A Randomized, Controlled Phase 3 Study of Cabozantinib (XL184) in Combination with Atezolizumab versus Sorafenib in Subjects with Advanced Hepatocellular Carcinoma Who Have Not Received Previous Systemic Anticancer Therapy

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56004

Source
ToetsingOnline

Brief title
COSMIC-312

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
advanced hepatocellular carcinoma / liver cancer

Research involving

Human

Sponsors and support

Primary sponsor: Exelixis, Inc.
Source(s) of monetary or material Support: The sponsor;Exelixis;Inc.

Intervention

Keyword: Cabozantinib, Controlled, Hepatocellular Carcinoma

Outcome measures

Primary outcome

Primary Efficacy Endpoints:

• Duration of PFS per RECIST 1.1, by BIRC for the experimental arm

(cabozantinib + atezolizumab) vs the control arm (sorafenib)

• Duration of OS for the experimental arm (cabozantinib + atezolizumab) vs the

control arm (sorafenib)

Secondary outcome

Secondary efficacy endpoint:

• PFS per RECIST 1.1 by BIRC for the single-agent cabozantinib arm vs the

control arm (sorafenib)

Additional endpoints:

• ORR, time to progression (TTP), and DOR per RECIST 1.1 by BIRC and

Investigator

• Evaluation of radiographic response per modified RECIST (mRECIST)

• Safety through the evaluation of AEs, including irAEs and other AESIs.

• Characterization of the pharmacokinetics (PK) of cabozantinib in subjects

with previously untreated HCC

• Immunogenicity of atezolizumab given in combination with cabozantinib

• Change in serum AFP from baseline

• Correlation of biomarker analyses with clinical outcomes

• Health-related quality of life (HRQOL) as assessed by the EuroQol Health

questionnaire instrument (EQ-5D-5L)

• Healthcare resource utilization

Study description

Background summary

Liver cancer is the second most frequent cause of cancer deaths worldwide (Ferlay et al 2015). Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for approximately 90% of cases. In 2015, 854,000 new liver cancer cases were reported worldwide and 810,000 deaths occurred (Global Burden of Disease Liver Cancer 2017; EASL 2018). The estimated incidence and mortality rates of liver cancer in the USA in 2016 were approximately 42,000 and 30,000 cases, respectively (American Cancer Society 2018); incidence and mortality in the EU in 2012 were 52,000 and 48,000 cases, respectively (Ferlay et al 2013). Surgical resection and transplantation are potential curative treatment modalities for HCC. Ablative therapies (eg, radiofrequency ablation [RFA], microwave ablation [MWA], and percutaneous ethanol injection [PEI]) are being used for early stage unresectable HCC. Transarterial chemoembolization (TACE) is used generally for intermediate stage disease. The current standard of care for first line treatment of advanced unresectable HCC is sorafenib, which is a small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR) and other protein kinases. In a randomized placebo-controlled Phase 3 study (SHARP), sorafenib improved the primary endpoint of overall survival (OS) in subjects with advanced HCC (Child-Pugh A) who had not received prior systemic therapy (Llovet et al 2008). Median OS was 10.7 months in the sorafenib arm and 7.9 months in the placebo arm (hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.55, 0.87; p-value < 0.001). A similar HR was observed (with a shorter duration of OS than in the SHARP trial) in a corresponding placebo-controlled Phase 3 trial conducted in an Asian-Pacific population in which infection with hepatitis B virus (HBV) was the main cause of HCC: median OS was 6.5 months vs 4.2 months (HR 0.68; 95% CI: 0.50, 0.93; p-value = 0.014) (Cheng et al 2009). Recently, the

