

**Original Paper**

# Efficacy and Safety of Ramucirumab in Asian and Non-Asian Patients with Advanced Hepatocellular Carcinoma and Elevated Alpha-Fetoprotein: Pooled Individual Data Analysis of Two Randomized Studies

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**Keywords**

Asian patients · Hepatocellular carcinoma · Ramucirumab

**Abstract**

**Objective:** REACH-2 and REACH were randomized, placebo-controlled, double-blind, multicenter phase 3 trials which showed survival benefits of ramucirumab treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated alpha-fetoprotein (AFP). We evaluated the efficacy and safety of ramucirumab in Asian and non-Asian patients with AFP  $\geq 400$  ng/mL from REACH-2 and REACH. **Methods:** We pooled Asian and non-Asian patients from the REACH-2 and REACH trials and performed an individual patient data meta-analysis. Overall survival (OS) and progression-free survival were evaluated using the Kaplan-Meier method. Hazard ratios (HRs) were estimated with a stratified Cox regression model. **Results:** In the pooled REACH-2 and REACH patient population, 291 Asian patients were randomly as-

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signed to receive ramucirumab ( $n = 168$ ) or placebo ( $n = 123$ ), and 251 non-Asian patients received ramucirumab ( $n = 148$ ) or placebo ( $n = 103$ ). The median OS was significantly longer in the ramucirumab arm in comparison to the placebo arm for Asian patients (8.08 vs. 4.76 months, stratified HR 0.73 [95% CI 0.56–0.95],  $p = 0.0189$ ) and non-Asian patients (7.98 vs. 5.22 months, stratified HR 0.65 [95% CI 0.49–0.86],  $p = 0.0028$ ). The overall response rate (ORR) and disease control rate (DCR) were significantly higher in the ramucirumab arm compared to the placebo arm for Asian patients (ORR: 4.2 vs. 0.8%; DCR: 53.6 vs. 33.3%) and non-Asian patients (ORR: 6.8 vs. 1.0%; DCR: 59.5 vs. 41.7%). The most common grade  $\geq 3$  treatment-emergent adverse events reported in the ramucirumab arm were hypertension (7.7%), decreased appetite (1.2%), and ascites (1.2%) for Asian patients and hypertension (16.9%), ascites (8.8%), asthenia (4.7%), and fatigue (5.4%) for non-Asian patients. **Discussion and Conclusion:** This pooled analysis of the REACH-2/REACH trials demonstrates significant benefits, with a manageable safety profile, of ramucirumab treatment in Asian and non-Asian patients with advanced HCC and baseline AFP  $\geq 400$  ng/mL.

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## Introduction

Worldwide, liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer deaths. Of all primary liver cancer cases, hepatocellular carcinoma (HCC) comprises 75–85% [1]. The incidence and mortality rate is particularly high in East and Southeast Asia. The risk factors for developing HCC vary by region. In many high-risk regions, such as China, the main risk factor for HCC is chronic infection with the hepatitis B virus, whereas hepatitis C is the predominant risk factor in Japan [1]. Other common causes include cirrhosis resulting from alcohol abuse and metabolic conditions including diabetes [2, 3]. Baseline alpha-fetoprotein (AFP) levels  $>400$  ng/mL are associated with poor prognosis in HCC, and tumors expressing high AFP commonly demonstrate high cell proliferation, high angiogenesis, and low apoptosis [4–6].

Vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR-2) signaling play an important role in angiogenesis and tumor growth [7–9]. VEGF is overexpressed in HCC, indicating that it may play a pivotal role in HCC development and progression [10–12]. Ramucirumab is a human immunoglobulin G1 monoclonal antibody targeting VEGFR-2 [13], a key mediator of VEGF-induced angiogenesis [14]. REACH was a global, randomized, phase 3 trial examining the efficacy and safety of ramucirumab monotherapy in patients with advanced HCC after first-line sorafenib treatment [15]. In an unselected population, second-line treatment with ramucirumab did not significantly improve survival in comparison to placebo-treated patients. However, a significant improvement in overall survival (OS) was observed on a prespecified analysis in the ramucirumab arm in comparison to the placebo arm in patients with baseline AFP concentrations  $\geq 400$  ng/mL [15].

To confirm the observed survival benefits in patients with elevated AFP, the REACH-2 trial was designed. This global, randomized, phase 3 trial demonstrated improved OS in ramucirumab-treated HCC patients with AFP levels  $\geq 400$  ng/mL and was the first positive phase 3 trial performed in a biomarker-selected population with advanced HCC [16].

An individual patient data meta-analysis of REACH-2 and REACH provides a larger dataset for evaluation and supports the significant and clinically meaningful benefit, with a favorable safety profile, of ramucirumab treatment in comparison to placebo for patients with HCC after first-line sorafenib therapy [17]. Ethnicity is a significant factor influencing the efficacy, tolerability, and safety of anticancer treatments [18, 19]. There is also significant

regional heterogeneity in the etiology, and management, of HCC. We conducted a pooled subgroup analysis to investigate the efficacy and safety of ramucirumab, in comparison to placebo, in Asian and non-Asian patients with elevated AFP from REACH-2 and REACH.

## Subjects and Methods

### *Study Design and Participants*

REACH-2 (NCT02435433) and REACH (NCT01140347) were both randomized, placebo-controlled, double-blind, multicenter phase 3 trials [15, 16]. The study designs for REACH and REACH-2 have been previously described. For both trials, eligible patients were aged 18 years or older and diagnosed with HCC via histopathological or cytological findings, or diagnosed with cirrhosis and HCC via classical imaging characteristics. Patients were previously treated with sorafenib and discontinued treatment at least 14 days before randomization. Patients had documented disease progression during or after sorafenib therapy. For REACH-2 only, patients were eligible if they had serum AFP concentrations  $\geq 400$  ng/mL [16].

We performed a meta-analysis by pooling Asian patients from REACH-2 and REACH (AFP  $\geq 400$  ng/mL). The Asian population was defined based on race (Asian vs. white vs. Black or African American) and included patients from Korea, China, Hong Kong, Taiwan, and Japan. Similarly, non-Asian patients from the two studies were also pooled.

