Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): final results of a randomised phase 3 study

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Summary

Background The aim of the COSMIC-312 trial was to evaluate cabozantinib plus atezolizumab versus sorafenib in patients with previously untreated advanced hepatocellular carcinoma. In the initial analysis, cabozantinib plus atezolizumab significantly prolonged progression-free survival versus sorafenib. Here, we report the pre-planned final overall survival analysis and updated safety and efficacy results following longer follow-up.

Methods COSMIC-312 was an open-label, randomised, phase 3 study done across 178 centres in 32 countries. Patients aged 18 years or older with previously untreated advanced hepatocellular carcinoma were eligible. Patients must have had measurable disease per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1), and adequate marrow and organ function, including Child–Pugh class A liver function; those with fibrolamellar carcinoma, sarcomatoid hepatocellular carcinoma, or combined hepatocellular cholangiocarcinoma were ineligible. Patients were randomly assigned (2:1:1) using a web-based interactive response system to a combination of oral cabozantinib 40 mg once daily plus intravenous atezolizumab 1200 mg every 3 weeks, oral sorafenib 400 mg twice daily, or oral single-agent cabozantinib 60 mg once daily. Randomisation was stratified by disease aetiology, geographical region, and presence of extrahepatic disease or macrovascular invasion. Dual primary endpoints were for cabozantinib plus atezolizumab versus sorafenib: progression-free survival per RECIST 1.1, as assessed by a blinded independent radiology committee, in the first 372 randomly assigned patients (previously reported) and overall survival in all patients randomly assigned to cabozantinib plus atezolizumab or sorafenib. The secondary endpoint was progression-free survival in all patients randomly assigned to cabozantinib versus sorafenib. Outcomes in all randomly assigned patients, including final overall survival, are presented. Safety was assessed in all randomly assigned patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT03755791.

Findings Between Dec 7, 2018, and Aug 27, 2020, 432 patients were randomly assigned to combination treatment, 217 to sorafenib, and 188 to single-agent cabozantinib, and included in all efficacy analyses. 704 (84%) patients were male and 133 (16%) were female. 824 of these patients received at least one dose of study treatment and were included in the safety population. Median follow-up was 22·1 months (IQR 19·3–24·8). Median overall survival was 16·5 months (96% CI 14·5–18·7) for the combination treatment group and 15·5 months (12·2–20·0) for the sorafenib group (hazard ratio [HR] 0·98 [0·78–1·24]; stratified log-rank p=0·87). Median progression-free survival was 6·9 months (99% CI 5·7–8·2) for the combination treatment group, 4·3 months (2·9–6·1) for the sorafenib group, and 5·8 months (99% CI 5·4–8·2) for the single-agent cabozantinib group (HR 0·74 [0·56–0·97] for combination treatment *vs* sorafenib; HR 0·78 [99% CI 0·56–1·09], p=0·05, for single-agent cabozantinib *vs* sorafenib). Grade 3 or 4 adverse events occurred in 281 (66%) of 429 patients in the combination treatment group, 100 (48%) of 207 patients in the sorafenib group, and 108 (57%) of 188 patients in the single-agent cabozantinib group; the most common were hypertension (37 [9%] *vs* 17 [8%] *vs* 23 [12%]), palmar-plantar erythrodysaesthesia (36 [8%] *vs* 18 [9%] *vs* 16 [9%]), aspartate aminotransferase increased (42 [10%] *vs* eight [4%] *vs* 17 [9%]), and alanine aminotransferase increased (40 [9%] *vs* six [3%] *vs* 13 [7%]). Serious adverse events occurred in 223 (52%) patients in the combination treatment group, 84 (41%) patients in the sorafenib group, and 87 (46%) patients in the single agent cabozantinib group. Treatment-related deaths occurred in six (1%) patients in the combination treatment group (encephalopathy, hepatic failure, drug-induced liver injury, oesophageal varices haemorrhage, multiple organ dysfunction syndrome, and tumour lysis syndrome), one (<1%) in the sorafenib group (general physical health deterioration), and four (2%) in the single-agent cabozantinib group (asthenia, gastrointestinal haemorrhage, sepsis, and gastric perforation).

Interpretation First-line cabozantinib plus atezolizumab did not improve overall survival versus sorafenib in patients with advanced hepatocellular carcinoma. The progression-free survival benefit of the combination versus sorafenib was maintained, with no new safety signals.

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Introduction

Systemic hepatocellular carcinoma treatment has evolved from multikinase inhibitors, such as sorafenib and lenvatinib, to immunotherapy-based regimens with combination approaches.[1–5] Multikinase inhibitors have shown modest overall survival benefits,[6,7] whereas PD-1 and PD-L1 immune checkpoint inhibitors (ICIs) have demonstrated durable responses and survival benefits in a subset of patients.[3,8,9] However, single-agent ICIs have not improved overall survival in randomised studies.[3,9] In the past 6 years, combination regimens have been evaluated to improve the efficacy of PD-1 and PD-L1 ICIs. Atezolizumab plus bevacizumab and tremelimumab plus durvalumab according to the STRIDE regimen (single tremelimumab regular interval durvalumab) have shown enhanced antitumour activity,

Research in context

Evidence before this study

We searched PubMed for articles that were published between database conception and Sept 25, 2023, using the terms "tyrosine kinase inhibitor" OR "axitinib" OR "sorafenib" OR "lenvatinib" OR "cabozantinib" OR "regorafenib" AND "immune checkpoint inhibitor" OR "avelumab" OR "pembrolizumab" OR "durvalumab" OR "nivolumab" OR "atezolizumab" OR "tremelimumab" OR "tislelizumab" AND "hepatocellular carcinoma." The search was not limited to English language publications. The search yielded 618 articles and 34 were identified to report results from clinical trials. We then reviewed prospective clinical trials that evaluated combination therapy including an immune checkpoint inhibitor (ICI) in patients with hepatocellular carcinoma. Four studies were identified to report results of a tyrosine kinase inhibitor (TKI) plus an ICI in patient with hepatocellular carcinoma, including cabozantinib plus durvalumab (phase 1b CAMILLA), cabozantinib plus nivolumab with or without ipilimumab (phase 1/2 CheckMate 040), cabozantinib plus atezolizumab (phase 3 COSMIC-312), and lenvatinib plus pembrolizumab (phase 1b). Antitumour activity with the combination regimens was observed in each of these studies. In the primary analysis of COSMIC-312, cabozantinib plus atezolizumab significantly improved progression-free survival versus sorafenib in patients with previously untreated advanced hepatocellular carcinoma. Four articles reported outcomes from studies of atezolizumab plus bevacizumab; a phase 1b study reported improved progression-free survival with this combination versus atezolizumab alone, and three articles reported results from the phase 3 IMbrave150 study, which demonstrated the efficacy of first-line atezolizumab plus bevacizumab versus sorafenib, including significant improvements in progression-free survival and overall survival. Two studies reported antitumour activity with the dual ICI combinations durvalumab plus tremelimumab (phase 1/2) and nivolumab plus ipilimumab (phase 1/2 CheckMate 040). The remaining articles reported results from single-agent ICI or TKI studies or from health-economics outcomes, patient-reported outcomes, or biomarker studies.

Added value of this study

Multiple early phase studies have evaluated TKI and ICI combinations and shown efficacy in patients with hepatocellular carcinoma. COSMIC-312 randomised patients with previously untreated, advanced hepatocellular carcinoma to treatment with cabozantinib plus atezolizumab, sorafenib, or single-agent cabozantinib. To our knowledge, COSMIC-312 is the first phase 3 study to evaluate a TKI plus ICI regimen in this population. The primary analysis showed a progression-free survival benefit with cabozantinib plus atezolizumab versus sorafenib in the first 372 randomised patients while there was no difference in overall survival at interim analysis in the intention-to-treat population. In the updated analysis of COSMIC-312 reported here, cabozantinib did not demonstrate an overall survival benefit versus sorafenib in the intention-to-treat population, although subgroup analyses indicated a potential benefit with the combination in patients with hepatitis B aetiology and in patients with a baseline alpha-fetoprotein of 400 ng/mL or more. The progression-free survival benefit of the combination was maintained after longer follow up and in the larger intention-to-treat population. Activity of single-agent cabozantinib in first-line was also explored in this study; although not statistically significant, cabozantinib alone demonstrated a numerical increase in progression-free survival versus sorafenib with early separation of the Kaplan–Meier curve, suggesting that cabozantinib may contribute to the early disease control and prolonged progression-free survival observed with the combination.

