A Randomised Phase 3 Trial of Lenvatinib vs. Sorafenib in First-line Treatment of Patients With Unresectable Hepatocellular Carcinoma

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BACKGROUND

In a phase 2 trial, lenvatinib, an inhibitor of vascular endothelial growth factor receptor 1–3, fibroblast growth factor receptor 1–4, platelet-derived growth factor receptor alpha, RET, and KIT, showed activity in hepatocellular carcinoma (HCC). We aimed to compare overall survival in patients treated with lenvatinib versus sorafenib as first-line treatment for unresectable HCC.

METHODS

This open-label, phase 3, multicentre, noninferiority trial involving patients with unresectable HCC who had not received treatment for advanced disease randomised 478 to lenvatinib (body weight ≥60 kg: 12 mg/day; <60 kg: 8 mg/day) and 476 to twice-daily sorafenib 400 mg. The primary endpoint was overall survival. The noninferiority margin was set at 1·08. Registered with ClinicalTrials.gov, number: NCT01761266.

FINDINGS

Patients were enrolled from March 1, 2013 through July 30, 2015. The study met its primary endpoint of noninferiority in overall survival for lenvatinib versus sorafenib (medians: lenvatinib, 13·6 months vs. sorafenib, 12·3 months; hazard ratio [HR]: 0·92; 95% confidence interval [CI], 0·79 to 1·06). The most common any-grade adverse events were hypertension (201 [42·2%]), diarrhoea (184 [38·7%]), decreased appetite (162 [34·0%]), and decreased weight (147 [30·9%]) for lenvatinib, and palmar-plantar erythrodysaesthesia (249 [52·4%]), diarrhoea (220 [46·3%]), hypertension (144 [30·3%]), and decreased appetite (127 [26·7%]) for sorafenib. In the EORTC-QLQ-based analysis, there were 5 outcomes, including pain and diarrhoea with nominal $p<0.05$, all of which favoured lenvatinib compared to sorafenib.

INTERPRETATION

Lenvatinib was noninferior to sorafenib in overall survival in untreated advanced HCC. The safety and tolerability profiles of lenvatinib were consistent with those previously observed.

FUNDING: Eisai

Research in Context

Evidence before this study

A PubMed literature search (March 16, 2017) for “phase 3” [Title/Abstract] OR “phase III” [Title/Abstract] AND “hepatocellular carcinoma” [MeSH Terms], restricted to clinical trials, yielded 65 reports. Of these, 21 publications described the use of targeted agents for the treatment of hepatocellular carcinoma, 11 of which were studies of single-agent sorafenib and 3 of which were studies of sorafenib in combination with another agent. There were 5 trials investigating targeted agents following treatment with sorafenib and 4 trials in first-line treatment of hepatocellular carcinoma with sorafenib as the comparator. None of these 4 trials met their primary endpoints of noninferiority or superiority over sorafenib in overall survival.

Added value of this study

This is the first global phase 3 trial to meet its primary endpoint of noninferiority in overall survival against sorafenib as first-line treatment for hepatocellular carcinoma in 10 years. Furthermore, lenvatinib demonstrated statistically significant and clinically meaningful improvement in 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.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide and is responsible for nearly 745,000 deaths each year.[1] It usually occurs in a background of chronic liver disease, particularly in cirrhosis, which limits the feasibility of surgical resection.[2,3] Sorafenib, an oral multikinase inhibitor, is the only systemic therapy that has been proven to extend overall survival when used as a first-line treatment for HCC, demonstrating 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 who were taking sorafenib, the median improvement in overall survival over placebo was 2·3 months (6·5 months vs 4·2 months; HR 0·68; p=0·014).[5]

Drug development in HCC in the past 10 years is marked by 4 failed global phase 3 trials (of sunitinib, brivanib, linifanib, and erlotinib plus sorafenib) that did not demonstrate noninferiority[6-8] or superiority[9] to sorafenib in overall survival in first-line treatment of HCC. There are currently no approved first-line systemic treatments available for advanced unresectable HCC other than sorafenib. Only regorafenib is approved as second-line systemic treatment for patients who failed to respond to sorafenib.[10] Best supportive care or participation in clinical trials is currently recommended by the treatment guidelines in the second-line setting.[11] Therefore, due to the current paucity of systemic treatment options for patients with advanced HCC, a critical need exists to develop new agents for the effective management of this disease.

Lenvatinib is an oral multikinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors 1, 2, and 3; fibroblast growth factor (FGF) receptors 1, 2, 3, and 4; platelet-derived growth factor receptor α (PDFGRα), RET, and KIT.[12-15] Lenvatinib monotherapy was approved for the treatment of radioiodine-refractory differentiated thyroid cancer.[16] Lenvatinib and everolimus were approved as a combined treatment for advanced renal cell carcinoma following 1 prior anti-angiogenic therapy.[17] In a

phase 2 study of patients with advanced HCC, lenvatinib at a dose of 12 mg once daily showed clinical activity and had an acceptable safety profile.[18] Based on dose adjustments depending on body weights as well as pharmacokinetic modelling data,[19] a starting dose of lenvatinib based on body weight was adopted (12 mg and 8 mg once daily for patients with body weights ≥60 kg and <60 kg, respectively) for further clinical development in HCC. Given the efficacy signal observed in this phase 2 study, we performed a phase 3 randomised, open-label, noninferiority study to compare the efficacy and safety of lenvatinib versus sorafenib as first-line treatment for unresectable HCC.

