Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

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Summary

Background In a phase 2 trial, lenvatinib, an inhibitor of VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α, RET, and KIT, showed activity in hepatocellular carcinoma. We aimed to compare overall survival in patients treated with lenvatinib versus sorafenib as a first-line treatment for unresectable hepatocellular carcinoma.

Methods This was an open-label, phase 3, multicentre, non-inferiority trial that recruited patients with unresectable hepatocellular carcinoma, who had not received treatment for advanced disease, at 154 sites in 20 countries throughout the Asia-Pacific, European, and North American regions. Patients were randomly assigned (1:1) via an interactive voice–web response system—with region; macroscopic portal vein invasion, extrahepatic spread, or both; Eastern Cooperative Oncology Group performance status; and bodyweight as stratification factors—to receive oral lenvatinib (12 mg/day for bodyweight ≥60 kg or 8 mg/day for bodyweight <60 kg) or sorafenib 400 mg twice-daily in 28-day cycles. The primary endpoint was overall survival, measured from the date of randomisation until the date of death from any cause. The efficacy analysis followed the intention-to-treat principle, and only patients who received treatment were included in the safety analysis. The non-inferiority margin was set at 1·08. The trial is registered with ClinicalTrials.gov, number NCT01761266.

Findings Between March 1, 2013 and July 30, 2015, 1492 patients were recruited. 954 eligible patients were randomly assigned to lenvatinib (n=478) or sorafenib (n=476). Median survival time for lenvatinib of 13·6 months (95% CI 12·1–14·9) was non-inferior to sorafenib (12·3 months, 10·4–13·9; hazard ratio 0·92, 95% CI 0·79–1·06), meeting criteria for non-inferiority. The most common any-grade adverse events were hypertension (201 [42%]), diarrhoea (184 [39%]), decreased appetite (162 [34%]), and decreased weight (147 [31%]) for lenvatinib, and palmar-plantar erythrodysaesthesia (249 [52%]), diarrhoea (220 [46%]), hypertension (144 [30%]), and decreased appetite (127 [27%]) for sorafenib.

Interpretation Lenvatinib was non-inferior to sorafenib in overall survival in untreated advanced hepatocellular carcinoma. The safety and tolerability profiles of lenvatinib were consistent with those previously observed.

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Introduction

Hepatocellular carcinoma is the most common type of liver cancer, which is the third leading cause of cancer deaths worldwide, causing nearly 745 000 deaths each year.[1] The disease usually occurs in people with chronic liver disease, particularly cirrhosis, which limits the feasibility of surgical resection.[2,3] Sorafenib, an oral multikinase inhibitor, is the only systemic therapy proven to extend overall survival when used as a first-line treatment, showing a median improvement of 2·8 months compared with placebo (10·7 months *vs* 7·9 months; hazard ratio [HR] 0·69; p<0·001), despite a low response rate of 2%.[4] In patients from the Asia-Pacific region taking sorafenib, the median improvement in overall survival compared with placebo was 2·3 months (6·5 months *vs* 4·2 months; HR 0·68; p=0·014).[5]

Drug development for hepatocellular carcinoma in the past 10 years has been marked by four failed global phase 3 trials (of sunitinib, brivanib, linifanib, and erlotinib plus sorafenib) that did not show non-inferiority[6–8] or superiority[9] to sorafenib in terms of overall survival in first-line treatment of hepatocellular carcinoma. No approved first-line systemic treatments are available for advanced unresectable hepatocellular carcinoma other than sorafenib. Only regorafenib and nivolumab are approved as second-line systemic treatments for patients who do not respond to sorafenib.[10] Otherwise, best supportive care or participation in clinical trials is recommended in the second-line setting by treatment guidelines.[11] Therefore, because of the paucity of systemic treatment options for patients with advanced hepatocellular carcinoma, a need exists to develop new drugs for effective management of this disease.

Lenvatinib is an oral multikinase inhibitor that targets VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α, RET, and KIT.[12–15] Lenvatinib monotherapy is approved for

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Research in context

Evidence before this study

We searched PubMed from inception up to March 16, 2017 using the search terms "phase 3" [Title/Abstract] OR "phase III" [Title/Abstract] AND "hepatocellular carcinoma" [MeSH Terms]. The search was restricted to clinical trials in English language only and yielded 65 reports. Of these publications, 21 described the use of targeted drugs for treatment of hepatocellular carcinoma, 11 were studies of single-drug sorafenib treatment, and three were studies of sorafenib in combination with another drug. Five trials investigated targeted agents following treatment with sorafenib and four trials investigated first-line treatment of hepatocellular carcinoma with sorafenib as the comparator. None of these four trials met their primary endpoints of non-inferiority or superiority over sorafenib in terms of overall survival.

Added value of this study

To our knowledge, this is the first global phase 3 trial in 10 years to meet its primary endpoint of non-inferiority in terms of overall survival against sorafenib as a first-line treatment for hepatocellular carcinoma. Furthermore, lenvatinib showed statistically significant and clinically meaningful improvement in terms of all secondary endpoints (progression-free survival, time to progression, and objective response rate) with a reasonable safety profile.

Implications of all the available evidence

The results of this study support lenvatinib as a first-line treatment option for patients with unresectable hepatocellular carcinoma.

treatment of radioiodine-refractory differentiated thyroid cancer.[16] Lenvatinib and everolimus are approved as a combined treatment for advanced renal cell carcinoma following one previous antiangiogenic therapy.[17] In a phase 2 study of patients with advanced hepatocellular carcinoma, 12 mg lenvatinib once-daily showed clinical activity and had an acceptable safety profile.[18] Based on dose adjustments depending on bodyweight and pharmacokinetic modelling data,[19] a starting dose of lenvatinib was adopted (12 mg for patients ≥60 kg and 8 mg for patients <60 kg once-daily) for further clinical development in hepatocellular carcinoma. Given the efficacy signal observed in this phase 2 study,[18] we did a phase 3 randomised, open-label, non-inferiority study to compare the efficacy and safety of lenvatinib versus sorafenib as a first-line treatment for unresectable hepatocellular carcinoma.

See Online for appendix

Methods

Study design and participants

This multicentre, phase 3, randomised, open-label, non-inferiority study was done at 154 sites in 20 countries throughout the Asia-Pacific, European, and North American regions (China, Hong Kong, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, Belgium, Canada, France, Germany, Israel, Italy, Poland, Russia, Spain, UK, and USA).