VEGFR-targeting tyrosine kinase inhibitor (TKI) lenvatinib was shown to be non-inferior to sorafenib in a Phase 3 study enrolling subjects with advanced HCC who had not received prior systemic therapy (Kudo et al 2018) leading to US and EU approval in this population. In that study, median OS for lenvatinib was 13.6 months compared with 12.3 months for sorafenib (HR 0.92; 95% CI 0.79, 1.06). Cabozantinib is an orally bioavailable small molecule TKI that potently inhibits VEGFR, MET, AXL, and RET, as well as a number of other receptor tyrosine kinases (RTKs) that have also been implicated in tumor pathobiology, including KIT and FLT3. Cabozantinib suppresses MET and VEGFR2 signaling, rapidly inducing apoptosis of endothelial and tumor cells, resulting in tumor regression in a variety of xenograft models. Cabozantinib capsules (140 mg) are approved in the United States for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) and in the European Union for the treatment of patients with progressive, unresectable locally advanced or metastatic MTC (Cometriq* US prescribing information [US PI] and European Medicines Agency Summary of Product Characteristics [EMA SmPC]). Cabozantinib tablets (60 mg) are approved in the United States, Europe, and other regions for advanced renal cell carcinoma (RCC; different patient populations depending on region; Cabometyx* US PI and EMA SmPC). Based on the results from the studies below, cabozantinib tablets (60 mg) as a single agent have also been approved in the US and EU for the treatment of HCC in patients who have previously been treated with sorafenib (Cabometyx US PI and EMA SmPC). The clinical activity and safety of single agent cabozantinib (60 mg, tablets) in HCC has been demonstrated in a randomized placebo-controlled Phase 3 study (CELESTIAL) in subjects who had received prior therapy with sorafenib (subjects were required to have progressed during or following prior systemic therapy and up to 2 prior lines of systemic therapy were allowed; Abou- Alfa et al 2018). The primary endpoint of the study was OS. At the second pre-planned interim analysis, the prespecified event-driven primary efficacy endpoint analysis of the 707 subjects enrolled at the data cutoff (470 cabozantinib, 237 placebo) demonstrated a statistically significant improvement in OS for subjects in the cabozantinib arm compared with placebo (Intent-to-Treat [ITT] population): the HR, adjusted for stratification factors, was 0.76 (95% CI 0.63, 0.92; stratified log-rank p-value = 0.0049; critical p-value to reject the null hypothesis of equal OS = 0.021). The Kaplan-Meier estimates for median duration of OS were 10.2 months in the cabozantinib arm vs 8.0 months in the placebo arm. The secondary endpoint analysis of progression-free survival (PFS) as determined by the investigator yielded a median duration of PFS of 5.2 months in the cabozantinib arm and 1.9 months in the placebo arm. The HR, adjusted for stratification factors, was 0.44 (95% CI 0.36, 0.52, stratified log-rank p-value < 0.0001). Investigator-determined objective response rate (ORR) was 4% and 0.4% for subjects in the cabozantinib and placebo arms, respectively (unstratified Fisher exact test p-value = 0.0059); all were partial responses (PRs). In addition, there was a high rate of stable disease (SD) in the cabozantinib arm relative to placebo (60% vs 33%). Adverse events reported for >= 20% of subjects in the cabozantinib arm by decreasing frequency were diarrhea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), fatigue,

