Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial

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Summary

Background Cabozantinib has shown clinical activity in combination with checkpoint inhibitors in solid tumours. The COSMIC-312 trial assessed cabozantinib plus atezolizumab versus sorafenib as first-line systemic treatment for advanced hepatocellular carcinoma.

Methods COSMIC-312 is an open-label, randomised, phase 3 trial that enrolled patients aged 18 years or older with advanced hepatocellular carcinoma not amenable to curative or locoregional therapy and previously untreated with systemic anticancer therapy at 178 centres in 32 countries. Patients with fibrolamellar carcinoma, sarcomatoid hepatocellular carcinoma, or combined hepatocellular cholangiocarcinoma were not eligible. Tumours involving major blood vessels, including the main portal vein, were permitted. Patients were required to have measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), Barcelona Clinic Liver Cancer stage B or C disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ and marrow function, and Child-Pugh class A. Previous resection, tumour ablation, radiotherapy, or arterial chemotherapy was allowed if more than 28 days before randomisation. Patients were randomly assigned (2:1:1) via a web-based interactive response system to cabozantinib 40 mg orally once daily plus atezolizumab 1200 mg intravenously every 3 weeks, sorafenib 400 mg orally twice daily, or single-agent cabozantinib 60 mg orally once daily. Randomisation was stratified by disease aetiology, geographical region, and presence of extrahepatic disease or macrovascular invasion. Dual primary endpoints were progression-free survival per RECIST 1.1 as assessed by a blinded independent radiology committee in the first 372 patients randomly assigned to the combination treatment of cabozantinib plus atezolizumab or sorafenib (progression-free survival intention-to-treat [ITT] population), and overall survival in all patients randomly assigned to cabozantinib plus atezolizumab or sorafenib (ITT population). Final progression-free survival and concurrent interim overall survival analyses are presented. This trial is registered with ClinicalTrials.gov, NCT03755791.

Findings Analyses at data cut-off (March 8, 2021) included the first 837 patients randomly assigned between Dec 7, 2018, and Aug 27, 2020, to combination treatment of cabozantinib plus atezolizumab (n=432), sorafenib (n=217), or single-agent cabozantinib (n=188). Median follow-up was 15·8 months (IQR 14·5–17·2) in the progression-free survival ITT population and 13·3 months (10·5–16·0) in the ITT population. Median progression-free survival was 6·8 months (99% CI 5·6–8·3) in the combination treatment group versus 4·2 months (2·8–7·0) in the sorafenib group (hazard ratio [HR] 0·63, 99% CI 0·44–0·91, p=0·0012). Median overall survival (interim analysis) was 15·4 months (96% CI 13·7–17·7) in the combination treatment group versus 15·5 months (12·1–not estimable) in the sorafenib group (HR 0·90, 96% CI 0·69–1·18; p=0·44). The most common grade 3 or 4 adverse events were alanine aminotransferase increase (38 [9%] of 429 patients in the combination treatment group vs six [3%] of 207 in the sorafenib group vs 12 [6%] of 188 in the single-agent cabozantinib group), hypertension (37 [9%] vs 17 [8%] vs 23 [12%]), aspartate aminotransferase increase (37 [9%] vs eight [4%] vs 18 [10%]), and palmar-plantar erythrodysaesthesia (35 [8%] vs 17 [8%] vs 16 [9%]); serious treatment-related adverse events occurred in 78 (18%) patients in the combination treatment group, 16 (8%) patients in the sorafenib group, and 24 (13%) in the single-agent cabozantinib group. Treatment-related grade 5 events 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 one (<1%) patient in the single-agent cabozantinib group (gastrointestinal haemorrhage).

Interpretation Cabozantinib plus atezolizumab might be a treatment option for select patients with advanced hepatocellular carcinoma, but additional studies are needed.

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Introduction

Hepatocellular carcinoma accounts for approximately 90% of cases of liver cancer worldwide.[1] As hepatocellular carcinoma is an angiogenic tumour, vascular endothelial growth factor receptor (VEGFR)-targeting tyrosine kinase inhibitors (TKIs) have been developed, improving survival outcomes in various studies.[1] Sorafenib was the first TKI approved as a first-line treatment, on the basis of improved overall survival versus placebo in the phase 3 SHARP trial.[2]

Subsequently, immune checkpoint inhibitors have shown clinical benefit in patients with hepatocellular carcinoma. In the first-line setting, immune checkpoint inhibitor monotherapies can elicit durable tumour responses in a subset of patients with advanced hepatocellular carcinoma,[3,4] but have not improved overall survival in global, randomised trials.[4] Several immune checkpoint inhibitor combination strategies have been studied for their potential to augment an antitumour immune response.[5–10]

Hepatocellular carcinoma is associated with immune tolerance, which is potentially related to overexpression of cytokine pathways in the tumour microenvironment, resulting in the recruitment of immunosuppressive cells and the inhibition of cells associated with immune response. VEGF overexpression can inhibit T-cell function, increase myeloid-derived suppressor cells and regulatory

Research in context

Evidence before this study

We searched PubMed for articles published between database conception and Jan 20, 2022, with 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 478 results. Studies were reviewed if they reported results of clinical trials in patients with hepatocellular carcinoma treated with a combination regimen that included an immune checkpoint inhibitor. Observational studies and studies that did not assess an immune checkpoint inhibitor combination therapy were excluded from review. 37 results were identified as possibly reporting clinical trial results. Further investigation yielded two clinical trials reporting results of a tyrosine kinase inhibitor (TKI) plus an immune checkpoint inhibitor in patients with hepatocellular carcinoma. One was a phase 1b study (VEGF Liver 100) evaluating avelumab plus axitinib in patients with advanced hepatocellular carcinoma and showed modest clinical activity. The second trial was a phase 1b study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma, and showed promising antitumour activity with the combination treatment. Six articles reported outcomes assessing the combination of atezolizumab plus bevacizumab, including a phase 1b study in which patients with unresectable hepatocellular carcinoma were randomly assigned to first-line atezolizumab plus bevacizumab or to atezolizumab monotherapy; progression-free survival was longer with the combination treatment. This study was followed by a phase 3 study (IMbrave150) evaluating atezolizumab plus bevacizumab versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma; the combination therapy improved overall survival and progression-free survival. Multiple articles also reported promising clinical activity with immune checkpoint inhibitor combinations, including nivolumab plus ipilimumab and tremelimumab plus durvalumab. The remaining articles reported results from clinical trials of immune checkpoint inhibitors or TKIs as single-agent treatments. We did not find any phase 3 studies assessing a TKI plus immune checkpoint inhibitor in patients with hepatocellular carcinoma. The existing evidence shows promising activity with TKI–immune checkpoint inhibitor combination therapies with manageable safety profiles, but no reported phase 3 trials.

Added value of this study

TKI and immune checkpoint inhibitor combinations have shown efficacy in several solid tumour types; however, this treatment strategy has not been assessed in phase 3 trials in patients with hepatocellular carcinoma. To our knowledge, COSMIC-312 is the first phase 3 trial to assess a TKI and immune checkpoint inhibitor combination in this setting. In COSMIC-312, cabozantinib plus atezolizumab significantly improved the primary endpoint of progression-free survival versus sorafenib in patients with hepatocellular carcinoma not amenable to curative treatment or locoregional therapy and previously untreated with systemic anticancer therapy. A statistically significant benefit was not shown for overall survival.