METHODS

Study Design

This multicentre, phase 3, randomised, open-label, noninferiority study was conducted at 154 sites in 20 countries throughout the Asia-Pacific, European, and North American regions. Within stratification factors, patients were randomly assigned (1:1) to receive oral lenvatinib at a dose of 12 mg per day (for body weight ≥60 kg) or 8 mg per day (for body weights <60 kg) or sorafenib at doses of 400 mg twice daily in 28-day cycles. Dosage interruptions followed by reductions for lenvatinib-related toxicities (to 8 and 4 mg per day, or 4 mg every other day) were permitted. Modifications to sorafenib dosage were implemented according to prescribing information in each region (all patients in the sorafenib arm received a starting dose of 400 mg orally twice per day).

Study Eligibility

Patients who were eligible for enrolment had unresectable HCC with diagnosis confirmed histologically or cytologically or with diagnosis confirmed clinically in accordance with the American Association for

the Study of Liver Diseases criteria. Included patients also had 1 or more measurable target lesion (lesions previously treated with radiotherapy or locoregional therapy had to show radiographic evidence of disease progression to be deemed a target lesion), 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 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 (defined as: 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 blood (hemoglobin ≥ 8·5 g/dL, platelet count ≥ 75 × 109/L, and international normalized ratio ≤2·3), renal, and pancreatic function. Patients with ≥50% liver occupation, obvious invasion of the bile duct, or portal vein invasion at the main portal vein were excluded. Patients also were excluded if they had received prior systemic therapy for HCC.

Study Oversight

The study was approved by all relevant institutional review boards and was conducted in accordance with the Declaration of Helsinki and local laws. The trial was registered before the start of patient enrolment. All patients provided written informed consent before undergoing any study-specific procedures. The study was funded by Eisai (Woodcliff Lake, NJ) and designed in collaboration with the principal investigators. The study was overseen by an independent data monitoring committee. All parties vouch for the accuracy and completeness of the data and analyses and for adherence to the study protocol. The manuscript was prepared by the authors with assistance from professional medical writers who were funded by Eisai. Revisions were contributed by the authors.

Randomisation and Masking

Patients were randomly allocated in a 1:1 ratio to receive either lenvatinib or sorafenib. The funder provided lenvatinib. Because the study was open label, the treatments allocated were not masked to the patients or investigators. Allocation was performed with an interactive voice/web-response system with region (Asia-Pacific or Western) macroscopic portal vein invasion or extrahepatic spread or both (yes or no), Eastern Cooperative Oncology Group performance status (0 or 1), and body weight (<60 kg or ≥60 kg) as stratification factors.

Endpoints and Assessments

The primary endpoint was overall survival. Secondary endpoints included progression-free survival, time to progression, objective response rate, quality-of-life measurements including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30)[22,23] and the HCC-specific EORTC QLQ-HCC18[24] health questionnaires, and plasma pharmacokinetic exposure parameters. All efficacy evaluations were based on the full analysis set (all randomised patients).

The investigators evaluated tumours in each treatment arm in accordance with mRECIST.[20,25] The liver was examined with computed tomography or magnetic resonance imaging using a triphasic scanning technique. Assessments were performed every 8 weeks (irrespective of dosage interruptions) until radiologic disease progression. Patients who discontinued from study treatment without disease progression continued to have tumour assessments performed every 8 weeks or until disease progression or the start of another anticancer treatment. Quality-of-life questionnaires were administered at baseline, on day 1 of each subsequent treatment cycle, and at the off-treatment visit.

Safety assessments included recording of vital signs, haematologic, 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 1 dose of study treatment). Post hoc exploratory tumour assessments using mRECIST and RECIST v1·1 were performed by blinded central independent imaging review (IIR).

A population pharmacokinetic analysis for lenvatinib was conducted to derive individual pharmacokinetic parameters and lenvatinib exposures for this study. The dataset used in the analysis included lenvatinib plasma concentrations from 468 patients with HCC in this study and lenvatinib plasma concentrations pooled from 12 additional studies (phase 1 to 3) in healthy individuals and in patients with other tumor types (e.g. differentiated thyroid cancer).

Statistical Analysis

The primary endpoint of overall survival was first tested for noninferiority, then for superiority. The required number of events for the primary analysis was 700 deaths.

The HR and its 95% confidence interval (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 the primary and for the subgroup analyses where it is appropriate. For the subgroup analysis, the analyses were performed within each subgroup. The noninferiority margin was set at 1·08 based on previous phase 3 trials of sorafenib.[4,5] Noninferiority was declared if the upper limit of the 2-sided 95% CI for HR was <1·08.

A fixed-sequence procedure was followed to control the overall type I error rate of analyses for both the primary and secondary efficacy endpoints at α=0·05 (2-sided). After noninferiority 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 its 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 chi-square test with randomisation stratification factors as strata, with associated odds ratio and its 95% CI. To assess futility, two interim analyses (at 30% and 70% of the target number of events) were performed using Bayesian predictive probability in a noninferiority design by the independent data monitoring committee. Programming and statistical analyses were performed with SAS version 9 or higher.