### *Randomization and Procedures*

Patient randomization and procedures for REACH and REACH-2 have been previously described [15, 16]. In the REACH trial, patients were randomized 1:1 to receive either ramucirumab or placebo. Randomization in REACH was stratified by geographical region and cause of liver disease. As the REACH trial showed potential ramucirumab benefits in patients with increased AFP, REACH-2 used a 2:1 randomization ratio to allocate a smaller percentage of patients to placebo. Randomization in REACH-2 was stratified by geographical region, macrovascular invasion, and Eastern Cooperative Oncology Group performance status.

In both trials, patients received ramucirumab 8 mg/kg or placebo intravenously over 1 h, every 14 days, until disease progression, unacceptable toxicity, or withdrawal of consent. All patients received best supportive care. Disease assessment and imaging studies were performed according to RECIST (version 1.1) every 6 weeks during the first 6 months and every 9 weeks thereafter.

### *Outcomes*

The primary and secondary outcome measures for REACH-2 and REACH have been described previously [15, 16]. In this pooled analysis of REACH-2 and REACH (AFP  $\geq 400$  ng/mL), we describe OS, progression-free survival (PFS), time to tumor progression, overall response rate (ORR), time to deterioration of FACT-Hepatobiliary Symptom Index-8 (FHSI-8) score, disease control rate (DCR), and safety in Asian and non-Asian patients.

### *Statistical Analysis*

Statistical analyses were performed as previously described for REACH-2 and REACH [15, 16]. In this analysis, Asian and non-Asian patients from the REACH-2 and REACH (AFP  $\geq 400$  ng/mL) trials were pooled and analyzed at the individual patient data level. OS and PFS for Asian and non-Asian patients were evaluated using the Kaplan-Meier method. Hazard ratios (HRs) were estimated with a Cox regression model stratified by study. All safety analyses were performed in the safety population, defined as any patient who received any dose of ramucirumab or placebo.

## Results

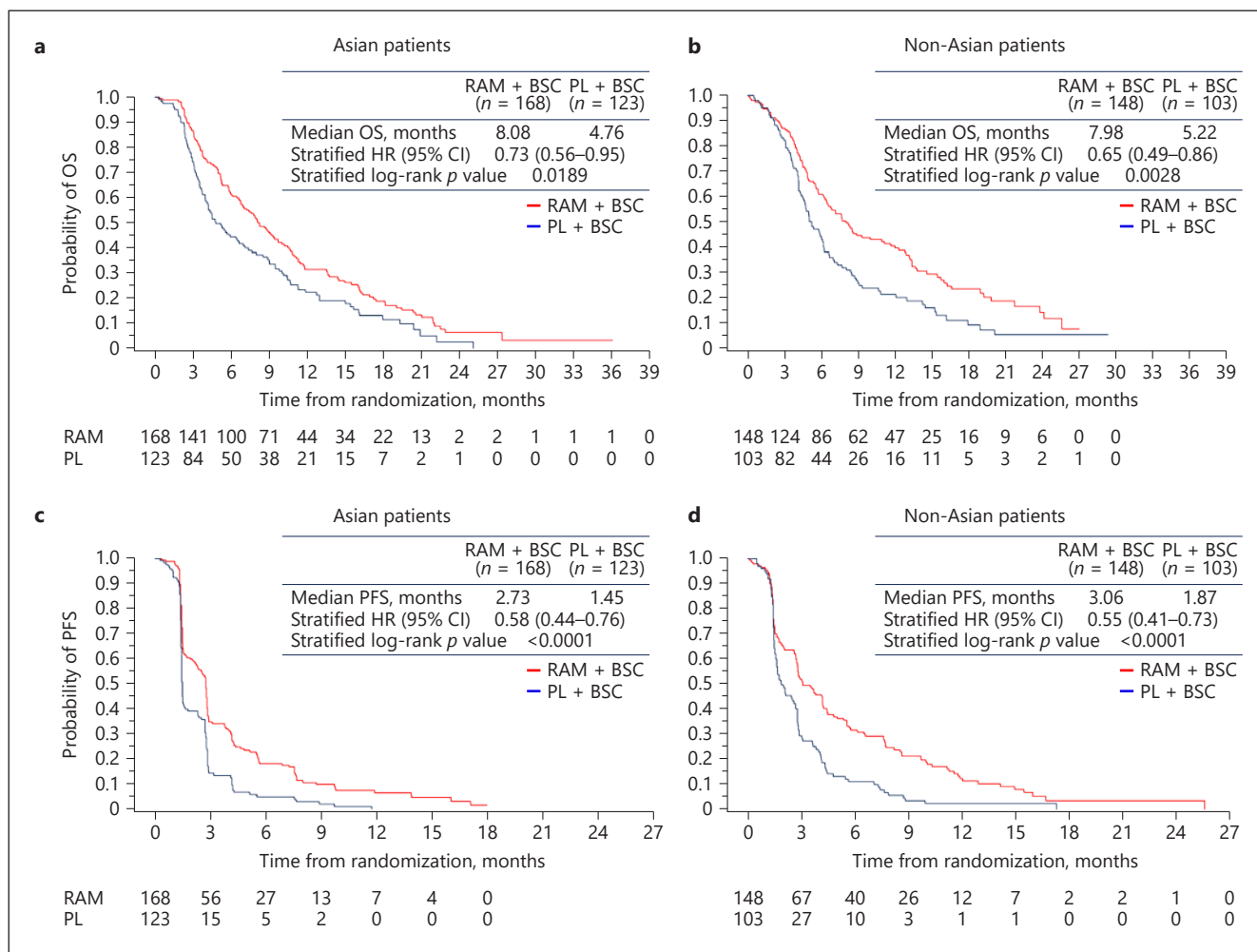
### *Patients*

In the pooled REACH and REACH-2 patient population, a total of 291 Asian patients received ramucirumab ( $n = 168$ ) or placebo ( $n = 123$ ), with a total of 251 non-Asian patients receiving ramucirumab ( $n = 148$ ) or placebo ( $n = 103$ ).