Eligible patients had unresectable hepatocellular carcinoma, with diagnoses confirmed histologically or cytologically, or confirmed clinically in accordance with American Association for the Study of Liver Diseases criteria. Included patients also had one or more measurable target lesions (lesions previously treated with radiotherapy or locoregional therapy had to show radiographic evidence of disease progression to be deemed target lesions) based on modified Response Evaluation Criteria in Solid Tumours (mRECIST),[20] Barcelona Clinic Liver Cancer stage B or C categorisation,[21] Child-Pugh class A, and an Eastern Cooperative Oncology Group performance status score of 0 or 1. All eligible patients had controlled blood pressure (≤150/90 mm Hg), adequate liver function (albumin ≥2·8 g/dL, bilirubin ≤3·0 mg/dL, and aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase ≤5 times the upper limit of normal), and adequate bone marrow (haemoglobin ≥8·5 g/dL, platelet count ≥75×10⁹ per L, and absolute neutrophil count ≥1·5×10⁹ per L), blood (international normalised ratio ≤2·3), renal, and pancreatic function (see appendix for a full list of inclusion criteria). Patients with 50% or higher liver occupation, obvious invasion of the bile duct, or invasion at the main portal vein were excluded from the study. Patients were also excluded if they had received previous systemic therapy for hepatocellular carcinoma (see appendix for a full list of exclusion criteria).

All patients provided written informed consent before undergoing any study-specific procedures. All relevant institutional review boards approved the study, which was done in accordance with the Declaration of Helsinki and local laws.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive either lenvatinib or sorafenib. Allocation of treatment group was done with an interactive voice–web response system, which also functioned as the allocation concealment method, with region (Asia-Pacific [defined as China, Hong Kong, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand] or western [defined as Belgium, UK, Spain, Germany, Italy, Poland, France, USA, Canada, Israel, and Russia]), macroscopic portal vein invasion, extrahepatic spread, or both (yes or no), Eastern Cooperative Oncology Group performance status (0 or 1), and bodyweight (<60 kg or ≥60 kg) as stratification factors. A randomisation block size of 2 was used. The randomisation sequence was generated by an independent statistician by the system vendor, and the investigators obtained the randomisation assignments from the system directly. Because the study was open

label, the treatments were not masked to the patients or investigators.

Procedures

Patients received oral lenvatinib (Eisai Inc., Woodcliff Lake, NJ, USA) 12 mg/day (for bodyweight ≥60 kg) or 8 mg/day (for bodyweight <60 kg) or sorafenib (Bayer, Leverkusen, Germany) 400 mg twice-daily in 28-day cycles. Dose interruptions followed by reductions for lenvatinib-related toxicities (to 8 mg and 4 mg/day, or 4 mg every other day) were permitted. Modifications to sorafenib doses were implemented according to prescribing information in each region (all patients in the sorafenib arm received a starting dose of 400 mg orally twice-daily).

Local investigators evaluated tumours in each treatment arm in accordance with mRECIST.[20,22] The liver was examined with CT or MRI by use of a triphasic scanning technique. Tumour assessments were done every 8 weeks (irrespective of dose interruptions) until radiological disease progression. Patients who discontinued study treatment without disease progression had tumour assessments every 8 weeks or until disease progression or the start of another anticancer treatment. Safety assessments were done throughout the study. Quality-of-life questionnaires were administered at baseline, on day 1 of each subsequent treatment cycle, and at the off-treatment visit, which occurred within 30 days of the final administration of study drug. Quality of life was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)[23,24] and the hepatocellular carcinoma-specific EORTC QLQ-HCC18[25] health questionnaires.

The follow-up period began immediately after the off-treatment visit and was planned to continue if the patient was alive or until the sponsor terminated the study, or the patient withdrew consent. Patients were planned to be followed up for survival every 12 weeks, and all anticancer treatments received were reported.

Outcomes

The primary endpoint was overall survival, measured from the date of randomisation until the date of death from any cause. Patients who were lost to follow-up were censored at the last date they were known to be alive, and patients who remained alive were censored at the time of data cutoff.

Secondary endpoints were progression-free survival, time to progression, objective response rate, quality-of-life measurements, and plasma pharmacokinetics lenvatinib exposure parameters. All efficacy evaluations were based on the full analysis set (all randomised patients).

Safety assessments included recording of vital signs, haematological and biochemical laboratory testing, urinalysis, and electrocardiography. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[26] All safety evaluations were based on the safety analysis set (all patients who received at least one dose of study treatment). Post-hoc exploratory tumour assessments using mRECIST and RECIST version 1.1 were done by masked central independent imaging review.

A population pharmacokinetic analysis for lenvatinib was done to derive individual pharmacokinetic parameters and lenvatinib exposure for this study. The dataset used in the analysis included lenvatinib plasma concentrations from 468 patients with hepatocellular carcinoma in this study, and lenvatinib plasma concentration pooled from 12 additional studies (phase 1–3) in healthy people and patients with other tumour types (eg, differentiated thyroid cancer).

Statistical analysis

The primary endpoint of overall survival was first tested for non-inferiority, then for superiority. Using a non-inferiority test by the 95% CI lower-limit method on log HR for overall survival with assumed true HR of 0·80 and a non-inferiority margin of 1·08 (corresponding to

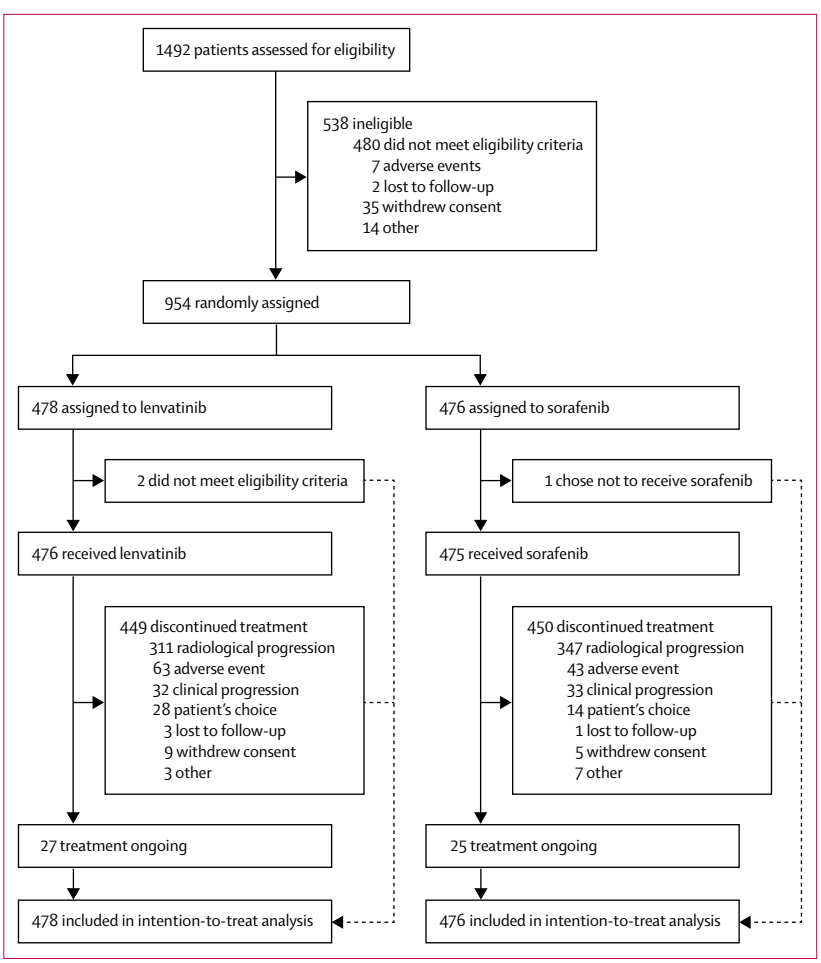


Figure 1: **Trial profile**
At the time of data cutoff (Nov 13, 2016; for the required 700 death events), 701 deaths had occurred (351 in the lenvatinib arm, 350 in the sorafenib arm).