Implications of all the available evidence

First-line cabozantinib plus atezolizumab demonstrated superiority over sorafenib by significantly improving progression-free survival in the primary analysis of COSMIC-312, and this improvement was also observed in the current analysis with longer follow-up. The lack of an overall survival benefit with the combination in the intention-to-treat population and the availability of other ICI-based combinations does not support cabozantinib plus atezolizumab in a general population of patients with advanced hepatocellular carcinoma. Subgroup analyses suggest a potential role for cabozantinib plus atezolizumab in selected patient populations, such as patients with hepatitis B aetiology, but further studies are needed to confirm these findings.

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as evidenced by improved survival versus sorafenib in previously untreated advanced hepatocellular carcinoma.[1,2]

Cabozantinib is a multikinase inhibitor approved for treatment of advanced hepatocellular carcinoma post sorafenib.[10] It inhibits VEGFR, MET, and the TAM family of kinases (TYRO3, AXL, and MER), which are involved in tumour angiogenesis, metastasis, survival, and immunosuppression.[11] By inhibiting these kinases, cabozantinib might promote an immune-permissive tumour microenvironment and enhance the activity of ICIs, which led to its investigation in combination regimens.[11] A phase 1b study of cabozantinib plus atezolizumab in various tumour types, including hepatocellular carcinoma, showed promising clinical activity.[12–14] In the phase 3 CheckMate 9ER study, cabozantinib plus nivolumab improved progression-free survival and overall survival versus sunitinib in patients with advanced renal cell carcinoma.[15] In the phase 1/2 CheckMate 040 study, cabozantinib plus nivolumab with or without ipilimumab also showed encouraging clinical activity in the cohort of patients with advanced hepatocellular carcinoma.[16]

COSMIC-312 (NCT03755791) is a phase 3 study that evaluated cabozantinib plus atezolizumab versus sorafenib in patients with previously untreated advanced hepatocellular carcinoma. The dual primary endpoints were progression-free survival in the first 372 patients randomly assigned to cabozantinib plus atezolizumab or sorafenib (the progression-free survival intention-to-treat [ITT] population) and overall survival in all patients randomly assigned to cabozantinib plus atezolizumab or sorafenib.[17] A single-agent cabozantinib group was included to assess the contribution of cabozantinib, and the secondary endpoint evaluated progression-free survival in all patients randomly assigned to sorafenib or single-agent cabozantinib.

The progression-free survival endpoint was met at the time of initial analysis after 257 events occurred in the progression-free survival ITT population (median follow-up 15·8 months [IQR 14·5–17·2]), with a median progression-free survival of 6·8 months (99% CI 5·6–8·3) for the combination treatment group versus 4·2 months (2·8–7·0) for the sorafenib group (hazard ratio [HR] 0·63 [0·44–0·91]; p=0·0012).[17] Concurrent interim analyses of overall survival and secondary progression-free survival were conducted in the ITT population (median follow-up 13·3 months [IQR 10·5–16·0]; n=837). Median overall survival was 15·4 months (96% CI 13·7–17·7) for the combination versus 15·5 months (12·1–not estimable) for sorafenib (HR 0·90 [0·69–1·18]; p=0·44), and median progression-free survival was 5·8 months (99% CI 5·4–8·2) with single-agent cabozantinib versus 4·3 months (2·9–6·1) with sorafenib (HR 0·71 [0·51–1·01]; p=0·011).[17]

Here, we present the pre-planned final overall survival analysis for cabozantinib plus atezolizumab versus sorafenib and pre-planned final progression-free survival analysis for single-agent cabozantinib versus sorafenib. Updated results after longer follow-up for other key endpoints, including progression-free survival for the combination versus sorafenib in the ITT population, pre-planned subgroup analyses, and safety are also reported.

Methods

Study design and participants

COSMIC-312 was an open-label, randomised, phase 3 study done across 178 centres in 32 countries. The study design and eligibility criteria have been previously described.[17] Briefly, eligible patients were aged 18 years or older with a confirmed diagnosis of hepatocellular carcinoma (pathological diagnosis or a radiological diagnosis in patients with cirrhosis per accepted guidelines[18,19]) and no previous systemic anticancer therapy for advanced disease, measurable disease per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) and not amenable to curative treatment or locoregional therapy, Barcelona Clinic Liver Cancer stage B or C disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ and marrow function, and preserved liver function (Child–Pugh class A, assessment for fibrosis or cirrhosis not required). Patients with fibrolamellar carcinoma, sarcomatoid hepatocellular carcinoma, or combined hepatocellular cholangiocarcinoma were excluded. Patients with gastric or oesophageal varices previously treated with endoscopic therapy per institutional standards were eligible, provided there was no recurrent bleeding for at least 6 months before randomisation. Endoscopy was not required. Documented hepatic encephalopathy or clinically meaningful ascites within 6 months before randomisation were not allowed. Sex data were collected by the investigator from patients' medical records or directly from the patient. Laboratory tests required within 14 days before randomisation were serum alpha-fetoprotein, haematology, serum chemistry, coagulation, urinalysis, urine chemistry, thyroid function test, and follicle-stimulating hormone; a negative serum or urine pregnancy test was required within 7 days before randomisation.

See Online for appendix

The study protocol (appendix pp 30–257) was approved by the institutional review board or ethics committee at each centre. The study was performed in compliance with Good Clinical Practice, the International Conference on Harmonisation, the Declaration of Helsinki, and local regulatory requirements. All patients provided written informed consent.

Randomisation and masking

Randomisation and masking were previously described.[17] Briefly, patients were randomly assigned (2:1:1) to open-label cabozantinib plus atezolizumab, sorafenib, or single-agent cabozantinib. Allocation concealment and randomisation were performed using web-based interactive response technology, which assigned patients a unique patient number. Trial centres enrolled patients,

and the web-based interactive response technology system randomly assigned them to treatment groups. An external clinical research organisation developed the randomisation schedule and uploaded it to a secure server of the interactive response technology vendor. Stratified randomisation was done using permuted blocks over 12 strata based on all combinations of three stratification factors: disease aetiology (hepatitis B virus [HBV] with or without hepatitis C virus [HCV] *vs* HCV without HBV *vs* non-viral), geographical region (Asia *vs* other), and presence of extrahepatic disease or macrovascular invasion (yes *vs* no). Patients, investigators, study centres, and the sponsor were not masked to study treatment.

Procedures

Patients received oral cabozantinib 40 mg once daily plus intravenous atezolizumab 1200 mg once every 3 weeks, oral sorafenib 400 mg twice daily, or oral single-agent cabozantinib 60 mg once daily. Patients were treated until lack of clinical benefit, as determined by the investigator, or unacceptable toxicity. Two dose reductions were permitted for cabozantinib and sorafenib, and all agents could be interrupted to manage adverse events, as described in the appendix (pp 6–7). Details regarding discontinuation of study treatment are provided in the appendix (p 5).

Tumour response was assessed by investigators and a blinded independent radiology committee (BIRC) according to RECIST 1.1 using CT or MRI every 6 weeks after randomisation up to week 49, then every 12 weeks thereafter. Safety and tolerability were monitored by investigators every 3 weeks during the treatment period. Incidence of treatment-emergent and immune-mediated adverse events, changes in laboratory parameters, vital signs, and ECOG performance status were recorded at safety assessments. Immune-mediated adverse events were adverse events of special interest and were individually reviewed to identify those requiring systemic immunosuppressive treatment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Post-treatment follow-up occurred at 30 days and 100 days after treatment discontinuation, and patients were followed up at least every 12 weeks for survival after the last safety assessment.

