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

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1  **A Randomised Phase 3 Trial of Lenvatinib vs. Sorafenib in First-line Treatment of Patients With**

2  **Unresectable Hepatocellular Carcinoma**

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35    **Word limit:** 3381/3000

36    **References:** 31/30 maximum

37    **Abstract:** 251/300 words maximum

38    **Running head:** Lenvatinib in advanced hepatocellular carcinoma

39    **ClinicalTrials.gov Identifier:** NCT01761266

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42  **BACKGROUND**

43  In a phase 2 trial, lenvatinib, an inhibitor of vascular endothelial growth factor receptor 1–3, fibroblast

44  growth factor receptor 1–4, platelet-derived growth factor receptor alpha, RET, and KIT, showed activity

45  in hepatocellular carcinoma (HCC). We aimed to compare overall survival in patients treated with

46  lenvatinib versus sorafenib as first-line treatment for unresectable HCC.

47  **METHODS**

48  This open-label, phase 3, multicentre, noninferiority trial involving patients with unresectable HCC who

49  had not received treatment for advanced disease randomised 478 to lenvatinib (body weight ≥60 kg: 12

50  mg/day; <60 kg: 8 mg/day) and 476 to twice-daily sorafenib 400 mg. The primary endpoint was overall

51  survival. The noninferiority margin was set at 1·08. Registered with ClinicalTrials.gov, number:

52  NCT01761266.

53  **FINDINGS**

54  Patients were enrolled from March 1, 2013 through July 30, 2015. The study met its primary endpoint of

55  noninferiority in overall survival for lenvatinib versus sorafenib (medians: lenvatinib, 13·6 months vs.

56  sorafenib, 12·3 months; hazard ratio [HR]: 0·92; 95% confidence interval [CI], 0·79 to 1·06). The most

57  common any-grade adverse events were hypertension (201 [42·2%]), diarrhoea (184 [38·7%]),

58  decreased appetite (162 [34·0%]), and decreased weight (147 [30·9%]) for lenvatinib, and palmar-

59  plantar erythrodysaesthesia (249 [52·4%]), diarrhoea (220 [46·3%]), hypertension (144 [30·3%]), and

60  decreased appetite (127 [26·7%]) for sorafenib. In the EORTC-QLQ-based analysis, there were 5

61  outcomes, including pain and diarrhoea with nominal p<0.05, all of which favoured lenvatinib compared

62  to sorafenib.

63  **INTERPRETATION**

64  Lenvatinib was noninferior to sorafenib in overall survival in untreated advanced HCC. The safety and

65  tolerability profiles of lenvatinib were consistent with those previously observed.

66  **FUNDING:** Eisai

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69 **Research in Context**

70 *Evidence before this study*

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

79 *Added value of this study*

80 This is the first global phase 3 trial to meet its primary endpoint of noninferiority in overall survival
81 against sorafenib as first-line treatment for hepatocellular carcinoma in 10 years. Furthermore,
82 lenvatinib demonstrated statistically significant and clinically meaningful improvement in all secondary
83 endpoints (progression-free survival, time to progression, and objective response rate) with a
84 reasonable safety profile.

85 *Implications of all the available evidence*

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

88

89

90      **INTRODUCTION**

91      Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide and is responsible

92      for nearly 745,000 deaths each year.[1] It usually occurs in a background of chronic liver disease,

93      particularly in cirrhosis, which limits the feasibility of surgical resection.[2,3] Sorafenib, an oral multikinase

94      inhibitor, is the only systemic therapy that has been proven to extend overall survival when used as a

95      first-line treatment for HCC, demonstrating a median improvement of 2.8 months compared with

96      placebo (10·7 months vs 7·9 months; hazard ratio [HR] 0·69; p<0·001) despite a low response rate of

97      2%.[4] In patients from the Asia-Pacific region who were taking sorafenib, the median improvement in

98      overall survival over placebo was 2·3 months (6·5 months vs 4·2 months; HR 0·68; p=0·014).[5]

99      Drug development in HCC in the past 10 years is marked by 4 failed global phase 3 trials (of sunitinib,

100     brivanib, linifanib, and erlotinib plus sorafenib) that did not demonstrate noninferiority[6-8] or superiority[9]

101     to sorafenib in overall survival in first-line treatment of HCC. There are currently no approved first-line

102     systemic treatments available for advanced unresectable HCC other than sorafenib. Only regorafenib is

103     approved as second-line systemic treatment for patients who failed to respond to sorafenib.[10] Best

104     supportive care or participation in clinical trials is currently recommended by the treatment guidelines in

105     the second-line setting.[11] Therefore, due to the current paucity of systemic treatment options for

106     patients with advanced HCC, a critical need exists to develop new agents for the effective management

107     of this disease.

