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Characterization of Tumor Responses in Patients with Unresectable Hepatocellular Carcinoma Treated with Lenvatinib in the Phase 3 Randomized Trial: REFLECT

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Keywords
Hepatocellular carcinoma · Objective response · Lenvatinib

Abstract

Introduction: In REFLECT, lenvatinib was noninferior to sorafenib in terms of overall survival (OS) in patients with unresectable hepatocellular carcinoma (uHCC; median 13.6 vs. 12.3 months; HR 0.92, 95% CI 0.79–1.06). The objective response rate (ORR) with lenvatinib was 18.8% by blinded independent imaging review (IIR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); per modified RECIST (mRECIST), the ORR was 40.6%. We sought to further characterize these tumor responses and explore ORR's importance among outcomes for patients with HCC. ***Methods:*** Efficacy assessments included all patients randomly assigned to receive lenvatinib treatment (if bodyweight ≥60 kg, 12 mg/day; if <60 kg, 8 mg/day). Time to first objective response (TTR) and duration of response (DOR) included patients who achieved a partial or complete tumor response. Tumors were assessed by IIR per RECIST v1.1 or mRECIST. ***Results:*** Four hundred seventy-eight patients were randomly assigned to receive lenvatinib. By IIR, 90 patients (18.8%) achieved an objective response per RECIST v1.1, and 194 (40.6%) had an objective response per mRECIST. Median TTR/DOR were 2.8 months/7.4 months in responders per RECIST v1.1, and 1.9 months/7.3 months in responders per mRECIST, respectively. Per baseline disease characteristics, ORRs by Child-Pugh score (A5/A6) were 21.2%/11.2% per RECIST v1.1 and 42.9%/33.6% per mRECIST, respectively. By baseline alpha-fetoprotein level (<400/≥400 ng/mL), ORRs were 21.4%/15.4%

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per RECIST v1.1 and 45.6%/33.8% per mRECIST, respectively. Incidences of treatment-related treatment-emergent adverse events were 98.9% in responders per RECIST v1.1 and 97.9% in responders per mRECIST. ***Conclusions:*** Responses were seen even in those patients with more severe disease at baseline. Tumor responses occurred early and were durable.

Introduction

Liver cancer, particularly hepatocellular carcinoma (HCC), is a substantial contributor to cancer deaths worldwide [1–3]. HCC comprises the majority of liver cancer cases, and people with HCC generally have a poor 5-year prognosis [3].

Lenvatinib is an oral multikinase inhibitor approved globally as first-line therapy for patients with advanced or unresectable HCC (uHCC) based on the results from the phase 3 multicenter REFLECT trial (NCT01761266) [4–6]. REFLECT met its primary endpoint, demonstrating that lenvatinib was noninferior to sorafenib for patients with uHCC based on the analysis of overall survival (OS; median 13.6 vs. 12.3 months; hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.79–1.06) [5]. In REFLECT, the objective response rates (ORR) with lenvatinib by blinded independent imaging review (IIR) were 40.6% per modified Response Evaluation Criteria in Solid Tumors (mRECIST) and 18.8% per RECIST version 1.1 (RECIST v1.1) [5]. Since the publication of these findings, several immunotherapy-based regimens have been introduced for the treatment of HCC that are characterized by a consistent double-digit ORR [7–11].

Objective responses and baseline characteristics (e.g., baseline alpha-fetoprotein [AFP] and macroscopic portal vein invasion [MPVI]) have been found to predict the survival of patients with advanced HCC who received systemic treatment [12–15]. Further, there are differences in how RECIST v1.1 and mRECIST evaluate tumors – RECIST utilizes a unidirectional measurement of lesion size; mRECIST attempts to correct for the presence of necrotic tissue through the use of contrast-enhanced radiologic imaging [16, 17]. Given this and considering the introduction of immunotherapy-based regimens which have demonstrated efficacy in treating HCC, we conducted exploratory analyses of the REFLECT trial data to characterize patients who responded to front-line lenvatinib treatment (per RECIST v1.1 and mRECIST) by baseline factors, duration of response (DOR), time to response, survival, and other efficacy and safety measures.

Materials and Methods

Study Design and Patients

The study design of REFLECT and patient eligibility criteria have been described previously [5]. Briefly, patients with uHCC, ≥1 measurable target lesion, and no prior systemic treatment were randomly assigned 1:1 to receive either lenvatinib (dosage based on bodyweight as either 12 mg/day for patients weighing ≥60 kg or 8 mg/day for patients weighing <60 kg) or sorafenib (400 mg twice daily) in 28-day cycles [5]. Patients were stratified by region (Asia-Pacific or Western); MVPI, extrahepatic spread (EHS), or both (yes or no); Eastern Cooperative Oncology Group performance status (ECOG PS) score (0 or 1); and bodyweight (<60 kg or ≥60 kg).

Endpoints of the REFLECT Study

The primary endpoint of REFLECT was OS; secondary endpoints included progression-free survival (PFS), time to progression, and ORR (according to mRECIST by investigator review). These endpoints were reported in Kudo et al. Lancet 2018 [5].

Post hoc Exploratory Analyses

Patients randomly assigned to lenvatinib who had an objective response (defined as a complete response or partial response) by masked central IIR per RECIST v1.1 or per mRECIST were characterized by baseline characteristics, as well as by maximum percentage of tumor reduction, time to first objective response (TTR), DOR, OS, PFS, incidence of treatment-related treatment-emergent adverse events (TEAEs), and duration of treatment. PFS was assessed by IIR per RECIST v1.1 and per mRECIST.

