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Ramucirumab in elderly patients with hepatocellular carcinoma and elevated alpha-fetoprotein after sorafenib in REACH and REACH-2

Masatoshi Kudo[1] | Peter R. Galle[2] | Josep M. Llovet[3,4] | Richard S. Finn[5] | Arndt Vogel[6] | Kenta Motomura[7] | Eric Assenat[8] | Philippe Merle[9] | Giovanni Brandi[10] | Bruno Daniele[11] | Takuji Okusaka[12] | Jiří Tomášek[13] | Christophe Borg[14] | Vincenzo Dadduzio[15] | Manabu Morimoto[16] | Marc Pracht[17] | Min-Hua Jen[18] | Nora Drove Ubreva[19] | Ryan C. Widau[20] | Kenta Shinozaki[19] | Reigetsu Yoshikawa[19] | Andrew X. Zhu[21]

[1]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan

[2]Department of Internal Medicine, Mainz University Medical Center, Mainz, Germany

[3]Translational Research in Hepatic Oncology Group, Liver Unit, IDIBAPS, Hospital Clinic Barcelona, University of Barcelona, Barcelona, Catalonia, Spain

[4]Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[5]Department of Medicine, Division of Hematology/Oncology, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[6]Department of Hepatology, Gastroenterology and Endocrinology, Medizinische Hochschule Hannover, Hannover, Germany

[7]Department of Hepatology, Aso Iizuka Hospital, Fukuoka, Japan

[8]Department of Medical Oncology, CHU de Montpellier, Montpellier, France

[9]Hepatology and Gastroenterology Unit, Croix-Rousse Hospital, Northern Lyon Hospital Group, Lyon, France

[10]Department of Experimental, Diagnostic and Speciality Medicicne, University Hospital S.Orsola-Malpighi, Bologna, Italy

[11]Department of Oncology, Azienda Ospedaliera Gaetano Rummo, Benevento, Italy

[12]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan

[13]Department of Complex Oncology Care, Masaryk Memorial Cancer Institute, Masaryk University, Brno, Czech Republic

[14]Department of Medical Oncology, University Hospital of Besançon, Besançon, France

[15]Department of Clinical and Experimental Oncology, Medical Oncology Unit-1, Veneto Institute of Oncology (IOV) – IRCCS, Padua, Italy

[16]Department of Hepatobiliary and Pancreatic Oncology, Kanagawa Cancer Center, Yokohama, Japan

[17]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France

[18]Global Statistical Sciences, Eli Lilly and Company, Surrey, UK

[19]Medicines Development Unit Japan, Eli Lilly Japan K.K, Kobe, Japan

[20]Oncology, Eli Lilly and Company, Indianapolis, IN, USA

[21]Department of Medicine, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

Abbreviations: AE, adverse event; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; $C_{min}1$, minimum concentration after administration of first dose; CPI, checkpoint inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; FHSI, Functional Hepatobiliary Symptoms Index; HCC, hepatocellular carcinoma; HR, hazard ratio; max, maximum; MedDRA, Medical Dictionary for Regulatory Activities; min, minimum; mTKI, multitargeted tyrosine kinase inhibitor; NASH, non-alcoholic steatohepatitis; NE, not evaluable; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; PS, performance status; RDI, relative dose intensity; TEAE, treatment-emergent adverse event; TtD, time to deterioration; TTP, time to progression; VEGFR2, vascular endothelial growth factor receptor 2.

Correspondence
Masatoshi Kudo, Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511 Japan.
Email: m-kudo@med.kinki.ac.jp

Present address
Bruno Daniele, Oncology Unit, Ospedale del Mare, Napoli, Italy

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Abstract

Background & Aims: Limited data on treatment of elderly patients with hepatocellular carcinoma (HCC) increase the unmet need. REACH and REACH-2 were global phase III studies of ramucirumab in patients with HCC after prior sorafenib, where patients with alpha-fetoprotein (AFP) ≥400 ng/mL showed an overall ssurvival (OS) benefit for ramucirumab. These post-hoc analyses examined efficacy and safety of ramucirumab in patients with HCC and baseline AFP ≥ 400 ng/mL by three prespecified age subgroups (<65, ≥65 to <75 and ≥75 years).

Methods: Individual patient data were pooled from REACH (baseline AFP ≥400 ng/mL) and REACH-2. Kaplan-Meier and Cox proportional hazards regression methods (stratified by study) assessed OS, progression-free survival (PFS), time to progression (TTP) and patient-reported outcomes (Functional Hepatobiliary System Index-8 [FHSI-8] score).

Results: A total of 542 patients (<65 years: n = 302; ≥65 to <75 years: n = 160; ≥75 years: n = 80) showed similar baseline characteristics between ramucirumab and placebo. Older subgroups had higher hepatitis C and steatohepatitis incidences, and lower AFP levels, than the <65 years subgroup. Ramucirumab prolonged OS in patients <65 years (hazard ratio [HR], 0.753; 95% CI 0.581-0.975), ≥65 to <75 years (0.602; 0.419-0.866) and ≥75 years (0.709; 0.420-1.199), PFS and TTP irrespective of age. Ramucirumab showed similar overall safety profiles across subgroups, with a consistent median relative dose intensity ≥97.8%. A trend towards a delay in symptom deterioration in FHSI-8 with ramucirumab was observed in all subgroups.

Conclusions: In this post-hoc analysis, ramucirumab showed a survival benefit across age subgroups with a tolerable safety profile, supporting its use in advanced HCC with elevated AFP, irrespective of age, including ≥75 years.

