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Overall survival and objective response in advanced unresectable hepatocellular carcinoma: A subanalysis of the REFLECT study

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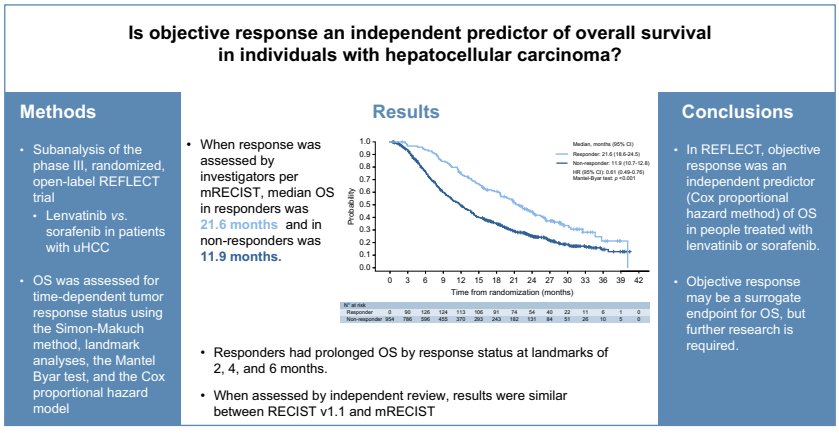
Graphical abstract



Highlights

- A post hoc analysis of REFLECT: Is objective response associated with OS in uHCC?
- In lenvatinib- or sorafenib-treated patients, OS was assessed by response status using landmark analyses per the Simon-Makuch method.
- Responders had longer median OS (21.6 months) vs non-responders (11.9 months).
- Responders had significantly prolonged OS by response status at 2, 4, and 6 months.
- Objective response was an independent predictor of OS in individuals with uHCC.

Impact and implications

This analysis of data taken from a completed clinical trial (REFLECT) looked for any link between objective response and overall survival time in individuals with unresectable HCC receiving anti-angiogenic treatments. Significantly longer median overall survival was found for responders (21.6 months) *vs.* non-responders (11.9 months). Overall survival was also significantly longer for responders *vs.* non-responders (based on objective response status at 2, 4, and 6 months) in the landmark analysis. Our results indicate that objective response is an independent predictor of overall survival in this setting, confirming its validity as a rapid marker of efficacy that can be applied in phase II trials; however, further validation is required to determine is validity for other systemic treatments (*e.g.* immunotherapies), or as a surrogate of overall survival.

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Overall survival and objective response in advanced unresectable hepatocellular carcinoma: A subanalysis of the REFLECT study

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Background & Aims: Validated surrogate endpoints for overall survival (OS) are important for expediting the clinical study and drug-development processes. Herein, we aimed to validate objective response as an independent predictor of OS in individuals with unresectable hepatocellular carcinoma (HCC) receiving systemic anti-angiogenic therapy.
Methods: We investigated the association between objective response (investigator-assessed mRECIST, independent radiologic review [IRR] mRECIST and RECIST v1.1) and OS in REFLECT, a phase III study of lenvatinib *vs.* sorafenib. We conducted landmark analyses (Simon-Makuch) of OS by objective response at 2, 4, and 6 months after randomization.
Results: Median OS was 21.6 months (95% CI 18.6–24.5) for responders (investigator-assessed mRECIST) *vs.* 11.9 months (95% CI 10.7–12.8) for non-responders (hazard ratio [HR] 0.61; 95% CI 0.49–0.76; p <0.001). Objective response by IRR per mRECIST and RECIST v1.1 supported the association with OS (HR 0.61; 95% CI 0.51–0.72; p <0.001 and HR 0.50; 95% CI 0.39–0.65; p <0.001, respectively). OS was significantly prolonged for responders *vs.* non-responders (investigator-assessed mRECIST) at the 2-month (HR 0.61; 95% CI 0.49–0.76; p <0.001), 4-month (HR 0.63; 95% CI 0.51–0.80; p <0.001), and 6-month (HR 0.68; 95% CI 0.54–0.86; p <0.001) landmarks. Results were similar when assessed by IRR, with both mRECIST and RECIST v1.1. An exploratory multivariate Cox regression analysis identified objective response by investigator-assessed mRECIST (HR 0.55; 95% CI 0.44–0.68; p <0.0001) and IRR-assessed RECIST v1.1 (HR 0.49; 95% CI, 0.38–0.64; p <0.0001) as independent predictors of OS in individuals with unresectable HCC.
Conclusions: Objective response was an independent predictor of OS in individuals with unresectable HCC in REFLECT; additional studies are needed to confirm surrogacy. Participants achieving a complete or partial response by mRECIST or RECIST v1.1 had significantly longer survival *vs.* those with stable/progressive/non-evaluable disease.
ClinicalTrials.gov number: NCT01761266.

