

# Pattern of progression in advanced hepatocellular carcinoma treated with ramucirumab

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## Abstract

**Background & Aims:** Radiological progression patterns to first-line sorafenib have been associated with post-progression and overall survival in advanced hepatocellular carcinoma, but these associations remain unknown for therapies in second- and later-line settings. This post hoc analysis of REACH and REACH-2 examined outcomes by radiological progression patterns in the second-line setting of patients with advanced hepatocellular carcinoma treated with ramucirumab or placebo.

**Methods:** Patients with advanced hepatocellular carcinoma, Child-Pugh A and Eastern Cooperative Oncology Group Performance Status 0 or 1 with prior sorafenib were randomized to receive ramucirumab 8mg/kg or placebo every 2 weeks. Among 625 patients with  $\geq 1$  progression pattern (new extrahepatic lesion [including new macrovascular invasion], new intrahepatic lesion, extrahepatic growth or intrahepatic growth), data were analysed by trial and for pooled individual patient data for REACH-2 and REACH (alpha-fetoprotein  $\geq 400$  ng/mL). Cox models evaluated prognostic implications of progression patterns on overall and post-progression survival.

**Results:** Post-progression survival was worse among those with new extrahepatic lesions in REACH (HR 2.33, 95% CI 1.51-3.60), REACH-2 (HR 1.49, 95% CI 0.72-3.08) and the pooled population (HR 1.75, 95% CI 1.12-2.74) compared to other progression patterns. Overall survival was also significantly reduced in those with new extrahepatic lesions across studies. Ramucirumab provided an overall survival benefit across progression patterns, including patients with new extrahepatic lesions (HR 0.56, 95% CI 0.39-0.80) in the pooled population.

**Conclusions:** The emergence of new extrahepatic lesions in the second-line setting is a poor prognostic factor for post-progression survival. The benefit of ramucirumab for overall survival was consistent across progression patterns.

**Abbreviations:** AFP, alpha-fetoprotein; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; HR, hazard ratio; mRECIST, modified response evaluation criteria in solid tumours; OS, overall survival; PPS, post-progression survival; RECIST, response evaluation criteria in solid tumours; VEGF, vascular endothelial growth factor; VEGFRs, vascular endothelial growth factor receptors.

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## KEY WORDS

best supportive care, disease progression patterns, new extrahepatic lesion, post-progression survival, ramucirumab

## 1 | INTRODUCTION

Vascular endothelial growth factor (VEGF) is overexpressed in hepatocellular carcinoma (HCC), and thus VEGF receptors (VEGFRs) 1 and 2 and their ligands play an important role in tumour angiogenesis and contribute to the pathogenesis and progression of advanced HCC.<sup>1</sup> Several antiangiogenic multikinase inhibitors targeting this pathway have demonstrated clinical benefits in the phase 3 setting, including sorafenib and lenvatinib in the first-line, regorafenib for sorafenib-tolerant patients, and cabozantinib in patients intolerant or refractory to sorafenib.<sup>2-4</sup> Ramucirumab (an immunoglobulin G1 VEGFR-2 antagonist) is the first and only treatment approved in a biomarker-selected population with alpha-fetoprotein (AFP) concentrations  $\geq 400$  ng/mL in advanced HCC.<sup>5,6</sup> Global approvals were based on evidence from the phase 3 REACH and REACH-2 studies in which ramucirumab, compared to placebo, demonstrated superior overall survival (OS) in patients with baseline AFP concentrations  $\geq 400$  ng/mL following sorafenib.<sup>4,7,8</sup>

Among patients with advanced HCC, radiological progression patterns, specifically the presence of new extrahepatic lesions and/or vascular invasion on first-line sorafenib, have been associated with poorer OS and post-progression survival (PPS) compared to other radiological progression patterns.<sup>3,9-11</sup> Pattern of progression on first-line sorafenib was prognostic of poorer survival in other trials of second-line regorafenib<sup>12</sup> and tivantinib cohorts.<sup>13</sup> However, these second-line studies were limited in that progression patterns were examined only in first-line sorafenib and not during second-line treatment.

The response evaluation criteria in solid tumours (RECIST) version 1.1,<sup>14</sup> and modified RECIST (mRECIST)<sup>15</sup> are commonly used to evaluate time to tumour progression in HCC trials. However, neither RECIST nor mRECIST use progression patterns in evaluating tumour progression, which could refine the characterization of both, as suggested by the prognostic value in the first-line sorafenib setting.<sup>9-13</sup> Determining the utility of radiological progression patterns as a stratification or prognostic factor is critical for improving the design and analysis of second-line and later advanced HCC trials.<sup>9,11,12</sup>

The objective of this study was to examine the incidence of radiological progression patterns in the second-line advanced HCC setting and to determine whether there is a relationship between progression pattern and OS and PPS in patients treated with ramucirumab or placebo.