Role of the funding source:

The funder employed CD, MG, KS, SK, TT, and MR, who played a significant role in study design, data collection, data analysis, data interpretation, and writing of the report (see Contributors for details). The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Patients

Patients were recruited from March 1, 2013 through July 30, 2015. A total of 954 patients from 20 countries were randomly assigned to receive lenvatinib (478 patients) or sorafenib (476 patients) (Figure S1 in the Supplementary Appendix). The required number of 700 deaths occurred after the completion of enrolment. The efficacy analysis followed the intent-to-treat principle. Only patients who received treatment (lenvatinib, n=476 patients; sorafenib, n=475 patients) were included in the safety analysis. Patient characteristics at baseline were well balanced between treatment groups, with the exception of baseline hepatitis C aetiology and alpha-fetoprotein levels (Table 1). At the time of data cutoff (November 13, 2016), the median duration of follow-up was 27·7 months (interquartile range [IQR], 23·3 to 32·8) in the lenvatinib group and 27·2 months (IQR, 22·6 to 31·2) in the sorafenib group.

Efficacy

Lenvatinib demonstrated noninferiority in overall survival compared with sorafenib. The median overall survival was 13·6 months (95% CI, 12·1 to 14·9) with lenvatinib, compared with 12·3 months (95% CI, 10·4 to 13·9) with sorafenib (HR: 0·92; 95% CI, 0·79 to 1·06) (Figure 1A; results from the per protocol set are shown in Table S1 in the Supplementary Appendix). The effect of lenvatinib and sorafenib on median overall survival was consistent across the subgroups based on baseline characteristics (Figure 2A). While baseline alpha-fetoprotein level was not a pre-specified stratum, patients with baseline alpha-fetoprotein levels <200 ng/mL had longer overall survival than those with alpha-fetoprotein levels ≥200 ng/mL in both treatment groups (Figure 2A). There were more patients with baseline alpha-fetoprotein levels <200 ng/mL in the sorafenib arm (286, 60·1%) compared with the lenvatinib arm (255, 53·3%, Table 1).

Lenvatinib demonstrated a statistically significant improvement compared to sorafenib in all secondary efficacy endpoints as determined by investigators' tumour assessment based on mRECIST. Median progression-free survival for lenvatinib was 7·4 months (95% CI, 6·9 to 8·8 months) compared with 3·7 months (95% CI, 3·6 to 4·6 months) with sorafenib (HR: 0·66; 95% CI, 0·57 to 0·77; p<0·0001) (Figure 1B). The median time to progression was 8·9 months (95% CI, 7·4 to 9·2 months) for patients in the lenvatinib group compared with 3·7 months (95% CI, 3·6 to 5·4 months) for patients in the sorafenib group (HR: 0·63; 95% CI, 0·53 to 0·73; p<0·0001) (Table 2 and Figure S2 in the Supplementary Appendix). Lenvatinib showed an objective response rate of 24·1% versus 9·2% for sorafenib (odds ratio, 3·13; 95% CI, 2·15 to 4·56; p<0·0001) (Table 2 and Figure S3 in the Supplementary Appendix). The improvements in all secondary efficacy endpoints (progression-free survival, time to progression, and objective response rate) with lenvatinib over sorafenib are consistent across all predefined subgroups (Figure 2B, and Figures S4 and S5 in the Supplemental Appendix). Analysis for overall survival with predefined subgroups supports the robustness of the noninferiority result (Table S2 in the Supplementary Appendix). Blinded

IIR confirmed progression-free survival (HR: 0·64; 95% CI, 0·55–0·75; p<0·0001) and time to progression (HR: 0·60; 95% CI, 0·51–0·71; p<0·0001) based on investigator assessments according to mRECIST (Table 2). Similar progression-free survival and time to progression were observed for mRECIST and RECIST 1·1 based on blinded IIR. Blinded IIR confirmed a significantly higher objective response rate in the lenvatinib arm compared with the sorafenib arm by mRECIST (40·6% vs. 12·4%; odds ratio: 5·01; 95% CI, 3·59–7·01; p<0·0001) and RECIST 1·1 (18·8% vs. 6·5%; odds ratio: 3·34; 95% CI, 2·17–5·14; p<0·0001; Table 2).

Of note, 156 (32·6%) patients in the lenvatinib arm and 184 (38·7%) in the sorafenib arm received a post-study anticancer medication (including investigational therapy). Of these, 121 (25·3%) patients in the lenvatinib arm and 56 (11·8%) in the sorafenib arm, respectively, received sorafenib during survival follow-up. In the Western region, 41 (26·1%) patients in the lenvatinib arm received any anticancer medication during survival follow-up versus 61 (38·9%) in the sorafenib arm. In the lenvatinib arm, 11 (7·0%) patients in the Western region had any anticancer procedure during follow-up compared with 18 (11·5%) patients in the sorafenib arm in this region (Table S3 in the Supplementary Appendix).