KEYWORDS
alpha-fetoprotein (AFP), elderly, hepatocellular carcinoma, ramucirumab, sorafenib intolerance, VEGFR2

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is a relatively common cancer associated with significant morbidity and mortality.[1-3] In eastern Asia and Africa, HCC usually presents in younger patients, whereas in Japan and Western countries, HCC generally presents at an older age. This is partly because of differences in aetiology across regions. The risk of HCC increases with advancing age.[1-3] Different definitions exist to define "elderly"; however, 65 years is most commonly used; in recent HCC clinical trials, patients ≥75 years of age were considered.[4] In developed countries, increasing life expectancy is leading to a progressively aging population, resulting in higher numbers of elderly patients with HCC.[4,5]

Elderly patients are often fragile, have comorbidities, altered drug pharmacokinetics and a poor prognosis. Treatment of elderly patients with HCC remains an unresolved clinical challenge, with increasing unmet need, especially for those ≥70 years of age.[4-6] Despite recently available data supporting the efficacy of multitargeted tyrosine kinase inhibitors (mTKIs),[4-9] single-agent immune checkpoint inhibitors (CPI)[10,11] or CPI in combination with an anti-angiogenic agent,[12] data for elderly patients are scarce. Of note,

Key points

- In this analysis of two phase III studies (REACH and REACH-2), the effects of ramucirumab in relation to age, including elderly patients ≥75 years of age, in hepatocellular carcinoma (HCC) are described in detail.
- In patients with HCC and elevated alpha-fetoprotein with prior sorafenib use, ramucirumab improved survival with delayed deterioration of quality of life and an acceptable safety profile, irrespective of age, including patients ≥75 years of age.

where data are available, the use of mTKIs is associated with significant adverse effects[4,6,13] or unknown toxicity profiles[8,9] in this population. Most global trials enrol younger or fit older adults, which limits the application of their results to older adults in clinical practice. Additionally, most HCC treatment guidelines offer no specific guidance for the treatment of elderly patients owing to limited evidence-based data.[4,5]

Ramucirumab, a human immunoglobulin G1 monoclonal antibody that inhibits ligand activation of vascular endothelial growth factor receptor 2 (VEGFR2), was assessed for efficacy and safety vs placebo in patients with HCC after prior sorafenib in two global, randomized, double-blind, placebo-controlled phase III clinical trials (REACH and REACH-2).[14,15] A prespecified subgroup analysis of patients with HCC with baseline alpha-fetoprotein (AFP) levels ≥400 ng/mL in REACH showed a significant overall survival (OS) benefit in this subgroup (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.51-0.90)[15]; this was confirmed in the REACH-2 trial (HR, 0.710; 95% CI, 0.531-0.949; *P* = .0199), without compromising patient-reported disease symptoms as assessed by the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptoms Index (FHSI)-8.[14] Ramucirumab had an acceptable safety profile in these trials and therefore may be considered for HCC treatment in elderly patients. This post-hoc analysis evaluated the efficacy, safety and patient-reported outcomes (PROs) for ramucirumab in three prespecified age subgroups (<65, ≥65 to <75 and ≥75 years of age) using the pooled data of patients with baseline AFP ≥400 ng/mL from the REACH and REACH-2 trials.

2 | METHODS

2.1 | Study design and population

The REACH and REACH-2 study designs have been published elsewhere.[14,15] Both trials enrolled adults ≥18 years of age with histopathologically or cytologically confirmed HCC (or a diagnosis of cirrhosis and HCC with classical imaging characteristics), previously treated with sorafenib (≥14 days) that was discontinued because of disease progression/intolerance, Barcelona Clinic Liver Cancer stage B/C disease, Child-Pugh class A liver disease and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Both trials had similar eligibility criteria, except patients in REACH-2 had to have baseline AFP ≥400 ng/mL. Individual patient data (stratified by study) from REACH (AFP ≥400 ng/mL) and REACH-2 were pooled for this post-hoc analysis, which substantially increased the sample size, thus enabling a more precise assessment of ramucirumab treatment effect by different age groups. Both pooled analyses and age cut-off values of 65 and 75 years were prespecified in the protocol before REACH-2 database lock. Both trials were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guideline for Good Clinical Practice. The ethical review board of each participating site approved the protocol. All patients provided informed consent before treatment. Both trials were registered at www.clinicaltrials.gov (NCT01140347, NCT02435433).

2.2 | Treatment and procedures

Patients were randomly assigned (1:1 ratio in REACH; 2:1 ratio in REACH-2) to receive ramucirumab or placebo. In REACH, randomization was stratified by geographical region and aetiology of liver disease (hepatitis B vs hepatitis C vs other aetiologies).[15] In REACH-2, randomization was stratified by macrovascular invasion, geographical region and ECOG performance status.[14] Patients received ramucirumab (8 mg/kg) or placebo intravenously on Day 1 of each 14-day cycle plus best supportive care until disease progression, unacceptable toxicity or withdrawal of consent. Tumour response was assessed every 6 weeks during the first 6 months and every 9 weeks thereafter, according to Response Evaluation Criteria in Solid Tumors v1.1. The FHSI-8 was used to assess PROs.[16] Estimates of exposure (minimum concentration after administration of first dose [C_{min},1]) were calculated using population pharmacokinetic analysis.[17]

2.3 | Statistical analyses

This post-hoc analysis of pooled individual patient data (stratified by study) from REACH (patients with baseline AFP ≥400 ng/mL) and REACH-2 assessed the efficacy, safety and health-related quality of life outcomes for ramucirumab vs placebo in three prespecified age subgroups (<65, ≥65 to <75 and ≥75 years of age). Efficacy was assessed in all randomized patients with baseline AFP ≥400 ng/mL. Survival curves and medians with 95% CIs for OS, progression-free survival (PFS) and time to progression (TTP) were estimated using the Kaplan-Meier method, with the stratified (by study) Cox regression model used to estimate HRs. Deterioration in FHSI-8 was defined as a ≥3-point decrease in total score. Time to deterioration (TtD) was defined as time from randomization date to deterioration date. Safety was assessed in all patients who received at least one dose of study drug. Treatment-emergent adverse events (TEAEs) were graded using Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Analyses were conducted using SAS® 9.4 (SAS Institute Inc, Cary, NC, USA).

3 | RESULTS

3.1 | Demographic and baseline clinical characteristics

This subgroup analysis included 542 patients with AFP ≥400 ng/mL (REACH: 250; REACH-2:292). All randomized patients received study treatment and were included in the efficacy and safety analyses. Baseline characteristics were generally similar between treatment arms and across the age subgroups (Table 1).