## 2 | PATIENTS AND METHODS

### 2.1 | Study design

Phase 3 REACH and REACH-2 study designs have been previously reported in detail (Figure S1).<sup>7,8</sup> Briefly, 565 patients ( $n = 283$  in the

### Lay Summary

- Development of new extrahepatic lesions in the second-line setting is associated with worse overall survival and post-progression survival in patients with advanced hepatocellular carcinoma receiving ramucirumab or placebo.
- Patterns of progression may help refine risk characterization in the design and analysis of second-line and later trials.

ramucirumab arm and  $n = 282$  in the placebo arm) were enrolled in the randomized, placebo-controlled, double-blind REACH trial, 250 of whom had AFP concentrations  $\geq 400$  ng/mL. In REACH-2, a randomized, double-blind, placebo-controlled trial, 292 patients were enrolled ( $n = 197$  in the ramucirumab arm and  $n = 95$  in the placebo arm).<sup>7</sup> Patients in REACH and REACH-2 had advanced HCC and Barcelona Clinic Liver Cancer stage B or C that was refractory or not amenable to locoregional therapy, Child-Pugh A liver disease and Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1;<sup>7,8</sup> REACH-2 had an additional inclusion criterion of serum AFP concentration  $\geq 400$  ng/mL.<sup>7</sup> In both trials, patients were randomly assigned (1:1 REACH and 2:1 REACH-2) to receive either ramucirumab 8 mg/kg or placebo intravenously for 1 hour every 2 weeks until disease progression, unacceptable toxicity or withdrawal of consent.<sup>7,8</sup> Patients in REACH and REACH-2 were from several geographic regions, including the Americas, Europe, Australia and Israel (collectively Region 1); Asia, excluding Japan (Region 2); and Japan (Region 3). Both trials complied with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable local regulations. Ethics committees at all participating centres approved the protocol, and all patients provided written informed consent.

### 2.2 | Outcomes and assessments

Tumour response was assessed according to RECIST version 1.1.<sup>14</sup> Radiological assessments of tumours were conducted at baseline, every 6 weeks during the first 6 months of treatment and every 9 weeks thereafter. Radiological progression patterns on ramucirumab or placebo in the second-line setting were classified into four non-mutually exclusive categories of new extrahepatic lesion, new intrahepatic lesion, extrahepatic growth or intrahepatic growth based on previously published definitions<sup>11</sup> and RECIST

data entered into case report forms. The categories were defined as follows: new extrahepatic lesion (including new macrovascular invasion), patients developed new lesion(s) outside the liver during ramucirumab or placebo treatment; new intrahepatic lesion, patients developed new lesion(s) if the tumour was inside the liver (ie hepatic, liver or liver fissure) during ramucirumab or placebo treatment; extrahepatic growth, patients experienced  $\geq 20\%$  growth in the target tumour outside the liver during ramucirumab or placebo treatment; and intrahepatic growth, patients experienced  $\geq 20\%$  growth in the target tumour inside the liver during ramucirumab or placebo treatment.<sup>11</sup> Overall survival was defined as time from randomization to death from any cause. Using radiological lesion data captured on the case report form, radiological progression patterns on ramucirumab or placebo in REACH and REACH-2 were calculated at the time of RECIST progression, with a method consistent with prior studies.<sup>11,12</sup> Post-progression survival was defined as time from progression (per RECIST version 1.1) to time of death.

### 2.3 | Statistical analyses

Two hundred thirty-two patients from REACH ( $n = 151$ ) and REACH-2 ( $n = 81$ ) who did not have a radiological progression pattern during the study were excluded from this analysis (Figure 1). Reasons for missing progression pattern included patient who did not exhibit progression (ie still receiving benefit of study treatment), death without progression, withdrawal of consent,  $\geq 2$  missed study visits, no documented death or progressive disease, patient started a new anticancer therapy, patient was lost to follow-up or a patient had no documented post-baseline tumour assessments.

All patients included in analyses had at least one radiological progression pattern on ramucirumab or placebo in the second-line setting, and patients could have  $\geq 1$  progression site. Patient data were analysed by trial and in a pooled meta-analysis of individual patient data from REACH and REACH-2. It should be noted that for analyses conducted by trial, patients enrolled in REACH

were included regardless of baseline AFP level, while in the pooled analyses, only patients who had AFP concentration  $\geq 400$  ng/mL were included. 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, as previously described.<sup>7</sup> Cox models evaluated the effect of progression pattern in the second-line setting on OS, adjusting for baseline ECOG PS, AFP concentration, macrovascular invasion and study arm. Cox models also evaluated the effect of progression pattern in the second-line setting on PPS (third-line setting), adjusting for ECOG PS and AFP concentration at progression.