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide.[1,2] Although curative treatment options exist for those with early-stage HCC, the majority of individuals present with advanced HCC at the time of diagnosis.[3,4] Currently, sorafenib and lenvatinib are the only targeted therapies approved for the first-line treatment of advanced unresectable HCC.[5]

Sorafenib, a multikinase inhibitor, demonstrated a survival benefit in the phase III sorafenib hepatocellular carcinoma assessment randomized protocol (SHARP) and Asia-Pacific studies.[6,7] Lenvatinib is a multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT.[8–11] In the randomized, open-label, phase III trial to compare the efficacy and safety of lenvatinib vs. sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma (REFLECT), lenvatinib met its primary endpoint by demonstrating a treatment effect on overall survival (OS) statistically confirmed by non-inferiority to sorafenib.[12] The median OS for patients treated with lenvatinib compared with sorafenib was 13.6 months *vs.* 12.3 months, respectively (hazard ratio [HR] 0.92; 95% CI 0.79–1.06). Lenvatinib also led to significant improvements in the objective response rate (ORR). ORR by investigator-

Keywords: landmark analysis; lenvatinib; mRECIST; response status; surrogate endpoint.
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assessed modified RECIST (mRECIST) for patients treated with lenvatinib compared with sorafenib was 24.1% *vs.* 9.2%, respectively (odds ratio 3.13; 95% CI 2.15–4.56; p <0.0001).

There has been a poor correlation between OS and objective response using RECIST version 1.0 in the setting of multi-targeted anti-angiogenic therapy in HCC.[13,14] RECIST utilizes a unidimensional measurement of tumor size; however, anti-angiogenic targeted therapies can cause tumor necrosis without changing the overall tumor size. mRECIST evaluates tumor response based on intratumoral arterial enhancement (measured using contrast-enhanced radiologic imaging, which aims to differentiate between the viable and necrotic tissue) rather than overall tumor size.[2,13–15] While mRECIST has been widely used to assess response in those receiving locoregional or systemic therapies for HCC, additional studies are needed to validate this approach.

Though OS is considered to be the most reliable and clinically meaningful endpoint in oncology clinical trials, it is challenging to evaluate because it requires a large number of participants and an extended follow-up period. There are also an increasing number of subsequent treatments available, and their use can impact the evaluation of OS, making it difficult to determine if the survival benefit was from the trial or from subsequent treatments.[16] Therefore, the identification of validated surrogate endpoints for OS may expedite the clinical study and drug-development processes.[13,14] Previous studies have demonstrated that objective response by mRECIST is an independent predictor of OS in individuals with HCC.[13,14,17] This is particularly useful in the setting of phase II trials, where the use of objective response by mRECIST may serve as a rapid marker of efficacy and may ultimately aid in the determination of which HCC treatments are best suited for further evaluation in a phase III trial. However, the European Association for the Study of the Liver clinical practice guidelines advised that additional studies are needed to further validate the predictive value of tumor response.[2] In this *post hoc* subanalysis using data from REFLECT, we investigated the relationship between objective response (by mRECIST and RECIST version 1.1) and OS.

Patients and methods

Study design and participants

REFLECT was a phase III multicenter, open-label, non-inferiority study in participants with unresectable HCC.[12] Full details of the study design and methodology for REFLECT have been reported previously (ClinicalTrials.gov number: NCT01761266).[12]

Randomization and masking

REFLECT was an open-label study where patients were randomly assigned 1:1 to receive either lenvatinib or sorafenib, based on stratification. Patients were stratified by region (Asia-Pacific or Western); macroscopic portal vein invasion, extrahepatic spread, or both (yes or no); Eastern Cooperative Oncology Group performance status score (0 or 1); and bodyweight (<60 kg or ≥60 kg).

Treatments

The starting dose for lenvatinib was based on baseline bodyweight. Patients weighing ≥60 kg received lenvatinib 12 mg/day; patients weighing <60 kg received lenvatinib 8 mg/day.[18] Patients randomly assigned to receive sorafenib received 400 mg twice-daily in 28-day cycles.

Clinical assessments

The primary endpoint was OS, defined as the time from randomization to death from any cause. The secondary efficacy endpoints were progression-free survival, time to progression, and ORR according to investigator-assessed mRECIST. Tumor measurements were performed every 8 weeks using computed tomography or magnetic resonance imaging, regardless of dose interruptions, and until radiologic disease progression. Retrospectively, tumor assessments were performed by independent radiologic review (IRR), per both mRECIST and RECIST version 1.1. The independent review was performed by a panel of board-certified radiologists sub-specialized in liver imaging, who were specifically trained for the study. Two independent radiologists reviewed the available scans for each patient. If there was disagreement between the two primary reviewers in the response assessment at any timepoint, a third adjudicating radiologist reviewed the case and the results from the first two reviewers and decided which of the two primary radiological assessments was preferred. The decision of the adjudicator was the final decision.

All participants provided written informed consent. The study protocol, protocol amendments, and informed consent forms were reviewed and approved by the relevant institutional review boards and independent ethics committees. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.

Statistical analysis

This *post hoc*, retrospective subanalysis of REFLECT examined the association between objective response based on investigator-assessed mRECIST and OS for participants randomly assigned to receive lenvatinib or sorafenib. Additionally, as a sensitivity analysis, the association between OS and objective response in REFLECT by IRR was assessed per both mRECIST and RECIST version 1.1 criteria in the overall population of REFLECT and in participants from each treatment arm. Responders were defined as participants who achieved a complete or partial response per mRECIST or RECIST version 1.1 criteria as noted. Non-responders were defined as participants who had stable disease (SD) or progressive disease (PD) or whose response status was unknown or not evaluable. Radiological evaluation for response was performed every 8 weeks.