Implications of all the available evidence

The improvement in progression-free survival with cabozantinib plus atezolizumab in this study shows that the combination confers clinical benefit for patients with advanced hepatocellular carcinoma previously untreated with systemic anticancer therapy. The absence of a benefit in overall survival, along with the availability of atezolizumab in combination with bevacizumab, indicates the need for additional studies to determine if cabozantinib plus atezolizumab would be an appropriate first-line treatment option in select patient populations.

T cells, and inhibit the differentiation of dendritic cells, limiting antitumour immune responses.[11,12] Combining immune checkpoint inhibitors with VEGF pathway inhibitors and other immune-modulating pathways might promote an immune-permissive environment and enhance immune checkpoint inhibitor response. The combination of atezolizumab (anti-PD-L1 antibody) plus bevacizumab (anti-VEGFA antibody) improved progression-free survival and overall survival versus sorafenib in patients with unresectable hepatocellular carcinoma in the phase 3 IMbrave150 study.[5]

Cabozantinib is a TKI that shows immunomodulatory activity. Cabozantinib targets multiple receptor tyrosine kinases involved in tumour pathogenesis, including the proangiogenic growth factors VEGFR and MET and the TAM family of kinases (TYRO3, AXL, MER), which contribute to immunosuppression in the tumour microenvironment.[13,14] Cabozantinib is approved for patients with hepatocellular carcinoma after previous sorafenib treatment on the basis of improved overall survival and progression-free survival versus placebo in the phase 3 CELESTIAL trial.[15] Cabozantinib in combination with immune checkpoint inhibitors has shown promising clinical activity in several solid tumours, including improved progression-free survival and overall survival versus sunitinib as first-line treatment for renal cell carcinoma in the phase 3 CheckMate 9ER study.[16–18] A phase 1b trial of cabozantinib plus atezolizumab showed clinical activity in several different solid tumours and determined the recommended dose of the combination for further development.[17–19]

COSMIC-312 is a phase 3 trial assessing the efficacy and safety of cabozantinib plus atezolizumab versus sorafenib for patients with advanced hepatocellular carcinoma in the first-line setting. Single-agent cabozantinib is also being investigated to assess the contribution of cabozantinib. Reported here are the final analysis of progression-free survival and the interim analysis of overall survival for cabozantinib plus atezolizumab versus sorafenib, and the interim analysis of secondary progression-free survival for single-agent cabozantinib versus sorafenib.

Methods
Study design and participants
COSMIC-312 is an open-label, randomised, phase 3 trial done at 178 sites in 32 countries (appendix pp 2–4). Eligible patients were aged 18 years or older and had a pathological diagnosis of hepatocellular carcinoma or a radiological diagnosis of hepatocellular carcinoma in patients with cirrhosis per accepted guidelines.[20,21] Patients with fibrolamellar carcinoma, sarcomatoid hepatocellular carcinoma, or combined hepatocellular cholangiocarcinoma were not eligible. Patients had disease not amenable to curative treatment or loco-regional therapy and previously untreated with systemic anticancer therapy. Tumours involving major blood vessels, including the main portal vein, were permitted. Patients were required to have measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), 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); these were determined by the investigator. Patients with hepatitis B virus infection were eligible if hepatitis B virus DNA was less than 500 IU/mL on antiviral therapy. Patients with active hepatitis C virus infection were eligible provided liver function met eligibility criteria and their disease was managed per local institutional practice (antiviral treatment was allowed). Patients with gastric or oesophageal varices previously treated with endoscopic therapy according to institutional standards were eligible, provided there was no recurrent bleeding for at least 6 months before randomisation. Endoscopy was not required. 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.

Patients were excluded if they had received previous systemic anticancer therapy for advanced hepatocellular carcinoma, although previous resection, tumour ablation, radiotherapy, or arterial chemotherapy was allowed if more than 28 days before randomisation. Patients with documented hepatic encephalopathy or clinically meaningful ascites within 6 months before randomisation were also excluded. Additional eligibility criteria are listed in the appendix (pp 5–9).

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

Randomisation and masking
The initial study design randomly assigned patients in a 6:3:1 ratio to open-label cabozantinib plus atezolizumab, sorafenib, or single-agent cabozantinib. The single-agent cabozantinib group was included to explore the safety and activity of single-agent cabozantinib. On the basis of regulatory feedback, an approved protocol amendment (on April 12, 2019) modified progression-free survival for single-agent cabozantinib versus sorafenib from an exploratory to an inferential secondary endpoint; the randomisation scheme was adjusted to 2:1:1 to ensure adequate enrolment of 185 patients into the single-agent cabozantinib group (appendix p 13).

Patients were assigned a unique patient number using web-based interactive response technology. Stratified randomisation was done using permuted blocks over 12 strata based on all combinations of three stratification factors: disease aetiology (hepatitis B virus with or without hepatitis C virus vs hepatitis C virus without hepatitis B virus vs non-viral hepatocellular carcinoma), geographical region (Asia vs other), and presence of extrahepatic disease or macrovascular invasion (yes vs no). 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. Patients, investigators, study centres, and the sponsor were not masked to study treatment. Access to efficacy data was limited within the sponsor, and these data were only summarised at prespecified timepoints. Investigators and a blinded independent radiology committee (BIRC) performed radiographical assessments.

Procedures
Patients received cabozantinib tablets 40 mg orally once daily plus atezolizumab 1200 mg intravenously every 3 weeks, sorafenib 400 mg orally twice daily, or single-agent cabozantinib tablets 60 mg orally once daily. Treatment was continued if patients had ongoing clinical benefit determined by the investigator or until unacceptable toxicity, need for subsequent systemic anticancer therapy, or other protocol-defined reasons for discontinuation (appendix p 10).

Safety and tolerability were monitored by an independent data monitoring committee and assessed by the incidence of treatment-emergent and immune-mediated adverse events, changes in laboratory parameters, vital signs, and ECOG performance status. To manage adverse events, dose modification and supportive care were allowed (appendix pp 11–12); two dose reductions were permitted for cabozantinib to manage adverse events—from 40 mg daily to 20 mg daily then 20 mg every other day for the combination treatment group, and from 60 mg daily to 40 mg daily then 20 mg daily for the single-agent group. Sorafenib could be reduced from 400 mg twice daily to 400 mg daily, then 400 mg every other day. Dose reduction was not allowed for atezolizumab. Cabozantinib, sorafenib, and atezolizumab could be interrupted to manage adverse events.

Tumour assessments were done by CT or MRI every 6 weeks after randomisation until week 49, then every 12 weeks thereafter. Images were evaluated by investigators and BIRC according to RECIST 1.1. Safety assessments were done by investigators every 3 weeks. After discontinuation of study treatment, post-treatment follow-up occurred at 30 days and 100 days. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Immune-mediated adverse events were adverse events of special interest and were individually reviewed to identify those requiring systemic immunosuppressive treatment. Patients were followed up at least every 12 weeks for survival after the last safety assessment.

Two additional protocol amendments (on April 9, 2020, and May 14, 2021) introduced study-related measures for the COVID-19 pandemic, including guidance for managing COVID-19 infections and administration of vaccines. These accommodations were temporary as conditions allowed. The amendments were formulated by the Sponsor Study Execution Team and reviewed and approved by the Sponsor COVID Taskforce.