## 3 | RESULTS

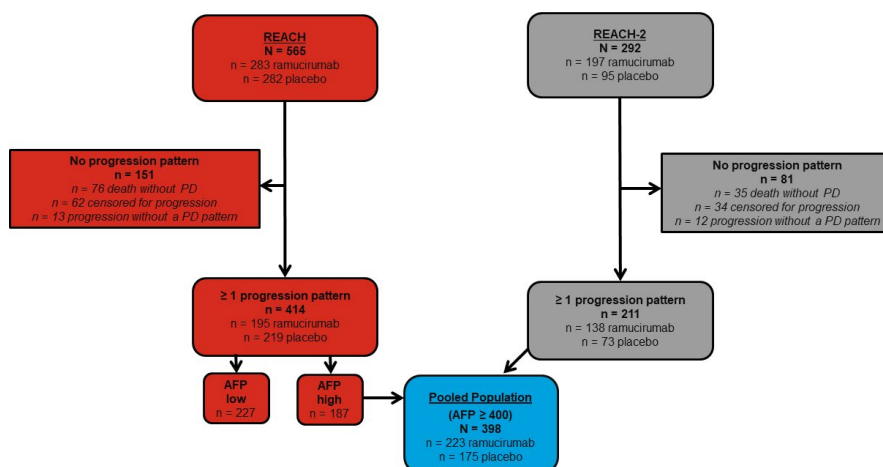
### 3.1 | Baseline characteristics

This exploratory analysis included 625 randomized patients with advanced HCC who had  $\geq 1$  radiological progression pattern on ramucirumab or placebo within the second-line setting (Figure 1). The proportion of patients with each progression pattern was similar between study arms for each trial and the pooled population (Table 1). Demographic and disease characteristics by progression pattern were generally balanced between treatment arms (Table 2).

### 3.2 | Overall survival

In an unadjusted Kaplan-Meier analysis, development of new extrahepatic lesions was significantly associated with poorer OS compared to patients who did not develop new extrahepatic lesions (5.3 months vs 8.6 months; stratified HR 1.45, 95% CI 1.16-1.82; Figure 2).

When adjusting for baseline prognostic factors that were statistically significant for OS (baseline macrovascular invasion, ECOG PS, AFP concentration) and treatment arm, development of new



**FIGURE 1** Flowchart showing derivation of analytic samples for analyses in REACH, REACH-2 and the pooled population. AFP, alpha-fetoprotein; N, number of participants in overall population; n, number of participants in sample of population; PD, progressive disease

**TABLE 1** Radiological progression patterns on ramucirumab or placebo during REACH and REACH-2

Progression during REACH and REACH-2 n (%) <sup>a</sup>	REACH N = 414		REACH-2 N = 211		Pooled (≥400 ng/mL) N = 398	
	RAM n = 195	PL n = 219	RAM n = 138	PL n = 73	RAM n = 223	PL n = 175
New extrahepatic lesion	81 (42)	72 (33)	48 (35)	24 (33)	85 (38)	72 (41)
New intrahepatic lesion	49 (25)	67 (31)	30 (22)	14 (19)	50 (22)	44 (25)
Extrahepatic growth	66 (34)	76 (35)	61 (44)	32 (44)	89 (40)	68 (39)
Intrahepatic growth	77 (40)	96 (44)	45 (33)	32 (44)	79 (35)	70 (40)

Abbreviations: n, number of patients per category; N, number of patients overall; PL, placebo; RAM, ramucirumab.

<sup>a</sup>Patients could have had ≥1 pattern of progression.

extrahepatic lesions during the study was prognostic for OS in REACH [HR 1.84, 95% CI 1.24-2.73, REACH-2 (HR 1.94, 95% CI 1.05-3.60)] and the pooled population (HR 1.89, 95% CI 1.27-2.83; Table 3). No other progression pattern demonstrated a statistically significant difference in OS across the study populations (Table 3).

Overall survival by progression pattern on ramucirumab demonstrated that patients who received ramucirumab had a consistent OS benefit compared to those who received placebo in the pooled population: new extrahepatic lesion (HR 0.56, 95% CI 0.39-0.80), new intrahepatic lesion (HR 0.70, 95% CI 0.43-1.15), extrahepatic growth (HR 0.62, 95% CI 0.43-0.88) and intrahepatic growth (HR 0.68, 95% CI 0.48-0.97; Table 4 and Figure 3). Results were similar in REACH and REACH-2, although they did not reach statistical significance in REACH-2 (Table S1).

### 3.3 | Post-progression survival

Post-progression survival by radiographic progression patterns was examined in 398 patients in REACH, 205 patients in REACH-2 and 386 patients in the pooled population; 22 patients were excluded because of loss to follow-up or withdrawal of consent for follow-up after progression. After adjusting for prognostic factors at the time of radiological progression (ECOG PS and AFP concentration at progression), development of new extrahepatic lesions during the study was prognostic for PPS in REACH (HR 2.33, 95% CI 1.51-3.60) and the pooled population (HR 1.75, 95% CI 1.12-2.74; Table 5), but did not reach statistical significance in REACH-2 (HR 1.49, 95% CI 0.72-3.08; Table 5). No other progression pattern demonstrated a statistical difference in PPS across the study populations. Post-progression survival by progression pattern demonstrated consistent ramucirumab benefit in PPS, irrespective of progression pattern (Table S2).