OS for responders and non-responders in the overall REFLECT population, irrespective of treatment, was estimated using the Simon-Makuch method[19] and was compared using the Mantel-Byar test. HRs and associated CIs were calculated using a Cox proportional hazard model with objective response as a time-dependent covariate.

Landmark analyses of OS by objective response status at 2, 4, and 6 months after randomization were conducted. Participants who died before the landmark point were excluded from that analysis; participants who were still in the study at the landmark point being analyzed were initially classified by best response until that point. Landmark survival curves were estimated using the Simon-Makuch method and compared using

Mantel-Byar tests; the corresponding HRs and associated CIs were calculated using a Cox proportional hazard model, stratified by treatment, with objective response as a time-dependent covariate.

Multivariate Cox regression analyses for predictors of survival were performed, with objective response (by investigator per mRECIST) and increase in Child-Pugh score from baseline to ≥7 as time-dependent covariates. The stepwise selection procedure was used for all candidate factors, and factors were selected for entry and retention in the multivariate model based on a significance level of 5%.

OS for responders and participants with SD or PD in the overall REFLECT population was estimated using the Simon-Makuch method and compared using the Mantel-Byar test. HRs and associated CIs were calculated using a Cox proportional hazard model with objective response as a time-dependent covariate.

Following the approach presented by Burzykowski *et al.*, the individual-level association θ (95% CI) between objective response (binary surrogate outcome) and OS (true outcome) was estimated without any landmark times (i.e., with no consideration for potential guarantee-time bias) and with 2-, 4-, and 6-month landmark times.[20]

Because this was a post hoc retrospective analysis, *p* values without multiplicity adjustment were provided for descriptive purposes.

Results

Participant characteristics

Of the 954 participants enrolled in REFLECT, 478 received lenvatinib and 476 received sorafenib. As previously reported, baseline characteristics were similar between treatment arms, except for baseline hepatitis C virus etiology and alpha-fetoprotein concentrations.[12]

Overall, 159 (16.7%) participants were classified as responders and 795 (83.3%) were classified as non-responders. Of the responders, 8 (5.0%) had a complete response (CR) and 151 (95.0%) had a partial response (PR). Of the non-responders, 490 (61.6%) had SD, 218 (27.4%) had PD, and 87 (10.9%) had a disease state that was unknown or indeterminable.

Participants' baseline and clinical characteristics by response status are summarized in Table 1. Baseline characteristics between responders and non-responders were similar. However, a greater proportion of non-responders had extrahepatic spread and/or macroscopic portal vein invasion, as well as advanced Barcelona Clinic Liver Cancer stage and greater number of involved disease sites. A greater proportion of responders had hepatitis C virus etiology.

Efficacy

Median OS for the total REFLECT population was 13.0 months (95% CI 11.9–14.1). Simon-Makuch estimates of OS for responders and non-responders (as assessed by investigator per mRECIST) in REFLECT are shown in Fig. 1. Median OS was 21.6 months (95% CI 18.6–24.5) for responders, compared with 11.9 months (95% CI 10.7–12.8) for non-responders (HR 0.61; 95% CI 0.49–0.76; p <0.001). When response was assessed by IRR per mRECIST, median OS was 20.5 months

Table 1. Baseline and clinical characteristics by response status.

Characteristic	Responders (n = 159)	Non-responders (n = 795)
Median age, years (range)	63 (26, 85)	62 (20, 88)
Sex		
Male	131 (82.4)	675 (84.9)
Female	28 (17.6)	120 (15.1)
Region		
Western	50 (31.4)	264 (33.2)
Asia-Pacific	109 (68.6)	531 (66.8)
Bodyweight		
<60 kg	46 (28.9)	253 (31.8)
≥60 kg	113 (71.1)	542 (68.2)
ECOG performance status		
0	111 (69.8)	494 (62.1)
1	48 (30.2)	301 (37.9)
Macroscopic portal vein invasion		
Yes	26 (16.4)	173 (21.8)
No	133 (83.6)	622 (78.2)
Extrahepatic spread		
Yes	86 (54.1)	500 (62.9)
No	73 (45.9)	295 (37.1)
Macroscopic portal vein invasion, extrahepatic spread, or both		
Yes	99 (62.3)	566 (71.2)
No	60 (37.7)	229 (28.8)
BCLC stage		
B (intermediate stage)	48 (30.2)	148 (18.6)
C (advanced stage)	111 (69.8)	647 (81.4)
Number of involved disease sites per patient[a]		
1	85 (53.5)	329 (41.4)
2	53 (33.3)	297 (37.4)
≥3	21 (13.2)	168 (21.1)
Missing	0	1 (<1)
Presence of HCC in the liver		
Yes	142 (89.3)	729 (91.7)
No	17 (10.7)	66 (8.3)
Etiology HBV		
Yes	74 (46.5)	429 (54.0)
No	85 (53.5)	366 (46.0)
Etiology HCV		
Yes	50 (31.4)	188 (23.6)
No	109 (68.6)	607 (76.4)
Etiology alcohol		
Yes	6 (3.8)	50 (6.3)
No	153 (96.2)	745 (93.7)
Cirrhosis present[b]		
Yes	82 (51.6)	392 (49.3)
No	77 (48.4)	403 (50.7)
Baseline serum AFP		
<200 ng/ml	97 (61.0)	444 (55.8)
≥200 ng/ml	62 (39.0)	347 (43.6)
Missing	0	4 (0.01)
Concomitant systemic antiviral therapy for HBV/HCV		
Yes	51 (32.1)	261 (32.8)
No	108 (67.9)	534 (67.2)
Prior anticancer procedures		
Yes	111 (69.8)	560 (70.4)
No	48 (30.2)	235 (29.6)
Treatment		
Lenvatinib	115 (72.3)	363 (45.7)
Sorafenib	44 (27.7)	432 (54.3)
Median time on treatment[c], months	11.0	3.7
Median duration on follow-up, months	27.0	27.8