**Table 1.** Baseline patient characteristics in Asian and non-Asian patients

Characteristics	Asian patients (n = 168)		Non-Asian patients (n = 148)		placebo (n = 103)	
	ramucirumab	placebo	ramucirumab	placebo	ramucirumab	placebo
Male sex	133 (79.2%)	105 (85.4%)	113 (76.4%)	84 (81.6%)	67.0 (10.95)	72.0 (15.11)
Age, years	60.5 (11.65)	58.0 (11.65)	66.0 (9.57)	67.0 (10.95)	67.0 (10.95)	72.0 (15.11)
Body weight, kg	60.8 (10.28)	63.4 (10.44)	72.2 (14.94)	72.2 (14.94)	67.0 (10.95)	72.0 (15.11)
Race						
Asian	168 (100.0%)	168 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
White	0 (0%)	0 (0%)	110 (74.3%)	80 (77.7%)	80 (77.7%)	80 (77.7%)
Black or African American	0 (0%)	0 (0%)	2 (1.4%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
Multiple	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
Other	0 (0%)	0 (0%)	2 (1.4%)	4 (3.9%)	4 (3.9%)	4 (3.9%)
Missing <sup>1</sup>	0 (0%)	0 (0%)	34 (23.0%)	17 (16.5%)	17 (16.5%)	17 (16.5%)
ECOG performance status						
0	100 (59.5%)	63 (51.2%)	73 (49.3%)	55 (53.4%)	55 (53.4%)	55 (53.4%)
1	68 (40.5%)	60 (48.8%)	75 (50.7%)	48 (46.6%)	48 (46.6%)	48 (46.6%)
Baseline BCLC stage						
B	19 (11.3%)	10 (8.1%)	26 (17.6%)	19 (18.4%)	19 (18.4%)	19 (18.4%)
C	149 (88.7%)	113 (91.9%)	122 (82.4%)	84 (81.6%)	84 (81.6%)	84 (81.6%)
Baseline Child-Pugh score A	167 (99.4%)	122 (99.2%)	145 (98.0%)	102 (99.0%)	102 (99.0%)	102 (99.0%)
Metastatic sites						
0	34 (20.2%)	20 (16.3%)	57 (38.5%)	36 (35.0%)	36 (35.0%)	36 (35.0%)
1	70 (41.7%)	52 (42.3%)	57 (38.5%)	37 (35.9%)	37 (35.9%)	37 (35.9%)
≥2	64 (38.1%)	51 (41.5%)	34 (23.0%)	30 (29.2%)	30 (29.2%)	30 (29.2%)
Etiology of liver disease						
Hepatitis B	108 (64.3%)	83 (67.5%)	16 (10.8%)	19 (18.4%)	19 (18.4%)	19 (18.4%)
Hepatitis C	43 (25.6%)	26 (21.1%)	40 (27.0%)	30 (29.1%)	30 (29.1%)	30 (29.1%)
Significant alcohol use	13 (7.7%)	9 (7.3%)	58 (39.2%)	34 (33.0%)	34 (33.0%)	34 (33.0%)
Macrovascular invasion present	55 (32.7%)	38 (30.9%)	58 (39.2%)	39 (37.9%)	39 (37.9%)	39 (37.9%)
Extrahepatic spread present	133 (79.2%)	102 (82.9%)	93 (62.8%)	69 (67.0%)	69 (67.0%)	69 (67.0%)
Baseline AFP, ng/mL	7,107.4 (90,508)	7,219.0 (74,694)	2,801.0 (56,390)	3,343.0 (63,285)	3,343.0 (63,285)	3,343.0 (63,285)
Prior TACE	117 (69.6%)	78 (63.4%)	55 (37.2%)	39 (37.9%)	39 (37.9%)	39 (37.9%)
Duration of prior sorafenib therapy						
<5 months	113 (67.3%)	79 (64.2%)	78 (52.7%)	59 (57.3%)	59 (57.3%)	59 (57.3%)
≥5 months	55 (32.7%)	44 (35.8%)	70 (47.3%)	44 (42.7%)	44 (42.7%)	44 (42.7%)
Median, months	2.97 (0.46–44.4)	3.78 (0.49–32.0)	4.70 (0.39–56.3)	4.27 (0.49–36.5)	4.27 (0.49–36.5)	4.27 (0.49–36.5)
Time from last sorafenib treatment to randomization						
<1 month	98 (58.3%)	82 (66.7%)	72 (48.6%)	50 (48.5%)	50 (48.5%)	50 (48.5%)
≥1 month	70 (41.7%)	41 (33.3%)	76 (51.4%)	53 (51.5%)	53 (51.5%)	53 (51.5%)
Reason for discontinuation of sorafenib						
Progressive disease	149 (88.7%)	110 (89.4%)	125 (84.5%)	88 (85.4%)	88 (85.4%)	88 (85.4%)
Intolerance	19 (11.3%)	13 (10.6%)	23 (15.5%)	15 (14.6%)	15 (14.6%)	15 (14.6%)