## 4 | DISCUSSION

This study examined the relationship between radiological progression patterns during treatment with ramucirumab or placebo

in the second-line setting and OS and PPS following radiological progression. After adjusting for known prognostic factors, development of new extrahepatic lesions was prognostic for poorer OS and PPS. These findings were consistent in a biomarker-selected population of patients (AFP concentration ≥400 ng/mL) with advanced HCC, which is notable given the potential for different tumour biology and poor prognosis in patients with elevated AFP.<sup>16,17</sup> These results are supportive of other studies that examined progression patterns on sorafenib in the first-line setting and demonstrated that the development of new extrahepatic lesions, compared to other patterns of progression, is associated with poor prognosis in patients with advanced HCC.<sup>9-11</sup> Compared to other radiological progression patterns, the development of new extrahepatic lesions on sorafenib was also associated with poor prognosis in second-line trials of regorafenib and tivantinib, regardless of treatment.<sup>12,13</sup> It is important to note that although patterns of progression on sorafenib have been investigated in second-line trials of regorafenib<sup>12</sup> and tivantinib,<sup>13</sup> these studies only identified the pattern of progression to first-line sorafenib treatment. To our knowledge, this is the first study to investigate progression patterns in the second-line setting and the potential effect on second-line therapy. Thus, more work is needed to confirm whether new extrahepatic lesions developed in these second-line settings are prognostic of PPS outcomes, as well as whether outcomes are similar in biomarker-defined populations. Stratification for patterns of progression has been considered for trial design in HCC in a recent consensus manuscript.<sup>18</sup>

The development of new extrahepatic lesions was associated with PPS for patients in REACH and the pooled population, but not in REACH-2. We believe this is possibly because of differing patient profiles in REACH and REACH-2. One REACH-2 inclusion criterion was an AFP ≥400 ng/mL at baseline; this inclusion criterion may indicate that patients enrolled in REACH-2 had differing disease severity or prognosis from time of enrolment into the clinical trial, which could influence the effects that new progression patterns exert on outcomes. Additionally, the analytic sample size of REACH-2 was smaller than that for REACH and the pooled population. It is possible that these results did not reach statistical significance given the smaller sample size.

**TABLE 2** Baseline demographic and disease characteristics of pooled patients with alpha-fetoprotein  $\geq 400$  ng/mL by radiological progression patterns on ramucirumab or placebo

n (%), except where indicated	New extrahepatic lesion		New intrahepatic lesion		Extrahepatic growth		Intrahepatic growth	
	RAM n = 85	PL n = 72	RAM n = 50	PL n = 44	RAM n = 89	PL n = 68	RAM n = 79	PL n = 70
Sex, male	70 (82)	60 (83)	44 (88)	34 (77)	63 (71)	58 (85)	57 (72)	56 (80)
Age (y), median	62	60	65	62	61	59	63	62
ECOG PS 0	41 (48)	45 (63)	26 (52)	29 (66)	54 (61)	37 (54)	42 (53)	36 (51)
Child-Pugh Score A-5	48 (57)	49 (68)	32 (64)	28 (64)	59 (66)	48 (71)	51 (65)	43 (61)
BCLC stage C	77 (91)	70 (97)	38 (76)	35 (80)	87 (98)	65 (96)	64 (81)	55 (79)
Macrovascular invasion	28 (33)	26 (36)	18 (36)	10 (23)	27 (30)	18 (27)	34 (43)	27 (39)
Extrahepatic spread	67 (79)	64 (89)	26 (52)	27 (61)	84 (94)	68 (100)	51 (65)	45 (64)
AFP, median (IQR), ng/mL	4299 (1196-23802)	4535 (1226-28054)	2166 (1015-16484)	3430 (987-27559)	5681 (1590-23345)	4361 (1091-21435)	7926 (1449-38628)	2993 (973-16949)
Geographic region								
Region 1 (Americas, EU, Australia, Israel)	40 (47)	31 (43)	29 (58)	27 (61)	31 (35)	14 (21)	34 (43)	36 (51)
Region 2 (Asia, excluding Japan)	31 (37)	29 (40)	14 (28)	7 (16)	38 (43)	41 (60)	25 (32)	24 (34)
Region 3 (Japan)	14 (17)	12 (17)	7 (14)	10 (23)	20 (23)	13 (19)	20 (25)	10 (14)
Aetiology of liver disease								
Hepatitis B virus	36 (42)	41 (57)	15 (30)	15 (34)	41 (46)	43 (63)	34 (43)	28 (40)
Hepatitis C virus	15 (18)	12 (17)	18 (36)	13 (30)	20 (23)	12 (18)	18 (23)	15 (21)
Significant alcohol use	19 (22)	9 (13)	11 (22)	7 (16)	19 (21)	7 (10)	14 (18)	15 (21)