60% retention of sorafenib effect *vs* placebo, and set based on previous phase 3 trials of sorafenib[4,5]), the power of the study to declare non-inferiority was approximately 97%. The power of the study to declare superiority of lenvatinib to sorafenib was approximately 82% using a superiority test with assumed true HR of 0·80. The overall false positive rate was set at 0·05 (two-sided). Non-inferiority was declared if the upper limit of the two-sided 95% CI for HR was less than 1·08. The required number of events for the primary analysis was 700 deaths, assuming 5% dropout. HR and 95% CI were estimated from a Cox proportional hazard model with treatment group as a factor, and with the analysis stratified according to the same factors applied for randomisation for primary and subgroup analyses where appropriate. For the subgroup analysis, analyses were done within each subgroup.

A fixed sequence procedure was used to control the overall type I error rate of analyses for both the primary and secondary efficacy endpoints at α=0·05 (two-sided). After non-inferiority was declared, secondary efficacy endpoints were tested. Differences in progression-free survival and time to progression were evaluated using a stratified log-rank test with randomisation stratification factors, with the associated HR and 95% CI. The same method was used to evaluate differences in progression-free survival and time to progression in the subgroup analyses. A difference in the objective response rate was evaluated using the Cochran-Mantel-Haenszel χ^2 test with randomisation stratification factors as strata, with associated odds ratio (OR) and 95% CI. To assess futility, two interim analyses (at 30% and 70% of the target number of events) were done using Bayesian predictive probability in a non-inferiority design.

The efficacy analysis followed the intention-to-treat principle. Only patients who received treatment were included in the safety analysis.

Programming and statistical analyses were done with SAS version 9 or higher. The study was overseen by an independent data monitoring committee. The study is registered with ClinicalTrials.gov, number NCT01761266.

	Lenvatinib (n=478)	Sorafenib (n=476)	Total (n=954)
Age (years), median (range)	63·0 (20–88)	62·0 (22–88)	62·0 (20–88)
Age group (years)			
<65	270 (56%)	283 (59%)	553 (58%)
≥65 to <75	150 (31%)	126 (26%)	276 (30%)
≥75	58 (12%)	67 (14%)	125 (13%)
Sex			
Male	405 (85%)	401 (84%)	806 (84%)
Female	73 (15%)	75 (16%)	148 (16%)
Region			
Western	157 (33%)	157 (33%)	314 (33%)
Asia-Pacific	321 (67%)	319 (67%)	640 (67%)
Race			
White	135 (28%)	141 (30%)	276 (29%)
Asian	334 (70%)	326 (68%)	660 (69%)
Other	9 (2%)	9 (2%)	18 (2%)
Bodyweight (kg)			
<60	153 (32%)	146 (31%)	299 (31%)
≥60	325 (68%)	330 (69%)	655 (69%)
Eastern Cooperative Oncology Group performance status			
0	304 (64%)	301 (63%)	605 (63%)
1	174 (36%)	175 (37%)	349 (37%)
Child-Pugh class			
A	475 (99%)	471 (99%)	946 (99%)
B	3 (1%)	5 (1%)	8 (1%)
Macroscopic portal vein invasion			
Yes	109 (23%)	90 (19%)	199 (21%)
No	369 (77%)	386 (81%)	755 (79%)
Extrahepatic spread			
Yes	291 (61%)	295 (62%)	586 (61%)
No	187 (39%)	181 (38%)	368 (39%)
Macroscopic portal vein invasion, extrahepatic spread, or both			
Yes	329 (69%)	336 (71%)	665 (70%)
No	149 (31%)	140 (29%)	289 (30%)
Underlying cirrhosis based on masked independent imaging review			
Yes	356 (74%)	364 (76%)	720 (75%)
No	122 (26%)	112 (24%)	234 (25%)
Barcelona Clinic Liver Cancer stage			
B (intermediate stage)	104 (22%)	92 (19%)	196 (21%)
C (advanced stage)	374 (78%)	384 (81%)	758 (79%)
Involved disease sites			
Liver	441 (92%)	430 (90%)	871 (91%)
Lung	163 (34%)	144 (30%)	307 (32%)
Involved disease sites per patient*			
1	207 (43%)	207 (43%)	414 (43%)
2	167 (35%)	183 (38%)	350 (37%)
≥3	103 (22%)	86 (18%)	189 (20%)

(Table 1 continues on next page)

Role of the funding source

The study was funded by Eisai Inc, (Woodcliff Lake, NJ, USA) and designed in collaboration with the principal investigators. The funder employed CD, MG, KS, SK, TT, and MR, who played a significant part in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 1, 2013, and July 30, 2015, 1492 patients were recruited. 954 eligible patients from 20 countries were randomly assigned to receive lenvatinib (n=478) or sorafenib (n=476, figure 1).

Patient baseline characteristics were similar between treatment groups, except for baseline hepatitis C aetiology and α-fetoprotein concentrations (table 1). At the time of data cutoff (Nov 13, 2016, at 701 deaths), the median duration of follow-up was 27·7 months

(IQR 23·3–32·8) in the lenvatinib group and 27·2 months (22·6–31·3) in the sorafenib group.

Lenvatinib showed non-inferiority in terms of overall survival compared with sorafenib (figure 2). Median overall survival duration was 13·6 months (95% CI 12·1–14·9) for 478 patients in the lenvatinib group, compared with 12·3 months (10·4–13·9) for 476 patients in the sorafenib group (HR 0·92, 95% CI 0·79–1·06, figure 2, table 2; results from the per-protocol analysis set are shown in the appendix). Overall survival superiority over sorafenib was not achieved. The effect of lenvatinib and sorafenib on median overall survival was consistent across subgroups based on baseline characteristics (figure 3). Although baseline α-fetoprotein concentration was not a prespecified stratum, patients with baseline α-fetoprotein concentrations less than 200 ng/mL had longer overall survival than did those with α-fetoprotein concentration of at least 200 ng/mL in both treatment groups (figure 3). More patients had baseline α-fetoprotein levels less than 200 ng/mL in the sorafenib arm compared with the lenvatinib arm (table 1).