Safety and Side-effect Profile

Median duration of study treatment for patients in the lenvatinib group was longer than for patients in the sorafenib group (5·7 vs. 3·7 months). Treatment-emergent adverse events occurred in 98·7% of patients who received lenvatinib and 99·4% of patients who received sorafenib. Adjusted by patient-years, the adverse event rate was 18·9 in the lenvatinib group and 19·7 in the sorafenib group. Treatment-emergent adverse events of grade 3 or higher occurred in 75·0% of patients who received lenvatinib and 66·5% of patients who received sorafenib (adverse event rate/patient-year: 3·2 vs. 3·3). The most common treatment-emergent adverse events among patients who received lenvatinib were

hypertension (201; 42·2%), diarrhoea (184; 38·7%), decreased appetite (162; 34·0%), and decreased weight (147; 30·9%). In the sorafenib arm, the most common treatment-emergent adverse events were palmar-plantar erythrodysaesthesia (52·4%), diarrhoea (46·3%), hypertension (30·3%), and decreased appetite (26·7%) (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 patients (2·3%) and included hepatic failure (3 patients), cerebral haemorrhage (3 patients), and respiratory failure (2 patients). In the sorafenib group, treatment-related fatal adverse events occurred in 4 patients (0·8%) and included tumour haemorrhage, ischaemic stroke, respiratory failure, and sudden death (1 event per patient).

Treatment-related treatment-emergent adverse events leading to lenvatinib drug interruption, dose reduction, and drug withdrawal occurred in 190 (39·9%), 176 (37·0%), and 42 (8·8%) patients, respectively. In the sorafenib arm, treatment-related treatment-emergent adverse events led to drug interruption, dose reduction, and drug withdrawal in 153 (32·2%), 181 (38·1%), and 34 (7·2%) patients, respectively. The mean lenvatinib dose intensity was 7·0 mg in the 8 mg/day group and 10·5 mg in the 12 mg/day group, corresponding to 87·7% and 87·5% of the planned starting doses, respectively. The mean sorafenib dose intensity was 663·8 mg, or 83·0% of the planned starting dose.

Quality of Life

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. The 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 QLQ-C30 and nutrition (nominal p=0.0113) and body image (nominal p=0.0051) from QLQ-HCC18 deterioration was observed earlier in

patients treated with sorafenib than with lenvatinib. For between-group comparison, the summary score was not significantly different between the treatment arms (HR 0·87; 95%CI 0·754–1·012; Figure S6 in the Supplementary Appendix).

Pharmacokinetics

Based on the individual model-derived, predicted lenvatinib area under the curve (AUC) values at steady state for patients with HCC in the current study, the median value and range of AUC are comparable between the group with a starting dose of 8 mg for body weight < 60 kg (median: 1820.2 ng·h/mL; min-max: 704.8–4980.7 ng·h/mL) and the group with a 12 mg starting dose for body weight ≥ 60 kg (median: 1996.0 ng·h/mL; min-max: 925.5 - 5427.9 ng·h/mL), which supports the starting dose of 8 mg for body weight < 60 kg, and confirms the weight-based dosing based on the pharmacokinetic analysis from the Phase 1/2 study in HCC subjects.[19] There were no differences in lenvatinib oral clearance or in AUC at steady state among Western, Asian, Chinese and Japanese populations in the current study.

DISCUSSION

This is the first positive global phase 3 trial (HR 0·92; upper bound of 95% CI 1·06) for overall survival compared with sorafenib in first-line treatment for HCC in 10 years and the first ever to be positive using an active-control arm. This study showed lenvatinib to be noninferior to sorafenib, currently the standard of care in HCC, for overall survival. Importantly, lenvatinib demonstrated statistically significant, clinically meaningful improvement for all secondary efficacy endpoints (progression-free survival, time to progression, and objective response rate) across subgroups, as well as in quality-of-life assessments. Together, these data support the overall survival result in this study.

The median overall survival of patients who received sorafenib in the current study (12·3 months) is longer than has been reported in any previous large randomised phase 3 study.[4–9] One possible explanation for this result is the higher proportion of post-sorafenib anticancer therapy observed in this

study. For example, 21% and 17% of patients receiving sorafenib in the previous phase study of brivanib vs. sorafenib received systemic and nonsystemic post-sorafenib treatments, respectively compared with 39% and 27% of patients receiving sorafenib in this study.[7] Continuous improvements in care for unresectable HCC have been made, and multimodality therapies, including locoregional treatment approaches, are now often used following progression because they may be efficacious even after systemic therapies such as sorafenib treatment.[27,28] If post-progression survival is prolonged by such post-study treatments, this may lead to a dilution of the observed overall survival treatment benefit. Hence, while still representing the gold standard, overall survival as an endpoint alone for trials in first line HCC may no longer capture the full extent of antitumour efficacy. The significant improvement in progression-free survival, time to progression, and objective response rate with lenvatinib in this study may indicate, as in some other tumours, the emergence of a broader paradigm in drug assessment and treatment in advanced HCC.

This study did not enroll patients with >50% liver involvement and main portal vein invasion because this exclusion criterion was used in the preceding phase 2 proof-of-concept study conducted in Japan as mandated by Japan Society of Hepatology consensus-based clinical practice guidelines.[17,29] This resulted in only 4.2% screen failures in the phase 3 study. While this could have only slightly changed the overall prognosis of the patient population, it did not affect distribution of patients between the study arms since this was controlled by the randomization.

The safety profile of lenvatinib is 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.