TABLE 1 Baseline demographic and disease characteristics of the pooled REACH (AFP ≥400 ng/mL) and REACH-2 age subgroups

	Age <65 years		Age ≥65 to <75 years		Age ≥75 years	
	Ramucirumab (n = 171)	Placebo (n = 131)	Ramucirumab (n = 93)	Placebo (n = 67)	Ramucirumab (n = 52)	Placebo (n = 28)
Gender (%)						
Male	83.6	82.4	71.0	86.6	71.2	82.1
Geographical region (%)						
America, Europe, Israel, Australia	39.8	35.1	59.1	64.2	59.6	67.9
Asia (excluding Japan)	46.2	52.7	17.2	10.5	11.5	7.1
Japan	14.0	12.2	23.7	25.4	28.9	25.0
ECOG PS (%)						
0	57.3	51.2	54.8	52.2	46.2	57.1
Child-Pugh score A-5 (%)	63.2	64.9	58.1	55.2	53.8	46.4
Baseline BCLC stage C (%)	87.1	90.1	84.9	86.6	82.7	75.0
Baseline AFP, ng/mL, median (interquartile range)	4689.1 (1476.0-23,089.0)	6722.0 (1322.1-24,453.0)	3920.0 (1104.0-24,494.0)	2936.0 (1000.0-23,750.0)	3213.5 (923.0-9689.0)	2715.3 (1524.7-7208.0)
Aetiology of liver disease (%)						
Hepatitis B	56.7	61.1	21.5	28.4	13.5	10.7
Hepatitis C	22.8	23.7	28.0	26.9	34.6	25.0
Significant alcohol use	18.1	16.0	26.9	28.4	28.8	10.7
Steatohepatitis (NASH, fatty liver)	3.5	3.1	12.9	4.5	15.4	14.3
Others	12.3	6.1	15.1	19.4	19.2	35.7
Presence of macrovascular invasion (%)	33.9	35.9	37.6	31.3	38.5	32.1
Presence of extrahepatic spread (%)	79.5	80.9	62.4	74.6	61.5	53.6
Duration of prior sorafenib treatment, months						
Mean	6.7	6.0	6.4	7.8	6.5	6.2
Median	3.7	3.5	3.5	5.0	4.3	3.7
Reason for sorafenib discontinuation, n (%)						
Progressive disease	152 (88.9)	116 (88.5)	75 (80.6)	59 (88.1)	47 (90.4)	23 (82.1)
Intolerance	19 (11.1)	15 (11.5)	18 (19.4)	8 (11.9)	5 (9.6)	5 (17.9)
ALBI grade, n (%)						
Grade 1	82 (48.0)	60 (45.8)	33 (35.5)	27 (40.3)	21 (40.4)	8 (28.6)
Grade 2	87 (50.9)	65 (49.6)	60 (64.5)	36 (53.7)	29 (55.8)	19 (67.9)
Grade 3[a]	1 (0.6)	3 (2.3)	0	3 (4.5)	0	0
Missing	1	3	0	1	2	1

Abbreviations: AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; NASH, non-alcoholic steatohepatitis.

[a]Subjects with ALBI grade 3 were from the REACH study only.

However, patients <65 years of age had higher incidences of hepatitis B and extrahepatic spread and higher median baseline AFP, whereas steatohepatitis was higher in the older subgroups (Table 1).

3.2 | Treatment exposure

The median relative dose intensity (RDI) of ramucirumab was consistently high (≥97.8%) in the three age subgroups (Table 2). Similarly,

the estimated mean minimum ramucirumab concentration (C_{min},1) was comparable across the age subgroups (≥24.1 ng/mL) (Table S1). The proportion of patients requiring a ramucirumab dose adjustment was similar in the subgroups (<65 years: 31% vs ≥65 to <75 years: 36.6% vs ≥75 years: 38.5%) (Table 2). Most dose adjustments were as a result of TEAEs. The median number of treatment cycles was 5, 5 and 7 in the <65, ≥65 to <75 and ≥75 years subgroups respectively.

3.3 | Efficacy

Ramucirumab prolonged OS vs placebo, with similar median OS in all three age subgroups (<65 years: 8.18 vs 4.76 months [HR, 0.753; 95% CI, 0.581-0.975]; ≥65 to <75 years: 7.62 vs 5.22 months [HR, 0.602; 95% CI, 0.419-0.866]; ≥75 years: 8.87 vs 6.31 months [HR, 0.709; 95% CI, 0.420-1.199]) (Figure 1). In the three age subgroups, compared with placebo, ramucirumab also improved PFS (<65 years: 2.73 vs 1.45 months [HR, 0.613; 95% CI, 0.472-0.796]; ≥65 to <75 years: 2.78 vs 1.84 months [HR, 0.563; 95% CI, 0.396-0.802]; ≥75 years: 4.17 vs 1.64 months [HR, 0.480; 95% CI, 0.282-0.817]) (Figure 2) and TTP (<65 years: 2.76 vs 1.45 months [HR, 0.591; 95% CI, 0.447-0.782]; ≥65 to <75 years: 2.79 vs 1.87 months [HR, 0.555; 95% CI, 0.377-0.818]; ≥75 years: 4.17 vs 2.04 months [HR, 0.443; 95% CI, 0.255-0.769]) (Figure 3). Post-discontinuation systemic therapies (PDT) were generally balanced between treatment arms, but the rate of overall PDT use was lower in elderly patients (≥75 years: 19.2%) than younger patients (<65 years: 32.2%; ≥65 to <75 years: 33.3%) (Table S2).

3.4 | Safety

The overall safety profile of ramucirumab, including incidences of grade ≥3 TEAEs, was comparable between the <65 and ≥65 to <75 years subgroups (Table 3). In the ≥75 years subgroup, the incidence of grade ≥3 TEAEs (hypertension and fatigue) was higher for ramucirumab (62%) than placebo (39%), but was comparable with ramucirumab in the two younger subgroups (54% and 60%) (Table 3). Common TEAEs leading to dose adjustments in the ramucirumab arm were proteinuria in patients <65 years of age (4.1%) and hypertension in the two older subgroups (7.5% and 5.8%). Adverse events of special interest in the ramucirumab arm, based on its known safety profile, were comparable between the age subgroups (Table S3).

3.5 | Patient-reported outcomes

A trend for a delay in the deterioration of symptoms as measured by FHSI-8 was observed in the ramucirumab arm across all age subgroups but was not statistically significant. Median TtD was numerically longer in the ramucirumab vs the placebo arms in all three age subgroups (Figure 4).

4 | DISCUSSION

This is the first detailed report that describes the efficacy, safety and PROs of a systemic drug in relation to age in HCC, including patients ≥75 years of age, in a clinical trial setting. Although mTKIs like lenvatinib and regorafenib have shown similar efficacy outcomes, and cabozantinib has shown similar efficacy and safety profiles[18] between patients with HCC aged <65 years vs those ≥65 years old, these retrospective reports did not further divide the elderly age groups, and the specific effects of these mTKIs in patients ≥70 and ≥75 years of age are unknown.[5-8] This post-hoc subgroup analysis in patients with HCC and AFP ≥400 ng/mL, who had progressed on or were intolerant to sorafenib, showed a survival benefit (improved OS, PFS and TTP) for ramucirumab and a comparable estimated ramucirumab exposure across three prespecified age subgroups, including ≥75 years, with a manageable safety profile and a trend for improvements in PROs. This finding is consistent with the subgroup analyses from the phase III placebo-controlled REGARD and RAINBOW studies, which showed a survival benefit of ramucirumab as monotherapy or in combination with paclitaxel in elderly patients (≥70 and ≥75 years of age) with advanced gastric cancer.[19] Together, these results suggest that ramucirumab can be used in patients with HCC irrespective of age, including elderly patients ≥75 years of age.