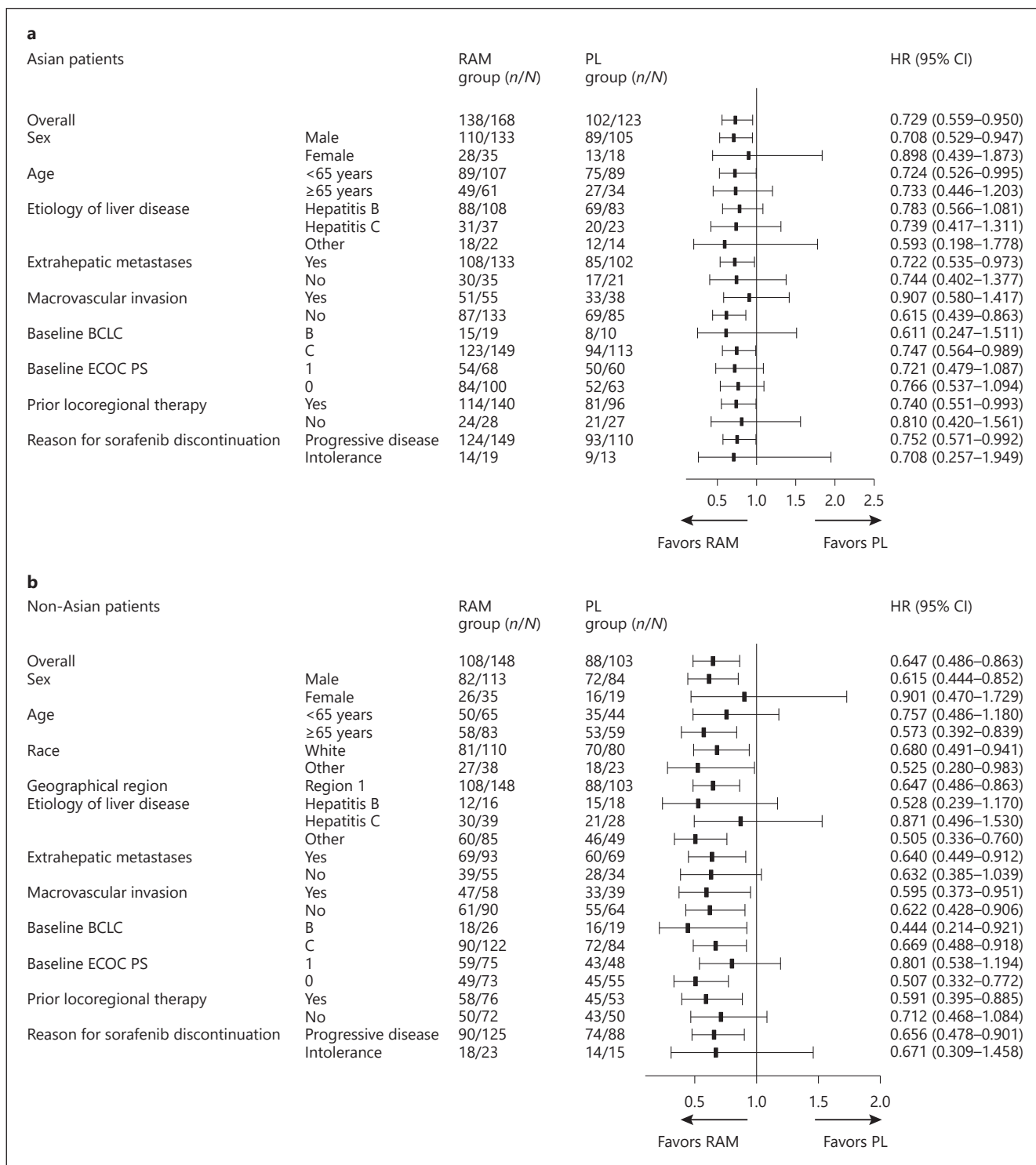
Values are presented as n (%), median (standard deviation), or median (range). AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; n, number of patients; TACE, transarterial chemoembolization. <sup>1</sup>Local regulations limited the collection of race data from all regions.



**Fig. 1.** Kaplan-Meier plots of OS (**a, b**) and PFS (**c, d**) for Asian (**a, c**) and non-Asian patients (**b, d**). BSC, best supportive care; n, number of patients; OS, overall survival; PFS, progression-free survival; PL, placebo; RAM, ramucirumab.

Baseline patient and disease characteristics for Asian and non-Asian patients are outlined in Table 1. Differences between Asian and non-Asian patients were observed for body weight (Asian patients were lighter), Barcelona Clinic Liver Cancer stage (more Asian patients were stage C), number of metastatic sites (more Asian patients exhibited  $\geq 2$  sites), etiology of liver disease (more Asian patients were diagnosed with hepatitis B), significant alcohol use (smaller number of Asian patients), extrahepatic spread (greater for Asian patients), baseline AFP (higher for Asian patients), prior transarterial chemoembolization (TACE) (higher for Asian patients), and duration of prior sorafenib (Asian patients generally had shorter duration). Baseline characteristics between treatment arms within each pool of Asian and non-Asian patients were generally well balanced.

The median duration of therapy in Asian patients was 9.7 weeks (range 2–84) in the ramucirumab arm and 6.0 weeks (range 2–52) in the placebo arm. For non-Asian patients, the median duration of therapy was 12.1 weeks (range 2–107) in the ramucirumab arm and 8.1 weeks (range 2–77) in the placebo arm. Median relative dose intensity was  $>98\%$  for all patients (Asian and non-Asian).



**Fig. 2.** Subgroup analysis of OS by patient and disease characteristics in Asian (a) and non-Asian patients (b). BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; n, number of events; N, number of patients in specified category; OS, overall survival; PL, placebo; RAM, ramucirumab.



**Table 2.** Overall response

	Asian patients			Non-Asian patients		
	ramucirumab (n = 168)	placebo (n = 123)	p value	ramucirumab (n = 148)	placebo (n = 103)	p value
Best overall response						
Complete response	0 (0%)	0 (0%)		1 (0.7%)	0 (0%)	
Partial response	7 (4.2%)	1 (0.8%)		9 (6.1%)	1 (1.0%)	
Stable disease	83 (49.4%)	40 (32.5%)		78 (52.7%)	42 (40.8%)	
Progressive disease	71 (42.3%)	70 (56.9%)		42 (28.4%)	47 (45.6%)	
Not evaluable	7 (4.2%)	12 (9.8%)		18 (12.2%)	13 (12.6%)	
ORR	7 (4.2%)	1 (0.8%)	0.1320	10 (6.8%)	1 (1.0%)	0.0270
DCR	90 (53.6%)	41 (33.3%)	0.0043	88 (59.5%)	43 (41.7%)	0.0067

Values are presented as n (%). DCR, disease control rate; n, number of patients; ORR, overall response rate.

### Efficacy

For Asian patients, median OS was significantly longer in the ramucirumab arm (8.08 months) in comparison to the placebo arm (4.76 months) (stratified HR 0.73 [95% CI 0.56–0.95],  $p = 0.0189$ ). Similarly, for non-Asian patients, median OS was significantly improved in the ramucirumab arm (7.98 months) compared to the placebo arm (5.22 months) (stratified HR 0.65 [95% CI 0.49–0.86],  $p = 0.0028$ ). Kaplan-Meier survival curves for OS are presented in Figure 1. Analysis of OS by patient and tumor characteristics consistently favored ramucirumab treatment in both Asian and non-Asian patients (Fig. 2).