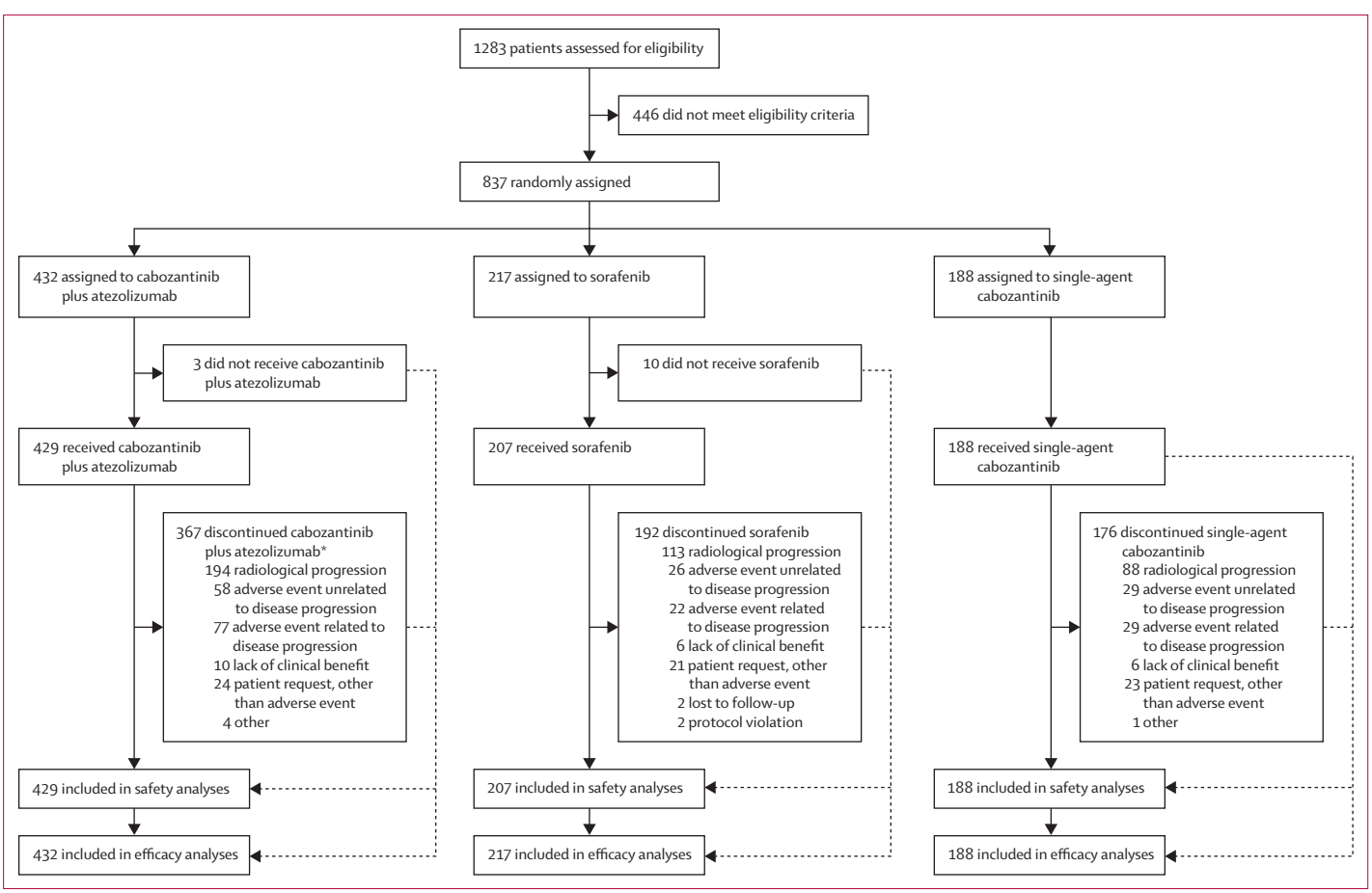


Figure 1: **Trial profile**
ITT=intention-to-treat. *Patients who discontinued both agents.

Outcomes

The dual primary endpoints were progression-free survival (defined as the time from randomisation to the earlier of disease progression per RECIST 1.1 assessed by the BIRC or death) in the first 372 patients randomly assigned to cabozantinib plus atezolizumab or sorafenib (progression-free survival ITT population) and overall survival (defined as the time from randomisation to death) in all patients randomly assigned to cabozantinib plus atezolizumab or sorafenib (ITT population).[17] Superiority of cabozantinib plus atezolizumab versus sorafenib would be declared if either primary endpoint was met.

	Cabozantinib plus atezolizumab group (n=432)	Sorafenib group (n=217)	Cabozantinib group (n=188)
Age, years	64 (58–70)	64 (57–71)	64 (58–71)
Sex			
Male	360 (83%)	186 (86%)	158 (84%)
Female	72 (17%)	31 (14%)	30 (16%)
Race*			
White	218 (50%)	113 (52%)	95 (51%)
Asian	127 (29%)	72 (33%)	64 (34%)
Other	36 (8%)	9 (4%)	17 (9%)
Not reported	52 (12%)	25 (12%)	12 (6%)
Geographical region			
Asia	120 (28%)	63 (29%)	58 (31%)
Other	312 (72%)	154 (71%)	130 (69%)
Aetiology			
HBV (with or without HCV)	127 (29%)	64 (29%)	59 (31%)
HCV (without HBV)	136 (31%)	67 (31%)	60 (32%)
Non-viral	169 (39%)	86 (40%)	69 (37%)
ECOG performance status			
0	276 (64%)	143 (66%)	126 (67%)
1	154 (36%)	74 (34%)	62 (33%)
2	1 (<1%)	0	0
Extrahepatic disease	232 (54%)	123 (57%)	103 (55%)
Macrovascular invasion	136 (31%)	61 (28%)	67 (36%)
Extrahepatic disease, macrovascular invasion, or both	298 (69%)	148 (68%)	128 (68%)
BCLC stage			
B	140 (32%)	72 (33%)	66 (35%)
C	292 (68%)	145 (67%)	122 (65%)
Alpha-fetoprotein			
<400 ng/mL	269 (62%)	152 (70%)	123 (65%)
≥400 ng/mL	163 (38%)	65 (30%)	65 (35%)
ALBI grade			
1	249 (58%)	123 (57%)	103 (55%)
2	182 (42%)	89 (41%)	82 (44%)
3	1 (<1%)	3 (1%)	2 (1%)

Data are median (IQR) or n (%). ALBI=albumin-bilirubin. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group. HBV=hepatitis B virus. HCV=hepatitis C virus. *More than one category could be self-reported by the patient.

Table 1: **Baseline demographics and clinical characteristics**

The secondary endpoint was progression-free survival per RECIST 1.1 assessed by the BIRC for single-agent cabozantinib versus sorafenib in all patients randomly assigned to these two groups. Progression-free survival per RECIST 1.1 assessed by the BIRC for cabozantinib plus atezolizumab versus sorafenib in the ITT population was a predefined exploratory endpoint. Additional predefined endpoints included overall survival for single-agent cabozantinib versus sorafenib, objective response rate (defined as the proportion of patients with a best overall response of complete or partial response [confirmed ≥28 days after initial documentation]), duration of response (defined as time from first documentation of a confirmed response to disease progression or death), and time to progression (defined as the time from randomisation until tumour progression), each of which have been previously reported and were assessed per RECIST 1.1 by BIRC and by investigator in the progression-free survival ITT and ITT populations. Safety was evaluated in the safety population (all patients who received at least one dose of study treatment). In this report, all efficacy endpoints are reported in the ITT population.

Statistical analysis

Details of the statistical plan for analysis of primary progression-free survival, interim analyses of overall survival and secondary progression-free survival, and analyses of additional endpoints have previously been published.[17] The total sample size was planned to be 740 patients randomly assigned in a 2:1:1 ratio (370 to combination treatment, 185 to sorafenib, and 185 to single-agent cabozantinib). However, enrolment commenced under a randomisation ratio of 6:3:1 according to the original protocol design. As a result, the needed enrolment of 185 patients in the single-agent cabozantinib group was not expected to be reached. Therefore, to ensure complete enrolment in each group, the total global enrolment was extended to accrue a total of approximately 840 patients. A modified Bonferroni procedure, gatekeeping technique, and the fallback method were used to control inflation of type I error associated with testing of multiple primary endpoints and a secondary efficacy endpoint. The study-wise two-sided alpha value of 5% was unequally allocated between the dual primary endpoints (1% for progression-free survival and 4% for overall survival). The secondary progression-free survival endpoint was tested at 1% using alpha reallocated from the primary progression-free survival analysis. Type I error associated with interim analyses were controlled using Lan–DeMets O'Brien–Fleming alpha-spending function. Actual critical p values for each overall survival analysis depended on the true number of events observed at each analysis.

For the primary endpoint of overall survival, it was estimated that 368 events in 555 patients randomly

assigned to the combination treatment or sorafenib would provide 90% power to detect an HR of 0·69 at an alpha value of 4% using a two-sided stratified log-rank test, with a critical p value of 0·03728. Two interim analyses of overall survival were planned at the 33% and 66% information fractions; however, only one interim analysis was performed at the 74·2% information fraction. Secondary progression-free survival was to be tested after the primary progression-free survival endpoint was met. It was estimated that 283 events in 370 patients randomly assigned to single-agent cabozantinib or sorafenib would provide 85% power to detect a clinically significant HR of 0·65 at a two-sided alpha value of 1%, with a critical p value of 0·00866. Power and sample size estimates were calculated using EAST (version 6.5) by Cytel software.