108     Lenvatinib is an oral multikinase inhibitor that targets vascular endothelial growth factor (VEGF)

109     receptors 1, 2, and 3; fibroblast growth factor (FGF) receptors 1, 2, 3, and 4; platelet-derived growth

110     factor receptor α (PDFGRα), RET, and KIT.[12-15] Lenvatinib monotherapy was approved for the treatment

111     of radioiodine-refractory differentiated thyroid cancer.[16] Lenvatinib and everolimus were approved as a

112     combined treatment for advanced renal cell carcinoma following 1 prior anti-angiogenic therapy.[17] In a

113    phase 2 study of patients with advanced HCC, lenvatinib at a dose of 12 mg once daily showed clinical

114    activity and had an acceptable safety profile.[18] Based on dose adjustments depending on body weights

115    as well as pharmacokinetic modelling data,[19] a starting dose of lenvatinib based on body weight was

116    adopted (12 mg and 8 mg once daily for patients with body weights ≥60 kg and <60 kg, respectively) for

117    further clinical development in HCC. Given the efficacy signal observed in this phase 2 study, we

118    performed a phase 3 randomised, open-label, noninferiority study to compare the efficacy and safety of

119    lenvatinib versus sorafenib as first-line treatment for unresectable HCC.

120

121    **METHODS**

122    **Study Design**

123    This multicentre, phase 3, randomised, open-label, noninferiority study was conducted at 154 sites in 20

124    countries throughout the Asia-Pacific, European, and North American regions. Within stratification

125    factors, patients were randomly assigned (1:1) to receive oral lenvatinib at a dose of 12 mg per day (for

126    body weight ≥60 kg) or 8 mg per day (for body weights <60 kg) or sorafenib at doses of 400 mg twice

127    daily in 28-day cycles. Dosage interruptions followed by reductions for lenvatinib-related toxicities (to 8

128    and 4 mg per day, or 4 mg every other day) were permitted. Modifications to sorafenib dosage were

129    implemented according to prescribing information in each region (all patients in the sorafenib arm

130    received a starting dose of 400 mg orally twice per day).

131

132    **Study Eligibility**

133    Patients who were eligible for enrolment had unresectable HCC with diagnosis confirmed histologically

134    or cytologically or with diagnosis confirmed clinically in accordance with the American Association for

135     the Study of Liver Diseases criteria. Included patients also had 1 or more measurable target lesion

136     (lesions previously treated with radiotherapy or locoregional therapy had to show radiographic evidence

137     of disease progression to be deemed a target lesion), based on modified Response Evaluation Criteria in

138     Solid Tumours (mRECIST)[20]; Barcelona Clinic Liver Cancer stage B or C categorisation[21]; Child-Pugh class

139     A; and Eastern Cooperative Oncology Group performance status score of 0 or 1. All eligible patients had

140     controlled blood pressure (≤150/90 mm Hg), adequate liver function (defined as: albumin ≥ 2·8 g/dL,

141     bilirubin ≤ 3·0 mg/dL, and aspartate aminotransferase, alkaline phosphatase, and alanine

142     aminotransferase ≤ 5 times the upper limit of normal), and adequate blood (hemoglobin ≥ 8·5 g/dL,

143     platelet count ≥ 75 × 109/L, and international normalized ratio ≤2·3), renal, and pancreatic function.

144     Patients with ≥50% liver occupation, obvious invasion of the bile duct, or portal vein invasion at the

145     main portal vein were excluded. Patients also were excluded if they had received prior systemic therapy

146     for HCC.

147     **Study Oversight**

148     The study was approved by all relevant institutional review boards and was conducted in accordance

149     with the Declaration of Helsinki and local laws. The trial was registered before the start of patient

150     enrolment. All patients provided written informed consent before undergoing any study-specific

151     procedures. The study was funded by Eisai (Woodcliff Lake, NJ) and designed in collaboration with the

152     principal investigators. The study was overseen by an independent data monitoring committee. All

153     parties vouch for the accuracy and completeness of the data and analyses and for adherence to the

154     study protocol. The manuscript was prepared by the authors with assistance from professional medical

155     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

179    Institute Common Terminology Criteria for Adverse Events version 4·0.[26] All safety evaluations were

180    based on the safety analysis set (all patients who received at least 1 dose of study treatment). Post hoc

181    exploratory tumour assessments using mRECIST and RECIST v1·1 were performed by blinded central

182    independent imaging review (IIR).