Unless otherwise stated values are expressed as n (%).
AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; mRECIST, modified RECIST.
[a]The number of involved disease sites refers to the liver, lung, lymph node, bone, and other.
[b]Per the investigators' own radiologic assessment.
[c]In the non-responder group, 3 participants did not receive study treatment and were excluded from the median time on treatment analysis (n = 792).

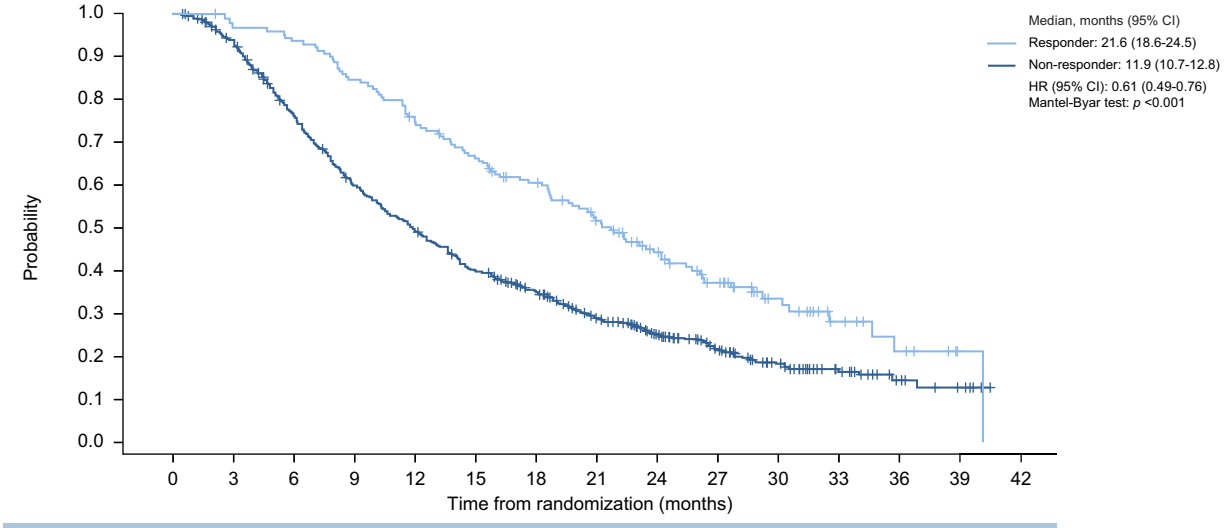
(95% CI 17.4–23.4) in responders and 11.1 months (95% CI 9.9–12.3) in non-responders (HR 0.61; 95% CI 0.51–0.72; p <0.001); and when response was assessed by IRR per RECIST version 1.1, median OS was 26.0 months (95% CI 22.4–28.6) in responders and 12.0 months (95% CI 10.9–13.1) in non-responders (HR 0.50; 95% CI 0.39–0.65; p <0.001 [Fig. S1]). Similarly, the median OS was higher in responders *vs.* non-responders, regardless of treatment arm, when assessed by investigator per mRECIST (lenvatinib, HR 0.73; 95% CI 0.56–0.94; sorafenib, HR 0.38; 95% CI 0.24–0.61) and when assessed by IRR per mRECIST (lenvatinib, HR 0.72; 95% CI 0.58–0.89; sorafenib, HR 0.35; 95% CI 0.23–0.53) or by RECIST version 1.1 (lenvatinib, HR 0.62; 95% CI 0.46–0.82; sorafenib, HR 0.22; 95% CI 0.11–0.44 [Fig. S2]).

The OS benefit for responders *vs.* non-responders was maintained at each landmark time point. OS was significantly prolonged for patients who achieved an objective response (assessed by investigator per mRECIST) compared with patients who did not at the 2-month landmark (HR 0.61; 95% CI 0.49–0.76; p <0.001; Fig. 2A), 4-month landmark (HR 0.63; 95% CI 0.51–0.80; p <0.001; Fig. 2B), and 6-month landmark (HR 0.68; 95% CI 0.54–0.86; p = 0.001; Fig. 2C). These results were generally consistent with those obtained by IRR, per mRECIST or RECIST version 1.1 (Fig. S3). Moreover, the OS benefit for responders *vs.* non-responders (assessed by investigator per mRECIST) was also maintained when assessed by treatment arm at the 2-month landmark (lenvatinib, HR 0.73; 95% CI 0.57–0.95; sorafenib, HR 0.38; 95% CI 0.24–0.61), the 4-month landmark (lenvatinib, HR 0.76; 95% CI 0.58–0.98; sorafenib, HR 0.41; 95% CI 0.26–0.66), and the 6-month landmark (lenvatinib, HR 0.81; 95% CI 0.62–1.07; sorafenib, HR 0.43; 95% CI 0.27–0.70 [Fig. S4]). When assessed by IRR, OS benefits in responders were also observed for both study drugs per mRECIST (Fig. S5) or RECIST version 1.1 (Fig. S6). Table S1 shows the exact numbers of responders and non-responders, as well as the numbers of patients who were excluded from each landmark analysis, per study drug when assessed by mRECIST per investigator, mRECIST per IRR, and RECIST version 1.1 per IRR.