nausea, hypertension, vomiting, aspartate aminotransferase (AST) increased, and asthenia. Grade 3 or 4 adverse events (AEs) regardless of causality were reported for 68% of subjects in the cabozantinib arm and 36% in the placebo arm. Grade 3 or 4 AEs reported for >= 5% of subjects in the cabozantinib arm by decreasing frequency were PPE, hypertension, AST increased, fatigue, diarrhea, asthenia, and decreased appetite. The results of this study formed the basis for regulatory applications to the US FDA and EMA to approve cabozantinib for treatment of patients with advanced HCC who have received prior therapy. Earlier clinical evaluation of cabozantinib in HCC was conducted in a Phase 2 study that included both previously-treated and treatment-nai*ve subjects with advanced HCC (n=41; Kelley et al 2017). Progression-free survival from first dose throughout the study was estimated for all HCC subjects using a piecewise method; median PFS was 5.2 months. Tumor regression appeared independent of prior sorafenib exposure. Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody which potently and selectively inhibits binding of programmed death ligand 1 (PD-L1) on tumor cells and tumor infiltrating immune cells in the tumor microenvironment (McDermott et al 2016). Through this interaction, atezolizumab interrupts the negative regulatory effects of PD-L1 on T-cell proliferation and function that result from PD-L1 binding to programmed death receptor 1 (PD-1) and B7.1 (CD80) expressed on T lymphocytes and other immune cells. The result is an increase in the susceptibility of tumor cells to T-cell-mediated immune response, an effect that has been demonstrated in clinical activity across several tumor types. Atezolizumab injection, for intravenous (IV) use (1200 mg once every 3 weeks [q3w]), has been approved in the United States and the European Union for the treatment of patients with advanced urothelial carcinoma (UC) after prior platinum containing chemotherapy or in a subset patients who are considered cisplatin-ineligible (different patient populations are indicated depending on region; Rosenberg et al 2016, Balar et al 2017). Atezolizumab is also approved for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy (Fehrenbacher et al 2016; Tecentriq* US PI and EMA SmPC). Recently, atezolizumab was also granted accelerated approval in the US for treatment in combination with paclitaxel proteinbound for adult patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC) whose tumors express PD-L1 (Schmid et al 2018) and was also approved for first-line treatment in combination with carboplatin and etoposide in adult patients with extensive-stage small cell lung cancer (ES-SCLC; Horn et al 2018, Tecentriq US PI). Treatment with atezolizumab is generally well-tolerated but can be associated with immune-related adverse events (irAEs). The clinical activity and safety of atezolizumab has been evaluated in subjects with advanced HCC either as single agent or in combination therapy. In a Phase 1b study of atezolizumab (1200 mg q3w) in combination with the anti-VEGF targeting antibody bevacizumab, 103 subjects with advanced HCC nai*ve to systemic therapy had been enrolled at the data cutoff of 26 July 2018 (NCT02715531; Pishvaian et al 2018). Among 73 efficacy-evaluable subjects, the median survival follow-up was 7.2 months. The ORR by independent radiology facility (IRF) was 27% (with 4 complete responses [CRs]) per Response Evaluation Criteria in Solid Tumors

version 1.1 (RECIST 1.1) and was 34% (with 8 CRs) per modified RECIST (mRECIST); ORR by Investigator per RECIST 1.1 was 32% with 1 CR. Confirmed responses were reported across the patient population regardless of HCC etiology, geographic region, baseline alpha-fetoprotein (AFP) levels, or extrahepatic spread of tumor. The investigator-assessed median PFS per RECIST 1.1 was 14.9 months, and the IRF-assessed median PFS per RECIST 1.1 was 7.5 months. Median estimates for duration of response (DOR) and OS were not yet reached at the data cutoff of 26 July 2018. Among the 103 safety evaluable subjects, treatment-related Grade 3 or 4 AEs were reported in 28 subjects (27%), most commonly hypertension (n = 10 [10%]). Five (5) Grade 5 AEs were observed, 2 of which were assessed as treatment related (one sepsis, one pneumonitis). A total of 19 subjects (18%) experienced treatment-related serious adverse events (SAEs). Adverse events of special interest (AESIs) of any grade for atezolizumab were reported for 54% of subjects, and AESIs of any grade for bevacizumab were reported for 47% of subjects. Immune-related AESIs for atezolizumab of >= Grade 3 requiring corticosteroid treatment included pneumonitis (2 subjects), autoimmune encephalitis, drug-induced liver injury (DILI), colitis, AST increased, γ-glutamyltranspeptidase (GGT) increased, diabetes mellitus, and pancreatitis (1 subject each). The high response rate observed suggested that the combination of atezolizumab with bevacizumab has synergistic activity in advanced HCC and compared favorably to early single-agent atezolizumab data in treatment-nai*ve HCC. Limited information is currently available for atezolizumab as a single agent in patients with advanced HCC. A total of 12 subjects were enrolled in two Phase 1 studies. In these two studies, few responses were observed: one study with 5 subjects had no responses (NCT01375842), and one study with 7 subjects had two confirmed responses per investigator assessment (NCT02825940). Targets of cabozantinib are also implicated in promoting tumor immune suppression including TYRO3, MER, and AXL (TAM family kinases). Preclinical studies (Kwilas et al 2014, Lu et al 2017) and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients (Apolo et al 2014) suggest that cabozantinib promotes an immunepermissive environment that may present an opportunity for synergistic effects from combined treatment with immune checkpoint inhibitors (ICIs). A Phase 1b study (NCT03170960) is currently evaluating the combination of cabozantinib with atezolizumab in multiple tumor cohorts. In the dose escalation stage of the study, cabozantinib dose levels of 40 mg and 60 mg once daily (qd) were evaluated in 6 subjects each (atezolizumab was administered at 1200 mg IV q3w for all subjects). At both cabozantinib dose levels in the dose-limiting toxicity (DLT) evaluation period of the dose escalation stage of the study there were no DLTs or SAEs (n=12 subjects total). The majority of AEs were of Grade 1 or 2 including irAEs. Grade 3 AEs included five events of hypertension, two events each of diarrhea and hypophosphatemia, and one event each of pulmonary embolism, hyperglycemia, GGT increased, AST increased, ALT increased, lymphocyte count decreased, lipase increased, muscular weakness, nephritis, and myositis (verbatim term). No Grade 4 or 5 AEs were reported. Among 10 subjects with clear cell RCC enrolled in the dose escalation stage, the investigator-assessed confirmed ORR was 70% with 1 CR and

