovet, B. Daniele, H. Lim, D. McIlwain, R. Yoshikawa, K. Nakamura, C. Wang, P. Abada, R. Widau, A. Zhu, M. Kudo, and R. Finn. Drafting of the work: M. Morimoto, K. Rau, H. Lim, D. McIlwain, K. Nakamura, and R. Widau. Critical revision of the work for important intellectual content: M. Ikeda, C. Yen, P. Galle, J. Llovet, B. Daniele, H. Lim, R. Yoshikawa, K. Nakamura, K. Liang, C. Wang, P. Abada, R. Widau, A. Zhu, M. Kudo, R. Finn.

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