An exploratory multivariate Cox regression analysis including objective response and increase in Child-Pugh score from baseline to ≥7 as time-dependent covariates (Table 2) identified objective response by mRECIST per investigator assessment as an independent predictor of OS for individuals with HCC in this study (HR 0.55; 95% CI 0.44–0.68, p <0.0001). Other independent predictors of OS included increase in Child-Pugh score to ≥7, sex, macroscopic portal vein invasion, baseline alpha-fetoprotein level, number of tumor sites at baseline, presence of HCC in the liver, hepatitis B virus etiology, and treatment (Table 2). Notably, objective response by mRECIST was an independent predictor of OS for individuals with HCC, regardless of whether they were in the lenvatinib or sorafenib treatment arm. A multivariate analysis with objective response assessed by IRR also consistently identified objective response as an independent predictor of OS (by RECIST version 1.1: HR 0.49; 95% CI, 0.38-0.64; p <0.0001; by mRECIST: HR 0.61; 95% CI, 0.50-0.74; p <0.0001).

We also assessed survival by response (CR+PR) *vs.* SD or PD status. Simon-Makuch estimates of OS for responders and participants with SD and PD in REFLECT are shown in Fig. S7. When responses were assessed by investigator per mRECIST, median OS was 21.6 months (95% CI 18.6–24.5) for responders, compared to 16.0 months (95% CI 14.3–18.5) for participants who had SD (HR [(CR+PR)/SD] 0.75; 95% CI 0.60–0.94; p = 0.013) and 6.4 months (95% CI 5.7–7.2) for those with PD (HR [(CR+PR)/PD] 0.35; 95% CI 0.27–0.45; p <0.001 [Fig. S7A]). Similar patterns were seen when responses were assessed by IRR, per mRECIST (Fig. S7B) or RECIST version 1.1 (Fig. S7C).

When individual-level association analyses between objective response and OS were estimated with or without any landmark times, the odds of surviving beyond a specified time



N° at risk															
Responder	0	90	126	124	113	106	91	74	54	40	22	11	6	1	0
Non-responder	954	786	596	455	370	293	243	182	131	84	51	26	10	5	0

Fig. 1. Simon-Makuch estimates of overall survival by response status (per investigator-assessed mRECIST) for the REFLECT population. HR, hazard ratio; mRECIST, modified RECIST.