Landmark analyses of OS by objective response status at 4 and 6 months were conducted in order to assess the association between tumor response and OS. Survival estimates in patients were presented as the time from the landmark time point. Only patients who were known to be alive at each specified landmark time point were included in the analysis.

Statistical Analyses

Incidence of treatment-related TEAEs was summarized for patients who received lenvatinib and had a response. TTR was calculated as the time from randomization to the patient's first objective response. DOR was calculated as the time from the patient's first objective response to progression or death, whichever occurs first. Median DOR, OS, and PFS were estimated with the Kaplan-Meier product-limit method; 95% CIs were estimated with a generalized Brookmeyer and Crowley method. Analyses presented herein were not powered.

Results

Baseline Demographics and Clinical Characteristics of Patients with an Objective Response

In REFLECT, 478 patients were randomly assigned to receive lenvatinib [5] (Table 1). Most patients assigned to receive lenvatinib (69%) had MPVI, EHS, or

Table 1. Baseline characteristics of patients in the lenvatinib arm and of those who had an objective response

Baseline characteristic	Overall, *n* (%)[a] (*N* = 478)	RECIST v1.1 (90 responders)		mRECIST (194 responders)	
		responders with characteristic among all 90 responders, *n* (%)[b]	responders with characteristic among all patients with characteristic, *n* (%)[c]	responders with characteristic among all 194 responders, *n* (%)[b]	responders with characteristic among all patients with characteristic, *n* (%)[c]
Age, years					
<65	270 (56.5)	47 (52.2)	47 (17.4)	105 (54.1)	105 (38.9)
≥65–<75	150 (31.4)	28 (31.1)	28 (18.7)	62 (32.0)	62 (41.3)
≥75	58 (12.1)	15 (16.7)	15 (25.9)	27 (13.9)	27 (46.6)
Sex					
Male	405 (84.7)	75 (83.3)	75 (18.5)	163 (84.0)	163 (40.2)
Female	73 (15.3)	15 (16.7)	15 (20.5)	31 (16.0)	31 (42.5)
Region[d]					
Asia-Pacific	321 (67.2)	66 (73.3)	66 (20.6)	134 (69.1)	134 (41.7)
Western regions	157 (32.8)	24 (26.7)	24 (15.3)	60 (30.9)	60 (38.2)
China	112 (23.4)	21 (23.3)	21 (18.8)	50 (25.8)	50 (44.6)
Rest of the world	366 (76.6)	69 (76.7)	69 (18.9)	144 (74.2)	144 (39.3)
Bodyweight, kg					
<60	153 (32.0)	25 (27.8)	25 (16.3)	63 (32.5)	63 (41.2)
≥60	325 (68.0)	65 (72.2)	65 (20.0)	131 (67.5)	131 (40.3)
ECOG PS					
0	304 (63.6)	66 (73.3)	66 (21.7)	129 (66.5)	129 (42.4)
1	174 (36.4)	24 (26.7)	24 (13.8)	65 (33.5)	65 (37.4)
Child-Pugh score					
A5	368 (77.0)	78 (86.7)	78 (21.2)	158 (81.4)	158 (42.9)
A6	107 (22.4)	12 (13.3)	12 (11.2)	36 (18.6)	36 (33.6)
AFP level at baseline, ng/mL					
<200	255 (53.3)	56 (62.2)	56 (22.0)	122 (62.9)	122 (47.8)
≥200	222 (46.4)	34 (37.8)	34 (15.3)	72 (37.1)	72 (32.4)
<400	281 (58.8)	60 (66.7)	60 (21.4)	128 (66.0)	128 (45.6)
≥400	195 (40.8)	30 (33.3)	30 (15.4)	66 (34.0)	66 (33.8)
ALBI score					
1	318 (66.5)	74 (82.2)	74 (23.3)	143 (73.7)	143 (45.0)
2	158 (33.1)	16 (17.8)	16 (10.1)	51 (26.3)	51 (32.3)
MPVI					
Yes	109 (22.8)	14 (15.6)	14 (12.8)	31 (16.0)	31 (28.4)
No	369 (77.2)	76 (84.4)	76 (20.6)	163 (84.0)	163 (44.2)
EHS					
Yes	291 (60.9)	57 (63.3)	57 (19.6)	101 (52.1)	101 (34.7)
No	187 (39.1)	33 (36.7)	33 (17.6)	93 (47.9)	93 (49.7)
MPVI, EHS, or both					
Yes	329 (68.8)	61 (67.8)	61 (18.5)	113 (58.2)	113 (34.3)
No	149 (31.2)	29 (32.2)	29 (19.5)	81 (41.8)	81 (54.4)
BCLC stage					
Stage B	104 (21.8)	23 (25.6)	23 (22.1)	59 (30.4)	59 (56.7)
Stage C	374 (78.2)	67 (74.4)	67 (17.9)	135 (69.6)	135 (36.1)

Table 1 (continued)

Baseline characteristic	Overall, *n* (%)[a] (*N* = 478)	RECIST v1.1 (90 responders)		mRECIST (194 responders)	
		responders with characteristic among all 90 responders, *n* (%)[b]	responders with characteristic among all patients with characteristic, *n* (%)[c]	responders with characteristic among all 194 responders, *n* (%)[b]	responders with characteristic among all patients with characteristic, *n* (%)[c]
Etiology					
Hepatitis B	259 (54.2)	44 (48.9)	44 (17.0)	99 (51.0)	99 (38.2)
Hepatitis C	103 (21.5)	27 (30.0)	27 (26.2)	49 (25.3)	49 (47.6)
Alcohol	33 (6.9)	5 (5.6)	5 (15.2)	11 (5.7)	11 (33.3)

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; IIR, independent imaging review; MPVI, macroscopic portal vein invasion; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. [a]Out of 478 patients in the lenvatinib arm. [b]Proportion of responders per baseline characteristic by number of responders (either *n* = 90 or *n* = 194), regardless of baseline characteristic. [c]Proportion of responders per characteristic by number of all patients with that characteristic, regardless of response status. [d]Asia-Pacific consists of China, Hong Kong, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand; Western regions consist of North America and Europe including Russia and Israel. A subdivision of the 478 patients in the lenvatinib arm is also shown for China versus the rest of the world (excluding China).

a combination of both. The most common etiologies of liver disease were hepatitis B (54.2%) and hepatitis C (21.5%).