Overall, ramucirumab had an acceptable safety profile across all three age subgroups, which is consistent with the previously reported safety profile of ramucirumab.[20] The higher incidence of grade ≥3 TEAEs (ie hypertension and fatigue) with ramucirumab in the ≥75 years subgroup may be owing to slightly longer treatment duration in this subgroup, allowing more time for recording TEAEs. Use of mTKIs in elderly patients is associated with significant adverse effects[4,6,18] or unknown toxicity profiles.[8,9] Ramucirumab may offer a favourable safety profile for elderly patients with HCC, particularly for hand-foot syndrome, diarrhoea and fatigue, which are common side effects of mTKIs in elderly patients.[13] Additionally, the median RDI (≥97.8%) and treatment duration for ramucirumab in the current analyses were maintained irrespective of age, suggesting good treatment administration compliance, and the proportion of patients requiring a dose adjustment in the ramucirumab arm was similar between the age subgroups, indicating favourable treatment tolerance.

The aetiology of HCC may affect treatment response.[4,6] In this analysis, patients <65 years of age were more likely to have hepatitis B–related HCC vs older patients, who were more likely to have hepatitis C–related HCC. This is consistent with previously described characteristics of HCC in young and elderly patients.[4-6,21] Longer treatment duration for ramucirumab in the ≥75 years of age subgroup than in the younger subgroups may be attributed to lower AFP levels in the ≥75 years subgroup, which are associated with less aggressive tumour types and a better prognosis (Tables 1 and 2). Finally, different geographical regions may be associated with different patient characteristics for age, HCC aetiology and AFP levels and, therefore, different treatment outcomes.

TABLE 2 Comparison Relative dose intensity, dose adjustment and treatment duration in the pooled REACH (AFP ≥400 ng/mL) and REACH-2 age subgroups

	Age <65 years		Age ≥65 to <75 years		Age ≥75 years	
	Ramucirumab (n = 171)	Placebo (n = 128)	Ramucirumab (n = 93)	Placebo (n = 67)	Ramucirumab (n = 52)	Placebo (n = 28)
Relative dose intensity (%) median (min-max)	98.6 (41.4-108.7)	99.8 (62.1-112.7)	98.0 (59.1-105.0)	100.0 (68.5-106.4)	97.8 (60.7-109.4)	98.6 (81.1-102.9)
Any dose adjustment (%)	31.0	14.1	36.6	16.4	38.5	21.4
Dose reduction	4.7	0.8	5.4	3.0	5.8	0
Dose delay	10.5	5.5	10.8	4.5	15.4	7.1
Dose omission	26.3	9.4	30.1	11.9	30.8	17.9
Dose adjustments owing to TEAEs (%)						
Any grade	24.6	8.6	36.6	22.4	38.5	14.3
Grade 3/4/5	14.6	5.5	20.4	17.9	15.4	7.1
Cycles received per patient, median (interquartile range)	5.0 (3.0-9.0)	3.0 (3.0-6.0)	5.0 (3.0-13.0)	3.0 (3.0-7.0)	7.0 (3.0-14.0)	4.5 (3.0-6.0)

Note: The data for any dose adjustment were obtained from exposure analysis and the data for dose adjustments owing to TEAEs were obtained from safety analysis, and the difference between both sets of data is owing to different definitions used in the respective analyses.

Abbreviations: AFP, alpha-fetoprotein; max, maximum; min, minimum; TEAE, treatment-emergent adverse event.

Comprehensive PRO data are lacking from randomized controlled trials of targeted therapy in HCC.[22] Some recent phase III trials in HCC have reported on quality of life; however, the use of different methodologies in these studies makes their interpretation difficult.[8,9,22] In this analysis, the effect of ramucirumab on PROs did not appear to be influenced by age, with a trend towards a delay in deterioration of symptoms (as assessed by FHSI-8) in all three age subgroups.

One of the strengths of this study is the use of pooled individual patient data from two similarly designed phase III trials, which substantially increased the sample size. Additionally, the age subgroups were prespecified. However, several aspects of this analysis represent notable limitations that reduce the robustness of the results. The main limitation is the post-hoc nature of this analysis, which was not designed or powered to show differences between ramucirumab and placebo across the age subgroups. Additionally, the number of patients in each subgroup, especially in the oldest subgroup (≥75 years), is limited, and the three subgroups are highly heterogeneous with respect to patient baseline characteristics. Another important limitation is the nature of the clinical trial, which underrepresents elderly patients and may have led to selection bias. Selection of elderly patients suitable for clinical trials for cancer treatments should be performed using appropriate geriatric assessments.[23] Therefore, these results must be interpreted with caution in clinical practice. Furthermore, the implications of these results in elderly non-Japanese Asian patients remain to be defined because of their underrepresentation in this study.

In conclusion, this post-hoc subgroup analysis in patients with HCC and elevated AFP, who had progressed on or were intolerant to sorafenib, showed that ramucirumab had a survival benefit with a trend for a delay in deterioration of PROs, irrespective of age, including patients ≥75 years of age. The overall safety profile of ramucirumab was comparable across the three age subgroups, with a high median RDI and similarly maintained treatment duration irrespective of age. Therefore, ramucirumab may offer an active and well-tolerated treatment option for elderly patients with HCC and elevated AFP levels. This post-hoc analysis provides valuable information for the treatment algorithm of elderly patients with HCC, especially those ≥75 years of age.