6 PRs. Cabozantinib 40 mg in combination with atezolizumab 1200 mg was selected as the recommended dose for the Expansion Stage cohorts because of its favorable safety profile over a prolonged time on study treatment with minimal dose reductions and encouraging preliminary efficacy, which was deemed to optimize the benefit/risk of the combination. The study is ongoing and currently enrolling expansion cohorts in multiple solid tumor types including subjects with advanced HCC who have not received prior systemic anticancer therapy. As of 05 February 2019, 157 additional subjects had been enrolled in the expansion cohorts evaluating cabozantinib (40 mg, qd) + atezolizumab (1200 mg IV q3w); information on the 141 subjects evaluable for safety as of 29 January 2019 is provided in Section 1.4. Targeting the VEGF signaling pathway with small molecule TKIs has improved the clinical outcome of patients with advanced HCC; however, the OS has been modest with a median OS between 10.7 and 13.6 months (SHARP trial, Llovet et al 2008; REFLECT trial, Kudo et al 2018). More recently ICI therapies are being evaluated as potential new treatment strategy in HCC. Both cabozantinib and atezolizumab have shown encouraging clinical activity in advanced HCC. Based on the potential synergistic effects the combination of cabozantinib with atezolizumab appears to be a promising treatment opportunity for subjects with advanced HCC. Therefore, further evaluation of cabozantinib in combination with atezolizumab in subjects with previously untreated advanced HCC is warranted. This Phase 3 study evaluates the safety and efficacy of cabozantinib in combination with atezolizumab (approximately 370 subjects) versus the standard of care sorafenib (approximately 185 subjects) in subjects with advanced HCC who have not received previous systemic anticancer therapy. A single-agent cabozantinib arm (approximately 185 subjects) will be enrolled in which subjects will receive single-agent cabozantinib in order to determine its contribution to the overall safety and efficacy of the combination with atezolizumab in this patient population. It is planned to include up to 148 subjects from mainland China in this study to assess safety and efficacy in the China subpopulation. In the event enrollment in mainland China is incomplete by the time the global enrollment phase has been completed, a Mainland China Extension Phase will be implemented to complete enrollment and facilitate subpopulation analyses as needed. The global population will include all subjects enrolled during the global enrollment phase (including subjects enrolled at sites in mainland China during that phase), and the China subpopulation will include all subjects enrolled at sites in China (ie, during both the global enrollment phase and the Mainland China Extension Phase). XL184-312 Protocol Amendment 2.0 introduced considerations and study-related measures necessary due to the COVID-19 pandemic. XL184-312 Protocol Amendment 3.0 expanded the COVID-19-related guidance to include instructions for managing subjects who become infected on study, considerations for administration of COVID-19 vaccines, and confirmation that the COVID-19 accommodations are temporary and will be repealed back to standard study conduct when conditions allow.