Ninety patients (18.8%) achieved objective response per RECIST v1.1 by IIR, and 194 (40.6%) patients achieved an objective response per mRECIST by IIR at the date of the primary analysis data cutoff (November 13, 2016) [5]. ORRs by Child-Pugh score (A5 and A6) were 21.2% and 11.2% per RECIST v1.1 and 42.9% and 33.6% per mRECIST (Table 1). ORRs by AFP levels (<400 or ≥400 ng/mL) were 21.4% and 15.4% per RECIST v1.1 and 45.6% and 33.8% per mRECIST; by albumin-bilirubin (ALBI) score (1 and 2), ORRs were 23.3% and 10.1% per RECIST v1.1 and 45.0% and 32.3% per mRECIST. ORRs of patients with prior MPVI were 12.8% per RECIST v1.1 and 28.4% per mRECIST; they were 20.6% per RECIST v1.1 and 44.2% per mRECIST in patients without prior MPVI. ORRs by additional baseline characteristics including age, sex, bodyweight, ECOG PS, MVPI/EHS, Barcelona Clinic Liver Cancer (BCLC) staging, and etiology are available in Table 1.

Efficacy Metrics of Responders

Among the patients randomly assigned to receive lenvatinib and who achieved an objective response per RECIST v1.1, the median TTR was 2.8 months (range 1–29) and the median DOR was 7.4 months (95% CI 5.6–9.2); per mRECIST, the median TTR was 1.9 months (range 1–15) and the median DOR was 7.3 months (95% CI 5.6–7.4) (Table 2). The maximum tumor reductions of responders in the lenvatinib arm are shown by their best overall response (per RECIST v1.1 and mRECIST by IIR) in Figure 1; reductions in tumor size from baseline were generally sustained over time for responders per RECIST v1.1 (Fig. 2a) and mRECIST (Fig. 2b). Among responders in the lenvatinib arm, median PFS was 11.0 months (95% CI 9.2–12.9) for responders per RECIST v1.1 (by IIR) and 9.2 months (95% CI 8.8–10.8) for responders per mRECIST (by IIR). The median OS was 24.1 months (95% CI 18.7–26.5) among responders per RECIST v1.1 (shown in Fig. 3a); the median OS was 18.7 months (95%

Table 2. Response outcomes per independent imaging review

Parameter	Patients (*N* = 478)	
	RECIST v1.1	mRECIST
Objective response rate, *n* (%) [5]	90 (18.8)	194 (40.6)
95% CI [5]	15.3–22.3	36.2–45.0
Median DOR, months	7.4	7.3
95% CI	5.6–9.2	5.6–7.4
Median time to response, months	2.8	1.9
Range	1–29	1–15