342 The median duration of lenvatinib treatment was 1·5 times longer than that of sorafenib, which may
343 have contributed to the higher incidence of adverse events. When adjusted for treatment duration,
344 almost all episodes were comparable for the lenvatinib and sorafenib arms. The dosages of lenvatinib
345 for HCC are lower than the lenvatinib dosage for radioiodine-refractory differentiated thyroid cancer (24
346 mg per day). In the phase 1 study of lenvatinib in HCC, patients with HCC who received 12 mg of
347 lenvatinib per day and patients with solid tumours who received 25 mg of lenvatinib per day had similar
348 lenvatinib plasma concentration at 24 hours, possibly because lenvatinib is metabolised in the liver.[31]
349 Unlike other cancer types, including differentiated thyroid cancer and renal cell carcinoma, lenvatinib
350 pharmacokinetics were affected by body weight to a clinically significant degree. The final
351 pharmacokinetic model for lenvatinib included body weight effect as an allometric constant on both
352 clearance and volume parameters, whereby both parameters increased with increasing body weight.
353 The clinical relevance of this finding is that, when administered equivalent doses, HCC subjects with low
354 body weights will have clinically significant higher exposures than patients with high body weights,
355 supporting body weight-based dosing.

356 This study was potentially limited by its open-label design. However, because of the distinct toxicities
357 and dose management requirements, the open-label design was essential to ensure patient safety. Still,
358 major protocol deviations were minimal and balanced, the percentage of patients experiencing clinical
359 progression and drug discontinuations were similar in both arms, and the results were confirmed by
360 blinded IIR. Therefore, we believe any bias introduced by the open-label design was minimal. It should
361 also be noted that the full analysis set was used as the primary analysis set as opposed to the per-
362 protocol set. However, the sample size calculation for this study was such that any factor introducing
363 bias toward the null hypothesis would reduce the power of the study. For this reason, use of the full
364 analysis set as the primary analysis set for noninferiority testing is a conservative approach in this study,

and, in fact, overall survival analysis based on the per-protocol set was completely consistent with that based on the full analysis set.

The use of mRECIST may also be considered as a limitation of the study. However, mRECIST has been established as a tool in HCC.[32,33] In addition, the exploratory post-hoc analysis confirms that progression-free survival and time to progression based on investigator assessment using mRECIST are similar to those observed based on IIR using both mRECIST and RECIST 1.1.

In conclusion, the results of this study demonstrated noninferiority of lenvatinib versus sorafenib in overall survival, and 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 this study appear consistent with the known safety profiles of these agents in HCC, and no new safety signals were identified. Based on these results, lenvatinib may be a potential new treatment option in advanced HCC.

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Contributors

M.K., R.F., S.Q., K-H.H., K.I., F.P., and A-L.C. are Protocol Steering Committee (PSC) members of this study, who made significant contributions in all aspects of the ICMJE criteria. Equal contribution was made by A.B., J-W.P., and G.H. (non-PSC member investigators). In particular, A.B. and J-W.P. contributed to helpful communications in study management and data acquisition with good quality;

and G.H. contributed to significant data acquisition with good quality and critical data interpretation of the Chinese patient population. J.J., J.F.B., A.V., D.K., T.R.J.E., and C.L. are national coordinating or representing investigators in European countries, who particularly contributed to study coordination and data acquisition with good quality. C.D., M.G., K.S., S.K., T.T., and M.R. are Eisai employees primarily involved in this study. M.K., R.F, S.Q., K-H.H., K.I., F.P., C.D., M.G., K.S., T.T., and A-L.C. contributed to the study design. M.G., K.S., and M.R. performed the statistical analysis. All authors meet all four criteria for authorship in the ICMJE Recommendations.

Declaration of interests:

Masatoshi Kudo, M.D., Ph.D.: Reports and honoraria from health care company (Bayer, Eisai, MSD, EA pharma).

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Table 1. Demographic and Disease Characteristics at Baseline.

	Lenvatinib (n = 478)	**Sorafenib (n = 476)**	**Total (N = 954)**
Age – y			
Mean	61·3	61·2	61·3
Standard Deviation	11·7	12·0	11·8
Age group — no. (%)			
<65 y	270 (56·5)	283 (59·5)	553 (58·0)
≥65 to <75 y	150 (31·4)	126 (26·5)	276 (28·9)
≥75 y	58 (12·1)	67 (14·1)	125 (13·1)
Sex — no. (%)			
Male	405 (84·7)	401 (84·2)	806 (84·5)
Female	73 (15·3)	75 (15·8)	148 (15·5)
Region — no. (%)			
Western	157 (32·8)	157 (33·0)	314 (32·9)
Asia-Pacific	321 (67·2)	319 (67·0)	640 (67·1)
Race — no. (%)			
White	135 (28·2)	141 (29·6)	276 (28·9)
Asian	334 (69·9)	326 (68·5)	660 (69·2)
Body weight (kg) — no. (%)			
<60	153 (32·0)	146 (30·7)	299 (31·3)
≥60	325 (68·0)	330 (69·3)	655 (68·7)