Outcomes
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 the combination treatment of cabozantinib plus atezolizumab or sorafenib. The ITT population included all patients randomly assigned to any treatment. Progression-free survival was defined as time from randomisation to the earlier of disease progression per RECIST 1.1 assessed by BIRC or death. Overall survival was defined as time from randomisation to death. Superiority of cabozantinib plus atezolizumab versus sorafenib would be declared if either primary endpoint was met.

The secondary endpoint was progression-free survival per RECIST 1.1 assessed by BIRC for single-agent cabozantinib versus sorafenib. Additional predefined endpoints included objective response rate, duration of response, time to progression, and safety. Objective response rate was 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 was defined as time from first documentation of a confirmed response to disease progression or death; time to progression was defined as the time from randomisation until tumour progression; each was assessed per RECIST 1.1 by BIRC and by investigator in the progression-free survival ITT and ITT populations. Safety and tolerability were assessed in all patients who received at least one dose of study treatment (safety population).

Other additional predefined endpoints included progression-free survival and proportion of patients with an objective response assessed by BIRC using modified RECIST,[22] pharmacokinetics of cabozantinib, immunogenicity of atezolizumab given in combination with cabozantinib, change in serum alpha-fetoprotein, biomarker analyses, health-related quality of life per the EuroQol Health questionnaire instrument (EQ-5D-5L), and health-care resource utilisation; analyses of these endpoints are ongoing.

Statistical analysis

It was estimated that 740 patients (370 in the combination cabozantinib plus atezolizumab group, 185 in the sorafenib group, and 185 in the single-agent cabozantinib group) would provide adequate power to assess both dual primary endpoints and secondary progression-free survival (appendix p 13). Because of the change of secondary progression-free survival from an exploratory to inferential endpoint, the sample size was increased to 840 patients to ensure that 185 patients were assigned to single-agent cabozantinib. The study used a modified Bonferroni procedure and parallel gatekeeping method to protect against inflation of type I error associated with testing of multiple endpoints and repeated testing at interim and final analyses. Initially, the two-sided alpha was allocated at 1% for primary progression-free survival and 4% for overall survival. Testing of secondary progression-free survival used alpha reallocated from the primary progression-free survival analysis.

For primary progression-free survival, it was estimated that 257 events would provide 90% power for a two-sided log-rank test with a 1% level of significance to detect a hypothesised hazard ratio (HR) of 0·6, with a critical p value of 0·01. Assuming an exponential distribution of progression-free survival, this corresponds to a 67% increase in median progression-free survival from 3·6 months anticipated with sorafenib to 6·0 months with the combination treatment. The total sample size required to evaluate progression-free survival (372 patients) was smaller than needed to evaluate overall survival. To minimise potential bias introduced by possible over-representation of early progressions among the planned number of events and to reliably estimate medians, the primary analysis of progression-free survival was prespecified to occur in the first 372 patients randomised (the progression-free survival ITT population). For the final overall survival analysis, it was estimated that 368 events in 555 patients randomly assigned to the combination treatment or sorafenib would provide a power of 90% to detect an HR of 0·69 at an alpha of 4%; this corresponds to a 45% increase in median overall survival from 12·3 months anticipated with sorafenib to 17·8 months with the combination treatment. For secondary progression-free survival, it was estimated that 283 events in 370 patients randomly assigned to single-agent cabozantinib or sorafenib would provide 85% power for a two-sided log-rank test with a 1% significance level to detect a clinically significant HR of 0·65, corresponding to a 53% increase in median progression-free survival from 3·6 months anticipated with sorafenib to 5·5 months with single-agent cabozantinib. If the null hypothesis was rejected for primary progression-free survival, then concurrent interim analyses of overall survival and secondary progression-free survival were planned with estimated information fractions of 33% (approximately 121 events) and 67% (approximately 190 events), respectively. Type I error associated with interim analyses

was controlled using Lan-DeMets O'Brien-Fleming alpha-spending functions. A second interim analysis of overall survival was planned at the 66% information fraction (approximately 243 events). A group sequential design was prespecified to test overall survival and secondary progression-free survival: if the null hypothesis was rejected for both primary and secondary progression-free survival endpoints, the 1% alpha for progression-free survival would be reallocated to overall survival to be tested at the 5% level. Based on the timing of the primary progression-free survival events, interim analyses of overall survival occurred at the 74·2% information fraction (273 events) and secondary progression-free survival occurred at the 84·5% information fraction (239 events), resulting in critical p values of 0·014 for overall survival at nominal alpha of 4% and 0·0045 for secondary progression-free survival at nominal alpha of 1%. Power and sample size estimates were calculated using EAST version 6.5 by Cytel software.

Median duration of progression-free survival and overall survival and associated CIs were estimated using the Kaplan-Meier method. Stratified HRs and associated CIs were estimated using a Cox proportional hazards model. The proportional hazards assumption for progression-free survival was evaluated by visual inspection of log-log plots. Prespecified subgroup analyses based on stratification factors (disease aetiology, geographical region, and presence of extrahepatic disease or macrovascular invasion) were done for the primary endpoints; CIs for subgroup analyses are considered descriptive. Three sensitivity analyses were done for primary progression-free survival to evaluate the effect of inconsistent tumour assessment intervals between groups, investigator assessment of progression, and missing tumour assessments. Only the sensitivity analysis of progression-free survival by investigator is reported. Analyses of progression-free survival and overall survival at 6 months and 12 months were post hoc.

Additional efficacy endpoints were analysed in the progression-free survival ITT and ITT populations using an appropriate two-sided statistical test without adjustment for multiplicity, with results considered supportive of the primary endpoint analyses. For objective response by BIRC and investigator assessment, two-sided CIs for the point estimate were calculated using exact methods. Waterfall plots displaying maximum percent reduction or minimum increase since baseline in sum of diameter of tumour target lesions per BIRC were generated in patients with tumour assessment at baseline and at least one post-baseline assessment. Duration of response was analysed using the Kaplan-Meier method. 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. Time to progression was analysed using the Kaplan-Meier method.