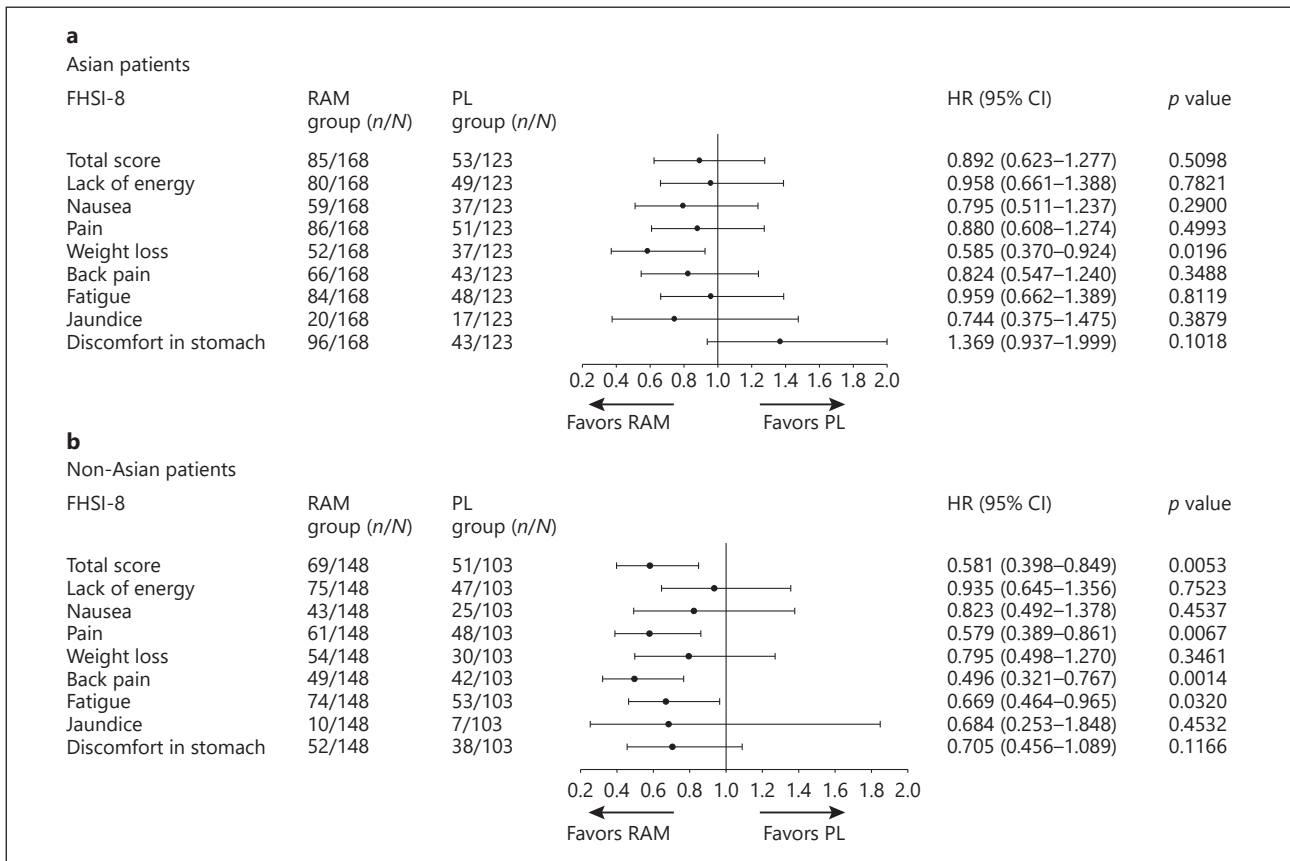
Median PFS for Asian patients was significantly improved in the ramucirumab arm (2.73 months) compared to the placebo arm (1.45 months) (stratified HR 0.58 [95% CI 0.44–0.76],  $p < 0.0001$ ). For non-Asian patients, median PFS was also significantly longer in the ramucirumab arm (3.06 months) compared to the placebo arm (1.87 months) (stratified HR 0.55 [95% CI 0.41–0.73],  $p < 0.0001$ ). Kaplan-Meier survival curves for PFS are presented in Figure 1.

The ORR in Asian patients was 4.2% in the ramucirumab arm (95% CI 1.1–7.2) and 0.8% in the placebo arm (95% CI 0.0–2.4) ( $p = 0.132$ ), and the DCR was significantly higher for ramucirumab-treated patients (53.6%, 95% CI 46.0–61.1) compared to placebo-treated patients (33.3%, 95% CI 25.0–41.7) ( $p = 0.0043$ ). For non-Asian patients, the ORR was 6.8% in the ramucirumab arm (95% CI 2.7–10.8) compared to 1.0% in the placebo arm (95% CI 0.0–2.9%) ( $p = 0.027$ ), and the DCR was significantly higher for ramucirumab-treated patients (59.5%, 95% CI 51.5–67.4) compared to placebo-treated patients (41.7%, 95% CI 32.2–51.3) ( $p = 0.0067$ ) (Table 2).

For Asian patients, median time to deterioration of FHSI-8 scores was 2.73 months (95% CI 1.51–4.17) in the ramucirumab arm and 1.87 months (95% CI 1.48–2.83) in the placebo arm (HR 0.89 [95% CI 0.62–1.28],  $p = 0.510$ ). For non-Asian patients, median time to deterioration of FHSI-8 scores was 4.17 months (95% CI 3.02–5.52) in the ramucirumab arm and 1.94 months (95% CI 1.61–2.83) in the placebo arm (HR 0.58 [95% CI 0.40–0.85],  $p = 0.005$ ). Time to deterioration for individual parameters was comparable between Asian and non-Asian patients for the majority of factors (Fig. 3).

### Safety

The Asian safety population included 168 patients in the ramucirumab arm and 121 in the placebo arm. For non-Asian patients, the safety population consisted of 148 patients in the ramucirumab arm and 102 patients in the placebo arm.



**Fig. 3.** Time to deterioration of patient-reported symptoms using the FHSI-8 in Asian (**a**) and non-Asian (**b**) patients. FHSI-8, FACT-Hepatobiliary Symptom Index-8; n, number of events; N, number of patients in intention to treat population (also number in category); PL, placebo; RAM, ramucirumab.