Lenvatinib showed a statistically significant improvement compared with sorafenib for all secondary efficacy endpoints as determined by investigator tumour assessments based on mRECIST. Median progression-free survival for lenvatinib was longer than that for sorafenib (table 2, figure 4). Median time to progression was 8·9 months (95% CI 7·4–9·2) for patients in the lenvatinib group compared to 3·7 months (3·6–5·4) for patients in the sorafenib group (table 2, appendix). Lenvatinib also showed a greater objective response rate than did sorafenib (table 2, appendix). Improvements in all secondary efficacy endpoints (progression-free survival, time to progression, and objective response) with lenvatinib compared to sorafenib were consistent across all predefined subgroups (figure 3, appendix). Analysis for overall survival with predefined subgroups supports the robustness of the non-inferiority result (appendix). Masked independent imaging review confirmed progression-free survival and time to progression based on investigator assessments according to mRECIST (table 2, figure 4). Similar progression-free survival and time-to-progression results were observed for mRECIST and RECIST 1.1 based on masked independent imaging review. Masked independent imaging review confirmed a significantly higher objective response rate in the lenvatinib arm than in the sorafenib arm by mRECIST and RECIST 1.1 (table 2).

156 (33%) patients in the lenvatinib arm and 184 (39%) in the sorafenib arm received post-study anticancer medication (including investigational therapy). Of these patients, 121 (25%) in the lenvatinib arm and 56 (12%) in the sorafenib arm received sorafenib during survival follow-up. In the western region, 41 (26%) patients in the lenvatinib arm received anticancer medication during survival follow-up versus 61 (39%) patients in the sorafenib arm. In the lenvatinib arm, 11 (7%) patients in the western region had an anticancer procedure during follow-up compared with 18 (11%) patients in the sorafenib arm in this region (appendix).

The median duration of study treatment for patients in the lenvatinib group was 5·7 months (IQR 2·9–11·1), compared with 3·7 months (1·8–7·4) in the sorafenib

	Lenvatinib (n=478)	Sorafenib (n=476)	Total (n=954)
(Continued from previous page)			
Aetiology of chronic liver disease			
Hepatitis B	251 (53%)	228 (48%)	479 (50%)
Hepatitis C	91 (19%)	126 (26%)	217 (23%)
Alcohol	36 (8%)	21 (4%)	57 (6%)
Other	38 (8%)	32 (7%)	70 (7%)
Unknown	62 (13%)	69 (14%)	131 (14%)
Baseline α-fetoprotein concentration (ng/mL)			
Number of patients	471 (99%)	463 (97%)	934 (98%)
Mean (SD)	17 507·5 (105 137·4)	16 678·5 (94 789·5)	17 096·5 (100 088·8)
Median (IQR)	133·1 (8·0–3730·6)	71·2 (5·2–1081·8)	89·0 (6·3–2120·2)
Baseline α-fetoprotein concentration group (ng/mL)			
<200	255 (53%)	286 (60%)	541 (57%)
≥200	222 (46%)	187 (39%)	409 (43%)
Missing	1 (<1%)	3 (1%)	4 (<1%)
Concomitant systemic antiviral therapy for hepatitis B or C	163 (34%)	149 (31%)	312 (33%)
Previous therapy			
Previous anticancer procedures	327 (68%)	344 (72%)	671 (70%)
Radiotherapy	49 (10%)	60 (13%)	109 (11%)

Data are mean (SD) or n (%) unless otherwise specified. *One patient had no baseline target lesion.

Table 1: **Demographic and disease characteristics at baseline**

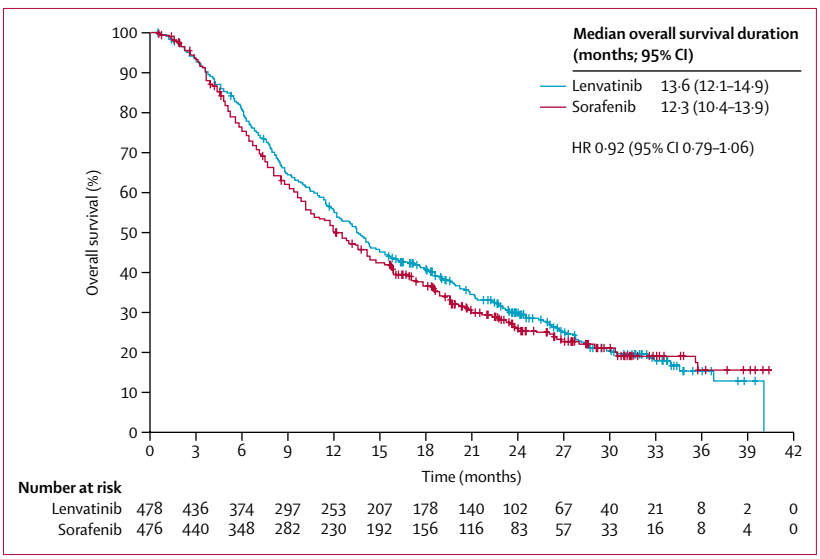


Figure 2: **Overall survival outcomes**
Kaplan-Meier estimates of overall survival by treatment group. HR=hazard ratio.

	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Investigator review according to mRECIST				
Overall survival (months)	13·6 (12·1–14·9)	12·3 (10·4–13·9)	HR 0·92 (0·79–1·06)	..
Progression-free survival (months)	7·4 (6·9–8·8)	3·7 (3·6–4·6)	HR 0·66 (0·57–0·77)	<0·0001
Time to progression (months)	8·9 (7·4–9·2)	3·7 (3·6–5·4)	HR 0·63 (0·53–0·73)	<0·0001
Objective response (%, 95% CI)	115 (24·1%, 20·2–27·9)	44 (9·2%, 6·6–11·8)	OR 3·13 (2·15–4·56)	<0·0001
Complete response	6 (1%)	2 (<1%)	..	..
Partial response	109 (23%)	42 (9%)	..	..
Stable disease	246 (51%)	244 (51%)	..	..
Durable stable disease lasting ≥23 weeks	167 (35%)	139 (29%)	..	..
Progressive disease	71 (15%)	147 (31%)	..	..
Unknown or not evaluable	46 (10%)	41 (9%)	..	..
Disease control rate (%, 95% CI)	361 (75·5%, 71·7–79·4)	288 (60·5%, 56·1–64·9)	..	..
Masked independent imaging review according to mRECIST				
Progression-free survival (months)	7·3 (5·6–7·5)	3·6 (3·6–3·7)	HR 0·64 (0·55–0·75)	<0·0001
Time to progression (months)	7·4 (7·2–9·1)	3·7 (3·6–3·9)	HR 0·60 (0·51–0·71)	<0·0001
Objective response (%, 95% CI)	194 (40·6%, 36·2–45·0)	59 (12·4%, 9·4–15·4)	OR 5·01 (3·59–7·01)	<0·0001
Complete response	10 (2%)	4 (1%)	..	..
Partial response	184 (38%)	55 (12%)	..	..
Stable disease	159 (33%)	219 (46%)	..	..
Durable stable disease lasting ≥23 weeks	84 (18%)	90 (19%)	..	..
Progressive disease	79 (17%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	46 (10%)	..	..
Disease control rate (%, 95% CI)	353 (73·8%, 69·9–77·8)	278 (58·4%, 54·0–62·8)	..	..
Masked independent imaging review according to RECIST 1.1				
Progression-free survival (months)	7·3 (5·6–7·5)	3·6 (3·6–3·9)	HR 0·65 (0·56–0·77)	<0·0001
Time to progression (months)	7·4 (7·3–9·1)	3·7 (3·6–5·4)	HR 0·61 (0·51–0·72)	<0·0001
Objective response (%, 95% CI)	90 (18·8%, 15·3–22·3)	31 (6·5%, 4·3–8·7)	OR 3·34 (2·17–5·14)	<0·0001
Complete response	2 (<1%)	1 (<1%)	..	..
Partial response	88 (18%)	30 (6%)	..	..
Stable disease	258 (54%)	250 (53%)	..	..
Durable stable disease lasting ≥23 weeks	163 (34%)	118 (25%)	..	..
Progressive disease	84 (18%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	43 (9%)	..	..
Disease control rate (%, 95% CI)	348 (72·8%, 68·8–76·8)	281 (59·0%, 54·6–63·5)	..	..