Median progression-free survival and overall survival and associated CIs were estimated using the Kaplan–Meier method. A Cox proportional hazards model estimated stratified HRs and associated CIs; the Cox proportional hazards model was stratified using the same stratification factors recorded in the interactive-response technology and used for randomisation. The proportional hazards assumption for progression-free survival and overall survival were evaluated by visual inspection of log–log plots. For the primary and secondary endpoints, CIs were reported using a 1 minus alpha confidence level (99% for the primary and secondary progression-free survival endpoints and 96% for overall survival); for the exploratory overall survival analysis of single-agent cabozantinib versus sorafenib, 95% CIs were reported. The 95% CI used for objective response rate was calculated using exact methods; patients without a baseline or post-baseline tumour assessment were not evaluable for radiographic response. The primary endpoints were also assessed in pre-specified subgroups based on the stratification factors (disease aetiology, geographical region, and presence of extrahepatic disease or macrovascular invasion) and prespecified exploratory subgroups of other baseline characteristics and variables, including age, sex, race, ethnicity, ECOG performance status, Barcelona Clinic Liver Cancer (BCLC) stage, baseline alpha-fetoprotein level, Child–Pugh classification, albumin-bilirubin grade, and presence of cirrhosis; 95% CIs were considered descriptive. Disease control was a post-hoc analysis defined as the proportion of patients with a best overall response of complete or partial response or stable disease per RECIST 1.1. All analyses were done with SAS (version 9.4). An independent data monitoring committee oversaw safety and tolerability.

This trial is registered with ClinicalTrials.gov, NCT03755791.

Role of the funding source

The funders provided cabozantinib and sorafenib, and were involved in the study design, data collection, data analysis and interpretation, manuscript preparation and approval, and provided financial support for medical writing. Atezolizumab was provided by Roche.

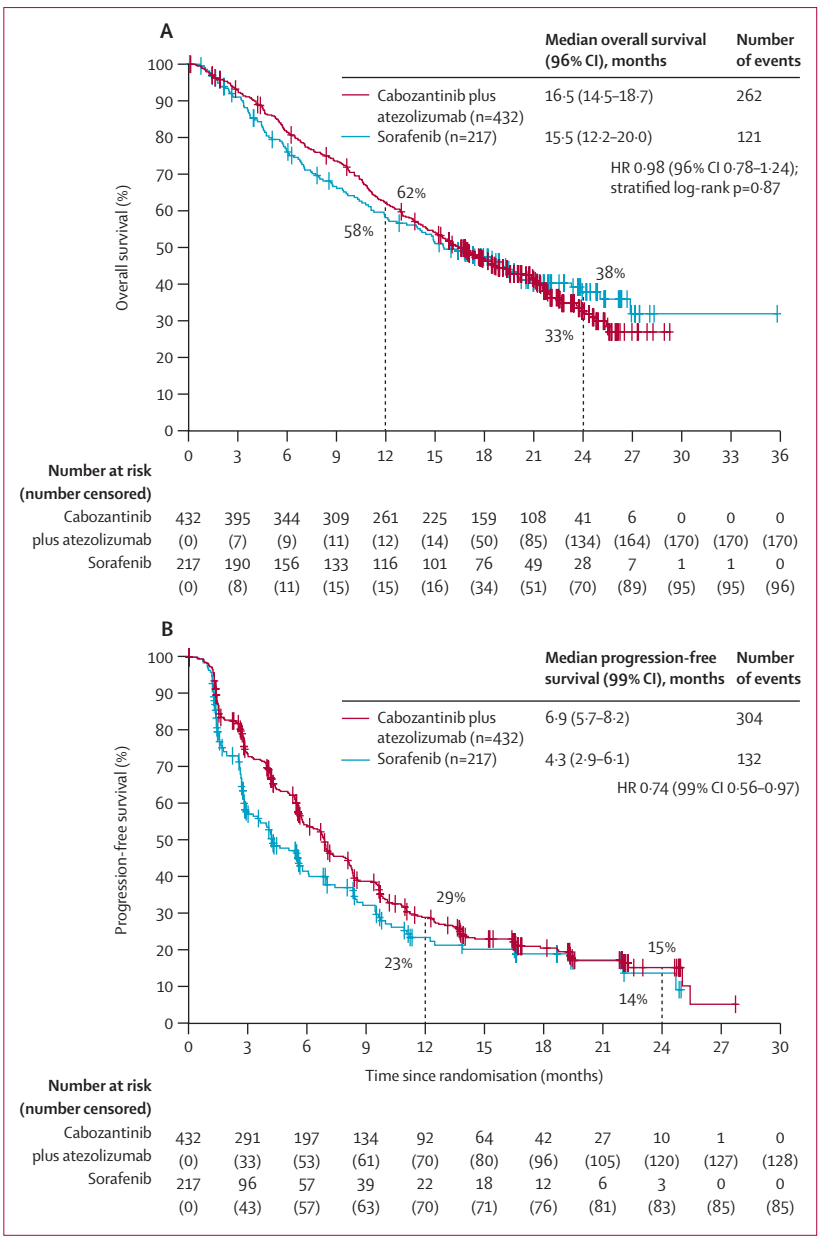


Figure 2: **Overall survival (A) and progression-free survival (B) per RECIST 1.1 by BIRC for cabozantinib plus atezolizumab versus sorafenib (ITT population)**
The HR was calculated from the stratified Cox regression model. Crosses denote censored patients. BIRC=blinded independent radiology committee. HR=hazard ratio. ITT=intention-to-treat. RECIST 1.1=Response Evaluation Criteria in Solid Tumours version 1.1.

Results

Between Dec 7, 2018, and Aug 27, 2020, 837 patients were enrolled and randomly assigned to cabozantinib plus atezolizumab (n=432), sorafenib (n=217), or single-agent cabozantinib (n=188) and included in ITT analyses. Reasons for over-enrolment of the combination and

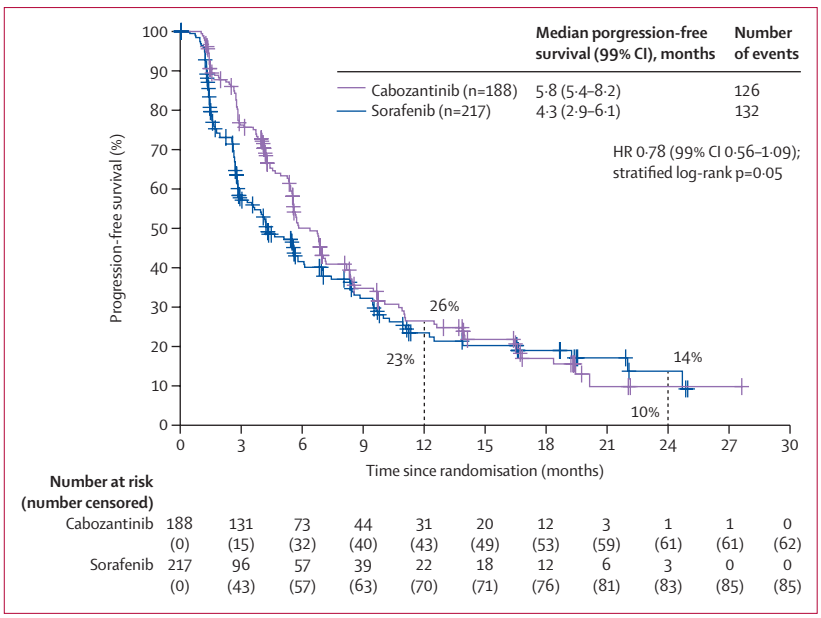


Figure 3: **Progression-free survival per RECIST 1.1 by BIRC for single-agent cabozantinib versus sorafenib (ITT population)**

The HR was calculated from the stratified Cox regression model. Crosses denote censored patients. BIRC=blinded independent radiology committee. HR=hazard ratio. ITT=intention-to-treat. RECIST 1.1=Response Evaluation Criteria in Solid Tumours version 1.1.

sorafenib groups have been previously described.[17] Of the patients who were randomly assigned, 824 received at least one dose of study treatment and were included in the safety population (figure 1). 640 (76%) of 837 patients overall had a histological or cytological diagnosis of hepatocellular carcinoma and 338 (40%) had a diagnosis by imaging per accepted guidelines (patients could have been diagnosed using both methods).[18,19] Key baseline characteristics for the ITT population are reported in table 1. 250 (30%) patients had an hepatocellular carcinoma aetiology of HBV (with or without HCV), 263 (31%) had HCV (without HBV), and 324 (39%) had non-viral hepatocellular carcinoma. Extrahepatic disease or macrovascular invasion was present in 574 (69%) of patients, and 596 (71%) were from regions other than Asia.