Overall, the incidence of all grade and grade  $\geq 3$  treatment-emergent adverse events (TEAEs) was higher in the ramucirumab arm compared to the placebo arm in both Asian and non-Asian patients. Any grade and grade  $\geq 3$  TEAEs reported in  $\geq 15\%$  of patients in the ramucirumab arm of Asian and non-Asian patients are shown in Table 3. For Asian patients, any grade TEAEs occurring in  $\geq 15\%$  of patients and at a higher rate in the ramucirumab arm (at least 10% difference) compared to the placebo arm were peripheral edema, proteinuria, and hypertension. The most common grade  $\geq 3$  TEAEs reported in the ramucirumab arm were hypertension (7.7%), decreased appetite (1.2%), and ascites (1.2%). For non-Asian patients, any grade TEAEs occurring in  $\geq 15\%$  patients and at a higher rate in the ramucirumab arm (at least 10% difference) compared to the placebo arm were peripheral edema, proteinuria, hypertension, asthenia, and headache. The most common grade  $\geq 3$  TEAEs reported in the ramucirumab arm were hypertension (16.9%), ascites (8.8%), asthenia (4.7%), and fatigue (5.4%). Peripheral edema was the most common TEAE (any grade), while hypertension was the most common grade  $\geq 3$  TEAE in the ramucirumab arm for both Asian and non-Asian patients.

The incidence of adverse events of special interest (AESI) occurring in Asian and non-Asian patients is shown in Table 3. Common AESI of any grade in the ramucirumab arm of both Asian and non-Asian patients were epistaxis, proteinuria, and hypertension. The frequency of high-grade AESI was similar between Asian and non-Asian patients. For Asian patients, serious adverse events were reported in 31.5% of patients in the ramucirumab arm



**Table 3.** Adverse events

	Ramucirumab		Placebo	
	any grade	grade ≥3	any grade	grade ≥3
<b>TEAEs in ≥15% in the ramucirumab arm</b>				
<i>Asian patients</i> <span style="float: right;">n = 168</span> <span style="float: right;">n = 121</span>				
Any	159 (94.6%)	80 (47.6%)	110 (90.9%)	58 (47.9%)
Peripheral edema	42 (25.0%)	0 (0%)	17 (14.0%)	0 (0%)
Proteinuria	34 (20.2%)	1 (0.6%)	9 (7.4%)	0 (0%)
Decreased appetite	33 (19.6%)	2 (1.2%)	27 (22.3%)	0 (0%)
Hypertension	31 (18.5%)	13 (7.7%)	8 (6.6%)	3 (2.5%)
Fatigue	30 (17.9%)	0 (0%)	14 (11.6%)	2 (1.7%)
Ascites	28 (16.7%)	2 (1.2%)	12 (9.9%)	4 (3.3%)
<i>Non-Asian patients</i> <span style="float: right;">n = 148</span> <span style="float: right;">n = 102</span>				
Any	147 (99.3%)	101 (68.2%)	96 (94.1%)	58 (56.9%)
Peripheral edema	50 (33.8%)	3 (2.0%)	21 (20.6%)	0 (0%)
Fatigue	46 (31.1%)	8 (5.4%)	25 (24.5%)	4 (3.9%)
Nausea	39 (26.4%)	0 (0%)	18 (17.6%)	0 (0%)
Ascites	38 (25.7%)	13 (8.8%)	21 (20.6%)	5 (4.9%)
Abdominal pain	38 (25.7%)	3 (2.0%)	25 (24.5%)	4 (3.9%)
Decreased appetite	37 (25.0%)	2 (1.4%)	19 (18.6%)	1 (1.0%)
Hypertension	35 (23.6%)	25 (16.9%)	12 (11.8%)	5 (4.9%)
Asthenia	34 (23.0%)	7 (4.7%)	13 (12.7%)	1 (1.0%)
Diarrhea	33 (22.3%)	1 (0.7%)	17 (16.7%)	1 (1.0%)
Headache	30 (20.3%)	0 (0%)	8 (7.8%)	0 (0%)
Proteinuria	22 (14.9%)	3 (2.0%)	3 (2.9%)	0 (0%)
<b>AESI</b>				
<i>Asian patients</i> <span style="float: right;">n = 168</span> <span style="float: right;">n = 121</span>				
Liver injury or failure <sup>1</sup>	63 (37.5%)	26 (15.5%)	38 (31.4%)	28 (23.1%)
Bleeding/hemorrhage <sup>1</sup>	45 (26.8%)	7 (4.2%)	20 (16.5%)	7 (5.8%)
Gastrointestinal hemorrhage events <sup>1</sup>	12 (7.1%)	5 (3.0%)	11 (9.1%)	5 (4.1%)
Infusion-related reaction	6 (3.6%)	0 (0%)	0 (0%)	0 (0%)
Venous thromboembolic events <sup>1</sup>	2 (1.2%)	0 (0%)	2 (1.7%)	1 (0.8%)
Arterial thromboembolic events <sup>1</sup>	1 (0.6%)	0 (0%)	1 (0.8%)	1 (0.8%)
Wound hemorrhage	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
<i>Non-Asian patients</i> <span style="float: right;">n = 148</span> <span style="float: right;">n = 102</span>				
Liver injury or failure <sup>1</sup>	77 (52.0%)	37 (25.0%)	49 (48.0%)	31 (30.4%)
Bleeding/hemorrhage <sup>1</sup>	34 (23.0%)	8 (5.4%)	20 (19.6%)	8 (7.8%)
Gastrointestinal hemorrhage events <sup>1</sup>	12 (8.1%)	6 (4.1%)	8 (7.8%)	7 (6.9%)
Arterial thromboembolic events <sup>1</sup>	4 (2.7%)	3 (2.0%)	2 (2.0%)	1 (1.0%)
Infusion-related reaction	4 (2.7%)	1 (0.7%)	1 (1.0%)	0 (0%)
Venous thromboembolic events <sup>1</sup>	1 (0.7%)	1 (0.7%)	4 (3.9%)	4 (3.9%)
Wound hemorrhage	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)

Values are presented as n (%). AESI, adverse events of special interest; n, number of patients; TEAEs, treatment-emergent adverse events. <sup>1</sup> Pooled adverse event terms.

and in 29.8% of patients in the placebo arm; 7.7 and 6.6%, respectively, were related to the study treatment. Similarly, for non-Asian patients, serious adverse events were reported in 39.9% in the ramucirumab arm and in 38.2% in the placebo arm; 12.8 and 8.8%, respectively, were related to the study treatment. In terms of study discontinuation due to any adverse event, 12.5% of Asian patients in the ramucirumab arm and 7.4% of patients in the placebo arm discontinued, with 7.7 and 3.3%, respectively, considered related to the study treatment.