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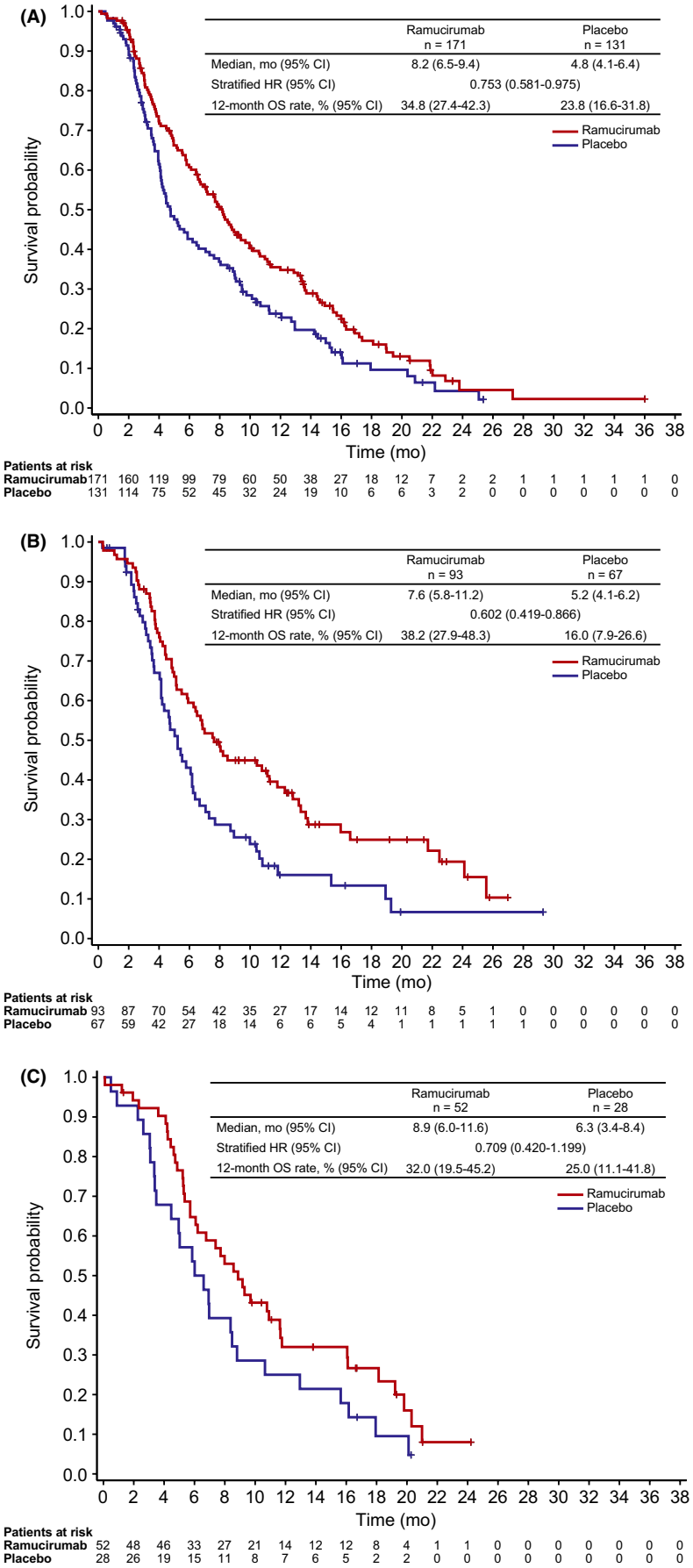


FIGURE 1 Kaplan-Meier plots of OS for patients receiving ramucirumab or placebo in the pooled REACH (patients with AFP ≥400 ng/mL) and REACH-2 age subgroups: (A) <65 years, (B) ≥65 to <75 years and (C) ≥75 years. CI, confidence interval; HR, hazard ratio; OS, overall survival