At data cutoff on Nov 30, 2021, for the final overall survival analysis, median follow-up was 22·1 months (IQR 19·3–24·8) in the ITT population, and 89 (11%) of 837 patients remained on any study treatment: 62 (14%) of 432 patients in the combination treatment group, 15 (7%) of 217 patients in the sorafenib group, and 12 (6%) of 188 patients in the single-agent cabozantinib group. Overall, the most common reason for treatment discontinuation was radiographic progression in 395 (47%) of 837 patients (figure 1).

Subsequent systemic anticancer therapy was used in 112 (26%) of 432 patients who received the combination, 92 (42%) of 217 who received sorafenib, and 66 (35%) of 188 who received single-agent cabozantinib (appendix p 8). Multikinase inhibitors were the most common subsequent therapy (80 [19%] patients in the combination treatment group, 56 [26%] in the sorafenib group, and 44 [23%] in the single-agent cabozantinib group). Subsequent ICIs were used by 26 (6%), 47 (22%), and 31 (16%) patients, respectively. The median time from randomisation to first subsequent systemic therapy was 8·3 months (IQR 5·8–12·6) for the combination treatment group, 4·5 months (2·1–7·9) for the sorafenib group, and 7·5 months (4·8–10·2) for the single-agent cabozantinib group.

For the final analysis of overall survival, median overall survival was 16·5 months (96% CI 14·5–18·7) in the combination treatment group and 15·5 months (12·2–20·0) in the sorafenib group (HR 0·98 [0·78–1·24]; stratified log-rank p=0·87; figure 2A). Median progression-free survival was 6·9 months (99% CI 5·7–8·2) in the combination treatment group and 4·3 months (2·9–6·1) in the sorafenib group (HR 0·74 [0·56–0·97]; figure 2B).

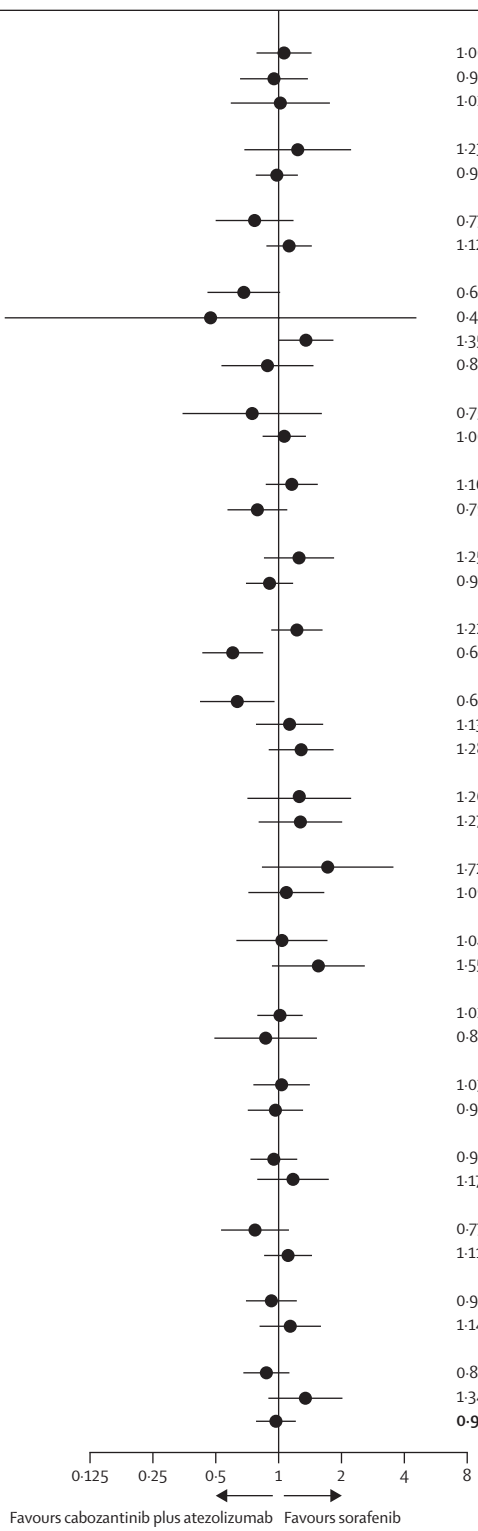
For the final secondary progression-free survival analysis, median progression-free survival was 5·8 months (99% CI 5·4–8·2) for the single-agent cabozantinib group versus 4·3 months (2·9–6·1) in the sorafenib group (HR 0·78 [0·56–1·09]; p=0·05; figure 3). Median overall survival was 14·5 months (95% CI 12·5–17·5) in the single-agent cabozantinib group versus 15·5 months (12·7–20·0) in the sorafenib group (HR 1·11 [0·85–1·43]). A log–log survival plot did not support the assumption of proportional hazards for overall survival of the combination treatment versus sorafenib or progression-free survival for single-agent cabozantinib versus sorafenib.

Tumour response data are reported in the appendix (p 9). The objective response rate was 13·0% (95% CI 9·9–16·5) for the combination treatment group, 4·6% (2·2–8·3) for the sorafenib group, and 7·4% (4·1–12·2) for the single-agent cabozantinib group. Disease control was achieved in 337 (78%) of 432 patients with combination treatment, 140 (65%) of 217 with sorafenib, and 157 (84%) of 188 with single-agent cabozantinib.

Figure 4 summarises overall survival and progression-free survival subgroup analyses for combination treatment versus sorafenib. Patients with HBV (with or without HCV) aetiology appeared to have longer overall survival and progression-free survival with combination treatment versus sorafenib. In this subgroup, median overall survival was 20·4 months (95% CI 16·9–24·2) with combination treatment versus 14·9 months (7·0–19·1) with sorafenib (HR 0·63 [0·42–0·95]); median progression-free survival was 6·8 months (95% CI 5·6–7·2) versus 2·7 months (1·6–4·1; HR 0·52 [0·37–0·75]; appendix p 28); and the objective response rate was 17·3% (95% CI 11·2–25·0) versus 0·0% (0·0–5·6). In the HCV (without HBV) subgroup, overall survival and progression-free survival results were consistent with the overall study population, and objective response rates were 12·9% (95% CI 7·7–19·8) for the combination treatment group and 3·0% (0·4–10·5) for the sorafenib group.

A

	Events/patients		HR (95% CI)
	Cabozantinib plus atezolizumab group	Sorafenib group	
Age, years			
<65	140/234	60/112	1·06 (0·78–1·44)
65 to <75	84/142	41/75	0·95 (0·65–1·38)
≥75	38/56	20/30	1·02 (0·59–1·76)
Sex			
Female	43/72	15/31	1·23 (0·69–2·22)
Male	219/360	106/186	0·98 (0·78–1·24)
Region			
Asia	59/120	33/63	0·77 (0·50–1·18)
Other	203/312	88/154	1·12 (0·87–1·44)
Race			
Asian	61/127	40/72	0·68 (0·46–1·02)
Black or African American	4/8	1/1	0·47 (0·05–4·57)
White	145/217	59/111	1·35 (1·00–1·83)
Other or not reported	52/80	21/33	0·88 (0·53–1·47)
Ethnicity			
Hispanic or Latino	24/42	9/15	0·75 (0·35–1·61)
Not Hispanic or Latino	212/352	99/183	1·06 (0·84–1·35)
ECOG performance status*			
0	155/276	67/143	1·16 (0·87–1·54)
1	105/154	54/74	0·79 (0·57–1·10)
BCLC stage			
Category B	85/140	37/72	1·25 (0·85–1·84)
Category C	177/292	84/145	0·90 (0·70–1·17)
Baseline alpha-fetoprotein, ng/mL			
<400	151/269	71/152	1·22 (0·92–1·62)
≥400	111/163	50/65	0·60 (0·43–0·84)
Disease aetiology			
HBV (with or without HCV)	65/127	38/64	0·63 (0·42–0·95)
HCV (without HBV)	91/136	41/67	1·13 (0·78–1·63)
Non-viral	106/169	42/86	1·28 (0·90–1·83)
Non-viral aetiology: alcoholism			
Yes	39/59	17/33	1·26 (0·71–2·22)
No	66/109	25/52	1·27 (0·80–2·02)
Non-viral aetiology: NASH or NAFLD			
Yes	28/48	10/22	1·72 (0·83–3·55)
No	75/113	31/59	1·09 (0·72–1·65)
Non-viral aetiology: other			
Yes	50/76	22/40	1·04 (0·63–1·71)
No	56/93	20/46	1·55 (0·93–2·59)
Child–Pugh classification			
A5	190/338	91/178	1·02 (0·79–1·30)
A6	61/78	15/20	0·87 (0·49–1·53)
ALBI grade			
Grade 1	127/249	58/123	1·03 (0·76–1·41)
Grade 2	134/182	60/89	0·97 (0·71–1·31)
Cirrhosis			
Yes	180/291	85/142	0·95 (0·73–1·23)
No	81/139	36/75	1·17 (0·79–1·74)
Macrovascular invasion			
Yes	88/136	40/61	0·77 (0·53–1·12)
No	174/296	81/156	1·11 (0·85–1·44)
Extrahepatic disease			
Yes	149/232	73/123	0·92 (0·70–1·22)
No	113/200	48/94	1·14 (0·81–1·59)
Extrahepatic disease or macrovascular invasion			
Yes	185/298	88/148	0·87 (0·68–1·13)
No	77/134	33/69	1·34 (0·89–2·02)
Overall	**262/432**	**121/217**	**0·98 (0·78–1·24)†**