CI, confidence interval; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

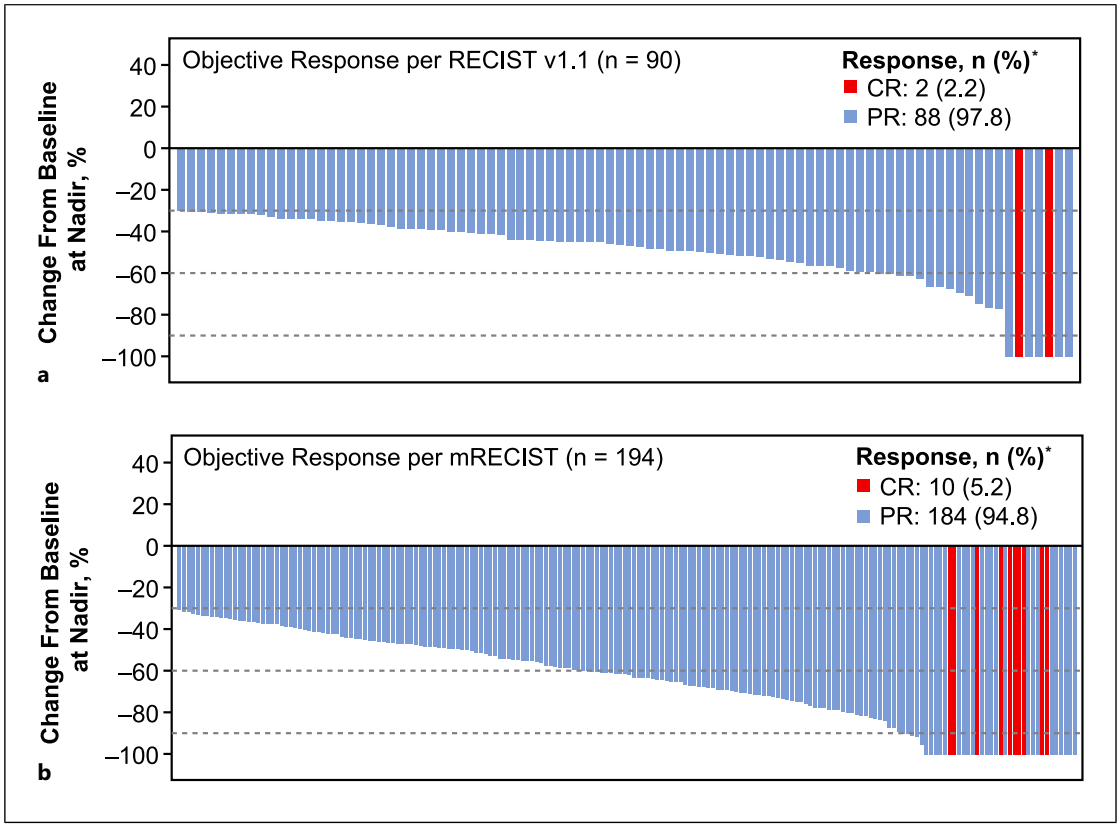

Fig. 1. Maximum tumor reduction of responders in the lenvatinib arm by IIR per RECIST v1.1 (**a**) and mRECIST (**b**). *Out of responders (CR or PR). CR, complete response; IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

CI 14.9–21.6) among responders per mRECIST (shown in Fig. 3b).

In the 4-month landmark analysis of OS by response status, patients who had an objective response per mRECIST v1.1 had a median OS of 19.4 months (95% CI 13.6–23.6); responders per RECIST had a median OS of 14.5 months (95% CI 10.4–18.3) (Fig. 4). Those patients who had stable disease at 4 months had a median OS of 13.4 months (95% CI 10.1–15.8) from the landmark time point per mRECIST v1.1 and 14.6 months (95% CI 10.3–17.2) per RECIST. Conversely, patients who had progressive disease (per mRECIST v1.1) by the 4-month landmark had a median OS of only 3.2 months (95% CI 2.3–4.6). These differences in OS by tumor response were similarly seen in the 6-month landmark analysis (shown in Fig. 5).

Safety/Tolerability of Responders

Of the 476 patients who received lenvatinib in the primary analysis, 447 (94%) had at least 1 treatment-related TEAE, 270 (57%) had at least 1 grade ≥3 severity treatment-related TEAE, and their median duration of treatment was 5.7 months [5]. In this analysis of responders per RECIST v1.1 (n = 90), 89 patients (98.9%) had at least 1 treatment-related TEAE, 59 (65.6%) had at least 1 grade ≥3 severity treatment-related TEAE, and their median duration of treatment was 10.3 months. Among the 194 patients who responded to lenvatinib treatment per mRECIST, 190 (97.9%) had at least 1 treatment-related TEAE, 122 (62.9%) had at least 1 grade ≥3 severity treatment-related TEAE, and their median duration of treatment was 9.2 months.

Discussion

Historically, tyrosine kinase inhibitors (TKIs) used to treat HCC have improved OS in either the first- or second-line setting by slowing progression; however, ORRs have typically been low (≤11%) [18, 19]. On the contrary, lenvatinib induced an ORR (18.8% per RECIST