For non-Asian patients, 20.9% of patients in the ramucirumab arm and 13.7% of patients in the placebo arm discontinued study treatment due to an adverse event, with 11.5 and 3.9%, respectively, considered related to the study treatment.

For Asian patients, deaths due to an adverse event occurred in 1 patient in each treatment arm, considered to be not related to the study treatment. For non-Asian patients, deaths due to an adverse event occurred in 4.7% of patients in the ramucirumab arm, with 2.7% considered to be due to the study treatment; 2.9% of non-Asian patients in the placebo arm died, but no deaths were considered to be related to the study treatment.

## Discussion and Conclusion

HCC is a heterogeneous disease, with treatment and prognosis dependent on many factors including cancer stage, underlying liver disease, and AFP levels [4, 20]. In addition, treatment approaches vary by region, further adding to heterogeneity in patient outcomes [21]. Sorafenib was the first drug to show improved median OS in patients with HCC and is widely used as a first-line treatment [22]. Significant survival benefits are observed in patients with advanced HCC who are treated with sorafenib [22]; however, the median OS in Asian patients is shorter compared to that in Western patients [22, 23]. In the present analysis, treatment with sorafenib was shorter in Asian patients in comparison to non-Asian patients. The shorter OS outcome in Asian compared to Western patients may be associated with differences in baseline characteristics, such as tumor burden or hepatitis infection, or regional differences in disease management [21, 24, 25]. Furthermore, sorafenib treatment is often accompanied by toxicities in all regions [23]. The overall incidence of drug-related adverse events in Asian patients treated with sorafenib was 81.9%, the most commonly reported events being hand and foot skin reactions, diarrhea, fatigue, rash, and hypertension [23]. Therefore, second-line treatments are needed for patients who progress after sorafenib therapy or are unable to continue with sorafenib due to toxicity.

This pooled subgroup analysis of the global, randomized, phase 3 REACH-2/REACH trials demonstrates statistically significant and consistent survival benefits of ramucirumab treatment in Asian and non-Asian patients with advanced HCC and baseline AFP  $\geq 400$  ng/mL. Time to deterioration of patient-reported symptoms favored ramucirumab treatment in both Asian and non-Asian patients. Despite differences in some baseline patient and disease characteristics between Asian and non-Asian patients, the survival benefit was consistent and robust across all subgroups. Some of these baseline differences were expected and related to ethnic/regional variances such as body weight, TACE utilization, and hepatitis B incidence. Notably, in Asian patients the benefits of ramucirumab are consistent regardless of hepatitis B or C etiology. Many of the differences observed in Asian compared to non-Asian patients are commonly associated with a poorer prognosis, such as increased number of metastatic sites, increased extrahepatic spread, and a higher proportion of patients at Barcelona Clinic Liver Cancer stage C.

Despite the poor prognosis of patients from the Asia-Pacific region, a similar treatment effect was observed in patients with HCC treated with sorafenib. HRs were comparable in patients from the Asia-Pacific region in comparison to the population from the SHARP trial, where patients were predominantly recruited from Europe and Australasia (HR 0.68 vs. 0.69) [22, 23]. However, the overall prognosis of patients from the Asia-Pacific trial differed from those of the SHARP trial, with shorter median OS for patients in the Asia-Pacific region (Asia-Pacific, 6.5 months [sorafenib] vs. 4.2 months [placebo]; SHARP, 10.7 months [sorafenib] vs. 7.9 months [placebo]). Conversely, we demonstrated that the prognosis and treatment benefit are comparable for Asian and non-Asian patients in terms of median OS (Asian, 8.08 months

[ramucirumab] vs. 4.76 months [placebo]; non-Asian, 7.98 months [ramucirumab] vs. 5.22 months [placebo]), and in alignment with the pooled analyses of total patients from REACH-2/REACH with baseline AFP  $\geq 400$  ng/mL (8.1 vs. 5.0 months). Overall, in terms of median OS and PFS, we did not observe any significant regional differences.

High AFP concentrations ( $\geq 400$  ng/mL) are associated with aggressive disease [5, 15, 26–29]. All patients in this analysis had an AFP concentration  $\geq 400$  ng/mL, but the East Asian population exhibited even higher AFP concentrations in comparison to non-East Asian patients. Despite higher AFP concentrations in the East Asian population, the prognosis and survival benefit of ramucirumab treatment was notably consistent between both East Asian and non-Asian patients. It has been suggested that tumors expressing AFP may represent a biologically distinct subtype of HCC associated with poor prognosis, more stem-cell-like features (such as epithelial cell adhesion molecule expression) [30, 31], increased VEGF pathway activity, and increased activity of VEGFR-2-targeted antibodies in preclinical models [32]. It is possible that the prognostic impact of AFP is lessened once AFP reaches significantly high levels where tumor behavior may become more homogeneous, and as a consequence the impact of differences in AFP observed between the East Asian and non-Asian populations are less apparent. However, as mentioned above, there are also well-known geographical differences in disease characteristics and management that may also have influenced the outcomes of patients. For example, hepatitis B is more prevalent in Asia and is also commonly associated with elevated serum AFP levels [33, 34], and some have suggested that it may impact disease prognosis.