183    A population pharmacokinetic analysis for lenvatinib was conducted to derive individual

184    pharmacokinetic parameters and lenvatinib exposures for this study. The dataset used in the analysis

185    included lenvatinib plasma concentrations from 468 patients with HCC in this study and lenvatinib

186    plasma concentrations pooled from 12 additional studies (phase 1 to 3) in healthy individuals and in

187    patients with other tumor types (e.g. differentiated thyroid cancer).

188

189    **Statistical Analysis**

190    The primary endpoint of overall survival was first tested for noninferiority, then for superiority. The

191    required number of events for the primary analysis was 700 deaths.

192    The HR and its 95% confidence interval (CI) were estimated from a Cox proportional hazard model

193    with treatment group as a factor and with the analysis stratified according to the same factors applied

194    for randomisation for the primary and for the subgroup analyses where it is appropriate. For the

195    subgroup analysis, the analyses were performed within each subgroup. The noninferiority margin was

196    set at 1·08 based on previous phase 3 trials of sorafenib.[4,5] Noninferiority was declared if the upper limit

197    of the 2-sided 95% CI for HR was <1·08.

198    A fixed-sequence procedure was followed to control the overall type I error rate of analyses for both the

199    primary and secondary efficacy endpoints at $\alpha=0·05$ (2-sided). After noninferiority was declared,

200    secondary efficacy endpoints were tested. Differences in progression-free survival and time to

201    progression were evaluated using a stratified log-rank test with randomisation stratification factors, with

202    the associated HR and its 95% CI. The same method was used to evaluate differences in progression-free

203    survival and time to progression in the subgroup analyses. A difference in the objective response rate

204    was evaluated using the Cochran-Mantel-Haenszel chi-square test with randomisation stratification

205    factors as strata, with associated odds ratio and its 95% CI. To assess futility, two interim analyses (at

206    30% and 70% of the target number of events) were performed using Bayesian predictive probability in a

207    noninferiority design by the independent data monitoring committee. Programming and statistical

208    analyses were performed with SAS version 9 or higher.

209    **Role of the funding source:**

210    The funder employed CD, MG, KS, SK, TT, and MR, who played a significant role in study design, data

211    collection, data analysis, data interpretation, and writing of the report (see Contributors for details). The

212    corresponding author had full access to all data in the study and had final responsibility for the decision

213    to submit for publication.

214    **RESULTS**

215    **Patients**

216    Patients were recruited from March 1, 2013 through July 30, 2015. A total of 954 patients from 20

217    countries were randomly assigned to receive lenvatinib (478 patients) or sorafenib (476 patients) (Figure

218    S1 in the Supplementary Appendix). The required number of 700 deaths occurred after the completion

219    of enrolment. The efficacy analysis followed the intent-to-treat principle. Only patients who received

220    treatment (lenvatinib, n=476 patients; sorafenib, n=475 patients) were included in the safety analysis.

221    Patient characteristics at baseline were well balanced between treatment groups, with the exception of

222    baseline hepatitis C aetiology and alpha-fetoprotein levels (Table 1). At the time of data cutoff

223    (November 13, 2016), the median duration of follow-up was 27·7 months (interquartile range [IQR], 23·3

224    to 32·8) in the lenvatinib group and 27·2 months (IQR, 22·6 to 31·2) in the sorafenib group.

225 **Efficacy**

226 Lenvatinib demonstrated noninferiority in overall survival compared with sorafenib. The median overall

227 survival was 13·6 months (95% CI, 12·1 to 14·9) with lenvatinib, compared with 12·3 months (95% CI,

228 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

229 are shown in Table S1 in the Supplementary Appendix). The effect of lenvatinib and sorafenib on median

230 overall survival was consistent across the subgroups based on baseline characteristics (Figure 2A). While

231 baseline alpha-fetoprotein level was not a pre-specified stratum, patients with baseline alpha-

232 fetoprotein levels <200 ng/mL had longer overall survival than those with alpha-fetoprotein levels ≥200

233 ng/mL in both treatment groups (Figure 2A). There were more patients with baseline alpha-fetoprotein

234 levels <200 ng/mL in the sorafenib arm (286, 60·1%) compared with the lenvatinib arm (255, 53·3%,

235 Table 1).

236 Lenvatinib demonstrated a statistically significant improvement compared to sorafenib in all secondary

237 efficacy endpoints as determined by investigators' tumour assessment based on mRECIST. Median

238 progression-free survival for lenvatinib was 7·4 months (95% CI, 6·9 to 8·8 months) compared with 3·7

239 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).