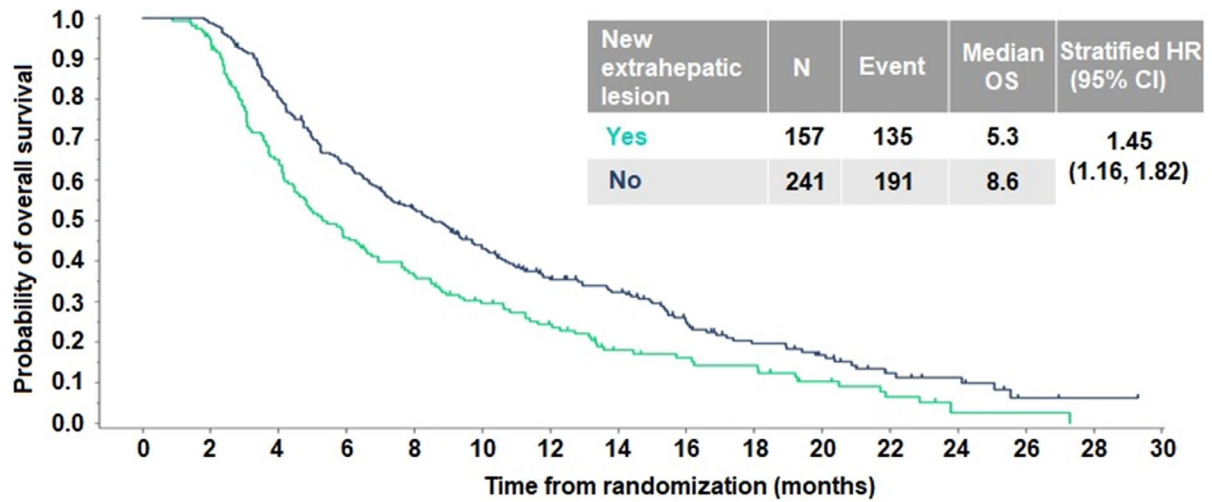
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EU, Europe; IQR, interquartile range; n, number of patients per category; PL, placebo; RAM, ramucirumab.

Hepatocellular carcinoma staging and risk assessment, occurring when a patient is diagnosed with advanced HCC, are critical to identifying optimal therapy and for disease prognosis.<sup>4</sup> However, there is a need to identify novel stratification or prognostic factors in the design and analysis of later trials to refine risk assessment in second-line and later trials. Taken together with prior studies,<sup>11-13</sup> data presented here suggest that radiological progression patterns should continue to be explored as a potential prognostic factor and validated in prospective trials.

There are no current data on radiological progression patterns and post-progression clinical outcomes for patients with advanced HCC who received immunotherapy-based treatments such as bevacizumab plus atezolizumab, nivolumab or pembrolizumab,<sup>19-24</sup> and it is unknown whether associations between progression patterns and PPS are similar after treatment with checkpoint inhibitors compared to VEGFR-targeted agents. Evidence from studies of

other solid tumours suggests impending challenges with immune checkpoint inhibitors for response assessment.<sup>22</sup> For example, patients may develop atypical response patterns and/or pseudo-progression, a phenomenon in which patients initially appear to progress but later show a decrease or stabilization in tumour burden.<sup>22</sup> Given that several immunotherapies are approved or pending approval for the treatment of advanced HCC, evaluating the impact of progression patterns with these novel therapies will be important in assessing whether they will be used in trial design or clinical practice.

Some limitations should be considered when interpreting these results. Although the data included 2 phase 3 trials and a meta-analysis of pooled data, which substantially increased the sample size, these post hoc analyses were not powered specifically for these types of analyses. In this study, we did not know the progression patterns of patients on first-line sorafenib or how they may have



<b>New extrahepatic lesion, yes</b>	157	145	98	69	54	41	32	20	17	15	9	5	1	1	0	0
<b>New extrahepatic lesion, no</b>	241	238	193	153	122	94	71	61	41	28	21	11	8	2	1	0

**FIGURE 2** FKaplan-Meier curves of overall survival by radiographic progression patterns. Data presented are combined arms (ramucirumab plus placebo) in the pooled population. CI, confidence interval; HR, hazard ratio; N, number of patients overall; OS, overall survival

**TABLE 3** Multivariate Cox regression analysis of overall survival by radiological progression patterns on ramucirumab or placebo