Presented here is the analysis of primary progression-free survival, the first of two planned interim analyses of
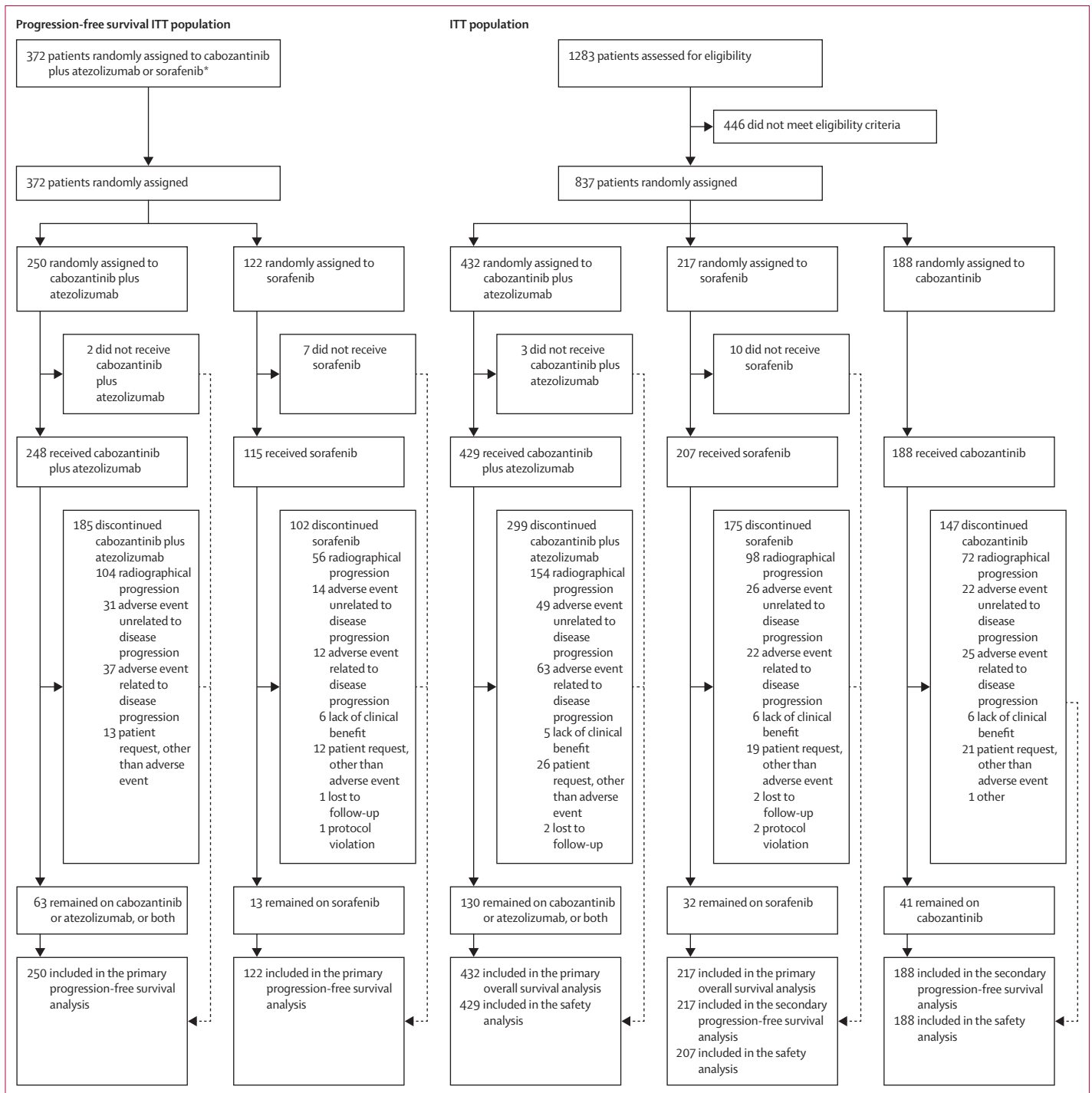
Figure 1: Trial profile

ITT=intention-to-treat. *The progression-free survival ITT population included the first 372 patients randomly assigned to cabozantinib plus atezolizumab or sorafenib.

overall survival, and a planned interim analysis of secondary progression-free survival.

All analyses were done with SAS version 9.4. This trial is registered with ClinicalTrials.gov, NCT03755791.

Role of the funding source

The funders provided cabozantinib and sorafenib, and participated in study design, data collection, and data analysis and interpretation. Roche provided atezolizumab. The funders were involved in trial design, manuscript

preparation, and approval for publication. The funders provided financial support for medical writing.

Results

Between Dec 7, 2018, and Aug 27, 2020, 837 patients were randomly assigned to receive the combination treatment of cabozantinib plus atezolizumab, sorafenib,

or single-agent cabozantinib (figure 1). Data reported here are as of March 8, 2021, when the first planned analyses were triggered by the prespecified number of progression-free survival events in the progression-free survival ITT population. The ITT population was over-enrolled in the combination treatment group (n=432) and the sorafenib group (n=217) as a result of the protocol

	Progression-free survival ITT population		ITT population		
	Cabozantinib plus atezolizumab (n=250)	Sorafenib (n=122)	Cabozantinib plus atezolizumab (n=432)	Sorafenib (n=217)	Cabozantinib (n=188)
Age, years	65 (58–70)	64 (58–71)	64 (58–70)	64 (57–71)	64 (58–71)
Sex					
Male	214 (86%)	107 (88%)	360 (83%)	186 (86%)	158 (84%)
Female	36 (14%)	15 (12%)	72 (17%)	31 (14%)	30 (16%)
Geographical region					
Asia*	63 (25%)	33 (27%)	120 (28%)	63 (29%)	58 (31%)
Other regions	187 (75%)	89 (73%)	312 (72%)	154 (71%)	130 (69%)
Europe	108 (43%)	45 (37%)	151 (35%)	67 (31%)	58 (31%)
Latin America	14 (6%)	8 (7%)	39 (9%)	17 (8%)	21 (11%)
North America	18 (7%)	7 (6%)	24 (6%)	15 (7%)	18 (10%)
Australia or New Zealand	11 (4%)	8 (7%)	24 (6%)	14 (6%)	6 (3%)
Other†	36 (14%)	21 (17%)	74 (17%)	41 (19%)	27 (14%)
Race‡					
Asian	67 (27%)	36 (30%)	127 (29%)	72 (33%)	64 (34%)
Other	136 (54%)	67 (55%)	253 (59%)	120 (55%)	112 (60%)
Native American or Alaska Native	4 (2%)	2 (2%)	11 (3%)	4 (2%)	7 (4%)
Black	2 (1%)	1 (1%)	8 (2%)	1 (<1%)	5 (3%)
Native Hawaiian or Pacific Islander	0	0	0	0	1 (1%)
White	124 (50%)	64 (52%)	218 (50%)	113 (52%)	95 (51%)
Other	7 (3%)	2 (2%)	17 (4%)	4 (2%)	4 (2%)
Not reported	47 (19%)	19 (16%)	52 (12%)	25 (12%)	12 (6%)
ECOG performance status					
0	162 (65%)	75 (61%)	277 (64%)	144 (66%)	126 (67%)
1	87 (35%)	47 (39%)	154 (36%)	73 (34%)	62 (33%)
2	1 (<1%)	0	1 (<1%)	0	0
Aetiology of disease§					
Hepatitis B virus (with or without hepatitis C virus)	74 (30%)	35 (29%)	127 (29%)	64 (29%)	59 (31%)
Hepatitis C virus (without hepatitis B virus)	71 (28%)	34 (28%)	136 (31%)	67 (31%)	60 (32%)
Non-viral	105 (42%)	53 (43%)	169 (39%)	86 (40%)	69 (37%)
Child-Pugh class¶					
A	250 (100%)	122 (100%)	432 (100%)	217 (100%)	188 (100%)
ALBI grade					
1	147 (59%)	69 (57%)	249 (58%)	123 (57%)	102 (54%)
2	102 (41%)	50 (41%)	182 (42%)	89 (41%)	82 (44%)
3	1 (<1%)	1 (1%)	1 (<1%)	3 (1%)	2 (1%)
Missing	0	2 (2%)	0	2 (1%)	2 (1%)
BCLC stage					
B (intermediate)	83 (33%)	42 (34%)	140 (32%)	72 (33%)	66 (35%)
C (advanced)	167 (67%)	80 (66%)	292 (68%)	145 (67%)	122 (65%)
Extrahepatic spread of disease	135 (54%)	69 (57%)	232 (54%)	122 (56%)	102 (54%)
				(Table 1 continues on next page)	