Eastern Cooperative Oncology Group performance status — no. (%)			
0	304 (63·6)	301 (63·2)	605 (63·4)
1	174 (36·4)	175 (36·8)	349 (36·6)
Child-Pugh class — no. (%)			
A	475 (99·4)	471 (98·9)	946 (99·2)
B	3 (0·6)	5 (1·1)	8 (0·8)
Macroscopic portal vein invasion — no. (%)			
Yes	109 (22·8)	90 (18·9)	199 (20·9)
No	369 (77·2)	386 (81·1)	755 (79·1)
Extrahepatic spread — no. (%)			
Yes	291 (60·9)	295 (62·0)	586 (61·4)
No	187 (39·1)	181 (38·0)	368 (38·6)
Macroscopic portal vein invasion, extrahepatic spread, or both — no. (%)			
Yes	329 (68·8)	336 (70·6)	665 (69·7)
No	149 (31·2)	140 (29·4)	289 (30·3)
Underlying cirrhosis based on blinded IIR — no. (%)			
Yes	356 (74·5)	364 (76·5)	720 (75·5)
No	122 (25·5)	112 (23·5)	234 (24·5)

Barcelona Clinic Liver Cancer stage — no. (%)			
B (intermediate stage)	104 (21·8)	92 (19·3)	196 (20·5)
C (advanced stage)	374 (78·2)	384 (80·7)	758 (79·5)
Involved disease sites — no. (%)			
Liver	441 (92·3)	430 (90·3)	871 (91·3)
Lung	163 (34·1)	144 (30·3)	307 (32·2)
Involved disease sites per patient — no. (%)			
1	207 (43·3)	207 (43·5)	414 (43·4)
2	167 (34·9)	183 (38·4)	350 (36·7)
≥3	103 (21·5)	86 (18·1)	189 (19·8)
Aetiology of chronic liver disease — no. (%)			
Hepatitis B	251 (52·5)	228 (47·9)	479 (50·2)
Hepatitis C	91 (19·0)	126 (26·5)	217 (22·7)
Alcohol	36 (7·5)	21 (4·4)	57 (6·0)
Other	38 (7·9)	32 (6·7)	70 (7·3)
Unknown	62 (13·0)	69 (14·5)	131 (13·7)
Baseline alpha-fetoprotein level — ng/mL			
No. of patients	471	463	934
Mean	17507·7	16678·5	17096·5
Standard deviation	105137·4	94789·5	100088·8

Median	133·1	71·2	89·0
Range	0–1567470	0–1446396	0–1567470
Baseline alpha-fetoprotein level group (ng/mL) — no. (%)			
<200	255 (53·3)	286 (60·1)	541 (56·7)
≥200	222 (46·4)	187 (39·3)	409 (42·9)
Missing	1 (0·2)	3 (0·6)	4 (0·4)
Concomitant systemic antiviral therapy for hepatitis B or C — no. (%)	163 (34·1)	149 (31·3)	312 (32·7)
Prior therapy — no. (%)			
Prior anticancer procedures	327 (68·4)	344 (72·3)	671 (70·3)
Radiotherapy	49 (10·3)	60 (12·6)	109 (11·4)

543 **Table 2.** Efficacy Measures.

Outcome	**Lenvatinib (n = 478)**	**Sorafenib (n = 476)**	**Hazard Ratio (95% CI)**
Investigator review per mRECIST			
Median (95% CI) overall survival — mo	13.6 (12·1–14·9)	12·3 (10·4–13·9)	0·92 (0·79–1·06)
Median (95% CI) progression-free survival — mo	7·4 (6·9–8·8)	3·7 (3·6–4·6)	0·66 (0·57–0·77) P<0·0001
Median (95% CI) time to progression — mo	8·9 (7·4–9·2)	3·7 (3·6–5·4)	0·63 (0·53–0·73) P<0·0001
Objective response rate* — no. (%)	115 (24·1)	44 (9·2)	3·13† (2·15–4·56)
95% CI	20·2–27·9	6·6–11·8	P<0·0001
Complete response	6 (1·3)	2 (0·4)	
Partial response	109 (22·8)	42 (8·8)	
Stable disease	246 (51·5)	244 (51·3)	
Durable stable disease lasting ≥23 weeks	167 (34·9)	139 (29·2)	
Progressive disease	71 (14·9)	147 (30·9)	
Unknown/not evaluable	46 (9·6)	41 (8·6)	
Disease control rate‡ — no. (%)	361 (75·5)	288 (60·5)	
95% CI	71·7–79·4	56·1–64·9	
Blinded independent imaging review per mRECIST			

Median (95% CI) progression-free survival — mo	7·3 (5·6–7·5)	3·6 (3·6–3·7)	0·64 (0·55–0·75) P<0·0001
Median (95% CI) time to progression — mo	7·4 (7·2–9·1)	3.7 (3·6–3·9)	0.60 (0·51–0·71) P<0·0001
Objective response rate* — no. (%)	194 (40·6)	59 (12·4)	5·01†
95% CI	36·2–45·0	9·4–15·4	(3·59–7·01)
Complete response	10 (2·1)	4 (0·8)	P<0·0001
Partial response	184 (38·5)	55 (11·6)	
Stable disease	159 (33·3)	219 (46·0)	
Durable stable disease lasting ≥23 weeks	84 (17·6)	90 (18·9)	
Progressive disease	79 (16·5)	152 (31·9)	
Unknown/not evaluable	46 (9·6)	46 (9·7)	
Disease control rate‡ — no. (%)	353 (73·8)	278 (58·4)	
95% CI	69·9–77·8	54·0–62·8	
Blinded independent imaging review per RECIST 1.1			
Median (95% CI) progression-free survival — mo	7·3 (5·6–7·5)	3·6 (3·6–3·9)	0·65 (0·56–0·77) P<0·0001
Median (95% CI) time to progression — mo	7·4 (7·3–9·1)	3·7 (3·6–5·4)	0·61 (0·51–0·72) P<0·0001
Objective response rate* — no. (%)	90 (18·8)	31 (6·5)	3·34†
95% CI	15·3–22·3	4·3–8·7	(2·17–5·14)
Complete response	2 (0·4)	1 (0·2)	P<0·0001