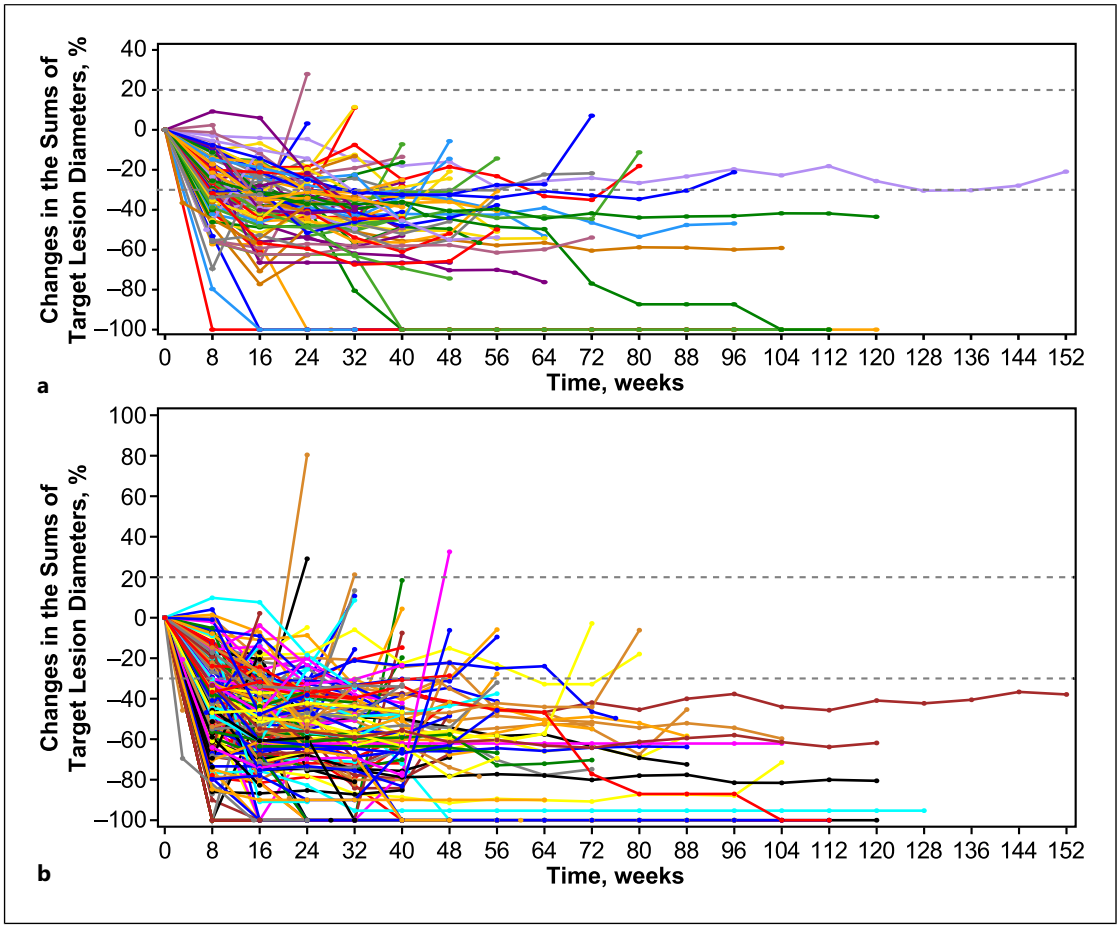

Fig. 2. Spider plot of changes in target lesion tumor sizes over time for responders in the lenvatinib arm by IIR per RECIST v1.1 (**a**) and mRECIST (**b**). IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

v1.1) in the REFLECT trial [5] that was generally comparable to single-agent immunotherapies [8, 11]. In our post hoc analysis of REFLECT, tumor responses with lenvatinib were observed early (median TTR per RECIST v1.1 and mRECIST: 2.8 and 1.9 months, respectively) and were durable (median DOR per RECIST v1.1 and mRECIST: 7.4 and 7.3 months, respectively).

Importantly, tumor responses in REFLECT were achieved irrespective of baseline characteristics, as assessed by either RECIST v1.1 or mRECIST. Baseline factors associated with numerically higher response rates to lenvatinib were an ECOG PS of 0 (vs. 1), a Child-Pugh score of A5 (vs. A6), an AFP level of <200 or <400 ng/mL (vs. ≥400), no MPVI, an ALBI score of 1 (vs. 2), a BCLC stage of B (vs. C), and hepatitis C as the etiology (vs. hepatitis B or alcohol) (Table 1). However, the ORR of patients with more-severe disease (e.g., ECOG PS of 1, MVPI, EHS, ALBI score 2, or BCLC stage C) was notably still above 10%.

Median PFS (11.0 and 9.2 months) and OS (24.1 and 18.7 months) in responders per RECIST v1.1 and mRECIST (respectively) were favorable compared with the median PFS (7.3 months per RECIST v1.1 and mRECIST) and OS (13.6 months) in the overall population. Landmark analyses of OS by response at 4 and 6 months by Kaplan-Meier analysis were similar to previous landmark analyses of REFLECT by the Simon-Makuch method [13] and further support the association between tumor response and improved OS.

Compared with the primary study, the incidence rates of any-grade and grade ≥3 severity treatment-related TEAEs were slightly higher in responders per RECIST v1.1 (98.9% and 65.6%, respectively) and mRECIST (97.9% and 62.9%, respectively) versus the overall population (94% and 57%, respectively) [5]. While this may have been due to the increased median duration of treatment among responders (RECIST v1.1: 10.3 months;