(Figure 4 continues on next page)

B

	Events/patients		HR (95% CI)
	Cabozantinib plus atezolizumab group	Sorafenib group	
Age, years			
<65	168/234	69/112	0·81 (0·61–1·07)
65 to <75	100/142	46/75	0·70 (0·49–1·00)
≥75	36/56	17/30	0·91 (0·51–1·63)
Sex			
Female	55/72	16/31	1·18 (0·67–2·06)
Male	249/360	116/186	0·71 (0·57–0·89)
Region			
Asia	82/120	41/63	0·54 (0·37–0·79)
Other	222/312	91/154	0·89 (0·69–1·13)
Race			
Asian	87/127	45/72	0·56 (0·39–0·81)
Black or African American	4/8	0/1	NE (NE–NE)
White	150/217	67/111	0·91 (0·68–1·22)
Other or not reported	63/80	20/33	0·85 (0·51–1·41)
Ethnicity			
Hispanic or Latino	29/42	10/15	0·58 (0·28–1·19)
Not Hispanic or Latino	242/352	109/183	0·79 (0·63–1·00)
ECOG performance status*			
0	195/276	86/143	0·74 (0·57–0·95)
1	107/154	46/74	0·85 (0·60–1·20)
BCLC stage			
Category B	104/140	41/72	1·03 (0·72–1·49)
Category C	200/292	91/145	0·66 (0·52–0·85)
Baseline alpha-fetoprotein, ng/mL			
<400	186/269	89/152	0·85 (0·66–1·10)
≥400	118/163	43/65	0·54 (0·38–0·77)
Disease aetiology			
HBV (with or without HCV)	94/127	45/64	0·52 (0·37–0·75)
HCV (without HBV)	89/136	39/67	0·78 (0·53–1·13)
Non-viral	121/169	48/86	0·99 (0·71–1·39)
Non-viral aetiology: alcoholism			
Yes	42/59	18/33	0·89 (0·51–1·55)
No	78/109	30/52	1·03 (0·67–1·57)
Non-viral aetiology: NASH or NAFLD			
Yes	33/48	11/22	1·32 (0·67–2·63)
No	85/113	33/59	1·00 (0·67–1·49)
Non-viral aetiology: other			
Yes	57/76	26/40	0·90 (0·56–1·44)
No	64/93	22/46	1·10 (0·68–1·79)
Child–Pugh classification			
A5	234/338	106/178	0·79 (0·63–0·99)
A6	60/78	12/20	0·96 (0·52–1·79)
ALBI grade			
Grade 1	165/249	66/123	0·87 (0·65–1·16)
Grade 2	138/182	63/89	0·65 (0·48–0·88)
Cirrhosis			
Yes	200/291	87/142	0·74 (0·58–0·96)
No	102/139	45/75	0·83 (0·59–1·19)
Macrovascular invasion			
Yes	94/136	43/61	0·51 (0·36–0·74)
No	210/296	89/156	0·90 (0·70–1·15)
Extrahepatic disease			
Yes	170/232	83/123	0·77 (0·59–1·00)
No	134/200	49/94	0·82 (0·59–1·14)
Extrahepatic disease or macrovascular invasion			
Yes	209/298	98/148	0·65 (0·51–0·83)
No	95/134	34/69	1·11 (0·75–1·65)
Overall	**304/432**	**132/217**	**0·74 (0·56–0·97)‡**

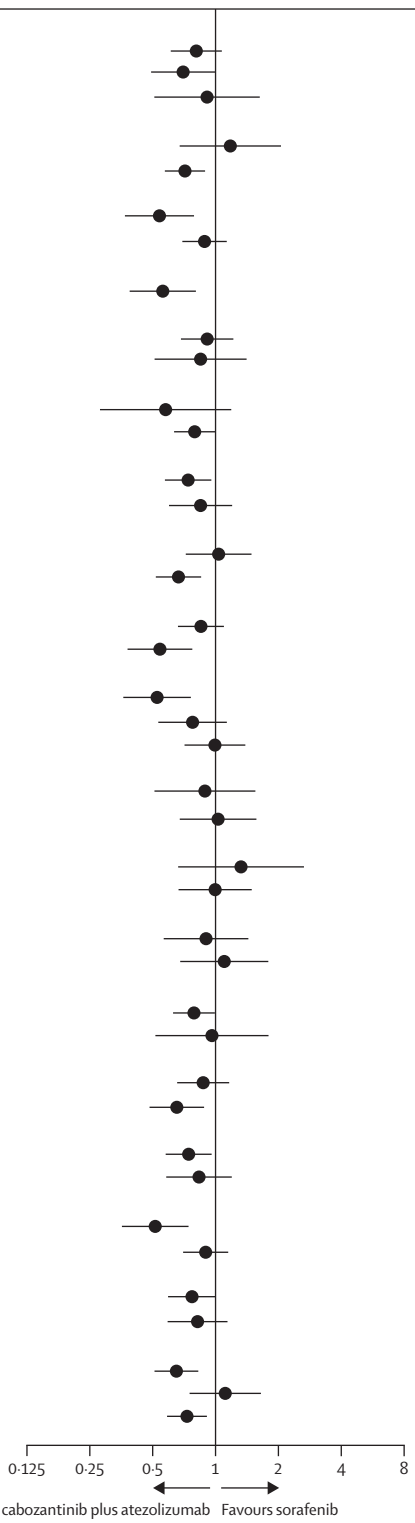


Figure 4: **Overall survival (A) and progression-free survival (B) per RECIST 1.1 by BIRC for cabozantinib plus atezolizumab versus sorafenib in prespecified subgroups (ITT population)**
ALBI=albumin-bilirubin. BCLC=Barcelona Clinic Liver Cancer. BIRC=blinded independent radiology committee. ECOG=Eastern Cooperative Oncology Group. HBV=hepatitis B virus. HCV=hepatitis C virus. HR=hazard ratio. ITT=intention-to-treat. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. NE=not estimable. RECIST 1.1=Response Evaluation Criteria in Solid Tumours version 1.1. *One patient had an ECOG performance status of 2 and one patient was missing in the cabozantinib plus atezolizumab group. †Stratified 96% CI. ‡Stratified 99% CI.

Overall survival and progression-free survival also appeared to be longer with combination treatment versus sorafenib in patients with an alpha-fetoprotein concentration of 400 ng/mL or higher (figure 4; appendix p 29), and progression-free survival appeared to be longer with combination treatment in subgroups defined by Asian race, BCLC stage C, and presence of extrahepatic disease or macrovascular invasion.

The median daily dose of oral study treatment was 23·2 mg (IQR 17·2–32·7) for cabozantinib in the combination treatment group, 614·0 mg (444·8–790·4) for sorafenib, and 38·7 mg (24·8–50·4) for single-agent cabozantinib (table 2). The median number of atezolizumab infusions received in the combination treatment group was 10 (IQR 4–20). Treatment-emergent adverse events led to dose reductions in 268 (62%) of 429 patients in the combination treatment group, 90 (43%) of 207 patients in the sorafenib group, and 124 (66%) of 188 patients in the single-agent cabozantinib group. More patients required one dose reduction versus two reductions (table 2).