240 The median time to progression was 8·9 months (95% CI, 7·4 to 9·2 months) for patients in the

241 lenvatinib group compared with 3·7 months (95% CI, 3·6 to 5·4 months) for patients in the sorafenib

242 group (HR: 0·63; 95% CI, 0·53 to 0·73; p<0·0001) (Table 2 and Figure S2 in the Supplementary Appendix).

243 Lenvatinib showed an objective response rate of 24·1% versus 9·2% for sorafenib (odds ratio, 3·13; 95%

244 CI, 2·15 to 4·56; p<0·0001) (Table 2 and Figure S3 in the Supplementary Appendix). The improvements in

245 all secondary efficacy endpoints (progression-free survival, time to progression, and objective response

246 rate) with lenvatinib over sorafenib are consistent across all predefined subgroups (Figure 2B, and

247 Figures S4 and S5 in the Supplemental Appendix). Analysis for overall survival with predefined subgroups

248 supports the robustness of the noninferiority result (Table S2 in the Supplementary Appendix). Blinded

249     IIR confirmed progression-free survival (HR: 0·64; 95% CI, 0·55–0·75; p<0·0001) and time to progression

250     (HR: 0·60; 95% CI, 0·51–0·71; p<0·0001) based on investigator assessments according to mRECIST (Table

251     2). Similar progression-free survival and time to progression were observed for mRECIST and RECIST 1·1

252     based on blinded IIR. Blinded IIR confirmed a significantly higher objective response rate in the

253     lenvatinib arm compared with the sorafenib arm by mRECIST (40·6% vs. 12·4%; odds ratio: 5·01; 95% CI,

254     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;

255     Table 2).

256     Of note, 156 (32·6%) patients in the lenvatinib arm and 184 (38·7%) in the sorafenib arm received a

257     post-study anticancer medication (including investigational therapy). Of these, 121 (25·3%) patients in

258     the lenvatinib arm and 56 (11·8%) in the sorafenib arm, respectively, received sorafenib during survival

259     follow-up. In the Western region, 41 (26·1%) patients in the lenvatinib arm received any anticancer

260     medication during survival follow-up versus 61 (38·9%) in the sorafenib arm. In the lenvatinib arm, 11

261     (7·0%) patients in the Western region had any anticancer procedure during follow-up compared with 18

262     (11·5%) patients in the sorafenib arm in this region (Table S3 in the Supplementary Appendix).

263

264     **Safety and Side-effect Profile**

265     Median duration of study treatment for patients in the lenvatinib group was longer than for patients in

266     the sorafenib group (5·7 vs. 3·7 months). Treatment-emergent adverse events occurred in 98·7% of

267     patients who received lenvatinib and 99·4% of patients who received sorafenib. Adjusted by patient-

268     years, the adverse event rate was 18·9 in the lenvatinib group and 19·7 in the sorafenib group.

269     Treatment-emergent adverse events of grade 3 or higher occurred in 75·0% of patients who received

270     lenvatinib and 66·5% of patients who received sorafenib (adverse event rate/patient-year: 3·2 vs. 3·3).

271     The most common treatment-emergent adverse events among patients who received lenvatinib were

272     hypertension (201; 42·2%), diarrhoea (184; 38·7%), decreased appetite (162; 34·0%), and decreased

273     weight (147; 30·9%). In the sorafenib arm, the most common treatment-emergent adverse events were

274     palmar-plantar erythrodysaesthesia (52·4%), diarrhoea (46·3%), hypertension (30·3%), and decreased

275     appetite (26·7%) (Table 3).

276     Fatal adverse events occurred throughout treatment and appeared to occur at similar rates in both

277     arms. Fatal adverse events determined by the investigator to be related to lenvatinib treatment

278     occurred in 11 patients (2·3%) and included hepatic failure (3 patients), cerebral haemorrhage

279     (3 patients), and respiratory failure (2 patients). In the sorafenib group, treatment-related fatal adverse

280     events occurred in 4 patients (0·8%) and included tumour haemorrhage, ischaemic stroke, respiratory

281     failure, and sudden death (1 event per patient).

