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Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial / Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blencowe J, Vogel A, Komov D, Evans TR, Lopez D, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. - In: THE LANCET. - ISSN 0140-6736. - STAMPA. - 391:10126(2018), pp. 1163-1173. [10.1016/S0140-6736(18)30207-1]

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

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This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Availability:

This version is available at: <https://hdl.handle.net/11585/647706> since: 2018-10-24

Published:

DOI: [http://doi.org/10.1016/S0140-6736\(18\)30207-1](http://doi.org/10.1016/S0140-6736(18)30207-1)

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Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL.

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

Lancet. 2018 Mar 24;391(10126):1163-1173.

The final published version is available online at: [https://doi.org/10.1016/S0140-6736\(18\)30207-1](https://doi.org/10.1016/S0140-6736(18)30207-1)

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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**

3

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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

40

41

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 erythrodysesthesia (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

67

68

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 noninferiority⁶⁻⁸ or superiority⁹
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 (PDGFR α), 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 categorisation²¹; 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 ($\leq 150/90$ 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 $\geq 75 \times 10^9/L$, and international normalized ratio ≤ 2.3), renal, and pancreatic function.
144 Patients with $\geq 50\%$ 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.

156 **Randomisation and Masking**

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

163 **Endpoints and Assessments**

164 The primary endpoint was overall survival. Secondary endpoints included progression-free survival, time
165 to progression, objective response rate, quality-of-life measurements including the European
166 Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-
167 C30)^{22,23} and the HCC-specific EORTC QLQ-HCC18²⁴ health questionnaires, and plasma pharmacokinetic
168 exposure parameters. All efficacy evaluations were based on the full analysis set (all randomised
169 patients).

170 The investigators evaluated tumours in each treatment arm in accordance with mRECIST.^{20,25} The liver
171 was examined with computed tomography or magnetic resonance imaging using a triphasic scanning
172 technique. Assessments were performed every 8 weeks (irrespective of dosage interruptions) until
173 radiologic disease progression. Patients who discontinued from study treatment without disease
174 progression continued to have tumour assessments performed every 8 weeks or until disease
175 progression or the start of another anticancer treatment. Quality-of-life questionnaires were
176 administered at baseline, on day 1 of each subsequent treatment cycle, and at the off-treatment visit.
177 Safety assessments included recording of vital signs, haematologic, and biochemical laboratory testing,
178 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 erythrodysesthesia (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 erythrodysesthesia, 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

378 **ACKNOWLEDGEMENTS**

379 The authors thank the patients, their families, the investigators, and the teams who participated in this
380 trial, and Terri Binder for overseeing the independent image review. Editorial assistance was provided by
381 Nicolette Belletier of Oxford PharmaGenesis (funded by Eisai).

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 Lilly 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 Jeffrey 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

428 support and other from Lilly, grants, personal fees, non-financial support and other from Daiichi Sankyo,
429 during the conduct of the study.

430 **Corina Dutcus, M.D.:** Employee of Eisai Inc.

431 **Matthew Guo, Ph.D.:** Employee of Eisai Inc.

432 **Kenichi Saito, M.S.:** Employee of Eisai Inc.

433 **Silvija Kraljevic, M.D.:** Employee of Eisai Ltd.

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435 **Min Ren, Ph.D.:** Employee of Eisai Inc.

436 **Ann-Lii Cheng, M.D., Ph.D.:** Reports personal fees from BMS, personal fees from Ono, personal fees from
437 Novartis, personal fees from Bayer, personal fees from Merck, personal fees from MSD, during the
438 conduct of the study.
439

440 **Role of the funding source:**

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

445

446

447 The corresponding author (Masatoshi Kudo, MD, PhD) confirms that he had full access to all of the data
448 in the study and had final responsibility for the decision to submit for publication.