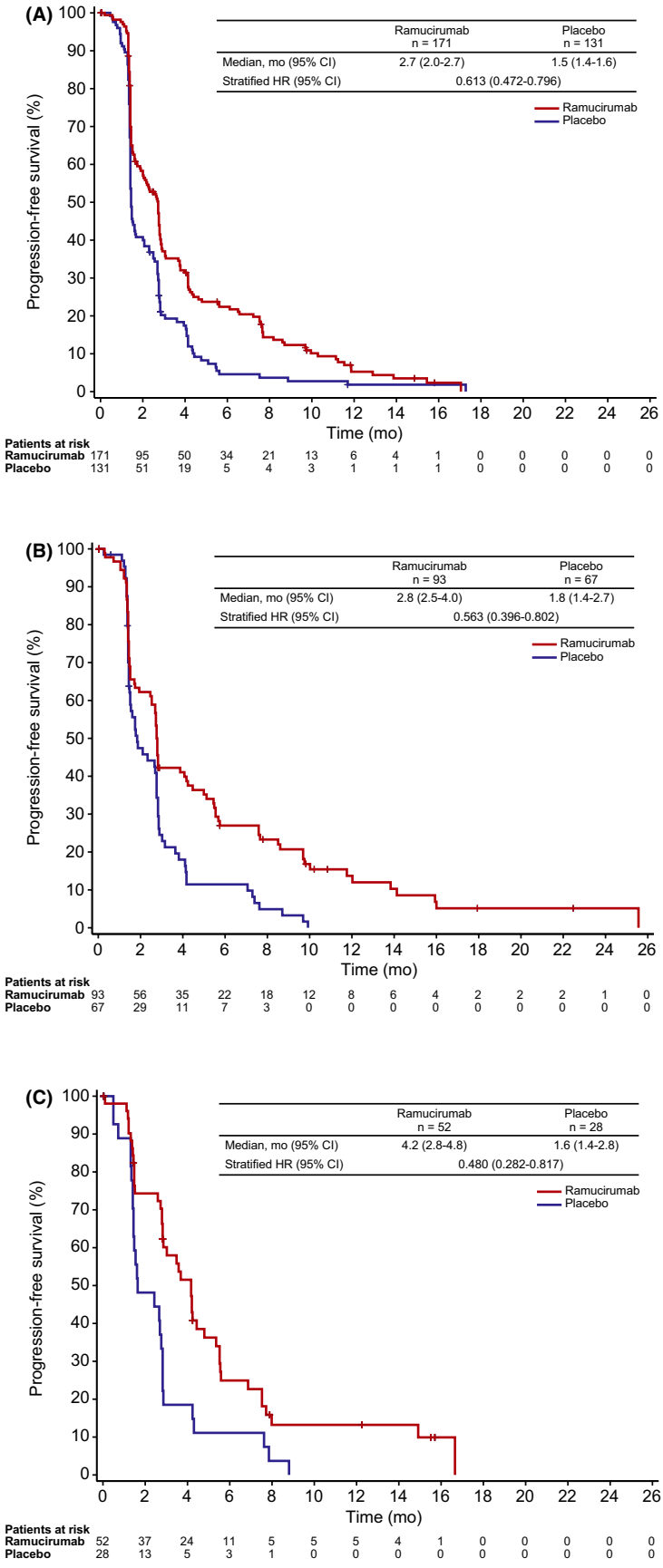
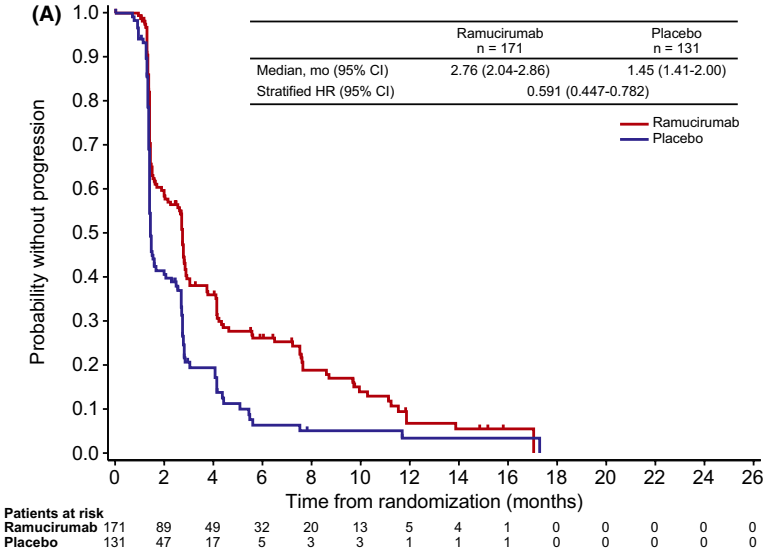
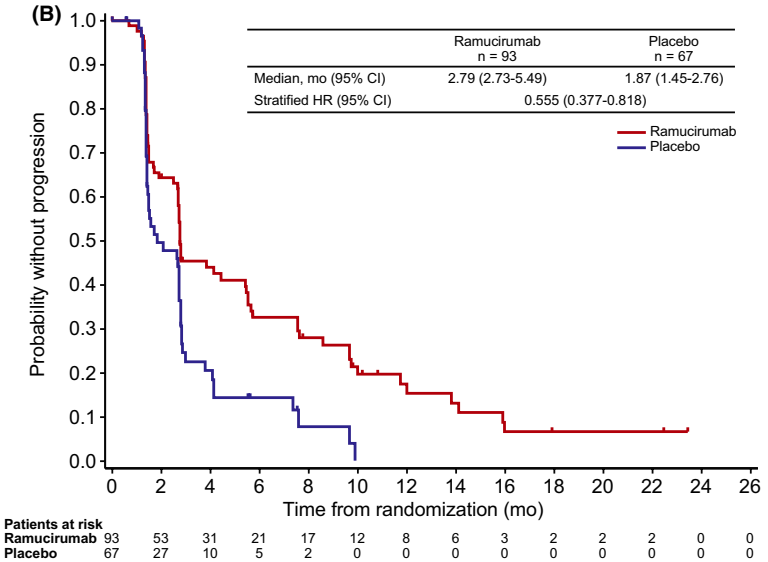


FIGURE 2 Kaplan-Meier plots of PFS for patients receiving ramucirumab or placebo in the pooled REACH (patients with AFP ≥400 ng/mL) and REACH-2 age subgroups: (A) <65 years, (B) ≥65 to <75 years and (C) ≥75 years. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival





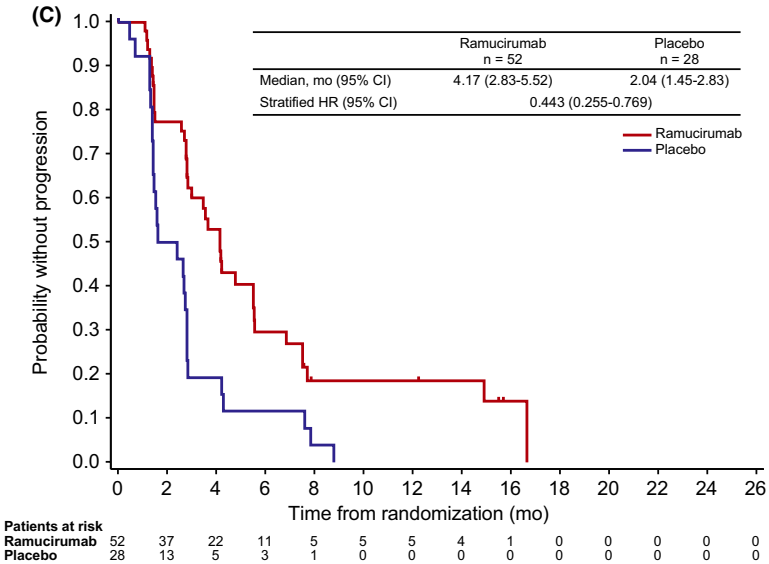


FIGURE 3 Kaplan-Meier plots of TTP for patients receiving ramucirumab or placebo in the pooled REACH (patients with AFP ≥400 ng/mL) and REACH-2 age subgroups: (A) <65 years, (B) ≥65 to <75 years and (C) ≥75 years. CI, confidence interval; HR, hazard ratio; TTP, time to progression

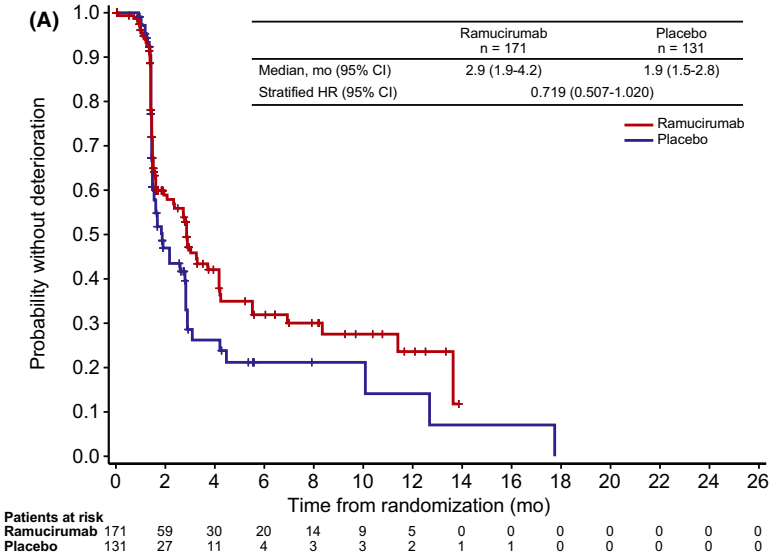
TABLE 3 Comparison Summary of AEs in the pooled REACH (AFP ≥400 ng/mL) and REACH-2 age subgroups