Overall, the survival benefits of ramucirumab were comparable between Asian and non-Asian patients. ORR and DCR were also comparable, with statistically significant benefits observed in both Asian and non-Asian patients treated with ramucirumab. Improvements in OS and PFS observed in this pooled analysis of Asian and non-Asian patients are comparable to the findings reported in REACH-2 [16] and in the pooled analysis of REACH-2/REACH [17]. In the East Asian subgroup analysis of the REACH trial, ramucirumab did not significantly prolong OS [35]. However, in patients with baseline AFP  $\geq 400$  ng/mL, a potentially larger survival benefit was observed for both East Asian and non-East Asian patients [35]. In this East Asian analysis from REACH, a lack of significance in terms of OS improvement [35] may have been attributed to the relatively small number of East Asian patients. With a larger cohort of Asian patients in the current REACH-2/REACH analysis, survival benefits now reach significance.

The efficacy benefits observed for Asian and non-Asian patients were achieved with a manageable safety profile. The majority of TEAEs and AESI in Asian patients were grade 3 or below, and the grade  $\geq 3$  TEAEs and AESI were generally comparable between Asian and non-Asian patients. The most common grade  $\geq 3$  TEAE in both Asian and non-Asian patients was hypertension. Liver injury and bleeding events are of particular concern in patients with HCC. Grade  $\geq 3$  bleeding/hemorrhage events were low, and comparable, between patients in the ramucirumab and placebo arms. The most common TEAE (any grade and grade  $\geq 3$ ) in both Asian and non-Asian patients was ascites. Importantly, there was no increase in high-grade AESI in Asian compared to non-Asian patients – this despite the prevalence of poor prognostic factors among Asian patients, potentially placing these patients at higher risk of developing adverse events following ramucirumab treatment, as well as the increased use of TACE in Asian patients, which may increase the risk of liver events. The overall observed safety profiles were consistent with those reported in other ramucirumab trials [16, 17, 36–39]. Note that for the REACH-2 trial, patients with an intolerance to sorafenib were enrolled. We demonstrated that these patients are able to tolerate ramucirumab treatment while maintaining quality of life.

A limitation of the REACH trials is that a biological link/mechanism of action between elevated AFP and ramucirumab has not been established. Interestingly, post hoc analysis of

the REACH trial demonstrated that treatment with ramucirumab prolonged time to AFP progression, slowed AFP increase, and was more likely to induce AFP response [40]. AFP expression and its relation to poor outcomes and aggressive tumor features is not well understood and warrants further investigation. Potentially, ramucirumab is more effective in certain HCC subtypes, and it has been suggested that AFP expression may define novel prognostic subtypes of HCC [30]. Indeed, a recent HCC biomarker study demonstrated that tumors with high AFP expression show significant activation of VEGF signaling, which provides further evidence of a mechanism for ramucirumab benefit in HCC patients with elevated AFP [41]. Potential heterogeneity between the REACH-2 and REACH trials in terms of previous therapy and patient characteristics should be noted, although no heterogeneity in treatment effect was observed in REACH-2 [16]. We report a post hoc subset analysis, and therefore caution should be used when interpreting the results. Despite this limitation, the efficacy observations in Asian and non-Asian patients with AFP  $\geq 400$  ng/mL were consistent and therefore seem unlikely to be due to chance. Further studies focusing on the relationships between AFP concentration, prognosis, and treatment efficacy in HCC are warranted.

Ramucirumab is currently indicated for advanced/recurrent gastric cancer, colorectal cancer, and non-small-cell lung cancer and is used in routine clinical practice. Recently, based on the REACH-2 trial, ramucirumab was approved by the Food and Drug Administration and the European Medicines Agency as a single agent for HCC in patients with AFP  $\geq 400$  ng/mL and previous treatment with sorafenib. Similarly, in Asia, ramucirumab was recently approved by the Pharmaceutical and Medical Devices Agency and by the Taiwan Food and Drug Administration. Based on the findings of this subanalysis, we believe ramucirumab is likely to be beneficial in Asian patients with advanced HCC and elevated AFP level who are intolerant to, or have progressed on, sorafenib – a population associated with poor prognosis and aggressive disease.

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### **Statement of Ethics**

Both REACH and REACH-2 followed the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. Each center's institutional review board or ethics committee approved the study, and all patients provided written informed consent.

### **Disclosure Statement**

M. Kudo has had a consulting/advisory role with Bayer, Bristol-Myers Squibb, Eisai Co., Ltd., and MSD; has received honoraria from AbbVie Inc., Bayer, Bristol-Myers Squibb, EA Pharma Co., Ltd., Eisai Co., Ltd., Gilead Sciences Inc., Merck Serono, MSD, Novartis, Pfizer, and Taiho Pharmaceutical; and has received research funding from AbbVie Inc., Astellas Pharma Inc., Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and Taiho Pharmaceutical. H.-Y. Lim is a member of the steering committee of Bayer. He participated in advisory board meetings for Bayer, Ipsen, Eisai, and Ono. C.-H. Hsu declares advisory board membership for Bristol-Myers Squibb, Ono, Merck/Serono, and Roche/Genentech, and research funding from MSD. A. Vogel declares honoraria from Lilly, Bayer, MSD,

Roche, Novartis, AstraZeneca, and Beigene. R. Cheng, I.S. Nitu, and P. Abada are employees and stock holders at Eli Lilly and Company. Y. Hsu is a former employee of Eli Lilly and Company and declares stock ownership and a pending patent at Eli Lilly and Company. A.X. Zhu has had a consulting/advisory role with AstraZeneca Pharmaceuticals, Bayer, Bristol-Myers Squibb, Eisai Co., Ltd., Eli Lilly, Exelixis, Merck, Novartis, and Sanofi; and has received honoraria from Eli Lilly, Bayer, Bristol-Myers Squibb, Merck, and Novartis. Y.-K. Kang is a consultant for Eli Lilly and Company, BMS, Ono, Bayer, and Blueprint. All other authors report no conflicts of interest.

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## Author Contributions

P. Abada and A.X. Zhu were involved in study conception and design. C.-J. Yen, M. Kudo, H.-Y. Lim, A. Vogel, G. Brandi, P. Abada, and A.X. Zhu were involved in patient recruitment. M. Kudo, H.-Y. Lim, C.-H. Hsu, A. Vogel, G. Brandi, A.X. Zhu, and Y.-K. Kang were involved in data collection. All authors were involved in data review and analysis as well as drafting and critical review of the manuscript and provided final approval for submission.

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