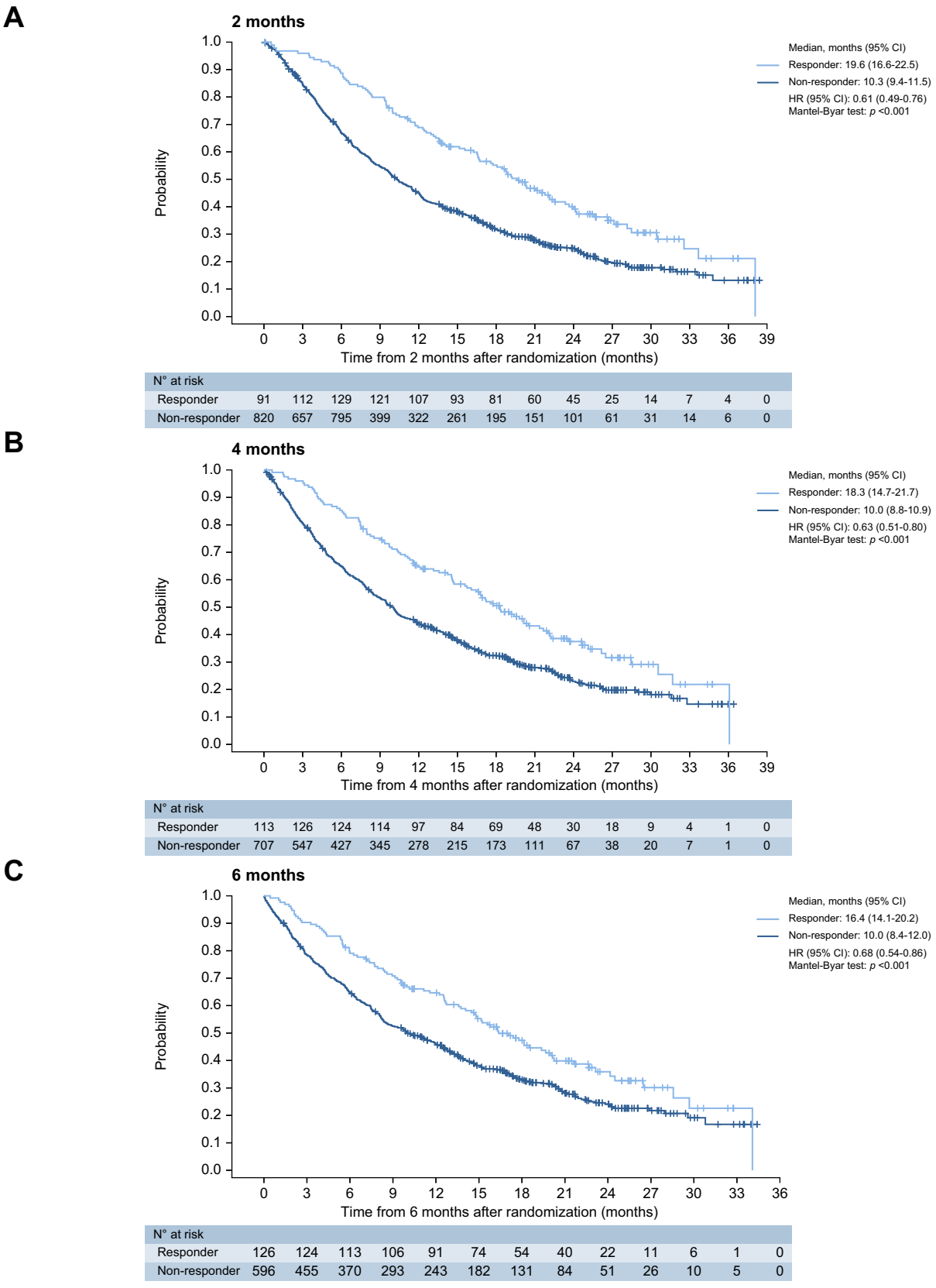


Fig. 2. Simon-Makuch estimates of overall survival by response status (per investigator-assessed mRECIST) for the REFLECT population using landmark times. Landmark times at (A) 2 months (B) 4 months, and (C) 6 months. HR, hazard ratio; mRECIST, modified RECIST.

Table 2. Multivariate cox regression analysis of factors associated with overall survival[a]

Parameter	β: log HR	SE	HR (95% CI)	*p* value
Overall REFLECT population				
Treatment (lenvatinib *vs.* sorafenib)	-0.174	0.078	0.84 (0.72–0.98)	0.0257
Objective response[b,c] (yes *vs.* no)	-0.605	0.113	0.55 (0.44–0.68)	<0.0001
Increase of Child-Pugh score to ≥7[c] (yes *vs.* no)	0.957	0.083	2.60 (2.21–3.06)	<0.0001
Sex (male *vs.* female)	0.216	0.105	1.24 (1.01–1.52)	0.0391
Macroscopic portal vein invasion (yes *vs.* no)	0.198	0.093	1.22 (1.02–1.46)	0.0325
AFP at baseline (<200 ng/ml *vs.* ≥ 200 ng/ml)	-0.544	0.079	0.58 (0.50–0.68)	<0.0001
Number of tumor sites at baseline (2 *vs.* 1)	0.362	0.088	1.44 (1.21–1.71)	<0.0001
Number of tumor sites at baseline (≥3 *vs.* 1)	0.740	0.101	2.10 (1.72–2.56)	<0.0001
Etiology HBV (yes *vs.* no)	0.224	0.078	1.25 (1.07–1.46)	0.0038
Presence of HCC in the liver (yes *vs.* no)	0.447	0.168	1.56 (1.12–2.17)	0.0080
Lenvatinib treatment arm				
Objective response[b,c] (yes *vs.* no)	-0.401	0.133	0.67 (0.52–0.87)	0.0026
Increase of Child-Pugh score to ≥7[c] (yes *vs.* no)	0.936	0.115	2.55 (2.03–3.20)	<0.0001
Sex (male *vs.* female)	0.278	0.149	1.32 (0.99–1.77)	0.0621
Macroscopic portal vein invasion (yes *vs.* no)	0.227	0.128	1.25 (0.98–1.61)	0.0768
AFP at baseline (<200 ng/ml *vs.* ≥200 ng/ml)	-0.522	0.113	0.59 (0.48–0.74)	<0.0001
Number of tumor sites at baseline (2 *vs.* 1)	0.343	0.126	1.41 (1.10–1.81)	0.0065
Number of tumor sites at baseline (≥3 *vs.* 1)	0.577	0.139	1.78 (1.36–2.34)	<0.0001
Etiology HBV (yes *vs.* no)	0.084	0.112	1.09 (0.87–1.36)	0.4522
Presence of HCC in the liver (yes *vs.* no)	0.569	0.269	1.77 (1.04–2.99)	0.0343
Sorafenib treatment arm				
Objective response[b,c] (yes *vs.* no)	-1.176	0.242	0.31 (0.19–0.50)	<0.0001
Increase of Child-Pugh score to ≥7[c] (yes *vs.* no)	1.000	0.121	2.72 (2.14–3.45)	<0.0001
Sex (male *vs.* female)	0.119	0.149	1.13 (0.84–1.51)	0.4244
Macroscopic portal vein invasion (yes *vs.* no)	0.208	0.136	1.23 (0.94–1.61)	0.1259
AFP at baseline (<200 ng/ml *vs.* ≥200 ng/ml)	-0.582	0.112	0.56 (0.45–0.70)	<0.0001
Number of tumor sites at baseline (2 *vs.* 1)	0.361	0.124	1.43 (1.12–1.83)	0.0037
Number of tumor sites at baseline (≥3 *vs.* 1)	0.875	0.148	2.40 (1.80–3.21)	<0.0001
Etiology HBV (yes *vs.* no)	0.351	0.110	1.42 (1.14–1.76)	0.0014
Presence of HCC in the liver (yes *vs.* no)	0.299	0.219	1.35 (0.88–2.07)	0.1733

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; mRECIST, modified RECIST; SE, standard error.