282     Treatment-related treatment-emergent adverse events leading to lenvatinib drug interruption, dose

283     reduction, and drug withdrawal occurred in 190 (39·9%), 176 (37·0%), and 42 (8·8%) patients,

284     respectively. In the sorafenib arm, treatment-related treatment-emergent adverse events led to drug

285     interruption, dose reduction, and drug withdrawal in 153 (32·2%), 181 (38·1%), and 34 (7·2%) patients,

286     respectively. The mean lenvatinib dose intensity was 7·0 mg in the 8 mg/day group and 10·5 mg in the

287     12 mg/day group, corresponding to 87·7% and 87·5% of the planned starting doses, respectively. The

288     mean sorafenib dose intensity was 663·8 mg, or 83·0% of the planned starting dose.

289     **Quality of Life**

290     Baseline scores on the EORTC QLQ-C30 and EORTC QLQ-HCC18 health questionnaires were similar in the

291     lenvatinib and sorafenib treatment groups. Following treatment, scores declined in both groups. The

292     analysis of time to clinically meaningful deterioration showed that role functioning (nominal p=0.0193),

293     pain (nominal p=0.0105), and diarrhoea (nominal p<0.0001) from QLQ-C30 and nutrition (nominal

294     p=0.0113) and body image (nominal p=0.0051) from QLQ-HCC18 deterioration was observed earlier in

295   patients treated with sorafenib than with lenvatinib. For between-group comparison, the summary

296   score was not significantly different between the treatment arms (HR 0·87; 95%CI 0·754–1·012; Figure

297   S6 in the Supplementary Appendix).

298   **Pharmacokinetics**

299   Based on the individual model-derived, predicted lenvatinib area under the curve (AUC) values at steady

300   state for patients with HCC in the current study, the median value and range of AUC are comparable

301   between the group with a starting dose of 8 mg for body weight < 60 kg (median: 1820.2 ng·h/mL; min-

302   max: 704.8–4980.7 ng·h/mL) and the group with a 12 mg starting dose for body weight ≥ 60 kg (median:

303   1996.0 ng·h/mL; min-max: 925.5 - 5427.9 ng·h/mL), which supports the starting dose of 8 mg for body

304   weight < 60 kg, and confirms the weight-based dosing based on the pharmacokinetic analysis from the

305   Phase 1/2 study in HCC subjects.[19] There were no differences in lenvatinib oral clearance or in AUC at

306   steady state among Western, Asian, Chinese and Japanese populations in the current study.

307   **DISCUSSION**

308   This is the first positive global phase 3 trial (HR 0·92; upper bound of 95% CI 1·06) for overall survival

309   compared with sorafenib in first-line treatment for HCC in 10 years and the first ever to be positive using

310   an active-control arm. This study showed lenvatinib to be noninferior to sorafenib, currently the

311   standard of care in HCC, for overall survival. Importantly, lenvatinib demonstrated statistically

312   significant, clinically meaningful improvement for all secondary efficacy endpoints (progression-free

313   survival, time to progression, and objective response rate) across subgroups, as well as in quality-of-life

314   assessments. Together, these data support the overall survival result in this study.

315   The median overall survival of patients who received sorafenib in the current study (12·3 months) is

316   longer than has been reported in any previous large randomised phase 3 study.[4–9] One possible

317   explanation for this result is the higher proportion of post-sorafenib anticancer therapy observed in this

318    study. For example, 21% and 17% of patients receiving sorafenib in the previous phase study of brivanib

319    vs. sorafenib received systemic and nonsystemic post-sorafenib treatments, respectively compared with

320    39% and 27% of patients receiving sorafenib in this study.[7] Continuous improvements in care for

321    unresectable HCC have been made, and multimodality therapies, including locoregional treatment

322    approaches, are now often used following progression because they may be efficacious even after

323    systemic therapies such as sorafenib treatment.[27,28] If post-progression survival is prolonged by such

324    post-study treatments, this may lead to a dilution of the observed overall survival treatment benefit.

325    Hence, while still representing the gold standard, overall survival as an endpoint alone for trials in first

326    line HCC may no longer capture the full extent of antitumour efficacy. The significant improvement in

327    progression-free survival, time to progression, and objective response rate with lenvatinib in this study

328    may indicate, as in some other tumours, the emergence of a broader paradigm in drug assessment and

329    treatment in advanced HCC.

330    This study did not enroll patients with >50% liver involvement and main portal vein invasion

331    because this exclusion criterion was used in the preceding phase 2 proof-of-concept study conducted in

332    Japan as mandated by Japan Society of Hepatology consensus-based clinical practice guidelines.[17,29] This

333    resulted in only 4.2% screen failures in the phase 3 study. While this could have only slightly changed the

334    overall prognosis of the patient population, it did not affect distribution of patients between the study

335    arms since this was controlled by the randomization.