HR (95% CI) P-value	REACH N = 414	REACH-2 N = 211	Pooled (≥400 ng/mL) N = 398
Treatment RAM vs PL	0.63 (0.44-0.90) 0.0102	0.76 (0.41-1.44) 0.4035	0.56 (0.38-0.83) 0.0038
Macrovascular invasion at baseline Yes vs no	1.02 (0.69-1.51) 0.9135	1.28 (0.71-2.31) 0.4214	1.24 (0.83-1.85) 0.2919
ECOG PS at baseline 0 vs 1	0.71 (0.50-1.00) 0.0525	0.57 (0.31-1.04) 0.0686	0.55 (0.38-0.81) 0.0020
Baseline AFP (ng/mL) Log-transformed	1.23 (1.10-1.40) 0.0009	1.69 (1.16-2.44) 0.0058	1.52 (1.18-1.96) 0.0013
New extrahepatic lesion Yes vs no	1.84 (1.24-2.73) 0.0026	1.94 (1.05-3.60) 0.0353	1.89 (1.27-2.83) 0.0019
New intrahepatic lesion Yes vs no	1.10 (0.73-1.66) 0.6639	1.55 (0.67-3.58) 0.3104	1.24 (0.76-2.02) 0.3840
Extrahepatic growth Yes vs no	1.08 (0.75-1.55) 0.6848	1.31 (0.71-2.43) 0.3922	1.12 (0.75-1.67) 0.5955
Intrahepatic growth Yes vs No	1.08 (0.75-1.57) 0.6856	1.68 (0.95-2.97) 0.0764	1.48 (1.01-2.16) 0.0453

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; PL, placebo; RAM, ramucirumab.

Progression during REACH and REACH-2	n	Events	Median OS months		HR (95% CI) P-value
			RAM	PL	
New extrahepatic lesion					
Yes	157	135	7.6	4.3	0.56 (0.39-0.80) 0.0013
No	241	191	9.4	7.1	0.81 (0.61-1.09) 0.1666
New intrahepatic lesion					
Yes	94	72	11.1	4.7	0.70 (0.43-1.15) 0.1579
No	304	254	8.2	5.9	0.72 (0.56-0.93) 0.0115
Extrahepatic growth					
Yes	157	132	9.1	5.4	0.62 (0.43-0.88) 0.0076
No	89	70	6.5	4.3	0.54 (0.32-0.91) 0.0213
Intrahepatic growth					
Yes	149	127	8.0	5.2	0.68 (0.48-0.97) 0.0347
No	152	123	7.6	5.9	0.99 (0.68-1.44) 0.9657

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number of patients in category; OS, overall survival; PL, placebo; RAM, ramucirumab.

affected progression patterns of patients on ramucirumab or placebo; however, this was not an aim of these analyses. As reported in the Methods, patients who did not have a recorded progression pattern were excluded from analyses. For this reason, these results are only generalizable to patients who developed radiological progression. Since patients in REACH and REACH-2 had only received prior sorafenib, which was the only approved first-line treatment when these trials were developed,<sup>7,8</sup> the potential clinical benefit of ramucirumab after therapies other than sorafenib is also unknown, but is currently being investigated as a separate ongoing cohort within the REACH-2 study. Additionally, we do not currently have a clear understanding of what determines the pattern of progression. More work is needed to understand the biological and pathophysiological mechanisms contributing to the development of different progression patterns.