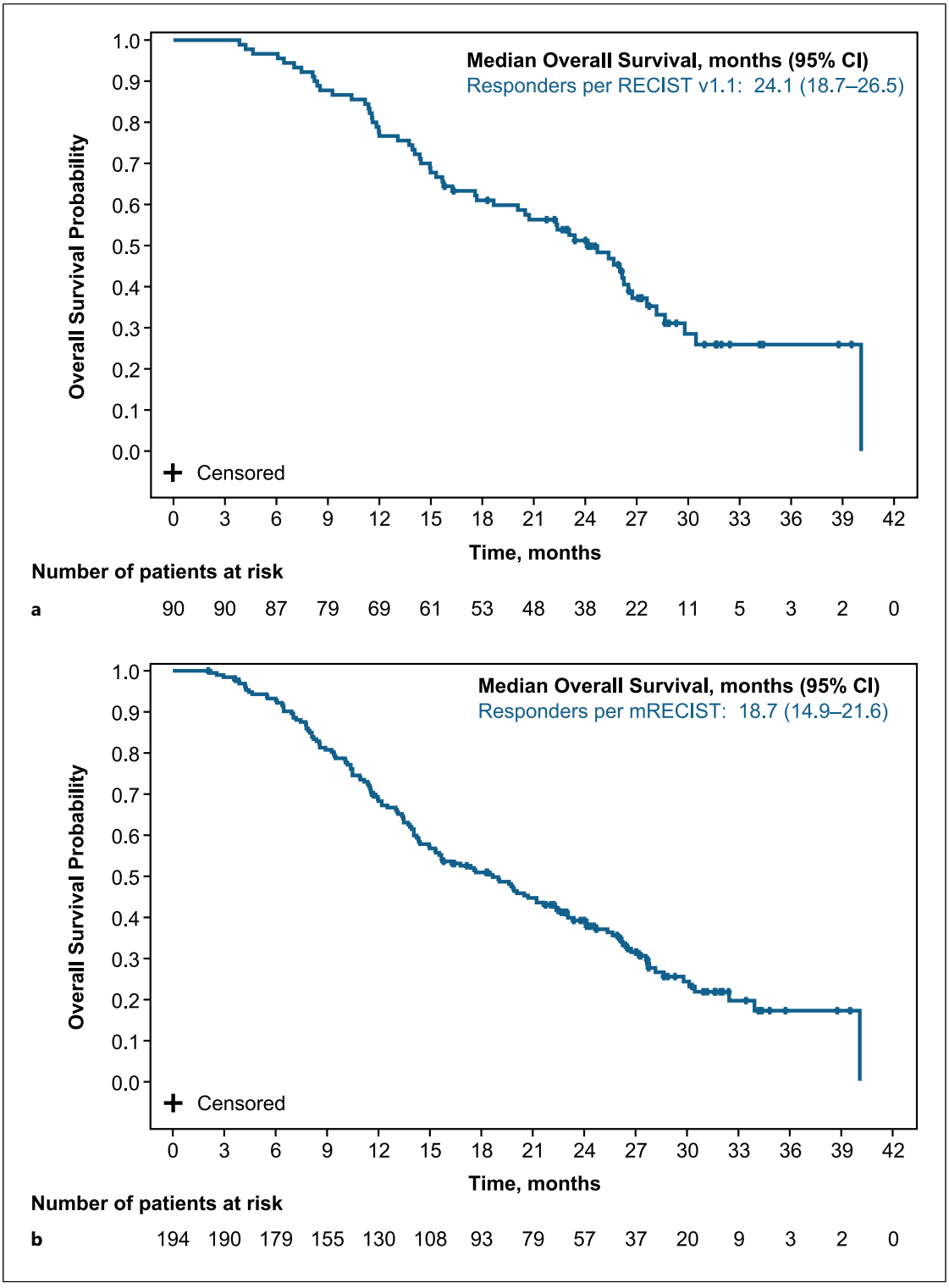

Fig. 3. Kaplan-Meier OS curves in patients in the lenvatinib arm with an objective response by IIR per RECIST v1.1 (**a**) and mRECIST (**b**). CI, confidence interval; IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

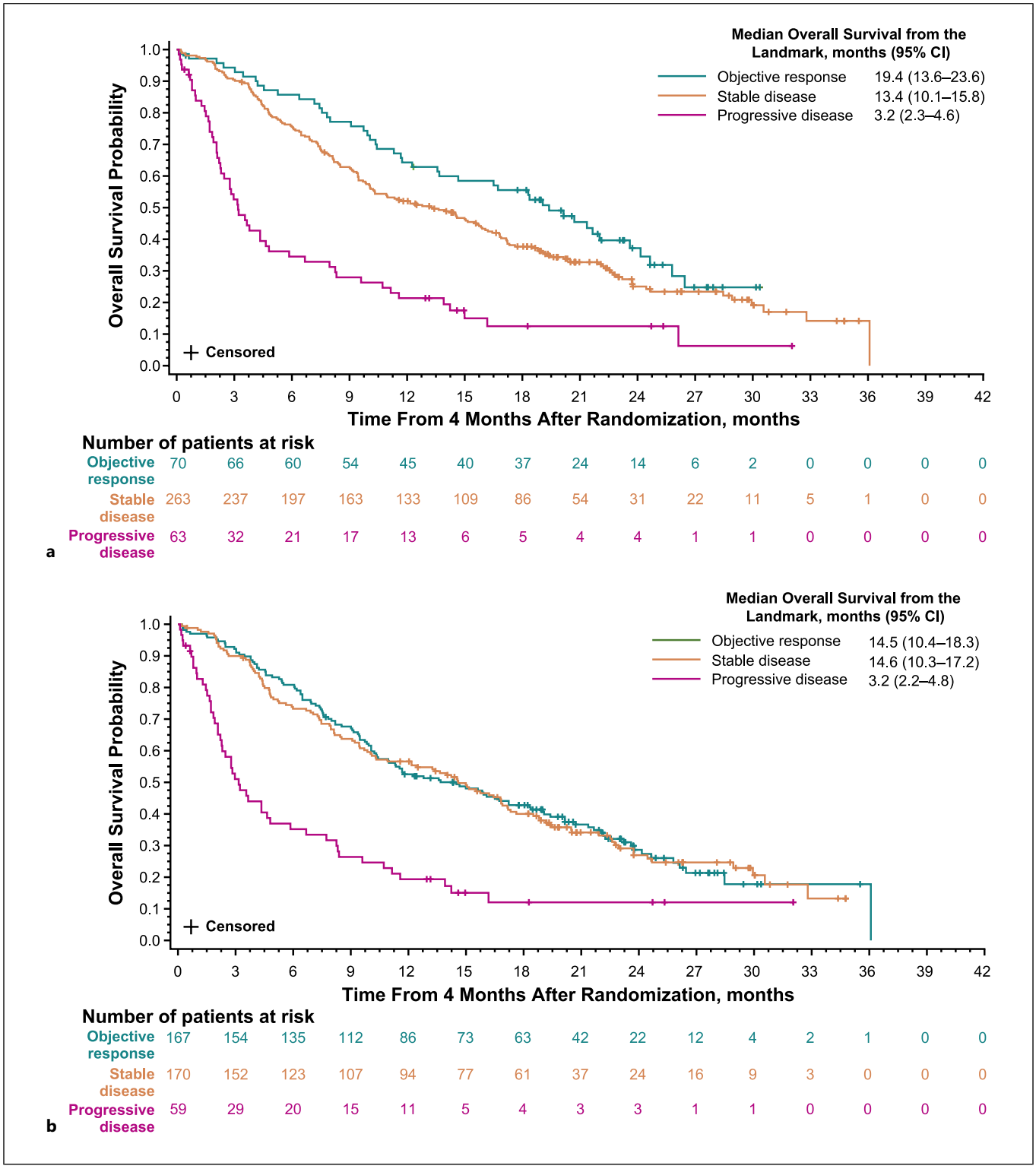

Fig. 4. Four-month landmark analysis of OS of patients in the lenvatinib arm with an objective response by IIR per mRECIST (**a**) and RECIST v1.1 (**b**). CI, confidence interval; CR, complete response; IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