Partial response	88 (18·4)	30 (6·3)	
Stable disease	258 (54·0)	250 (52·5)	
Durable stable disease lasting ≥23 weeks	163 (34·1)	118 (24·8)	
Progressive disease	84 (17·6)	152 (31·9)	
Unknown/not evaluable	46 (9·6)	43 (9·0)	
Disease control rate‡ — no. (%)	348 (72·8)	281 (59·0)	
95% CI	68·8–76·8	54·6–63·5	

*Objective response is defined as complete response + partial response, according to modified Response Evaluation Criteria in Solid Tumours or Response Evaluation Criteria in Solid Tumours v1·1.

†Odds ratio. ‡Disease control is defined as complete response + partial response + stable disease.

CI, confidence interval.

548 **Table 3.** Adverse Events.

	Lenvatinib (n = 476)		**Sorafenib (n = 475)**	
Total treatment-emergent adverse events— no. (%)	470 (98·7)		472 (99·4)	
Total treatment-related treatment-emergent adverse events— no. (%)	447 (93·9)		452 (95·2)	
Treatment-emergent adverse events of grade ≥3— no. (%)	357 (75·0)		316 (66·5)	
Treatment-related treatment-emergent adverse events of grade ≥3— no. (%)	270 (56·7)		231 (48·6)	
Serious treatment-emergent adverse events — no. (%)	205 (43·1)		144 (30·3)	
Serious treatment-related treatment-emergent adverse events — no. (%)	84 (17·6)		48 (10·1)	
Treatment-emergent adverse events occurring in ≥15% of patients in either treatment group	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3

Palmar-plantar erythrodysaesthesia	128 (26·9)	14 (2·9)	249 (52·4)	54 (11·4)
Diarrhoea	184 (38·7)	20 (4·2)	220 (46·3)	20 (4·2)
Hypertension	201 (42·2)	111 (23·3)	144 (30·3)	68 (14·3)
Decreased appetite	162 (34·0)	22 (4·6)	127 (26·7)	6 (1·3)
Decreased weight	147 (30·9)	36 (7·6)	106 (22·3)	14 (2·9)
Fatigue	141 (29·6)	18 (3·8)	119 (25·1)	17 (3·6)
Alopecia	14 (2·9)	0 (0)	119 (25·1)	0 (0)
Proteinuria	117 (24·6)	27 (5·7)	54 (11·4)	8 (1·7)
Dysphonia	113 (23·7)	1 (0·2)	57 (12·0)	0 (0)
Nausea	93 (19·5)	4 (0·8)	68 (14·3)	4 (0·8)
Abdominal pain	81 (17·0)	8 (1·7)	87 (18·3)	13 (2·7)
Decreased platelet count	87 (18·3)	26 (5·5)	58 (12·2)	16 (3·4)
Elevated aspartate aminotransferase	65 (13·7)	24 (5·0)	80 (16·8)	38 (8·0)
Hypothyroidism	78 (16·4)	0 (0)	8 (1·7)	0 (0)
Vomiting	77 (16·2)	6 (1·3)	36 (7·6)	5 (1·1)
Constipation	76 (16·0)	3 (0·6)	52 (10·9)	0 (0)
Rash	46 (9·7)	0 (0)	76 (16·0)	2 (0·4)

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Figure 1. Kaplan-Meier Estimate of Overall Survival and Progression-free Survival.

Kaplan-Meier estimates of overall survival by treatment group are shown in panel A. Panel B shows progression-free survival by modified Response Evaluation Criteria in Solid Tumours.

CI denotes confidence interval, and HR hazard ratio.

Figure 2. Forest Plots Indicating Hazard Ratios for Overall Survival and Progression-free Survival in Subgroup Analyses.

Subgroup analyses of overall survival indicating associated hazard ratio and 95% confidence interval are shown in panel A. Panel B shows subgroup analyses of progression-free survival indicating the associated hazard ratio and 95% confidence interval.

AFP denotes alpha-fetoprotein, BCLC Barcelona Clinic Liver Cancer, CI confidence interval, and HR hazard ratio.