	Progression-free survival ITT population		ITT population		
	Cabozantinib plus atezolizumab (n=250)	Sorafenib (n=122)	Cabozantinib plus atezolizumab (n=432)	Sorafenib (n=217)	Cabozantinib (n=188)
(Continued from previous page)					
Macrovascular invasion	84 (34%)	38 (31%)	136 (31%)	61 (28%)	67 (36%)
Main portal vein invasion or thrombus, or both	51 (20%)	20 (16%)	84 (19%)	35 (16%)	40 (21%)
Extrahepatic spread of disease or macrovascular invasion, or both	175 (70%)	85 (70%)	298 (69%)	148 (68%)	128 (68%)
Sites of disease					
Liver	228 (91%)	110 (90%)	405 (94%)	198 (91%)	175 (93%)
Bone	26 (10%)	12 (10%)	43 (10%)	22 (10%)	24 (13%)
Visceral (excluding liver and lymph nodes)	8 (3%)	5 (4%)	13 (3%)	8 (4%)	5 (3%)
Lung	7 (3%)	5 (4%)	12 (3%)	7 (3%)	5 (3%)
Adrenal gland	1 (<1%)	0	1 (<1%)	1 (<1%)	0
Lymph node	67 (27%)	42 (34%)	114 (26%)	68 (31%)	45 (24%)
Number of sites (including liver)					
1	71 (28%)	30 (25%)	117 (27%)	60 (28%)	61 (32%)
2	116 (46%)	69 (57%)	206 (48%)	111 (51%)	83 (44%)
≥3	61 (24%)	22 (18%)	106 (25%)	45 (21%)	44 (23%)
Missing	2 (1%)	1 (1%)	3 (1%)	1 (<1%)	0
Alpha-fetoprotein (ng/mL)					
<400	166 (66%)	86 (70%)	269 (62%)	152 (70%)	123 (65%)
≥400	84 (34%)	36 (30%)	163 (38%)	65 (30%)	65 (35%)
Previous chemoembolisation	93 (37%)	38 (31%)	139 (32%)	73 (34%)	58 (31%)
Previous radioembolisation	19 (8%)	6 (5%)	24 (6%)	12 (6%)	12 (6%)

Data are median (IQR) or n (%). ALBI=albumin-bilirubin. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group. ITT=intention-to-treat. *Asia included mainland China, Hong Kong, Philippines, Singapore, South Korea, Taiwan, and Thailand. †Other included Georgia, Israel, Russia, and Ukraine. ‡Race was self-reported by the patients; more than one race could be self-reported. §Some patients had more than one disease aetiology category. ¶Assessment for fibrosis or cirrhosis was not required.

Table 1: Baseline demographic and clinical characteristics

amendment that adjusted the randomisation ratio to 2:1:1 to ensure adequate patient numbers in the single-agent cabozantinib group (n=188). The safety population included 824 patients who received any amount of study treatment: 429 in the combination treatment group, 207 in the sorafenib group, and 188 in the single-agent cabozantinib group.

Baseline characteristics are shown in table 1 and the appendix (p 14).

At data cutoff, 130 patients in the combination treatment group remained on cabozantinib or atezolizumab, or both (figure 1); three were receiving cabozantinib only, six atezolizumab only, and 121 both agents. 32 patients in the sorafenib group and 41 in the single-agent cabozantinib group remained on treatment. The most common reason for treatment discontinuation was radiographical progression in all groups. Median follow-up was 15·8 months (IQR 14·5–17·2) in the progression-free survival ITT population and 13·3 months (10·5–16·0) in the ITT population.

In the progression-free survival ITT population, median progression-free survival per BIRC was 6·8 months (99% CI 5·6–8·3) in the combination cabozantinib plus atezolizumab treatment group versus 4·2 months (2·8–7·0) in the sorafenib group (HR 0·63, 99% CI 0·44–0·91, p=0·0012; figure 2). 6-month progression-free survival was 54·5% (95% CI 47·8–60·7) in the combination treatment group versus 40·0% (30·2–49·6) in the sorafenib group, and 12-month progression-free survival was 28·5% (95% CI 22·6–34·7) in the combination treatment group versus 18·0% (10·2–27·6) in the sorafenib group (post-hoc analyses). A log-log plot of the survivor functions supported the assumption of proportional hazards (appendix p 38). Progression-free survival outcomes were similar when assessed by investigator (appendix p 39).

For the interim analysis of overall survival in the ITT population (information fraction of 74·2%), median overall survival was 15·4 months (96% CI 13·7–17·7) in the combination treatment group of cabozantinib plus atezolizumab versus 15·5 months (12·1–not estimable) in the sorafenib group (HR 0·90, 96% CI 0·69–1·18; p=0·44; figure 2). 6-month overall survival was 81·4% (95% CI 77·3–84·8) in the combination treatment group versus 76·1% (69·7–81·3) in the sorafenib group, and 12-month overall survival was 61·8% (95% CI 56·6–66·6)

in the combination treatment group versus 58·2% (50·6–65·0) in the sorafenib group (post-hoc analyses).

In prespecified exploratory subgroup analyses of primary progression-free survival, progression-free survival appeared to be longer with the combination treatment versus sorafenib in the hepatitis B virus aetiology subgroup, in patients with extrahepatic disease or macrovascular invasion, and in patients enrolled in Asia, but not in any other prespecified subgroups (appendix pp 40–41). For the interim overall survival analysis, overall survival appeared to be longer with the combination treatment versus sorafenib in patients with hepatitis B virus aetiology, but not in any other prespecified subgroups (appendix pp 40–41).

For interim analysis of secondary progression-free survival, median progression-free survival was 5·8 months (99% CI 5·4–8·2) in the single-agent cabozantinib group versus 4·3 months (2·9–6·1) in the sorafenib group (HR 0·71, 99% CI 0·51–1·01, p=0·011; figure 3). 6-month progression-free survival in the ITT population was 49·9% (95% CI 42·0–57·4) in the single-agent cabozantinib group versus 41·4% (33·9–48·8) in the sorafenib group, and 12-month progression-free survival was 27·5% (95% CI 19·8–35·7) in the single-agent cabozantinib group versus 19·8% (12·9–27·8) in the sorafenib group (post-hoc analyses).

The additional endpoints of objective response, median time to response, median duration of response, median time to response, and disease control (post-hoc analysis) by BIRC in the progression-free survival ITT population and in the ITT population are shown in table 2. Reduction in sum of diameter of target lesions occurred in 255 (70%) of 364 evaluable patients in the combination treatment group, 93 (56%) of 167 in the sorafenib group, and 109 (69%) of 158 in the single-agent cabozantinib group (appendix p 42). Response outcomes per RECIST 1.1 by investigator assessment were generally consistent with those by BIRC (appendix p 15).

For patients who discontinued study treatment, subsequent systemic anticancer therapy was used in 87 (20%) of 432 patients in the combination treatment group, 80 (37%) of 217 in the sorafenib group, and 54 (29%) of 188 in the single-agent cabozantinib group. 17 (4%) patients in the combination treatment group received an immune checkpoint inhibitor, compared with 36 (17%) in the sorafenib group and 24 (13%) in the single-agent cabozantinib group (appendix p 16).