449

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538

539

540 **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)

541

542

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. (%) 95% CI Complete response Partial response Stable disease Durable stable disease lasting ≥23 weeks Progressive disease Unknown/not evaluable	194 (40.6) 36.2–45.0 10 (2.1) 184 (38.5) 159 (33.3) 84 (17.6) 79 (16.5) 46 (9.6)	59 (12.4) 9.4–15.4 4 (0.8) 55 (11.6) 219 (46.0) 90 (18.9) 152 (31.9) 46 (9.7)	5.01† (3.59–7.01) P<0.0001
Disease control rate‡ — no. (%) 95% CI	353 (73.8) 69.9–77.8	278 (58.4) 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. (%) 95% CI Complete response	90 (18.8) 15.3–22.3 2 (0.4)	31 (6.5) 4.3–8.7 1 (0.2)	3.34† (2.17–5.14) P<0.0001

Partial response	88 (18.4)	30 (6.3)	
Stable disease	258 (54.0)	250 (52.5)	
Durable stable disease lasting \geq 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 \ddagger — 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.

548 **Table 3.** Adverse Events.

	Lenvatinib		Sorafenib	
	(n = 476)		(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 $\geq 15\%$ of patients in either treatment group	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3

Palmar-plantar erythrodysesthesia	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

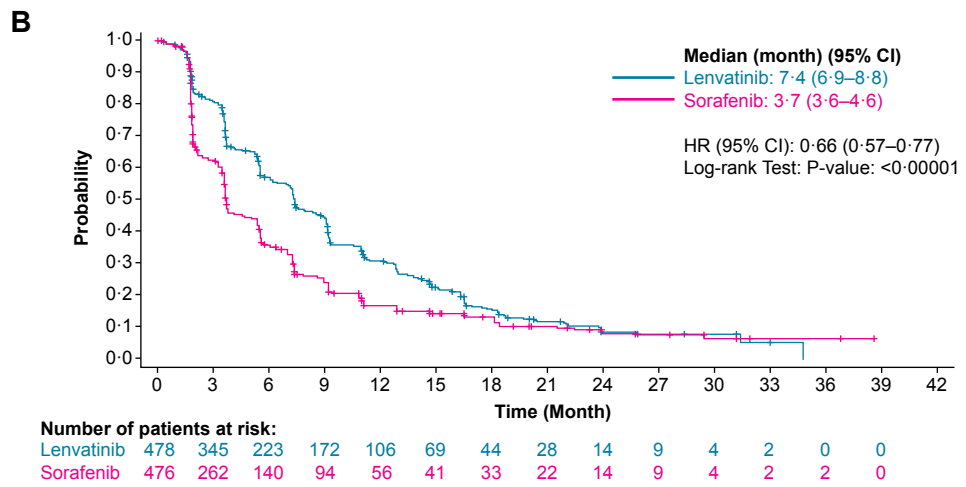
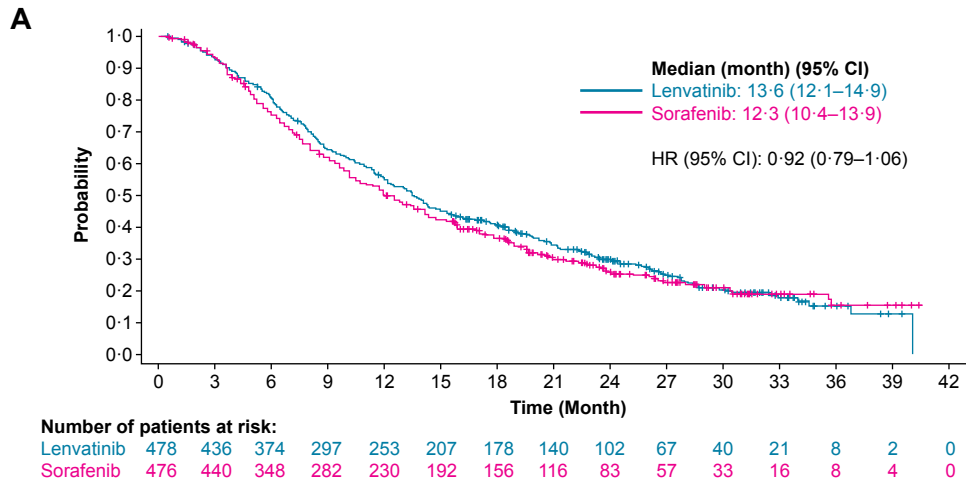