Treatment-emergent adverse events occurred in 99% or more of patients in each group (table 2). Grade 3 or 4 treatment-emergent adverse events occurred in 281 (66%) of 429 patients in the combination treatment group, 100 (48%) of 207 patients in the sorafenib group, and 108 (57%) of 188 patients in the single-agent cabozantinib group. The most common grade 3 or 4 treatment-emergent adverse events were hypertension (37 [9%] *vs* 17 [8%] *vs* 23 [12%]), palmar-plantar erythrodysaesthesia (36 [8%] *vs* 18 [9%] *vs* 16 [9%]), aspartate aminotransferase (AST) increased (42 [10%] *vs* eight [4%] *vs* 17 [9%]), and alanine aminotransferase (ALT) increased (40 [9%] *vs* six [3%] *vs* 13 [7%]; appendix p 10). Treatment-emergent adverse events led to discontinuation of any treatment component in 161 (38%) patients in the combination treatment group, 48 (23%) patients in the sorafenib group, and 58 (31%) patients in the single-agent cabozantinib group. Common treatment-emergent adverse events that led to discontinuation were AST increased (18 [4%] *vs* 0 *vs* one [1%]) and asthenia (13 [3%] *vs* seven [3%] *vs* four [2%]). Serious treatment-emergent adverse events occurred in 223 (52%) patients in the combination treatment group, 84 (41%) patients in the sorafenib group, and 87 (46%) patients in the single-agent cabozantinib group.

Treatment-related adverse events occurred in 399 (93%) of 429 patients in the combination treatment group, 188 (91%) of 207 patients in the sorafenib group, and 178 (95%) of 188 patients in the single-agent cabozantinib group. Grade 3 or 4 treatment-related adverse events occurred in 238 (55%) patients in the combination treatment group, 70 (34%) patients in the sorafenib group, and 102 (54%) patients in the single-agent cabozantinib group (appendix p 22). In the combination treatment group, 68 (16%) discontinued any treatment component due to a treatment-related adverse event and 32 (7%) discontinued both components; 15 (7%) patients discontinued sorafenib and 20 (11%) patients discontinued single-agent cabozantinib due to treatment-related adverse events. From the time of the first dose of study treatment until 30 days after the last dose, treatment-related deaths occurred in six (1%) patients in the combination treatment group (encephalopathy, hepatic failure, drug-induced liver injury, oesophageal varices haemorrhage, multiple organ dysfunction syndrome, and tumour lysis syndrome), one (<1%) patient in the sorafenib group (general physical health deterioration), and four (2%) patients in the single-agent cabozantinib group (asthenia, gastrointestinal haemorrhage, sepsis, and gastric perforation). There were two (<1%) additional treatment-related deaths in the combination treatment group up to 100 days after the last dose (rapid progression of hepatocellular carcinoma and deterioration of general physical health).

Immune-mediated adverse events that led to initiation of immunosuppressive treatment occurred in 31 (7%) of 429 patients in the combination treatment group and two (1%) of 207 patients in the sorafenib group. The most common immune-mediated adverse events in the combination treatment group were hepatitis (diagnosis

	Cabozantinib plus atezolizumab group (n=429)	Sorafenib group (n=207)	Cabozantinib group (n=188)
Duration of exposure, months	6·4 (2·6–13·5)*	4·2 (1·6–8·5)	6·3 (3·4–10·6)
Daily dose for cabozantinib or sorafenib, mg	23·2 (17·2–32·7)	614·0 (444·8–790·4)	38·7 (24·8–50·4)
Number of atezolizumab infusions received	10 (4–20)	NA	NA
Treatment-emergent adverse event			
Any grade	428 (>99%)	205 (99%)	187 (99%)
Grade 3–4	281 (66%)	100 (48%)	108 (57%)
Grade 5	59 (14%)	25 (12%)	38 (20%)
Serious adverse event	223 (52%)	84 (41%)	87 (46%)
Treatment-emergent adverse events leading to dose reduction	268 (62%)†	90 (43%)	124 (66%)
One reduction	206 (48%)	70 (34%)	64 (34%)
Two reductions	61 (14%)	21 (10%)	62 (33%)
Three reductions	0	1 (<1%)	3 (2%)
Treatment-emergent adverse events leading to dose interruption	362 (84%)	108 (52%)	142 (76%)
Cabozantinib or sorafenib interrupted	345 (80%)	111 (54%)	145 (77%)
Atezolizumab interrupted	202 (47%)	NA	NA
Treatment-emergent adverse events leading to discontinuation	161 (38%)‡	48 (23%)	58 (31%)
Immune-mediated adverse events leading to immunosuppressive treatment	31 (7%)	2 (1%)	0

Data are median (IQR) or n (%). NA=not applicable. *Duration of exposure on both agents. †Cabozantinib only because dose reductions were not allowed for atezolizumab. ‡Discontinuation of either agent.

Table 2: **Safety summary (safety population)**

and laboratory test abnormalities in 19 [4%] patients and laboratory test abnormalities in 13 [3%]) and pneumonitis in seven [2%] patients). The events in the sorafenib group were pneumonitis (n=1), hyperthyroidism (n=1), hypothyroidism (n=1), and rash (n=1).

Discussion

COSMIC-312 showed superiority of cabozantinib plus atezolizumab over sorafenib by meeting the primary progression-free survival endpoint at the initial analysis of the first 372 patients randomly assigned to the combination or sorafenib.[17] In this final analysis, the progression-free survival benefit with the combination treatment was maintained after longer follow-up in the larger ITT population. Nonetheless, the progression-free survival improvement did not translate into an overall survival benefit in the overall population at the interim analysis[17] or at the final analysis reported here.

The basis for the lack of alignment of progression-free survival with overall survival is unclear in our study. Multiple oncology trials have shown a poor correlation between progression-free survival and overall survival, and one hypothesis is that overall survival is negatively affected by decreased treatment exposure due to toxicity.[20] In COSMIC-312, a higher proportion of patients had treatment-emergent adverse events leading to dose reduction, dose interruption, or treatment discontinuation with the combination treatment than with sorafenib. Furthermore, median overall survival for sorafenib was 15·5 months, which is the longest observed in a phase 3 study for sorafenib. A higher proportion of patients in the sorafenib group received subsequent systemic therapies than in the combination treatment group, including ICIs, after disease progression. The reasons for the relatively low use of subsequent therapy in the combination treatment group in our study compared with other first-line trials might be multifactorial.[1,21] Patients might not have been fit to receive subsequent therapy, or treatments might not have been available in certain geographical regions. In addition, a higher proportion of patients remained on study treatment at data cutoff in the combination treatment group than in the sorafenib group, and subsequent therapy data were not collected for some patients who withdrew consent after progression. Use of subsequent therapy, together with increased availability of ICIs for subsequent therapy at the time of COSMIC-312 compared with when older trials were conducted might have contributed to a relatively long overall survival for sorafenib and confounded overall survival results.[1,2,6,7,22]

Other phase 3 studies have evaluated VEGF pathway agents plus ICIs in hepatocellular carcinoma. In IMbrave150, atezolizumab plus bevacizumab significantly prolonged overall survival versus sorafenib (median 19·2 months [95% CI 17·0–23·7] *vs* 13·4 months [11·4–16·9]; HR 0·66 [0·52–0·85], descriptive p<0·001);[22] a significant overall survival benefit was also observed with camrelizumab plus rivoceranib in CARES-310,[5] and in ORIENT-32, a study of sintilimab plus bevacizumab biosimilar in patients in China with HBV aetiology.[23] However, in LEAP-002, lenvatinib plus pembrolizumab did not significantly prolong overall survival versus lenvatinib (median 21·2 months [95% CI 19·0–23·6] *vs* 19·0 months [17·2–21·7]; HR 0·840 [0·708–0·997], p=0·0227).[21] Of note, the proportion of patients with HBV aetiology was lower in COSMIC-312 (30%) versus IMbrave150 (48%),[22] LEAP-002 (48%),[21] and CARES-310 (75%).[5] HBV has been associated with favourable survival outcomes with immunotherapy regimens versus other aetiologies,[2,24] including in COSMIC-312, IMbrave150,[22] and LEAP-002,[21] although there are confounding variables including post-progression factors that might affect these analyses.[25,26]