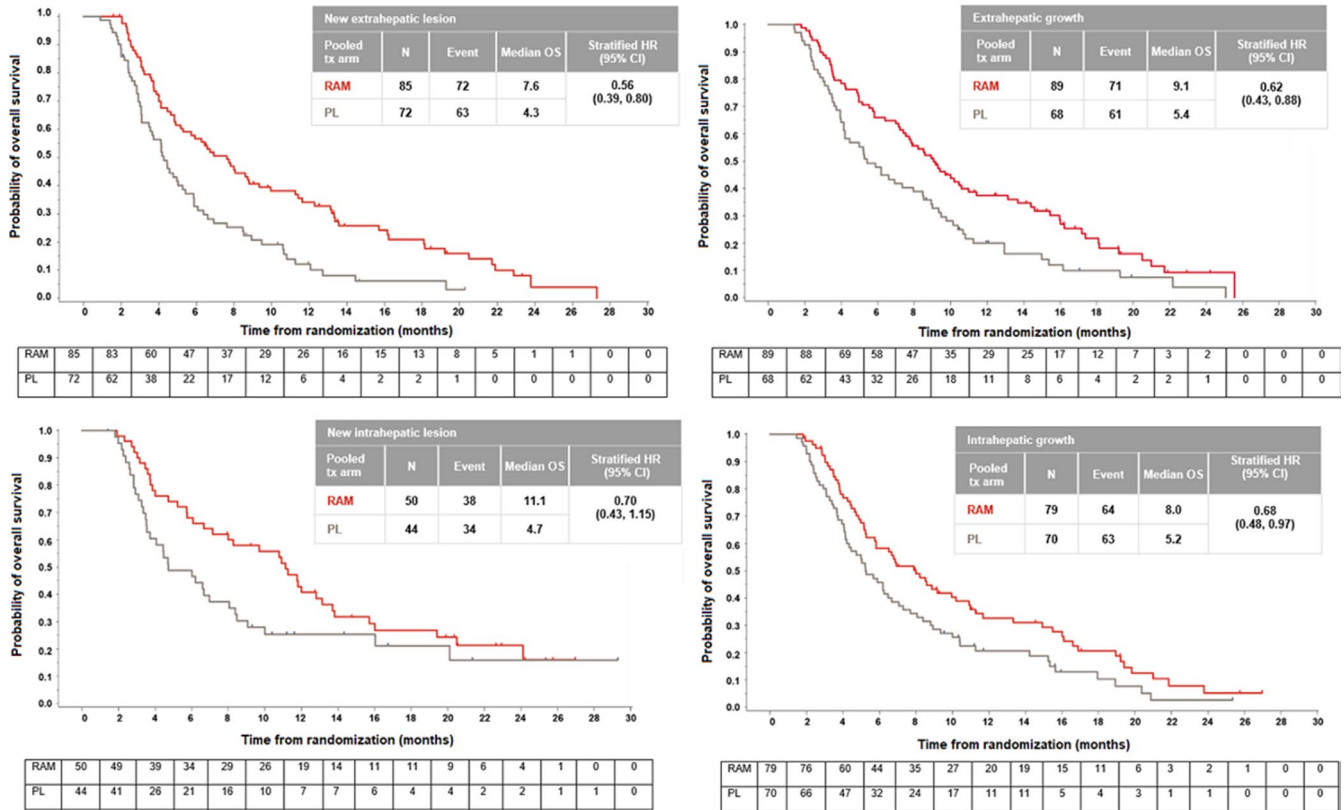
#### 4.1 | Conclusions

Acknowledging the limitations of post-randomization analysis, the emergence of new extrahepatic lesions during treatment with ramucirumab or placebo is an independent prognostic factor for OS and PPS. The OS benefit of ramucirumab in patients with advanced HCC and AFP concentrations  $\geq 400$  ng/mL was consistent across all radiological progression patterns. The results of these analyses warrant further study.

**TABLE 4** Subgroup analysis of overall survival on ramucirumab or placebo in the pooled population

#### DECLARATION OF POTENTIAL CONFLICTS OF INTEREST

Maria Reig reports receiving grants and other from Bayer Schering Pharma and Ipsen; and receiving consulting fees from Bristol-Myers Squibb, Roche, Ipsen, AstraZeneca, Roche, Eli Lilly and Company and Gilead Sciences. Peter R. Galle reports receiving grants and personal fees from Bayer and personal fees from Bayer, Bristol-Myers Squibb, AstraZeneca, Sirtex, Merck Sharp & Dohme, Eisai, Ipsen and Roche, all outside of the submitted work. Masatoshi Kudo reports receiving personal fees and other from Bayer and Merck Sharp & Dohme; receiving grants, personal fees and other from Eisai Co., Ltd.; other from Ono Pharmaceutical; and receiving grants from Daiichi Sankyo, Medico's Hirata, Otsuka Pharmaceutical, Taiho Oncology, Astellas Pharma, Chugai Pharmaceutical, Bristol-Myers Squibb, EA Pharma, Takeda and Gilead Sciences, all outside of the submitted work. Richard Finn reports serving as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly and Company, Merck, Novartis and Roche/Genentech. Josep M. Llovet reports receiving research support from Bayer HealthCare Pharmaceuticals, Eisai Inc, Bristol-Myers Squibb, Ipsen and Boehringer-Ingelheim; and receiving consulting fees from Eisai Inc, Merck, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Celsion Corporation, Eli Lilly and Company, Ipsen, Glycotest, Roche, AstraZeneca, Sirtex, and Nucleix. Andrea L. Metti is an employee of Syneos Health who contracts with Eli Lilly and Company. William R. Schelman is a former employee and shareholder of Eli Lilly and Company. Kun Liang,



**FIGURE 3** Kaplan-Meier curves of overall survival by radiographic progression patterns on ramucirumab or placebo during REACH and REACH-2. CI, confidence interval; HR, hazard ratio; N, number of patients overall; OS, overall survival; PL, placebo; RAM, ramucirumab; Tx, treatment

**TABLE 5** Multivariate Cox regression analysis of post-progression survival by radiographic patterns on ramucirumab or placebo