Details of treatment exposure, dose interruptions, dose reductions, and discontinuations in each group are in the appendix (p 17).

In the safety population, treatment-emergent adverse events of any grade occurred in 428 (>99%) of 429 patients in the combination treatment group, 205 (99%) of 207 in the sorafenib group, and 187 (99%) of 188 in the single-agent cabozantinib group (table 3), grade 3 or 4 events occurred in 273 (64%), 95 (46%), and 113 (60%), and grade 4 events occurred in
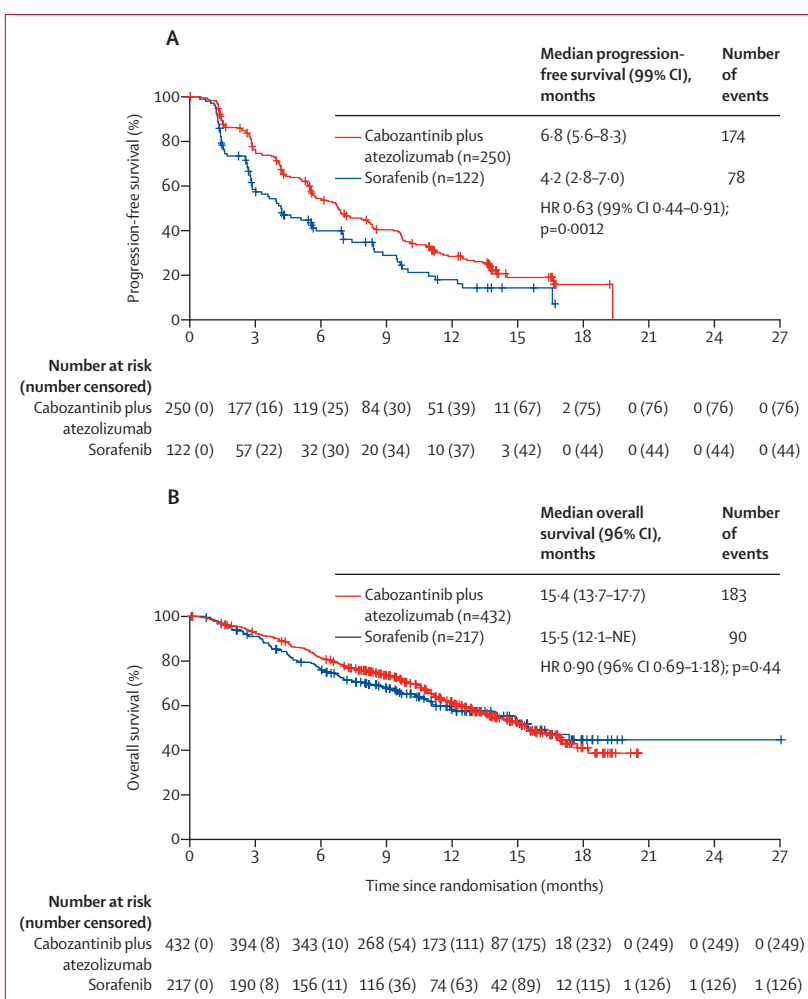
Figure 2: Progression-free survival (final analysis) and overall survival (interim analysis) for cabozantinib plus atezolizumab versus sorafenib

Kaplan-Meier estimates of cabozantinib plus atezolizumab versus sorafenib for the final analysis of progression-free survival in the progression-free survival ITT population (A) and the interim analysis of overall survival in the ITT population (B). Crosses denote censored patients. HR=hazard ratio. ITT=intention-to-treat. NE=not estimable.
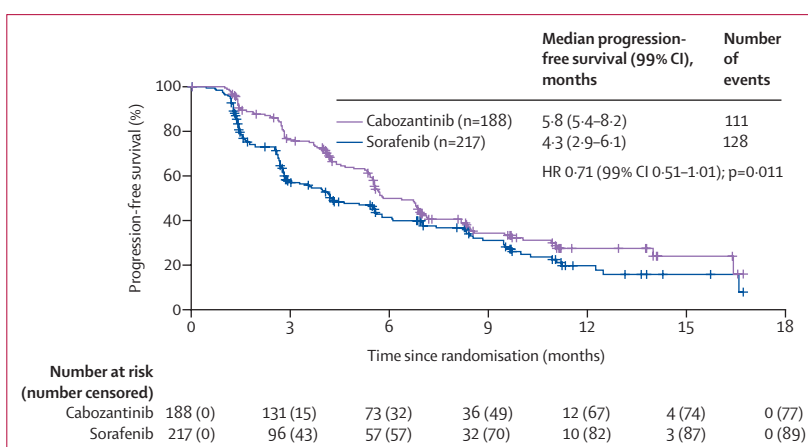
Figure 3: Interim analysis of progression-free survival for cabozantinib versus sorafenib in the ITT population
Crosses denote censored patients. HR=hazard ratio. ITT=intention-to-treat.

	Progression-free survival ITT population		ITT population		
	Cabozantinib plus atezolizumab (n=250)	Sorafenib (n=122)	Cabozantinib plus atezolizumab (n=432)	Sorafenib (n=217)	Cabozantinib (n=188)
Objective response, n (%, 95% CI)	32 (13%, 8·9–17·6)	6 (5%, 1·8–10·4)	47 (11%, 8·1–14·2)	8 (4%, 1·6–7·1)	12 (6%, 3·3–10·9)
Best overall response					
Complete response	1 (<1%)	0	1 (<1%)	0	0
Partial response	31 (12%)	6 (5%)	46 (11%)	8 (4%)	12 (6%)
Stable disease	172 (69%)	71 (58%)	290 (67%)	132 (61%)	145 (77%)
Progressive disease	32 (13%)	26 (21%)	61 (14%)	44 (20%)	20 (11%)
Unable to evaluate or missing	12 (5%)	19 (16%)	29 (7%)	32 (15%)	8 (4%)
No measurable disease	2 (1%)	0	5 (1%)	1 (<1%)	3 (2%)
Disease control*	204 (82%)	77 (63%)	337 (78%)	140 (65%)	157 (84%)
Median time to response (IQR), months	4·1 (2·5–8·4)	3·5 (1·5–4·5)	4·0 (2·6–8·3)	3·5 (2·1–4·4)	4·2 (2·1–5·6)
Median duration of response (95% CI), months	12·4 (9·8–NE)	8·4 (3·0–NE)	10·6 (7·1–12·7)	8·8 (3·0–NE)	15·1 (4·4–NE)
Median time to progression (95% CI), months	7·1 (6·3–8·5)	4·2 (2·9–7·0)	7·0 (6·7–8·3)	4·6 (3·6–6·1)	6·8 (5·6–8·2)

Data are n (%) unless otherwise indicated. ITT=intention-to-treat. NE=not estimable. RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1. *Disease control was defined as the proportion of patients with a complete response, partial response, or stable disease (post-hoc analysis). BIRC=blinded independent radiology committee.