Data are presented as median (95% CI) or n (%) unless otherwise indicated. mRECIST=modified Response Evaluation Criteria in Solid Tumours. HR=hazard ratio. OR=odds ratio.

Table 2: **Efficacy measures**

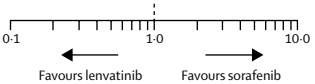
group. Treatment-emergent adverse events occurred in most patients who received lenvatinib or sorafenib (table 3). Adjusted by patient-years, the adverse event rate was 18·9 episodes per patient-year in the lenvatinib group and 19·7 episodes per patient-year in the sorafenib group. Treatment-emergent adverse events of grade 3 or higher occurred at similar rates in the lenvatinib and sorafenib arms (episodes per patient-year 3·2 *vs* 3·3). The most common treatment-emergent adverse events among patients who received lenvatinib were hypertension, diarrhoea, decreased appetite, and decreased weight. In the sorafenib arm, the most common treatment-emergent adverse events were palmar-plantar erythrodysaesthesia, diarrhoea, hypertension, and decreased appetite (table 3).

Fatal adverse events occurred throughout treatment and appeared to occur at similar rates in both arms. Fatal adverse events determined by the investigator to be related to lenvatinib treatment occurred in 11 (2%) patients and included hepatic failure (three patients), cerebral haemorrhage (three patients), and respiratory failure (two patients). In the sorafenib group, treatment-related fatal adverse events occurred in four (1%) patients and included tumour haemorrhage, ischaemic stroke, respiratory failure, and sudden death (one each).

Treatment-related treatment-emergent adverse events led to lenvatinib drug interruption in 190 (40%) patients, dose reduction in 176 (37%) patients, and drug withdrawal in 42 (9%) patients. In the sorafenib arm, treatment-related treatment-emergent adverse events led to drug interruption in 153 (32%) patients, dose reduction in 181 (38%), and drug withdrawal in 34 (7%) patients. The mean lenvatinib dose intensity was 7·0 mg in the

A

	Events/patients		HR (95% CI) lenvatinib *vs* sorafenib	Median (months)	
	Lenvatinib	Sorafenib		Lenvatinib	Sorafenib
Age (years)					
<65	203/270	204/283	0·94 (0·77–1·15)	12·4	11·4
≥65	148/208	146/193	0·84 (0·66–1·07)	14·6	13·4
Sex					
Male	293/405	293/401	0·91 (0·77–1·07)	13·4	12·4
Female	58/73	57/75	0·84 (0·56–1·26)	15·3	11·4
Region					
Asia-Pacific	243/321	248/319	0·86 (0·72–1·02)	13·5	11·0
Western	108/157	102/157	1·08 (0·82–1·42)	13·6	14·2
ECOG-PS					
PS=0	221/304	223/301	0·88 (0·73–1·06)	14·6	12·8
PS=1	130/174	127/175	0·97 (0·76–1·25)	10·7	10·3
Bodyweight (kg)					
<60	110/153	113/146	0·85 (0·65–1·11)	13·4	10·3
≥60	241/325	237/330	0·95 (0·79–1·14)	13·7	12·5
Macroscopic portal vein invasion, extrahepatic spread, or both					
Yes	250/329	259/336	0·87 (0·73–1·04)	11·5	9·8
No	101/149	91/140	1·05 (0·79–1·40)	18·0	18·0
AFP at baseline (ng/mL)					
<200	167/255	193/286	0·91 (0·74–1·12)	19·5	16·3
≥200	183/222	154/187	0·78 (0·63–0·98)	10·4	8·2
Aetiology					
HBV	196/259	186/244	0·83 (0·68–1·02)	13·4	10·2
HCV	75/103	97/135	0·91 (0·66–1·26)	15·3	14·1
Alcohol	22/33	15/23	1·03 (0·47–2·28)	14·1	11·9
BCLC staging					
Stage B	71/104	65/92	0·91 (0·65–1·28)	18·5	17·3
Stage C	280/374	285/384	0·92 (0·77–1·08)	11·8	10·3
Post-treatment anticancer therapy					
Yes	143/206	175/243	0·84 (0·67–1·06)	19·5	17·0
No	208/272	175/233	0·91 (0·74–1·11)	10·5	7·9
Post-treatment anticancer procedures					
Yes	63/99	82/112	0·71 (0·51–1·01)	23·0	19·6
No	288/379	268/364	0·94 (0·79–1·11)	11·6	10·1
Post-treatment anticancer medication					
Yes	110/156	132/184	0·87 (0·67–1·14)	20·8	17·0
No	241/322	218/292	0·90 (0·75–1·09)	11·5	9·1
Overall	**351/478**	**350/476**	**0·92 (0·79–1·06)**	**13·6**	**12·3**