Figure 2A

A. Overall Survival

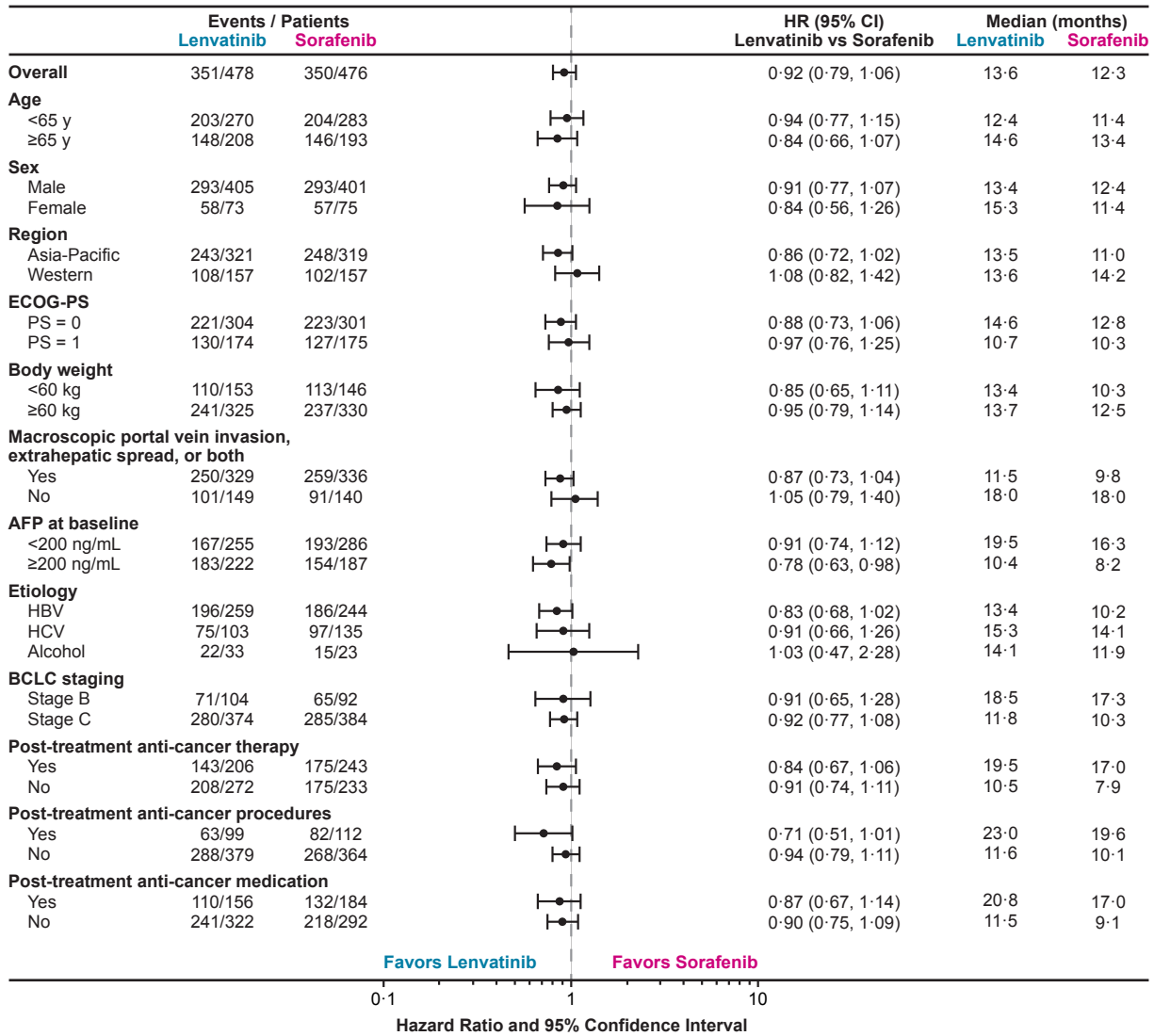


Figure 2B

B. Progression-free Survival