336    The safety profile of lenvatinib is consistent with that observed in previous studies.[16,18,30] Patients who

337    received lenvatinib experienced fewer instances of palmar-plantar erythrodysaesthesia, diarrhoea, and

338    alopecia, and more instances of hypertension, proteinuria, dysphonia, and hypothyroidism than did

339    patients who received sorafenib. Although quality-of-life scores declined in both groups after treatment,

340    a clinically meaningful delay in deterioration for multiple domains was observed with lenvatinib

341    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,

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

366 based on the full analysis set.

367 The use of mRECIST may also be considered as a limitation of the study. However, mRECIST has been

368 established as a tool in HCC.[32,33] In addition, the exploratory post-hoc analysis confirms that progression-

369 free survival and time to progression based on investigator assessment using mRECIST are similar to

370 those observed based on IIR using both mRECIST and RECIST 1.1.

371 In conclusion, the results of this study demonstrated noninferiority of lenvatinib versus sorafenib in

372 overall survival, and statistically significant and clinically meaningful improvement in progression-free

373 survival, time to progression, and objective response rate. The safety profiles of lenvatinib and sorafenib

374 in this study appear consistent with the known safety profiles of these agents in HCC, and no new safety

375 signals were identified. Based on these results, lenvatinib may be a potential new treatment option in

376 advanced HCC.

377

382 **Contributors**

383 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

384 study, who made significant contributions in all aspects of the ICMJE criteria. Equal contribution was

385 made by A.B., J-W.P., and G.H. (non-PSC member investigators). In particular, A.B. and J-W.P.

386 contributed to helpful communications in study management and data acquisition with good quality;

387    and G.H. contributed to significant data acquisition with good quality and critical data interpretation of

388    the Chinese patient population. J.J., J.F.B., A.V., D.K., T.R.J.E., and C.L. are national coordinating or

389    representing investigators in European countries, who particularly contributed to study coordination

390    and data acquisition with good quality. C.D., M.G., K.S., S.K., T.T., and M.R. are Eisai employees primarily

391    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

392    study design. M.G., K.S., and M.R. performed the statistical analysis. All authors meet all four criteria for

393    authorship in the ICMJE Recommendations.

394

395    **Declaration of interests:**

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

397    pharma).

398    **Richard Finn, M.D.:** Reports grants, personal fees and non-financial support from Eisai, Inc, during the

399    conduct of the study; grants, personal fees and non-financial support from Bayer, grants, personal fees

400    and non-financial support from Pfizer, grants, personal fees and non-financial support from Novartis,

401    grants, personal fees and non-financial support from Bristol Myers Squibb (BMS), grants, personal fees

402    and non-financial support from Merck, outside the submitted work.

403    **Shukui Qin, M.D.:** Nothing to disclose

404    **Kwang-Hyub Han, M.D.:** Reports grants and other from Eisai co., during the conduct of the study; grants

405    and other from KOWA, other from Bayer, outside the submitted work.

406    **Kenji Ikeda, M.D., Ph.D.:**  Reports honoraria from health care companies (Eisai Co. Ltd, Dainippon

407    Sumitomo Pharmaceutical Co. Ltd).

408    **Fabio Piscaglia, M.D.:** Reports personal fees from Eisai, during the conduct of the study; grants and

409    personal fees from Bayer, personal fees from Bracco, outside the submitted work.

410    **Ari Baron, M.D.:** Reports research funding from Eisai Inc.

411    **Joong-Won Park, M.D.:** Nothing to disclose

412    **Guohong Han, M.D.:** Nothing to disclose

413    **Jacek Jassem, M.D., Ph.D.:** Reports personal fees from Astra Zeneca, personal fees from Roche, personal

414    fees from Pfizer, personal fees from G1 Therapeutics, personal fees from Pierre Fabre, personal fees

415    from Celgene, personal fees from Merck, and personal fees from BMS, outside the submitted work.

416    **Jean Frederic Blanc, M.D.:** Reports personal fees from Bayer SP, personal fees from Eli Lily Oncology,

417    personal fees from Novartis, and personal fees from BMS, outside the submitted work.

418    **Arndt Vogel, M.D.:** Nothing to disclose.

419    **Dmitry Komov, M.D.:** Nothing to disclose.

420    **TR Jeffry Evans, M.D.:** Reports other from Eisai, during the conduct of the study; other from Bristol

421    Myers Squibb, other from Clovis, other from Karus Therapeutics, other from Baxalta, other from Bayer,

422    other from Celgene, other from Glaxo Smith Kline, other from Otsuka, other from Roche/Genentech,

423    other from TC Biopharm, other from Immunova, other from Basilea, other from e-Therapeutics, other

424    from Immunocore, other from Vertex, other from Verastem, other from Daiichi, and other from Merck,

425    outside the submitted work.