In subgroup analyses of COSMIC-312, patients with HBV (with or without HCV) appeared to consistently derive greater benefit with the combination across the endpoints of overall survival, progression-free survival, and objective response rate than other aetiologies evaluated. There was no overall survival or progression-free survival benefit with the combination treatment in patients with non-viral aetiology, who made up 39% of the COSMIC-312 study population, and overall survival outcomes appeared to favour sorafenib with a relatively prolonged median overall survival of 20·0 months in this subgroup of patients (appendix p 28). Similar results were observed with immunotherapy-based regimens in CheckMate 459,[9] KEYNOTE-240,[3] and IMbrave150,[2] suggesting that immunotherapy might be less effective in patients with non-viral aetiologies,[27] or that there might be differences in downstream therapy or other post-progression prognostic covariates that track with non-viral aetiology.[26] Given the proportion of patients with non-viral aetiology in COSMIC-312 (39%), the overall survival outcomes with sorafenib in this subgroup probably contributed to the relatively prolonged median overall survival in the overall sorafenib group. In the subgroup of patients with an alpha-fetoprotein concentration of 400 ng/mL or higher, combination treatment also appeared to be favoured versus sorafenib for overall survival and progression-free survival. Hepatocellular carcinoma is angiogenic, and high alpha-fetoprotein concentrations have been associated with increased VEGF expression and immunosuppression.[28] Subgroup analyses of progression-free survival in the current analysis were generally consistent with the previous analysis; progression-free survival subgroups not reported in the previous analysis that appeared to favour the combination treatment included Asian race and BCLC stage C.

COSMIC-312 included a single-agent cabozantinib group to inform the contribution of cabozantinib to the combination and evaluate the efficacy of first-line cabozantinib. Single-agent cabozantinib showed a numerical progression-free survival benefit versus

sorafenib at the interim and final analyses, and although not significant, this shows activity of cabozantinib as a single agent in the first-line setting. There was early separation of the Kaplan–Meier curves for single-agent cabozantinib versus sorafenib during the first 12 months, suggesting that cabozantinib might contribute to early disease control and prolonged progression-free survival observed with the combination.

Safety data from this longer follow-up were consistent with the initial analysis and the known safety profiles of the study drugs.[17] The most common grade 3 or 4 treatment-emergent adverse events with the combination were increased AST, increased ALT, hypertension, and palmar-plantar erythrodysaesthesia. In the single-agent cabozantinib group, patients received 60 mg daily (the approved dose for hepatocellular carcinoma treatment).[10] The recommended dose of cabozantinib 40 mg daily plus atezolizumab 1200 mg every 3 weeks was determined based on its acceptable safety profile in a dose-escalation study in advanced solid tumours.[29] In COSMIC-312, the proportion of patients who had two dose reductions of cabozantinib was higher in the single-agent group (60 mg starting dose) than in the combination treatment group (40 mg starting dose; 33% *vs* 14%), suggesting that the starting dose for the combination was appropriate from a safety perspective in this patient population.

There are important limitations of this study. COSMIC-312 was affected by the COVID-19 pandemic, which limited collection and reporting of quality-of-life data and affected study initiation in mainland China, resulting in relatively low enrolment of Asian and HBV-positive patients, who make up a large proportion of the population of patients with hepatocellular carcinoma.[30] Although Child–Pugh class A disease was an eligibility requirement, cirrhosis and fibrosis assessment was not required. In addition, subgroup analyses (except those for stratification factors) were limited by their post-hoc nature and relatively small sample sizes. The open-label design might have introduced bias, although BIRC-assessed efficacy outcomes should have mitigated some of this risk. Furthermore, the constant HR assumption underlying Cox regression was not met for the comparison of overall survival between the combination and sorafenib and the comparison of progression-free survival between cabozantinib and sorafenib. The reported HRs are an average of time-varying HRs and could depend on the duration of the study's follow-up.[31] Non-adherence to assigned treatment and missing outcome data could lead to bias using ITT estimates if censoring is related to missing values or treatment. Instrumental variable analysis[32] and G-estimation[33] can be used to provide causal effect estimates of the treatment under certain assumptions.

Cabozantinib plus atezolizumab showed superiority over sorafenib as first-line therapy in patients with advanced hepatocellular carcinoma based on significantly improved progression-free survival, a dual primary endpoint.[17] Although a significant overall survival benefit was not observed in the overall population, pre-planned subgroup results indicate the combination might favour certain patient populations, including patients with HBV aetiology, and this might inform future studies. After additional follow-up, no new safety concerns emerged, and the benefit of the combination on progression-free survival and disease control was maintained.

Contributors

TY, AK, A-LC, SQ, AXZ, FB, SM, RKK, and LR contributed to design of the study. TY, AK, A-LC, SQ, AXZ, SLC, TM, WS, VB, GV, EG, IB, JDGR, B-YR, TM, PM, RKK, and LR provided study materials or patients. All authors had full access to and verified all data, and were responsible for collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, and were accountable for all aspects of the work. TY had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

TY reports a consulting or advisory role with Bristol Myers Squibb, MSD, AstraZeneca, Eisai, and Ipsen; research funding from Bristol Myers Squibb, MSD, Exelixis, Eli Lilly, AstraZeneca, Roche, and Taiho; travel, accommodations, or expenses from Roche and Bayer; stock and other ownership interests in Moderna; and other financial or non-financial interests with Taiho and Ipsen. AK reports honoraria from Exelixis, Bristol Myers Squibb, Merck, Roche, and Eisai; a consulting or advisory role with Exelixis, Bristol Myers Squibb, Merck, Roche, and Eisai; research funding from Exelixis, Roche, Merck, Bristol Myers Squibb, AdaptImmune, and Tvardi; and travel, accommodations, or expenses from Exelixis, Bristol Myers Squibb, Merck, Roche, and Eisai. A-LC reports honoraria from Merck Sharp Dohme, Bristol Myers Squibb, Bayer Healthcare, AstraZeneca, Genentech/Roche, Ipsen Innovation, BeiGene, and Exelixis; a consulting or advisory role with Merck Sharp Dohme, Bristol Myers Squibb, Bayer Healthcare, AstraZeneca, Genentech/Roche, Ipsen Innovation, BeiGene, and Exelixis; and participation on a data safety monitoring board or advisory board for Abbisko Therapeutics Co. AXZ reports employment and leadership with I-Mab Biopharma; a consulting or advisory role with Lilly, Sanofi, Merck, Exelixis, Roche, Eisai, and Bayer; and stock and other ownership interests in I-Mab Biopharma. SLC reports honoraria from MSD, AstraZeneca, Eisai, Roche, and Bristol Myers Squibb; a consulting or advisory role with MSD, AstraZeneca, Eisai, Roche, and Bayer; and travel, accommodations, or expenses from Ipsen and Novartis. VB reports honoraria from AstraZeneca, Roche, Novartis, Eisai, Bristol Myers Squibb, and Pfizer; and participation on a data safety monitoring board or advisory board with AstraZeneca, Roche, Novartis, Eisai, Bristol Myers Squibb, and Pfizer. GV reports travel, accommodations, and expenses from Roche, Bayer, Terumo, and Ipsen; and participation on a data safety monitoring board or advisory board with Roche, Eisai, and AstraZeneca. EG reports participation on a data safety monitoring board or advisory board with Gilead, Janssen, and Aligos. IB reports honoraria from Roche, Servier, Ipsen, Eisai, and AstraZeneca; travel, accommodations, and expenses with Ipsen and Roche; and participation on a data safety monitoring board or advisory board with AstraZeneca. PM reports a consulting or advisory role with Roche, AstraZeneca, MSD, Bayer, and Ipsen; research funding from Ipsen; travel, accommodations, and expenses from Ipsen, Roche, MSD, and AstraZeneca; and participation on a data safety monitoring board or advisory board with Roche, MSD, Bayer, Ipsen, and AstraZeneca. FB reports employment and stock or other ownership interests with Ipsen. SM reports employment with Exelixis; and stock and other ownership interests in Exelixis, Amgen, and Fibrogen. ZW reports employment and stock and other ownership interests with Exelixis. DC reports employment and stock and other ownership interests with Exelixis. RKK reports a consulting or advisory role with Agios (paid to institution), AstraZeneca (paid to institution), Exelixis (paid to institution), Ipsen (paid to institution), Merck (paid to institution),

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Data sharing

Data collected during the study, including individual participant data, will not be made available.

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