B

	Events/patients		HR (95% CI) lenvatinib *vs* sorafenib	Median (months)	
	Lenvatinib	Sorafenib		Lenvatinib	Sorafenib
Age (years)					
<65	201/270	223/283	0·67 (0·55–0·82)	7·3	3·6
≥65	148/208	144/193	0·61 (0·48–0·78)	7·4	5·4
Sex					
Male	298/405	308/401	0·66 (0·56–0·77)	7·4	3·7
Female	51/73	59/75	0·75 (0·49–1·13)	7·4	4·6
Region					
Asia-Pacific	249/321	264/319	0·61 (0·51–0·73)	7·3	3·6
Western	100/157	103/157	0·81 (0·61–1·08)	7·4	5·5
ECOG-PS					
PS=0	220/304	233/301	0·63 (0·52–0·76)	7·4	3·7
PS=1	129/174	134/175	0·70 (0·55–0·90)	7·3	3·7
Bodyweight (kg)					
<60	111/153	121/146	0·61 (0·46–0·79)	7·4	3·6
≥60	238/325	246/330	0·69 (0·58–0·83)	7·4	3·7
Macroscopic portal vein invasion, extrahepatic spread, or both					
Yes	246/329	265/336	0·64 (0·54–0·77)	7·3	3·6
No	103/149	102/140	0·73 (0·55–0·97)	9·2	5·6
AFP at baseline (ng/mL)					
<200	186/255	209/286	0·68 (0·55–0·83)	9·0	5·4
≥200	163/222	157/187	0·59 (0·47–0·75)	5·5	2·4
Aetiology					
HBV	205/259	199/244	0·62 (0·50–0·75)	7·3	3·6
HCV	70/103	103/135	0·78 (0·56–1·09)	7·4	5·3
Alcohol	19/33	18/23	0·27 (0·11–0·66)	8·8	3·9
BCLC staging					
Stage B	72/104	66/92	0·70 (0·50–0·99)	9·1	5·5
Stage C	277/374	301/384	0·63 (0·53–0·75)	7·3	3·7
Post-treatment anticancer therapy					
Yes	177/206	204/243	0·58 (0·47–0·72)	7·2	3·6
No	172/272	163/233	0·70 (0·56–0·87)	8·0	3·7
Post-treatment anticancer procedures					
Yes	80/99	93/112	0·41 (0·29–0·57)	7·4	3·6
No	269/379	274/364	0·71 (0·59–0·84)	7·4	3·7
Post-treatment anticancer medication					
Yes	137/156	157/184	0·66 (0·51–0·85)	5·7	3·8
No	212/322	210/292	0·66 (0·54–0·80)	8·6	3·7
Overall	**349/478**	**367/476**	**0·66 (0·57–0·77)**	**7·4**	**3·7**

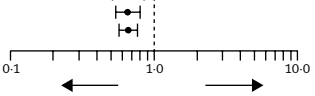


***Figure 3*: Forest plots of overall and progression-free survival in patient subgroups**
Subgroup analyses for overall survival (A) and progression-free survival (B). HR=hazard ratio. ECOG-PS=Eastern Cooperative Oncology Group performance status. AFP=α-fetoprotein. HBV=hepatitis B virus. HCV=hepatitis C virus. BCLC=Barcelona Clinic Liver Cancer.

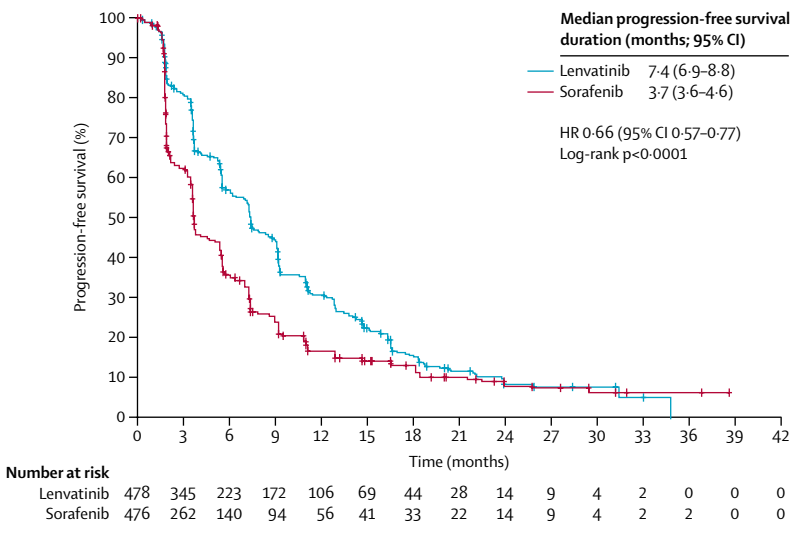


Figure 4: **Progression-free survival outcomes**
Kaplan-Meier estimates of progression-free survival by modified Response Evaluation Criteria in Solid Tumours. HR=hazard ratio.

	Lenvatinib (n=476)	Sorafenib (n=475)
Total treatment-emergent adverse events	470 (99%)	472 (99%)
Total treatment-related treatment-emergent adverse events	447 (94%)	452 (95%)
Treatment-emergent adverse events of grade ≥3	357 (75%)	316 (67%)
Treatment-related treatment-emergent adverse events of grade ≥3	270 (57%)	231 (49%)
Serious treatment-emergent adverse events	205 (43%)	144 (30%)
Serious treatment-related treatment-emergent adverse events	84 (18%)	48 (10%)
Treatment-emergent adverse events occurring in ≥15% of patients in either treatment group		
Palmar-plantar erythrodysaesthesia		
Any grade	128 (27%)	249 (52%)
Grade ≥3	14 (3%)	54 (11%)
Diarrhoea		
Any grade	184 (39%)	220 (46%)
Grade ≥3	20 (4%)	20 (4%)
Hypertension		
Any grade	201 (42%)	144 (30%)
Grade ≥3	111 (23%)	68 (14%)
Decreased appetite		
Any grade	162 (34%)	127 (27%)
Grade ≥3	22 (5%)	6 (1%)
Decreased weight		
Any grade	147 (31%)	106 (22%)
Grade ≥3	36 (8%)	14 (3%)
Fatigue		
Any grade	141 (30%)	119 (25%)
Grade ≥3	18 (4%)	17 (4%)

(Table 3 continues in next column)

	Lenvatinib (n=476)	Sorafenib (n=475)
(Continued from previous column)		
Alopecia		
Any grade	14 (3%)	119 (25%)
Grade ≥3	0	0
Proteinuria		
Any grade	117 (25%)	54 (11%)
Grade ≥3	27 (6%)	8 (2%)
Dysphonia		
Any grade	113 (24%)	57 (12%)
Grade ≥3	1 (<1%)	0
Nausea		
Any grade	93 (20%)	68 (14%)
Grade ≥3	4 (1%)	4 (1%)
Abdominal pain		
Any grade	81 (17%)	87 (18%)
Grade ≥3	8 (2%)	13 (3%)
Decreased platelet count		
Any grade	87 (18%)	58 (12%)
Grade ≥3	26 (5%)	16 (3%)
Elevated aspartate aminotransferase		
Any grade	65 (14%)	80 (17%)
Grade ≥3	24 (5%)	38 (8%)
Hypothyroidism		
Any grade	78 (16%)	8 (2%)
Grade ≥3	0	0
Vomiting		
Any grade	77 (16%)	36 (8%)
Grade ≥3	6 (1%)	5 (1%)
Constipation		
Any grade	76 (16%)	52 (11%)
Grade ≥3	3 (1%)	0
Rash		
Any grade	46 (10%)	76 (16%)
Grade ≥3	0	2 (<1%)
Increased blood bilirubin		
Any grade	71 (15%)	63 (13%)
Grade ≥3	31 (7%)	23 (5%)

Data are presented as n (%).

Table 3: **Adverse events**

8 mg/day group and 10·5 mg in the 12 mg/day group, corresponding to 88% of the planned starting dose in both cases. The mean sorafenib dose intensity was 663·8 mg, or 83% of the planned starting dose.