[a]Only factors selected by the stepwise selection method are shown. Factors not selected include age, region, extrahepatic spread, ECOG performance status, body weight, antiviral therapy for HBV or HCV, HCV etiology, alcoholism etiology, underlying cirrhosis, BCLC staging, and prior procedures.

[b]Response determined by investigator per mRECIST.

[c]Objective response and increase of Child-Pugh score to ≥7 are included in the Cox model as time-dependent covariates.

were higher for responders than for non-responders (Table S2). Thus, even after potential guarantee-time bias was considered, a consistent association between objective response and OS at the individual level was suggested.

While considering death due to hepatic failure among patients in REFLECT (n = 16) as a competing risk, we explored the association between objective response (time-dependent) and OS using the Fine-Gray subdistribution hazard model and a cause-specific hazard model. Importantly, the results of these analyses were consistent with those reported throughout the manuscript (Table S3).

When individual-level association analyses between progression-free survival (PFS) and OS were conducted, there was a moderate to strong correlation via iterative multiple imputation[21] between PFS and OS (as assessed per investigator via mRECIST and per IRR via mRECIST and RECIST version 1.1; Table S4).

Discussion

This retrospective analysis examined the relationship between objective response by investigator-assessed mRECIST and OS in the large-scale, phase III REFLECT study. Our findings show that objective response by mRECIST was an independent predictor of OS in patients undergoing systemic anti-angiogenic treatment for HCC. Objective response by IRR, per mRECIST or RECIST version 1.1, was also associated with improved OS in our analysis. Participants who achieved a CR or PR by mRECIST had significantly longer survival compared to those with stable, non-evaluable, or progressive disease. These results were generated using the Mantel-Byar method and Cox regression models, with objective response designated as a time-dependent covariate to reduce some of the bias related to differences in time to response and to take into consideration that the patient's response status may change over time.

Secondary analyses used the landmark method to evaluate survival by tumor response. This method was used to address the issue of guarantee-time bias via the selection of three fixed time points (i.e., 2, 4, and 6 months) after randomization as landmarks for conducting the analysis. Patients still in the study at the landmark time point were initially classified by best response until each landmark time point, and survival analyses from the landmark time point were performed combining the Simon-Makuch method. Patients who died before the landmark time point were excluded. Of note, Anderson and colleagues[22] remarked that "patients with poor survival prognosis who die early in the study will not have an opportunity to enter the responder group and will guarantee poorer survival rates for the non-response group." Thus, such patients are excluded to remove this confounding issue, which may introduce a guarantee-time bias. Utilization of the Simon-Makuch method addresses this by taking the patient's response status change

into consideration. In addition, this method allows for the selection of a starting timepoint after time zero, leading to more precise and meaningful results since the number of patients at risk in responders is usually smaller at earlier time points as patients may not have had the time to develop a response. On the other hand, we recognize that a landmark analysis at later time points could lead to a large loss of information and precision due to the large number of patients excluded. We have provided the number of responders and non-responders at each landmark in Table S1, but because number and timing of responses vary depending on how responses were assessed, these values should be interpreted with caution. However, multivariate Cox regression models with objective response as a time-dependent covariate are another established method for addressing the issue of guarantee-time bias.[22-24] This approach allowed for the evaluation of the effect of tumor response on survival, adjusting for other potential confounding factors.

Importantly, objective response status 2 months after randomization was predictive of survival, and these significant survival differences were also consistently demonstrated in objective response status at both 4 and 6 months after randomization. This suggests that study investigators may consider using objective response status by mRECIST shortly after commencing treatment as an early indicator of survival in clinical trials for unresectable HCC in an anti-angiogenic therapy setting. Similarly, this analysis may also support choosing an objective-response–based endpoint in early-phase trials for unresectable HCC. Because assessing OS requires a longer follow-up period than does objective response, intermediate endpoints such as objective response were examined. While difficult to validate as surrogate endpoints, objective response can be used as a supportive or primary endpoint in clinical trials to provide a more rapid assessment of therapeutic activity. This may ultimately lead to faster results from phase II trials, and quicker initiation of phase III trials, which, in turn, may speed up approvals and increase the availability of new treatment options for individuals with unresectable HCC. However, caution is warranted, particularly as this was an analysis comparing two kinase inhibitors, and potential surrogacy may not apply to other treatment classes. Surrogate endpoints should be fully validated with prospective studies to prevent inaccurate interpretation of the risk-benefit profile.[25]

Using this multivariate model, objective response as measured by mRECIST per investigator assessment was identified as an independent predictor of OS after adjustment for the effects of baseline characteristics and first-line systemic treatment. Objective response measured by mRECIST and RECIST version 1.1 per IRR was also considered a predictor of OS. Additional factors that were identified as independent predictors of OS by mRECIST per investigator assessment were: increase in Child-Pugh score to ≥7, sex, macroscopic portal vein invasion, baseline alpha-fetoprotein level, number of tumor sites at baseline, presence of HCC in the liver, hepatitis B virus etiology, and treatment with lenvatinib. Given the large difference in the number of responders vs. non-responders in the overall REFLECT population, more research is needed to validate these predictors.