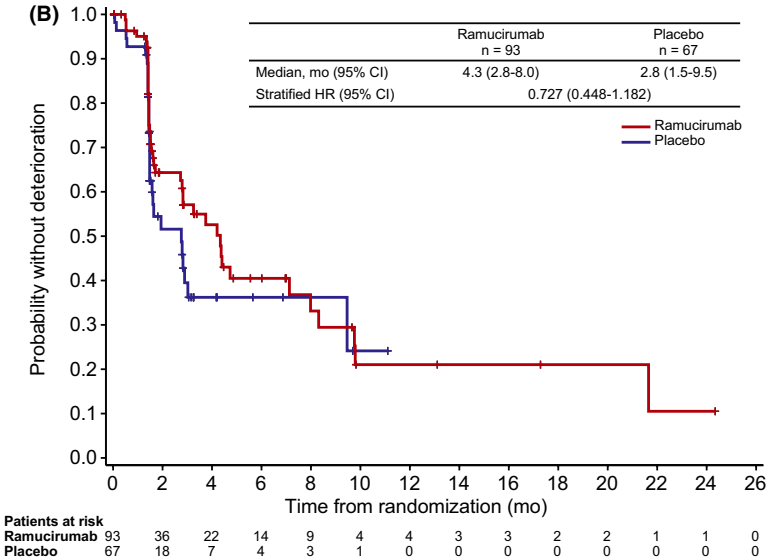
	Overall pooled population		Age <65 years		Age ≥65 to <75 years		Age ≥75 years	
	Ramucirumab (n = 316)	Placebo (n = 223)	Ramucirumab (n = 171)	Placebo (n = 128)	Ramucirumab (n = 93)	Placebo (n = 67)	Ramucirumab (n = 52)	Placebo (n = 28)
Any AE (%)	96.8	92.4	95.9	90.6	98.9	92.5	96.2	100.0
Any grade ≥ 3 AE (%)	57.3	52.0	54.4	49.2	60.2	62.7	61.5	39.3
Any AE leading to treatment discontinuation (%)	16.5	10.3	13.5	8.6	20.4	16.4	19.2	3.6

TEAEs in ≥15% of patients in ramucirumab arm (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Peripheral oedema	29.1	0.9	17.0	0	19.3	1.8	14.1	0	46.2	0	17.9	0	30.8	0	28.6	0
Fatigue	24.1	2.5	17.5	2.7	22.2	1.2	18.8	3.1	24.7	2.2	19.4	3.0	28.8	7.7	7.1	0
Decreased appetite	22.2	1.3	20.6	0.4	17.5	1.2	19.5	0.8	31.2	2.2	25.4	0	21.2	0	14.3	0
Ascites	20.9	4.7	14.8	4.0	18.1	4.1	16.4	3.1	24.7	5.4	14.9	7.5	23.1	5.8	7.1	0
Hypertension	20.9	12.0	9.0	3.6	15.8	8.2	7.0	3.1	25.8	17.2	9.0	4.5	28.8	15.4	17.9	3.6
Nausea	19.6	0	16.1	0	18.1	0	18.8	0	22.6	0	13.4	0	19.2	0	10.7	0
Abdominal pain	19.3	1.6	18.4	4.0	19.9	2.3	18.8	6.3	20.4	1.1	17.9	0	15.4	0	17.9	3.6
diarrhoea	18.4	0.3	11.7	0.4	18.7	0	7.8	0	16.1	0	17.9	1.5	21.2	1.9	14.3	0
Proteinuria	17.7	1.3	5.4	0	15.8	1.8	6.3	0	22.6	1.1	3.0	0	15.4	0	7.1	0

Note: All TEAE terms used above are preferred terms according to MedDRA Version 20.1.

Abbreviations: AE, adverse event; AFP, alpha-fetoprotein; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.





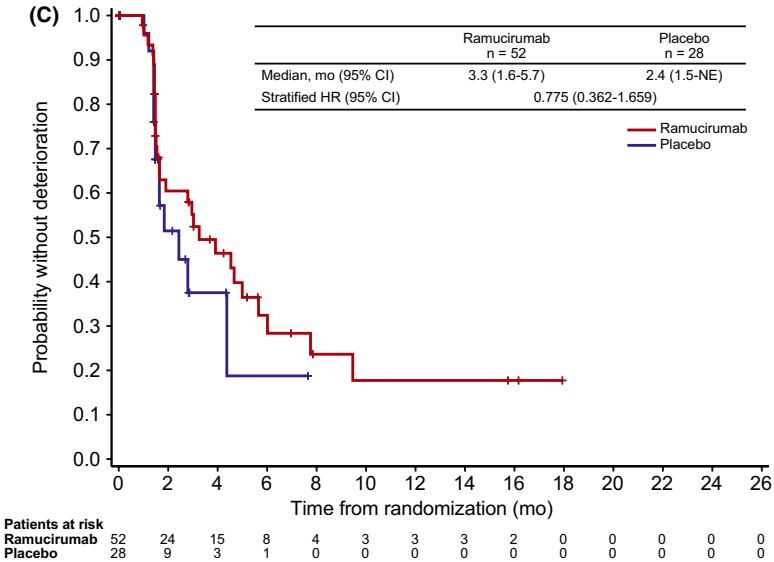


FIGURE 4 Kaplan-Meier plots of time to deterioration in FHSI-8 total scores for patients receiving ramucirumab or placebo in the pooled REACH (patients with AFP ≥400 ng/mL) and REACH-2 age subgroups: (A) <65 years, (B) ≥65 to <75 years and (C) ≥75 years. CI, confidence interval; FHSI-8, Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index-8; HR, hazard ratio; NE, not evaluable

KK were involved in the study design, data collection, data analysis and preparation of the manuscript.