426    **Carlos Lopez, M.D, Ph.D.:** Reports grants, personal fees, non-financial support and other from Eisai,

427    grants, personal fees, non-financial support and other from Bayer, grants, personal fees, non-financial

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538

539

540     **Table 1.** Demographic and Disease Characteristics at Baseline.

| | Lenvatinib<br>(n = 478) | Sorafenib<br>(n = 476) | Total<br>(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) |

541

542

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) P<0·0001 |
| 95% CI | 20·2–27·9 | 6·6–11·8 | |
| 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 | |

544     *Objective response is defined as complete response + partial response, according to modified

545     Response Evaluation Criteria in Solid Tumours or Response Evaluation Criteria in Solid Tumours v1·1.

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

547     CI, confidence interval.

**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) |

549

550

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

552

553    Kaplan-Meier estimates of overall survival by treatment group are shown in panel A. Panel B shows

554    progression-free survival by modified Response Evaluation Criteria in Solid Tumours.

555    CI denotes confidence interval, and HR hazard ratio.

556

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

558    Subgroup Analyses.

559

560    Subgroup analyses of overall survival indicating associated hazard ratio and 95% confidence interval are

561    shown in panel A. Panel B shows subgroup analyses of progression-free survival indicating the

562    associated hazard ratio and 95% confidence interval.

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

564    hazard ratio.