Of note, there are inherent limitations in assessing objective response by mRECIST because individual readings may be subjective due to the confounding effect of the arterial vasoconstriction induced by anti-angiogenic agents,[15] such as sorafenib and lenvatinib. However, post hoc exploratory analyses conducted by IRR, using both mRECIST and RECIST version 1.1, further support objective response as a predictor of OS, as results from these analyses were generally consistent with those from the investigator assessments by mRECIST. Median OS among responders was 21.6 months when assessed by investigator per mRECIST, 20.5 months when assessed by IRR per mRECIST, and 26.0 months when assessed by IRR per RECIST version 1.1. Although it is possible that some evaluators measured not only necrosis but also decreased blood flow, leading to potential false-positive results per mRECIST, we believe that mRECIST is more effective at predicting the prognosis of individual patients, because it considers the impact of necrosis within tumors. mRECIST is a well-established method that is often used in individuals with HCC to evaluate their response to transarterial chemoembolization[26,27] and molecular-targeted drugs that cause ischemia or necrosis.[28-30] Other clinical trials have also used mRECIST to assess tumor response in individuals with HCC.[14,31-33] RECIST version 1.1 only considers individuals as responders if they exhibit decreases in tumor size; it does not account for tumor necrosis. Thus, RECIST version 1.1 limits the pool of individuals who may be expected to experience an OS benefit. However, our data suggested that the HR of objective response *vs.* non-objective response by RECIST version 1.1 was lower than the HR by mRECIST, indicating that the survival benefit was more pronounced according to RECIST version 1.1 than mRECIST. It is thus important to consider the results of both methods of analysis when evaluating OS benefits in patients.

These findings are limited by the fact that investigator assessment using mRECIST was the primary assessment method for imaging-based endpoints used in this study, and thus it was used to make decisions about treatment discontinuation. The only available assessments by RECIST version 1.1 are based on retrospective exploratory tumor analyses performed by IRR according to both mRECIST and RECIST version 1.1. Therefore, results based on IRR should be carefully interpreted.

The association between objective response by mRECIST and OS was consistent with results reported in previous studies.[13,14,17] One of these studies conducted a time-dependent multivariate analysis using data from the phase III BRISK-PS study and showed that objective response by mRECIST was an independent predictor of OS in individuals with advanced HCC.[13] In addition, an analysis of two phase II studies in individuals with advanced HCC treated with either nintedanib or sorafenib showed that response by mRECIST or RECIST version 1.0 was associated with improved survival.[14] In the SILIUS study (a phase III trial that compared sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy *vs.* sorafenib alone in individuals with advanced HCC), those who responded to treatment had significantly longer median OS than non-responders (25.7 months vs. 9.3 months, respectively; p <0.0001).[17]

Because SD can be considered a benefit in a palliative setting, we compared survival in those with SD or PD to responders. Responders still had significantly longer OS than participants with either SD (16.0 months) or PD (6.4 months), when response was assessed by investigators per mRECIST. We did not directly compare participants with SD and PD to avoid a biased analysis.

In clinical practice, treatment decisions for each patient are made based on tumor response as well as evidence of SD. The absence of tumor growth is often viewed favorably by patients and could potentially lead to improvements in patients' quality of life; moreover, slower tumor progression may lead to slower progression of tumor-related symptoms. As such, PFS is also considered an important factor in clinical practice. Notably, in our analyses, there was a moderate to strong correlation between PFS and OS by mRECIST or RECIST version 1.1, further supporting the importance of PFS in the clinic.

In conclusion, our results from this *post hoc* analysis showed that objective response to first-line systemic therapy with lenvatinib or sorafenib, assessed by mRECIST or RECIST version 1.1, was associated with OS on an individual basis. However, additional studies, such as individual-patient pooled data analyses from several trials, are needed to further validate the association between objective response to systemic therapy and OS. Although this study also suggests that objective response may be a potential surrogate endpoint for OS in early-phase trials, its validity as a potential surrogate endpoint requires confirmation in additional prospective studies.

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Abbreviations

CR, complete response; HCC, hepatocellular carcinoma; HR, hazard ratio; IRR, independent radiologic review; mRECIST, modified RECIST; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; REFLECT, randomized, open-label, phase III trial to compare the efficacy and safety of lenvatinib *vs*. sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma; SD, stable disease; SHARP, sorafenib hepatocellular carcinoma assessment randomized protocol.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: MK, RL, CED, TT, and KS. Data curation and formal analysis: CED, TT, and KS. Investigation and data interpretation: All authors. Manuscript preparation (drafting/review and revision): All authors. Approved the final manuscript: All authors.

Data availability statement

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

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Supplementary data

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Author names in bold designate shared co-first authorship

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