Table 2: Tumour response per RECIST 1.1 assessed by BIRC

28 (7%), 11 (5%), and 12 (6%), respectively (appendix pp 18–27). The most common grade 3 or 4 events were alanine aminotransferase increase (38 [9%] in the combination treatment group vs six [3%] in the sorafenib group vs 12 [6%] in the single-agent cabozantinib group), aspartate aminotransferase increase (37 [9%] vs eight [4%] vs 18 [10%]), hypertension (37 [9%] vs 17 [8%] vs 23 [12%]), and palmar-plantar erythrodysaesthesia (35 [8%] vs 17 [8%] vs 16 [9%]). Treatment-emergent haemorrhagic events of any grade occurred in 71 (17%) patients in the combination treatment group, 29 (14%) in the sorafenib group, and 28 (15%) in the single-agent cabozantinib group; grade 3 or worse haemorrhagic events were infrequent in all treatment groups (12 [3%] in the combination treatment group, ten [5%] in the sorafenib group, and six [3%] in the single-agent cabozantinib group).

Treatment-related adverse events of any grade occurred in 399 (93%) of 429 patients in the combination treatment group, 186 (90%) of 207 in the sorafenib group, and 178 (95%) of 188 in the single-agent cabozantinib group (appendix pp 28–33). Serious treatment-related adverse events of any grade occurred in 78 (18%) patients in the combination treatment group, 16 (8%) in the sorafenib group, and 24 (13%) in the single-agent cabozantinib group (appendix pp 34–36).

Immune-mediated adverse events of any grade that required immunosuppressive treatment occurred in 31 (7%) of 429 patients in the combination treatment group; the most common were hepatitis (diagnosis and laboratory abnormalities, 19 [4%]; laboratory abnormalities, 14 [3%]) and pneumonitis (seven [2%]; appendix p 37).

In the combination treatment group, 58 (14%) of 429 patients discontinued any treatment component because of treatment-related adverse events and 26 (6%) of 429 discontinued both components; discontinuations because of treatment-related adverse events occurred in 16 (8%) of 207 patients in the sorafenib group and 16 (9%) of 188 in the single-agent cabozantinib group (appendix p 17).

Grade 5 treatment-emergent adverse events occurred in 51 (12%) of 429 patients in the combination treatment group, 23 (11%) of 207 in the sorafenib group, and 30 (16%) of 188 in the single-agent cabozantinib group (table 3, appendix pp 18–27). From the time of the first dose of study treatment until 30 days after the last dose, treatment-related grade 5 events 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 one (<1%) patient in the single-agent cabozantinib group (gastrointestinal haemorrhage; appendix pp 28–33). Two (<1%) additional patients had a treatment-related grade 5 event in the combination treatment group up to 100 days after the last dose (hepatocellular carcinoma and general physical health deterioration).

Discussion

The phase 3 COSMIC-312 study had dual primary endpoints of progression-free survival and overall survival for cabozantinib plus atezolizumab versus sorafenib as first-line systemic treatment for patients with advanced hepatocellular carcinoma not amenable to curative treatment or locoregional therapy. Primary progression-free survival was significantly longer in the combination treatment group versus the sorafenib group.

At interim analysis of overall survival presented here, an early separation in the Kaplan-Meier curves was seen,

	Cabozantinib plus atezolizumab (n=429)				Sorafenib (n=207)				Cabozantinib (n=188)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	104 (24%)	245 (57%)	28 (7%)	51 (12%)	87 (42%)	84 (41%)	11 (5%)	23 (11%)	44 (23%)	101 (54%)	12 (6%)	30 (16%)
Diarrhoea	190 (44%)	18 (4%)	0	0	93 (45%)	4 (2%)	0	0	91 (48%)	12 (6%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	148 (34%)	35 (8%)	0	0	75 (36%)	17 (8%)	0	0	66 (35%)	16 (9%)	0	0
Aspartate aminotransferase increased	92 (21%)	37 (9%)	0	0	22 (11%)	7 (3%)	1 (<1%)	0	43 (23%)	18 (10%)	0	0
Alanine aminotransferase increased	89 (21%)	35 (8%)	3 (1%)	0	17 (8%)	5 (2%)	1 (<1%)	0	43 (23%)	12 (6%)	0	0
Decreased appetite	109 (25%)	7 (2%)	0	0	37 (18%)	4 (2%)	0	0	69 (37%)	9 (5%)	0	0
Fatigue	91 (21%)	15 (3%)	0	0	25 (12%)	8 (4%)	0	0	52 (28%)	7 (4%)	0	0
Hypertension	63 (15%)	37 (9%)	0	0	21 (10%)	17 (8%)	0	0	32 (17%)	23 (12%)	0	0
Hypothyroidism	89 (21%)	0	0	0	7 (3%)	0	0	0	35 (19%)	0	0	0
Asthenia	56 (13%)	23 (5%)	1 (<1%)	0	28 (14%)	9 (4%)	0	0	27 (14%)	6 (3%)	0	0
Weight decreased	53 (12%)	20 (5%)	0	0	26 (13%)	2 (1%)	0	0	33 (18%)	13 (7%)	0	0
Abdominal pain	56 (13%)	7 (2%)	1 (<1%)	0	31 (15%)	10 (5%)	0	0	23 (12%)	4 (2%)	0	0
Nausea	62 (14%)	2 (<1%)	0	0	27 (13%)	1 (<1)	0	0	35 (19%)	4 (2%)	0	0
Constipation	59 (14%)	3 (1%)	0	0	22 (11%)	0	0	0	33 (18%)	0	0	0
Rash	56 (13%)	5 (1%)	0	0	36 (17%)	1 (<1%)	0	0	28 (15%)	1 (1%)	0	0
Pyrexia	53 (12%)	4 (1%)	0	0	25 (12%)	1 (<1%)	0	0	22 (12%)	0	0	0
Blood bilirubin increased	44 (10%)	11 (3%)	1 (<1%)	0	19 (9%)	5 (2%)	0	0	19 (10%)	5 (3%)	1 (1%)	0
Ascites	41 (10%)	14 (3%)	0	0	7 (3%)	5 (2%)	0	0	17 (9%)	5 (3%)	0	0
Platelet count decreased	44 (10%)	7 (2%)	1 (<1%)	0	11 (5%)	2 (1%)	0	0	20 (11%)	5 (3%)	0	0
Dysphonia	47 (11%)	1 (<1%)	0	0	14 (7%)	0	0	0	32 (17%)	1 (1%)	0	0
Mucosal inflammation	45 (10%)	1 (<1%)	0	0	12 (6%)	0	0	0	15 (8%)	6 (3%)	0	0
Oedema peripheral	46 (11%)	0	0	0	12 (6%)	0	0	0	20 (11%)	0	0	0
Vomiting	42 (10%)	2 (<1%)	0	0	13 (6%)	1 (<1%)	0	0	32 (17%)	3 (2%)	0	0
Pruritis	43 (10%)	0	0	0	14 (7%)	0	0	0	11 (6%)	1 (1%)	0	0
Stomatitis	29 (7%)	9 (2%)	0	0	8 (4%)	0	0	0	24 (13%)	1 (1%)	0	0
Upper abdominal pain	32 (7%)	3 (1%)	0	0	16 (8%)	1 (<1%)	0	0	19 (10%)	0	0	0
Alopecia	15 (3%)	0	0	0	31 (15%)	0	0	0	14 (7%)	0	0	0
Hepatocellular carcinoma	0	6 (1%)	5 (1%)	21 (5%)	1 (<1%)	3 (1%)	2 (1%)	9 (4%)	2 (1%)	1 (1%)	2 (1%)	19 (10%)

Data are n (%). Treatment-emergent adverse events, regardless of causality, that were reported in at least 10% of patients in any treatment group are shown. All events grade 3 or worse are reported in the appendix (pp 18–27). Patients are counted at the worst toxicity grade overall and at each preferred term.