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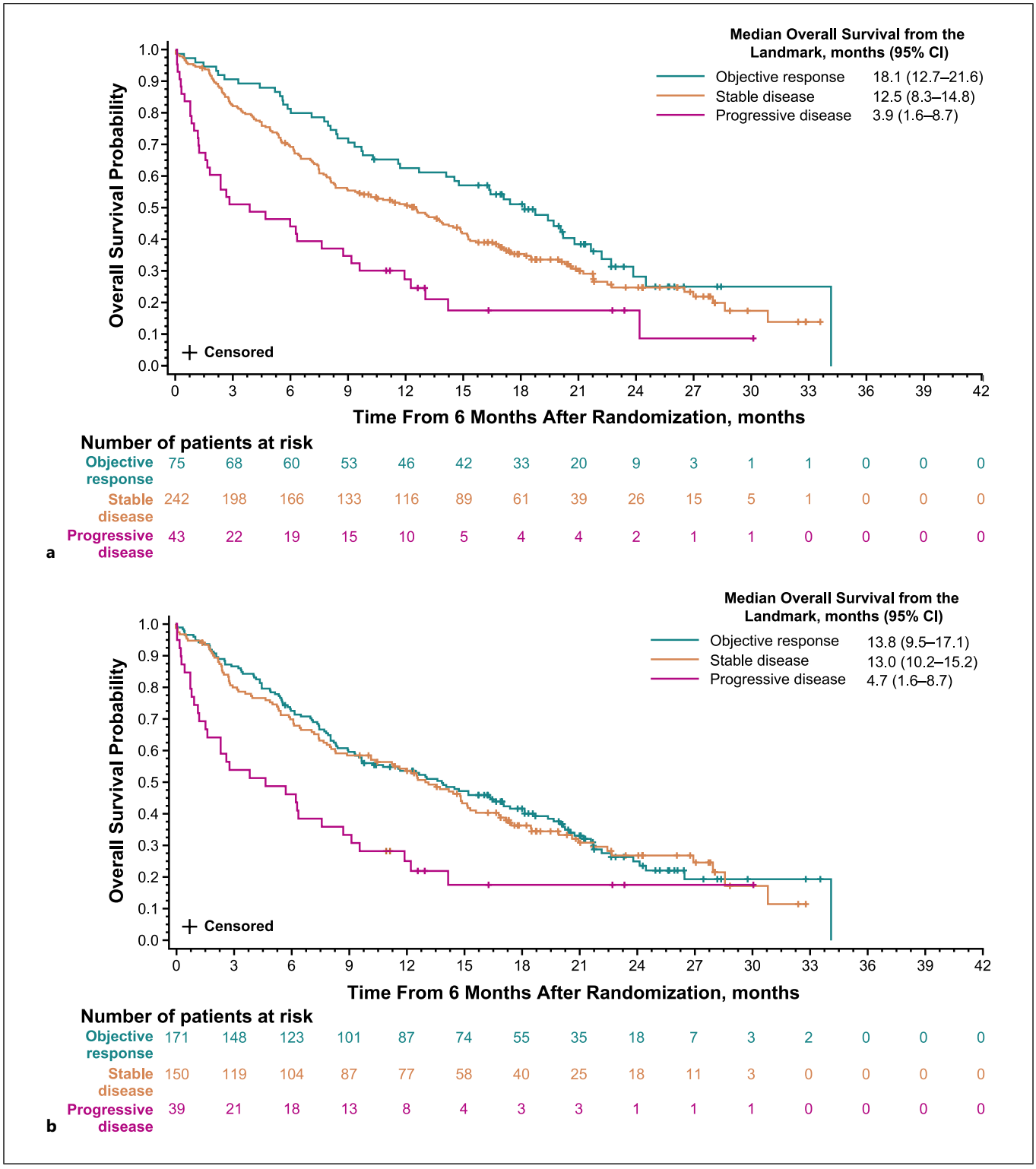

Fig. 5. Six-month landmark analysis of OS of patients in the lenvatinib arm with an objective response by IIR per mRECIST (**a**) and RECIST v1.1 (**b**). CI, confidence interval; CR, complete response; IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

mRECIST: 9.2 months) versus the overall population (5.7 months) [5], the differences in sample sizes (n = 90 and n = 194 vs. n = 476 [5], respectively) limit our ability to make direct comparisons.

Results of this unpowered post hoc analysis further support the improved survival among patients who achieved an objective response, which is notable as the ORR (per RECIST v1.1) is on par with recent studies of immune-checkpoint inhibitors (ICIs) or ICI combinations (18.8% vs. 11–27%) [7–10]. The limitations of cross-trial comparison are acknowledged, however; the efficacy of lenvatinib monotherapy in REFLECT was confirmed by lenvatinib monotherapy in the LEAP-002 study (ORR per RECIST v1.1: 17.5%) [20]. Together, these two studies show the efficacy of lenvatinib in uHCC.

In REFLECT, the ORR, TTR, and DOR of responders per RECIST v1.1 and mRECIST were notable in the context of first-line treatment for patients with uHCC; these, along with the PFS and OS reported previously [5], continue to support this regimen for the treatment of first-line uHCC. Although exploratory in nature, these analyses highlight the clinically relevant efficacy of lenvatinib across the subgroups assessed and support its use as a front-line option for patients with advanced HCC.