CONFLICT OF INTEREST

MK has received honoraria from Bayer AG, Eisai Co. Ltd. and Merck Sharp & Dohme (MSD), has served as an advisor and consultant for Bayer AG, Bristol-Myers Squibb, Eisai Co., Ltd., Eli Lilly and Company, MSD and Ono Pharmaceutical Co., Ltd., and has received research grants and funding from AbbVie Inc, Astellas Pharma Inc, Bayer AG, Bristol-Myers Squibb, Chugai Pharmaceuticals Co., Ltd., Daiichi Sankyo Company, Limited, EA Pharma Co., Ltd., Eisai Co. Ltd., Gilead Sciences Inc, MSD, Otsuka Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd and Takeda Pharmaceutical Company Ltd. PRG reports receipt of honoraria, and travel and accommodation fees from, and has served as an advisor and consultant for AstraZeneca plc, Bayer AG, Bristol-Myers Squibb, Eisai Co. Ltd., Eli Lilly and Company, Ipsen, MSD and Sirtex Medical Limited, has received lecture fees from Bayer AG, Eisai Co. Ltd., Eli Lilly and Company, Ipsen and Sirtex Medical Limited, and has received research funding from Bayer AG and Eli Lilly and Company. JML has received research grants support from Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai Inc and Ipsen, and consulting fees from Bayer Healthcare Pharmaceuticals, Bristol-Myers Squibb, Can-Fite Biopharma, Celsion Corporation, Eisai Inc, Eli Lilly and Company, Exelixis Inc, Fortress Biotech Inc, Glycotest Inc, Ipsen, Merck & Co., Inc, Midatech Ltd., Navigant, Nucleix Ltd., Spring Bank Pharmaceuticals, Inc and SVB Leerink LLC. RSF has received honoraria as well as research grant and funding from Eli Lilly and Company, and has served as a consultant and received personal fees and other fees from AstraZeneca plc, Bayer AG, Bristol-Myers Squibb, Eisai Co. Ltd., Eli Lilly and Company, Exelixis Inc, Merck & Co., Inc, Novartis International AG, Pfizer Inc and Roche/Genentech. AV has received honoraria from Amgen Inc, Bayer AG, Bristol-Myers Squibb, Delcath Systems, Inc, Eisai Co. Ltd., Eli Lilly and Company, MSD, Novartis International AG, Roche AG and Sanofi SA, has served as an advisor and consultant for Amgen Inc, Bayer AG, Bristol-Myers Squibb, Delcath Systems, Inc, Eisai Co. Ltd., Eli Lilly and Company, MSD, Novartis International AG, Roche AG and Sanofi SA, and has received research grant and funding, lecture fees, personal fees and other fees from Eli Lilly and Company. KM has received honoraria from Eisai Co. Ltd. EA has received honoraria and served as an advisor and consultant for Bayer AG, Ipsen, Novartis International AG, Sanofi SA, Servier Laboratories, Sirtex Medical Limited and TeraSphere™ by Boston Scientific Corporation, and has received research grants and funding from Eli Lilly and Company. PM has served on the advisory board for AstraZeneca plc, Bayer AG, Bristol-Myers Squibb, Eisai Co. Ltd., Ipsen, Exelixis, Inc, MSD, Onxeo S. A. and Roche AG, has received research grants from Onxeo S. A. and Eli Lilly and Company, and has received lecture and other fees from Eli Lilly and Company. GB has served as an advisor and consultant as well as received research funding, lecture and other fees from Eli Lilly and Company. BD has received personal fees for serving as an advisor and consultant from AstraZeneca plc, Bayer AG, Eisai Co. Ltd., Eli Lilly and Company, Ipsen, Incyte Corp, MSD and Sanofi S. A., has received non-financial support from Bayer AG, Ipsen and Sanofi S. A., and has received research grants, lecture fees and other fees from Eli Lilly and Company. TO has received honoraria from AbbVie Inc, AstraZeneca KK, Bayer Yakuhin, Ltd., Celgene, KK, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., EA Pharma Co., Ltd., Eisai Co., Ltd., Eli Lilly Japan KK, FUJIFILM RI Pharma Co., Ltd, Nobelpharma Co., Ltd., Novartis Pharma KK, Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc, Shire, Taiho Pharmaceutical Co., Ltd., Takara Bio Inc, Teijin Pharma Ltd. and Yakult Honsha Co., Ltd., has received research funding from Eisai Co., Ltd., Eli Lilly Japan KK, Kowa Company, Ltd, Novartis Pharma KK, Taiho Pharmaceutical Co., Ltd. and Yakult Honsha Co., Ltd. AstraZeneca KK, Baxter, Bayer Yakuhin Ltd., Chugai Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Nano Carrier Co., Ltd., Ono Pharmaceutical Co., Ltd. and Pfizer Japan Inc, and has served as an advisor and consultant for Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Taiho Pharmaceutical Co., Ltd. and Zeria Pharmaceutical Co., Ltd. JT has received lecture fees from Eli Lilly and Company. CB has served as an advisor and consultant for Bayer AG, Roche AG and Servier Laboratories. VD has served as a consultant and on the advisory panel for Bayer AG, Ipsen and MSD. MM has declared no conflicts of interest. MP has received research grant from Eli Lilly and Company. MHJ, RCW, NDU, KS and RY are full-time employees and shareholders of Eli Lilly and Company. AXZ has received honoraria and served as an advisor and consultant for AstraZeneca plc, Bayer AG, Eisai Co. Ltd., Eli Lilly and Company and Merck & Co., Ltd.

AUTHOR CONTRIBUTONS

MK, RSF, NDU and RY were involved in the concept and design of this study. Additionally, PRG and AXZ were also involved in study concept and GB was involved in the study design. All authors were involved in acquisition of data, except EA, BD, MP, MHJ, NDU, RCW and KS. MK, BD, TO and VD served as investigators of this study, and RSF, JML, AV, MHJ and RCW were involved in the statistical analyses. MK, PRG, RSF, JML, AV, EA, PM, GB, BD, MP, MHJ, NDU, RY, RCW, KS and AXZ were involved in the interpretation of the study data. NDU, RCW, KS and RY were involved in drafting this manuscript and all authors contributed to the critical review and approval of this manuscript.

ETHICS APPROVAL AND PATIENT CONSENT STATEMENT

The ethical review board of each participating site in both REACH and REACH-2 trials approved the respective study protocol and all patients provided informed consent before treatment.

ORCID

Masatoshi Kudo https://orcid.org/0000-0002-4102-3474

Peter R. Galle https://orcid.org/0000-0001-8294-0992
Richard S. Finn https://orcid.org/0000-0003-2494-2126
Kenta Motomura https://orcid.org/0000-0002-7515-099X
Takuji Okusaka https://orcid.org/0000-0003-1729-807X

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SUPPORTING INFORMATION

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

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