Table 3: **Treatment-emergent adverse events (safety population)**

but overall survival did not differ significantly between the treatment groups. Final overall survival analyses will be presented along with updated safety data in a future publication. At the interim analysis, a higher proportion of patients in the sorafenib group received subsequent systemic treatment, including immune checkpoint inhibitors, than did patients in the combination treatment group, and the median overall survival for sorafenib was the longest observed in a phase 3 study,[2,5,9,23,24] suggesting a possible effect from subsequent therapy. Subgroup analysis of overall survival also showed a range of outcomes that differed according to underlying disease features. Although combination therapy was favoured versus sorafenib for overall survival and progression-free survival in patients with hepatitis B virus and in patients with extrahepatic disease or macrovascular invasion at baseline, there was no clear benefit in patients with hepatocellular carcinoma of

non-viral aetiology. In the subgroup with hepatitis C virus, there did not appear to be a difference between the combination treatment and sorafenib groups for overall survival, which is at odds with findings from some other immunotherapy studies.[5] The phase 3 HIMALAYA study reported a significant overall survival benefit with first-line durvalumab plus tremelimumab versus sorafenib in patients with advanced hepatocellular carcinoma, but this benefit did not appear to be maintained in the subgroup with hepatitis C virus.[9] Clinical outcomes by aetiology subgroups have varied across immunotherapy studies, suggesting relevant effects of underlying liver disease and tumour characteristics that are only partly understood.[4,5,9] Hepatitis B virus-associated hepatocellular carcinoma tumours are more frequently associated with activated proliferation pathways, including the cabozantinib targets MET and AXL, which might have partly contributed to the favourable outcomes with

cabozantinib plus atezolizumab in the hepatitis B virus subgroup.[25,26] By contrast, hepatocellular carcinoma of non-viral cause is a heterogeneous group that includes hepatic steatosis, which might be less responsive to immunotherapy compared with other aetiologies of hepatocellular carcinoma.[27] In patients with hepatitis C virus, there are wide geographical variations in comorbidities, such as alcohol use and metabolic syndrome, and anticancer treatments that might affect survival through both hepatic and extrahepatic influences or through access to subsequent therapies.[28,29] Observational studies also suggest that antiviral therapy and sustained viral response are associated with improved overall survival in patients with hepatocellular carcinoma and hepatitis C virus.[30] Although control of hepatitis B virus with antiviral therapy was an eligibility requirement in COSMIC-312, this was optional for patients with hepatitis C virus. Generally, antiviral therapy for hepatitis C virus has not been required in hepatocellular carcinoma trials,[5,23] although most have required patients to have adequate hepatic reserve.

Cabozantinib has shown improvements in overall survival and progression-free survival compared with placebo in previously treated hepatocellular carcinoma.[15] To determine whether efficacy was also seen in first-line treatment and to evaluate the contribution of cabozantinib to the combination treatment, the secondary endpoint of COSMIC-312 was progression-free survival for the single-agent cabozantinib versus sorafenib. The interim analysis of secondary progression-free survival indicated a contributing role for cabozantinib in the efficacy of the combination treatment, and the early separation of Kaplan-Meier curves suggested rapid disease control. Final analysis of secondary progression-free survival is pending.

Responses for both the progression-free survival ITT and ITT populations were assessed by BIRC and by investigator and were generally consistent. In the ITT population, the proportion of patients with an objective response by BIRC was nearly three-times greater in the combination treatment group than in the sorafenib group (11% *vs* 4%). The proportion of patients with an objective response was lower with cabozantinib plus atezolizumab compared with atezolizumab plus bevacizumab (30%) in the IMbrave150 study[24] or with lenvatinib (18·8%) in the phase 3 REFLECT study,[23] but these studies also reported higher proportions of patients with an objective response in the sorafenib control groups (11% and 6·5%, respectively), suggesting differences in methods or patient populations. The proportion of patients with disease control was 78% in the combination treatment group in the ITT population, similar to the proportion reported for atezolizumab plus bevacizumab (74%)[24] and exceeding proportions reported with immune checkpoint inhibitor monotherapy and a dual immune checkpoint inhibitor combination.[4,6,9]

The baseline characteristics of patients enrolled in COSMIC-312 aligned with the general clinical characteristics of patients with advanced hepatocellular carcinoma, although some limitations are worth noting. Patients were required to have preserved liver function with a Child-Pugh class of A, although assessment for fibrosis or cirrhosis was not required and albumin-bilirubin grades indicated a range of underlying hepatic reserve. The study protocol sought to impose few other barriers to study entry. By contrast with other studies, previous endoscopy was not an eligibility requirement,[5] and patients with main portal vein tumour thrombus were not excluded.[9,23] The proportion of patients with hepatitis B virus aetiology and the proportion enrolled in Asia were lower than those in the IMbrave150 study,[5] resulting from lower rates of enrolment in mainland China, where study initiation was affected by the COVID-19 pandemic. Other limitations of the data reported here include the fact that the overall survival and secondary progression-free survival results are from interim analyses, rather than final analyses. However, final analysis of overall survival after longer follow-up has been completed and will be reported in a future publication. Follow-up is ongoing for the final analysis of secondary progression-free survival and for additional endpoints including quality of life. A study extension in mainland China is also ongoing.

The safety data of COSMIC-312 reflect the known safety profiles of the study drugs. The most common adverse events seen in patients treated with cabozantinib alone or with atezolizumab were similar to those reported in the CELESTIAL trial of cabozantinib versus placebo.[15] Immune-mediated adverse events requiring immunosuppressive treatment occurred in 7% of patients receiving the combination treatment, lower than in other immunotherapy studies.[9,31] Grade 3 or 4 treatment-related adverse events and dose modifications occurred more frequently in the combination and single-agent cabozantinib groups than in the sorafenib group, but adverse events leading to study treatment discontinuation were infrequent, indicating that these were manageable.

Underlying chronic liver disease is nearly universal in patients with hepatocellular carcinoma and the risk of gastrointestinal bleeding is high in this population, particularly if portal vein tumour thrombus is present. Despite not requiring endoscopy before enrolment, findings showed no excess of serious bleeding events in the treatment groups containing cabozantinib compared with sorafenib and proportions of grade 3 or worse haemorrhagic events were lowest in the combination treatment group. Fatal grade 5 treatment-related events were infrequent in all treatment groups and were generally consistent with those seen in patients with advanced chronic liver disease.

Despite the lack of improvement in overall survival, cabozantinib plus atezolizumab significantly improved progression-free survival and showed increased disease control and lower primary progression compared with sorafenib, which are also clinically meaningful endpoints.

For some patients, delaying progression and achieving rapid disease control is particularly important, such as in symptomatic patients with high disease burden or main portal vein occlusion at risk for impending complications. The observed improvement in progression-free survival in subgroups with more advanced malignancy, including those with extrahepatic disease or macrovascular invasion, reinforces the assessment of clinical benefit. Additional studies are needed to determine if cabozantinib plus atezolizumab might benefit select patient populations.

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