HR (95% CI) P-value	REACH N = 398 <sup>a</sup>	REACH-2 N = 205 <sup>†</sup>	Pooled (≥400 ng/ mL) N = 386 <sup>a</sup>
ECOG PS at progression 0 vs ≥1	0.54 (0.35-0.82) 0.0039	0.69 (0.34-1.37) 0.2854	0.64 (0.41-1.00) 0.0505
AFP (ng/mL) at progression Log-transformed	1.27 (1.11-1.44) 0.0004	1.84 (1.19-2.86) 0.0066	1.58 (1.20-2.07) 0.0011
New extrahepatic lesion Yes vs no	2.33 (1.51-3.60) 0.0001	1.49 (0.72-3.08) 0.2784	1.75 (1.12-2.74) 0.0135
New intrahepatic lesion Yes vs no	1.44 (0.91-2.29) 0.1166	1.40 (0.55-3.52) 0.4815	1.44 (0.85-2.44) 0.1760
Extrahepatic growth Yes vs no	1.40 (0.95-2.07) 0.0921	1.55 (0.76-3.19) 0.2286	1.28 (0.83-1.95) 0.2634
Intrahepatic growth Yes vs no	1.35 (0.90-2.04) 0.1467	1.40 (0.73-2.65) 0.3092	1.50 (0.97-2.33) 0.0663

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; N, number of patients overall.

<sup>a</sup>22 patients were excluded because of loss to follow-up or withdrawal of consent for follow-up after progression.

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## 6 | STATEMENT OF FINANCIAL SUPPORT

This study was sponsored by Eli Lilly and Company.

## 7 | TRIAL REGISTRATION NUMBERS

Clinicaltrials.gov: NCT01140347 (REACH) and NCT02435433 (REACH-2).

## 8 | ETHICS APPROVAL STATEMENT

Both trials complied with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable local regulations. Ethics committees at all participating centres approved the protocol.

## 9 | PATIENT CONSENT STATEMENT

All patients provided written informed consent.

## 10 | PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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## REFERENCES

- Zhu AX, Duda DG, Shahani DV, Jain RK. HCC and angiogenesis: possible targets and future directions. *Nat Rev Clin Oncol*. 2011;8:292-301.
- Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2018;15:599-616.
- Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378-390.
- Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv238-iv255.
- United States Food and Drug Administration. FDA approves ramucirumab for hepatocellular carcinoma. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ramucirumab-hepatocellular-carcinoma> [Accessed March 19, 2020]
- Bruix J, da Fonseca LG, Reig M. Insights into the success and failure of systemic therapy for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2019;16:617-630.
- Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased  $\alpha$ -fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:282-296.
- Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16:859-870.
- Iavarone M, Cabibbo G, Biolato M, et al. Predictors of survival in patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib. *Hepatology*. 2015;62:784-791.
- Ogasawara S, Chiba T, Ooka Y, et al. Post-progression survival in patients with advanced hepatocellular carcinoma resistant to sorafenib. *Invest New Drugs*. 2016;34:255-260.
- Reig M, Rimola J, Torres F, et al. Post-progression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. *Hepatology*. 2013;58:2023-2031.
- Bruix J, Merle P, Granito A, et al. Survival by pattern of tumor progression during prior sorafenib (SOR) treatment in patients with hepatocellular carcinoma (HCC) in the phase III RESORCE trial comparing second-line treatment with regorafenib (REG) or placebo [abstract]. *J Clin Oncol*. 2017;35(Suppl 4):Abstract 229.
- Rimassa L, Assenat E, Peck-Radosavljevic M, et al. Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study. *Lancet Oncol*. 2018;19:682-693.
- Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.
- Lencioni R, Montal R, Torres F, et al. Objective response by mRECIST as a predictor and potential surrogate end-point of overall survival in advanced HCC. *J Hepatol*. 2017;66:1166-1172.
- Nakazawa T, Hidaka H, Takada J, et al. Early increase in  $\alpha$ -fetoprotein for predicting unfavorable clinical outcomes in patients with advanced hepatocellular carcinoma treated with sorafenib. *Eur J Gastroenterol Hepatol*. 2013;25:683-689.
- Tangkijvanich P, Anukulkarnkusol N, Suwangool P, et al. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol*. 2000;31:302-308.
- Llovet JM, Villanueva A, Marrero JA, et al. Trial design and end-points in hepatocellular carcinoma: AASLD consensus conference. *Hepatology*. 2020. <https://doi.org/10.1002/hep.31327>
- El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389:2492-2502.
- Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894-1905.
- Finn RS, Ryoo B-Y, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in

- KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol.* 2020;38:193-202.
22. Forner A, Da Fonseca LG, Díaz-González A, Sanduzzi-Zamparelli M, Reig M, Bruix J. Controversies in the management of hepatocellular carcinoma. *JHEP Rep.* 2019;1:17-29.
  23. Yau T, Park JW, Finn RS, et al. CheckMate 459: a randomized multi-center phase 3 study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (PTS) with advanced hepatocellular carcinoma (AHCC) [abstract]. *Ann Oncol.* 2019;30(5):v874-v875. Abstract 6572.
  24. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol.* 2018;19:940-952.

#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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