Baseline scores on the EORTC QLQ-C30 and EORTC QLQ-HCC18 health questionnaires were similar in the lenvatinib and sorafenib treatment groups. Following treatment, scores declined in both groups. Analysis of time to clinically meaningful deterioration showed that role functioning (nominal p=0·0193), pain (nominal p=0·0105), and diarrhoea (nominal p<0·0001) from EORTC QLQ-C30, and nutrition (nominal p=0·0113) and body image

(nominal p=0·0051) from EORTC QLQ-HCC18 were observed earlier in patients treated with sorafenib than in those treated with lenvatinib. For between-group comparison, the summary score was not significantly different between the treatment arms (HR 0·87, 95% CI 0·754–1·013, appendix).

Based on individual model-derived predicted lenvatinib area under the curve (AUC) values at steady state for patients with hepatocellular carcinoma in our study, the median values and ranges of AUC between the group with a starting dose of 8 mg for bodyweight less than 60 kg (median 1820·2 ng·h/mL, range 704·8–4980·7) and the group with a 12 mg starting dose for bodyweight of at least 60 kg (1996·0 ng·h/mL, 925·5–5427·9) are comparable, which supports a starting dose of 8 mg for bodyweights less than 60 kg, and confirms the weight-based dosing reported in pharmacokinetic analyses from a previous study.[19] There were no differences in lenvatinib oral clearance or in AUC at steady state among Western, Asian, Chinese, and Japanese populations in our study.

Discussion

To our knowledge, our study is the first global phase 3 trial in 10 years to show a treatment effect on overall survival, and the first ever positive trial against an active control. Our study showed lenvatinib to be non-inferior to sorafenib—the current standard of care in hepatocellular carcinoma—for overall survival. Lenvatinib showed statistically significant clinically meaningful improvement for all secondary efficacy endpoints (progression-free survival, time to progression, and objective response) across subgroups, and in quality-of-life assessments. Together, these data support the overall survival result of our study.

The median overall survival time of patients who received sorafenib in our study is longer than that reported in any previous large randomised phase 3 study.[4–9] A possible explanation for this result is the high proportion of post-sorafenib anticancer therapy in our study. For example, in a previous phase 3 study[7] of brivanib versus sorafenib, 21% of patients who received sorafenib underwent systemic post-sorafenib treatments and 17% had non-systemic post-sorafenib treatments, compared with 39% of patients receiving systemic post-sorafenib treatments and 27% of patients receiving non-systemic post-sorafenib treatments in our study. Continuous improvements in care for unresectable hepatocellular carcinoma have been made, and multimodality therapies, including locoregional treatment approaches, are often used after disease progression because they might be efficacious, even after systemic therapies such as sorafenib treatment.[27,28] If post-progression survival is prolonged by such post-study treatments, this could lead to dilution of the observed overall survival treatment benefit. Hence, although still representing the gold standard, overall survival as an endpoint alone for trials in first-line hepatocellular carcinoma treatment might no longer capture the full extent of antitumour efficacy. The substantial improvement in progression-free survival, time to progression, and objective response with lenvatinib in our study might indicate, as in some other tumours, the emergence of a broader framework in drug assessment and treatment in advanced hepatocellular carcinoma.

Our study did not enrol patients with more than 50% liver involvement and main portal vein invasion because this exclusion criterion was used in the preceding phase 2 proof-of-concept study in Japan, as mandated by Japan Society of Hepatology consensus-based clinical practice guidelines.[17,29] This decision resulted in only 4·2% screen failures in the phase 3 study. Although this exclusion criterion could have slightly changed the overall prognosis of the patient population, it did not affect the distribution of patients between the study arms because this was controlled for by the randomisation.

The safety profile of lenvatinib was consistent with that observed in previous studies.[16,18,30] Patients who received lenvatinib experienced fewer instances of palmar-plantar erythrodysaesthesia, diarrhoea, and alopecia, and more instances of hypertension, proteinuria, dysphonia, and hypothyroidism than did patients who received sorafenib. Although quality-of-life scores declined in both groups after treatment, a clinically meaningful delay in deterioration for multiple domains was observed with lenvatinib compared with sorafenib.

The median duration of lenvatinib treatment was 1·5 times longer than that of sorafenib treatment, which might have contributed to the higher incidence of adverse events. When adjusted for treatment duration, almost all adverse event episodes were comparable for the lenvatinib and sorafenib arms. Doses of lenvatinib for hepatocellular carcinoma are lower than the dosage for radioiodine-refractory differentiated thyroid cancer (24 mg/day). In a phase 1 study of lenvatinib in hepatocellular carcinoma,[31] patients with hepatocellular carcinoma who received 12 mg of lenvatinib per day and patients with solid tumours who received 25 mg of lenvatinib per day had similar lenvatinib plasma concentrations at 24 h, possibly because lenvatinib is metabolised in the liver. In our study, similar clinical activities and safety profiles were observed for both the 8 mg/day and 12 mg/day lenvatinib starting doses.

Unlike other cancer types, including differentiated thyroid cancer and renal cell carcinoma, lenvatinib pharmacokinetics were affected by bodyweight to a clinically significant degree. The final pharmacokinetic model for lenvatinib included bodyweight effect as an allometric constant on both clearance and volume parameters, whereby both parameters increased with increasing bodyweight. The clinical relevance of this finding is that, when administered equivalent doses, patients with hepatocellular carcinoma with low bodyweight will have clinically significantly higher

exposures than will patients with high bodyweight, supporting bodyweight-based dosing.

Our study was potentially limited by its open-label design. However, because of the distinct toxicities and dose management requirements, this design was essential to ensure patient safety. Major protocol deviations were few and balanced, the percentage of patients having clinical progression and drug discontinuations were similar in both arms, and results were confirmed by masked independent imaging review. Therefore, we believe any bias introduced by the open-label design was minimal. The full analysis set was used as the primary analysis set as opposed to the per-protocol set. However, the sample size calculation for our study was such that any factor introducing bias toward the null hypothesis would reduce the power of the study. Therefore, use of the full analysis set as the primary analysis set for non-inferiority testing is a conservative approach, and, in fact, overall survival analysis based on the per-protocol set was completely consistent with that based on the full analysis set.

Use of mRECIST could also be considered as a limitation of this study. However, mRECIST is an established tool in hepatocellular carcinoma.[32,33] Furthermore, exploratory post-hoc analysis confirmed that progression-free survival and time to progression based on investigator assessment using mRECIST were similar to those observed based on independent imaging review using both mRECIST and RECIST 1.1.

In conclusion, this study showed non-inferiority of lenvatinib versus sorafenib in terms of overall survival, as well as statistically significant and clinically meaningful improvement in progression-free survival, time to progression, and objective response rate. The safety profiles of lenvatinib and sorafenib in our study appear consistent with the known safety profiles of these drugs in hepatocellular carcinoma, and no new safety signals were identified. Based on our results, lenvatinib might be a potential new treatment option for advanced hepatocellular carcinoma.