565

**Figure 1**



**A**



**B**
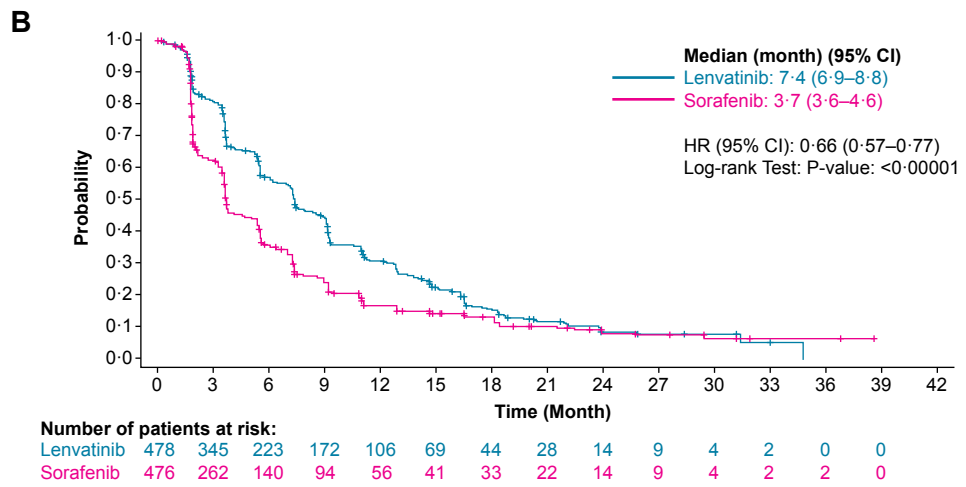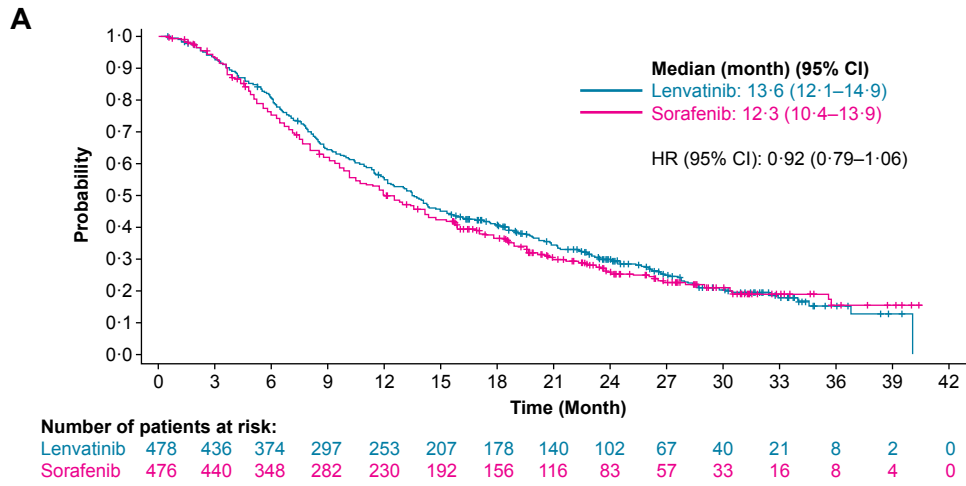
**Figure 2A**

## 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 |

Favors Lenvatinib        Favors Sorafenib

0·1          1          10

**Hazard Ratio and 95% Confidence Interval**
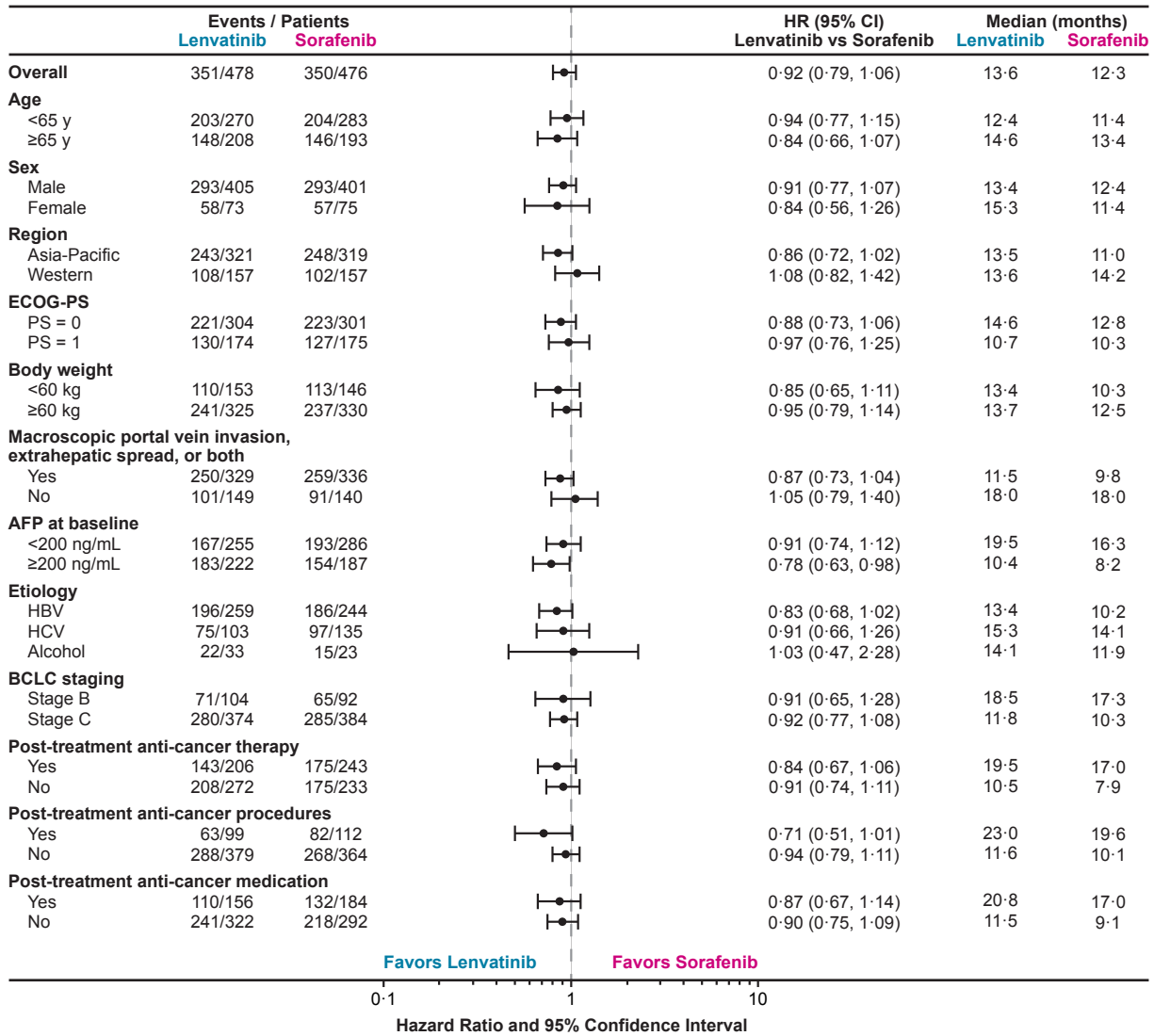
**Figure 2B**

## 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 |

Favors Lenvatinib    Favors Sorafenib

0·1    1    10

Hazard Ratio and 95% Confidence Interval