Figure 1

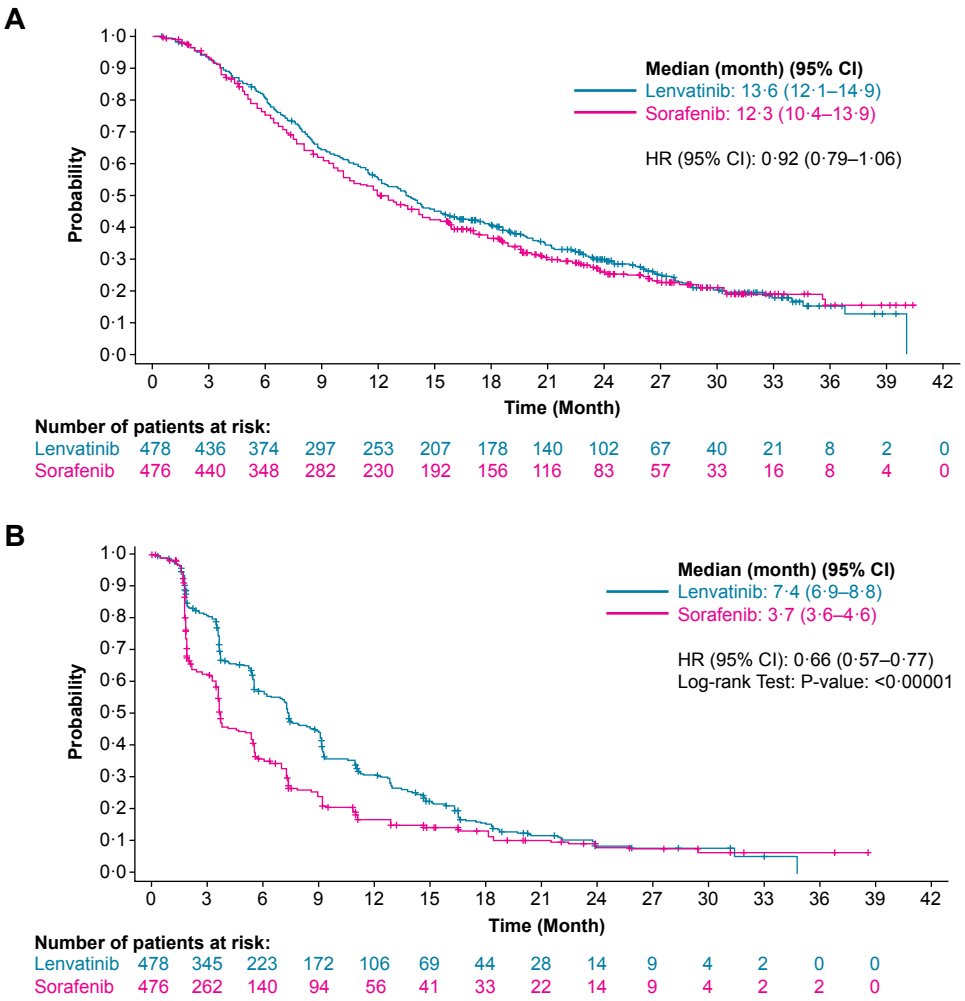
A
Probability
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0·0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42
Time (Month)
Median (month) (95% CI)
Lenvatinib: 13·6 (12·1–14·9)
Sorafenib: 12·3 (10·4–13·9)
HR (95% CI): 0·92 (0·79–1·06)
Number of patients at risk:
Lenvatinib 478 436 374 297 253 207 178 140 102 67 40 21 8 2 0
Sorafenib 476 440 348 282 230 192 156 116 83 57 33 16 8 4 0
B
Probability
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0·0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42
Time (Month)
Median (month) (95% CI)
Lenvatinib: 7·4 (6·9–8·8)
Sorafenib: 3·7 (3·6–4·6)
HR (95% CI): 0·66 (0·57–0·77)
Log-rank Test: P-value: <0·00001
Number of patients at risk:
Lenvatinib 478 345 223 172 106 69 44 28 14 9 4 2 0 0
Sorafenib 476 262 140 94 56 41 33 22 14 9 4 2 2 0

Figure 2A

A. Overall Survival

	Events / Patients		HR (95% CI)	Median (months)	
	Lenvatinib	Sorafenib	Lenvatinib vs Sorafenib	Lenvatinib	Sorafenib
Overall	351/478	350/476	0·92 (0·79, 1·06)	13·6	12·3
Age					
<65 y	203/270	204/283	0·94 (0·77, 1·15)	12·4	11·4
≥65 y	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
Body weight					
<60 kg	110/153	113/146	0·85 (0·65, 1·11)	13·4	10·3
≥60 kg	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					
<200 ng/mL	167/255	193/286	0·91 (0·74, 1·12)	19·5	16·3
≥200 ng/mL	183/222	154/187	0·78 (0·63, 0·98)	10·4	8·2
Etiology					
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 anti-cancer 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 anti-cancer 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 anti-cancer 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

Figure 2B

B. Progression-free Survival

	Events / Patients		HR (95% CI)	Median (months)	
	Lenvatinib	Sorafenib	Lenvatinib vs Sorafenib	Lenvatinib	Sorafenib
Overall	349/478	367/476	0·66 (0·57, 0·77)	7·4	3·7
Age					
<65 y	201/270	223/283	0·67 (0·55, 0·82)	7·3	3·6
≥65 y	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
Body weight					
<60 kg	111/153	121/146	0·61 (0·46, 0·79)	7·4	3·6
≥60 kg	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					
<200 ng/mL	186/255	209/286	0·68 (0·55, 0·83)	9·0	5·4
≥200 ng/mL	163/222	157/187	0·59 (0·47, 0·75)	5·5	2·4
Etiology					
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 anti-cancer 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 anti-cancer 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 anti-cancer 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