Contributors

MK, RSF, SQ, K-HH, KI, FP, and A-LC were protocol steering committee members and made substantial contributions in all aspects of ICMJE criteria. Equal contributions were made by AB, J-WP, and GH (non-protocol steering committee member investigators). AB and J-WP contributed to helpful communications in study management and acquisition of good quality data, and GH contributed to substantial good quality data acquisition and critical data interpretation of the Chinese patient population. JJ, JFB, AV, DK, TRJE, and CL were national coordinating or representing investigators in European countries, and particularly contributed to study coordination and acquisition of good quality data. CD, MG, KS, SK, TT, and MR 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. MK, RSF, SQ, K-HH, KI, FP, CD, MG, KS, TT, and A-LC contributed to the study design. MG, KS, and MR did the statistical analysis.

Declaration of interests

MK reports honoraria from Bayer, Eisai, MSD, and EA Pharma. RSF reports grants, personal fees and non-financial support from Eisai, Bayer, Pfizer, Novartis, Bristol Myers Squibb (BMS), and Merck outside the submitted work. K-HH reports grants and consultant fees from Eisai and KOWA, and consultant fees from Bayer, all outside the submitted work. KI reports honoraria from Eisai and Dainippon Sumitomo Pharma. FP reports personal fees from Eisai during the conduct of the study, and grants and personal fees from Bayer, and personal fees from Bracco, both outside the submitted work. AB reports research funding from Eisai. JJ reports personal fees from AstraZeneca, Roche, Pfizer, G1 Therapeutics, Pierre Fabre, Celgene, Merck, and BMS outside the submitted work. JFB reports personal fees from Bayer SP, Eli Lilly Oncology, Novartis, and BMS outside the submitted work. TRJE reports other fees (reimbursement of study costs of this clinical trial [to the institution]; advisory board honorarium [payable to the institution]) from Eisai during the conduct of the study, and other fees from BMS (financial support for clinical trials of novel anti-cancer drugs, honoraria for consultancies or speaker's fees, and support to attend international conferences), Clovis (support for clinical trials [to institution] and honorarium for advisory board), Karus Therapeutics (scientific advisory board [payable to the institution]), Baxalta (advisory board honorarium [payable to the institution]), Bayer (support for clinical trials and advisory board honorarium [payable to the institution]), Celgene (support for clinical trials and advisory board honorarium [payable to the institution]), GlaxoSmithKline (support for clinical trials and advisory board honorarium [payable to the institution]), Otsuka (support for clinical trials and advisory board honorarium [payable to the institution]), Roche/Genentech (support for clinical trials and advisory board honorarium [payable to the institution]), TC Biopharm (support for clinical trials), Immunova (advisory board honorarium [payable to the institution]), Basilea (support for clinical trials), e-Therapeutics (support for clinical trials), Immunocore (support for clinical trials), Vertex (support for clinical trials), Verastem (support for clinical trials), Daiichi (support for clinical trials), and Merck (support for clinical trials) outside the submitted work. CL reports grants, personal fees, non-financial support and advisory board fees from Eisai, Bayer, Lilly, and Daiichi Sankyo during the conduct of the study. CD, MG, KS, SK, TT, and MR are employees of Eisai. A-LC reports personal fees from BMS, Ono, Novartis, Bayer, Merck, and MSD during the conduct of the study. SQ, J-WP, GH, AV, and DK declare no competing interests.

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References

1 Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136:** E359–86.

2 El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; **132:** 2557–76.

3 Balogh J, Victor D 3rd, Asham EH, et al. Hepatocellular carcinoma: a review. *J Hepatocell Carcinoma* 2016; **3:** 41–53.

4 Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359:** 378–90.

5 Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10:** 25–34.

6 Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013; **31:** 4067–75.

7 Johnson PJ, Qin S, Park JW, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013; **31:** 3517–24.

8 Cainap C, Qin S, Huang WT, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015; **33:** 172–79.

9 Zhu AX, Rosmorduc O, Evans TR, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2015; **33:** 559–66.

10 Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389:** 55–66.

11 NCCN. Clinical practice guidelines in oncology, version 1: hepatobiliary cancers. Fort Washington, PA: National Comprehensive Cancer Network, 2017.

12 Matsui J, Yamamoto Y, Funahashi Y, et al. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. *Int J Cancer* 2008; **122:** 664–71.

13 Matsui J, Funahashi Y, Uenaka T, Watanabe T, Tsuruoka A, Asada M. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. *Clin Cancer Res* 2008; **14:** 5459–65.

14 Tohyama O, Matsui J, Kodama K, et al. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. *J Thyroid Res* 2014; **2014:** 638747.

15 Yamamoto Y, Matsui J, Matsushima T, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell* 2014; **6:** 18.

16 Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015; **372:** 621–30.

17 Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol* 2015; **16:** 1473–82.

18 Ikeda K, Kudo M, Kawazoe S, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. *J Gastroenterol* 2017; **52:** 512–19.

19 Tamai T, Hayato S, Hojo S, et al. Dose finding of lenvatinib in subjects with advanced hepatocellular carcinoma based on population pharmacokinetic and exposure-response analyses. *J Clin Pharmacol* 2017; **57:** 1138–47.

20 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30:** 52–60.

21 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53:** 1020–22.

22 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

23 Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol* 2011; **29:** 89–96.

24 Giesinger JM, Kieffer JM, Fayers PM, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *J Clin Epidemiol* 2016; **69:** 79–88.

25 Chie WC, Blazeby JM, Hsiao CF, et al. International cross-cultural field validation of an European Organization for Research and Treatment of Cancer questionnaire module for patients with primary liver cancer, the European Organization for Research and Treatment of Cancer quality-of-life questionnaire HCC18. *Hepatology* 2012; **55:** 1122–29.

26 National Cancer Institute. Protocol development. Cancer therapy evaluation program. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed March 21, 2017).

27 Terashima T, Yamashita T, Arai K, et al. Feasibility and efficacy of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma after sorafenib. *Hepatol Res* 2014; **44:** 1179–85.

28 Shao YY, Liang PC, Wu YM, et al. A pilot study of hepatic arterial infusion of chemotherapy for patients with advanced hepatocellular carcinoma who have failed anti-angiogenic therapy. *Liver Int* 2013; **33:** 1413–19.

29 Kudo M, Matsui O, Izumi N, et al. JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. *Liver Cancer* 2014; **3:** 458–68.

30 Boss DS, Glen H, Beijnen JH, et al. A phase I study of E7080, a multitargeted tyrosine kinase inhibitor, in patients with advanced solid tumours. *Br J Cancer* 2012; **106:** 1598–604.

31 Ikeda M, Okusaka T, Mitsunaga S, et al. Safety and pharmacokinetics of lenvatinib in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2016; **22:** 1385–94.

32 Lencioni R, Montal R, Torres F, et al. Objective response by mRECIST as a predictor and potential surrogate end-point of overall survival in advanced HCC. *J Hepatol* 2017; **66:** 1166–72.

33 Meyer T, Palmer DH, Cheng AL, Hocke J, Loembé AB, Yen CJ. mRECIST to predict survival in advanced hepatocellular carcinoma: analysis of two randomised phase II trials comparing nintedanib vs sorafenib. *Liver Int* 2017; **37:** 1047–55.