Statement of Ethics

All patients provided written informed consent. The study protocol, protocol amendments, and informed consent forms were reviewed and approved by all relevant institutional review boards approved the study in accordance with the Declaration of Helsinki and local laws. This study was approved by each research site's Institutional Review Board or Independent Ethics Committee; the name of the Ethics Committee at the leading recruitment site was Ethics Committee of Xijing Hospital (approval form number 20140114-2). A full list of participating sites was published in Kudo et al., Lancet 2018 [5].

Conflict of Interest Statement

R.S.F. reports receiving institutional research funding from Pfizer, Bayer, Novartis, Eisai, Lilly, Merck, Bristol Myers Squibb, and Roche/Genentech; receiving a consulting or advisory role from Pfizer, Bayer, Novartis, Bristol Myers Squibb, Merck, Eisai, Lilly, Genentech/Roche, AstraZeneca, Exelixis, and C Stone Pharma; and providing expert testimony to Novartis. S.Q. has no relationships to disclose. F.P. reports receiving honoraria for advisory boards, lecturing, or consultancies from AstraZeneca, Bayer, Bracco, ESAOTE, EISAI, Exact Sciences, IPSEN, MSD, Roche, Samsung, and Siemens Healthineers. A.V. reports honoraria from Roche, Amgen, Lilly, Bristol Myers Squibb, MSD, Pierre Fabre, Ipsen, Janssen, Incyte, AstraZeneca/MedImmune, Sirtex Medical, Daiichi Sankyo, Advanced Accelerator Applications/Imaging Equipment Ltd., Terumo, Taiho Oncology, Eisai, BeiGene, Boehringer Pharma GmbH, GlaxoSmithKline, Boston Scientific, Sirtex Medical, and Servier; consulting or advisory role for Novartis, Lilly, Roche, Amgen, Baxalta, AstraZeneca, Eisai, BTG, Ipsen, Pierre Fabre, Terumo, Daiichi Sankyo, Sirtex Medical, Boehringer Pharma GmbH, Incyte, and Taiho Oncology; research funding from Novartis; and travel/accommodations/expenses from Roche, Ipsen, AstraZeneca, MSD, and Lilly. T.R.J.E. reports honoraria from Ascelia, AstraZeneca, Bicycle Therapeutics, Bristol Myers Squibb, Eisai, Medivir, Merck Sharp & Dohme, NuCana, and Roche/Genentech; consulting or advisory role for Karus Therapeutics; speakers' bureau for AstraZeneca, Bristol Myers Squibb, Eisai, Medivir, Merck Sharp & Dohme, NuCana, Roche/Genentech, United Medical; research funding from Adaptimmune, Astellas Pharma, AstraZeneca, Athenex, Basilea, Beigene, Berg Pharma, Bicycle Therapeutics, BiolineRx, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Clovis Oncology, CytomX Therapeutics, Eisai, GlaxoSmithKline, Halozyme, Immunocore, iOnctura, Iovance Biotherapeutics, Janssen, Johnson & Johnson, Lilly, Medivir, Merck Serono, Merck Sharp & Dohme, MiNA Therapeutics, Modulate Pharma, Novartis, NuCana, Plexxikon, Roche/Genentech, Sanofi/Aventis, Sapience Therapeutics, Seagen, Sierra Pharma, Starpharma, UCB, Verastem, Vertex; expert testimony for Medivir; and travel/accommodations/expenses from Bristol Myers Squibb, Eisai, Merck Sharp & Dohme, NuCana, and Pierre Fabre. J.J.K. reports honoraria from AstraZeneca, Roche Canada; consulting or advisory role for AstraZeneca/MedImmune, Incyte, Lilly, and Merck; research funding from AstraZeneca, Ipsen, and Merck; and expert testimony from AstraZeneca. CLL reports consulting or advisory fees and research funding from Bristol Myers Squibb, Merck Sharp & Dohme, Eisai Co. Ltd., Merck Group, Servier, Sanofi S.A., Roche/Genentech, Exelixis, Daiichi Sankyo, Ipsen, and AstraZeneca and consulting or advisory fees from Bayer AG, Amgen Inc., Novartis, and Pfizer Inc. Z.R. was an employee of Eisai Inc., Nutley, NJ, USA. M.R. is an employee of Eisai Inc., Nutley, NJ, USA. K.M. is an employee of Eisai Inc., Nutley, NJ, USA. M.K. reports consulting or advisory fees and research funding from Chugai, Roche, Eisai, AstraZeneca, Otsuka, Taiho, GE Healthcare, AbbVie, and EA Pharma and honoraria from Chugai, Eisai, Eli Lilly, and Takeda.

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Author Contributions

M.K., R.S.F., S.Q., and F.P. were protocol steering committee members, made substantial contributions in all aspects of ICMJE criteria, and contributed to the study design. A.V., T.R.J.E., and C.L.L. were national coordinating or representing investigators in European countries and particularly contributed to study coordination and acquisition of good-quality data. Z.R., M.R., and K.M.

are Eisai employees primarily involved in the study and played a significant role in study design, data collection, data analysis, data interpretation, and writing of the report. M.R. performed the statistical analysis. R.S.F., S.Q., F.P., A.V., T.R.J.E., J.J.K., C.L.L., Z.R., M.R., K.M., and M.K. assisted in writing the manuscript and approved the final submitted version.

Data Availability Statement

The data will not be available for sharing at this time as they are commercially confidential. However, Eisai will consider written requests to share the data on a case-by-case basis. Inquiries can be directed to the corresponding author.

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