Study objective

The primary objective of this study is to evaluate the efficacy of cabozantinib in combination with atezolizumab versus sorafenib in subjects with advanced HCC who have not received previous systemic anticancer therapy. An secondary objective is to evaluate the activity of single-agent cabozantinib compared with sorafenib in this patient population.

Study design

This is a multicenter, randomized, open-label, controlled Phase 3 trial of cabozantinib in combination with atezolizumab versus sorafenib in subjects with advanced HCC who have not received previous systemic anticancer therapy. The multiple primary efficacy endpoints are PFS
and OS for the experimental arm (cabozantinib + atezolizumab) vs the control arm (sorafenib).
Additionally there will be a third arm to evaluate the safety and clinical activity of single-agent cabozantinib. Approximately 740 eligible subjects with advanced HCC were planned to be randomized in a 2:1:1 ratio at approximately 250 sites in this trial in the global enrollment phase of the study. However, enrollment commenced under a randomization ratio of 6:3:1 per the original protocol design, and there was a dynamic transition in randomization allocation over time. As a result, the needed enrollment of 185 subjects in the single-agent cabozantinib arm was not expected to be reached at the planned total global enrollment phase sample size of 740 subjects. Therefore, to ensure complete enrollment in the single-agent cabozantinib arm, the total global enrollment phase was extended to accrue a total of approximately 840 subjects.

After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China Extension Phase at sites in mainland China for evaluation in a China subpopulation. If initiated, subjects recruited in the Mainland China Extension Phase will be randomized according to the same 2:1:1 scheme as subjects in the global enrollment phase. The global population will include all subjects enrolled during the global enrollment phase (including subjects enrolled at sites in mainland China during that phase), and the China subpopulation will include all subjects enrolled at sites in China (ie, during both the global enrollment phase and the Mainland China Extension Phase).
The sample size for the global study may be increased up to an additional 25% if a review of the accumulating data suggests that the COVID-19 pandemic has caused the rate of study dropout or non-compliance to increase to a degree that the ability to adequately evaluate study endpoints may be undermined. The Mainland China Extension Phase will not be expanded beyond 148 subjects.

The trial consists of the
following phases:
Pre-Treatment Period: Potential subjects will be screened to determine if they meet the required eligibility criteria. Qualifying screening assessments must be performed within 28 days before randomization unless otherwise specified.

Treatment Period: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1:1 manner to receive study treatment as follows:
Experimental arm (at least 370 subjects):
cabozantinib (40 mg oral, qd) +
atezolizumab (1200 mg infusion, q3w)

Control arm (at least 185 subjects):
sorafenib (400 mg, twice a day [bid])
Single-Agent Cabozantinib Arm (approximately 185 subjects):
cabozantinib (60 mg qd)
Randomization will be stratified by the following factors established at screening:
• Disease etiology (HBV [with or without hepatitis C virus {HCV}], HCV [without HBV], or Other)
• Region (Asia, Other)
• Presence of extrahepatic disease and/or macrovascular invasion (Yes, No)
Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator or until there is unacceptable toxicity, the need for subsequent systemic anticancer treatment, or any other reasons for the treatment discontinuation listed in the protocol. Treatment may continue after radiographic progression per RECIST 1.1 according to the criteria outlined in Section 5.7.6.3. Subjects on the experimental arm (cabozantinib and atezolizumab) are allowed to discontinue one component of the study treatment but continue to receive the other. Escalation of cabozantinib from 40 mg qd to 60 mg qd in the experimental arm is allowed after Sponsor approval for subjects who are tolerating the 40 mg cabozantinib dose level well and have been treated on this dose level for at least 4 weeks. In general, subjects who develop clinically relevant adverse events (eg, Grade 3 or 4 AEs) are not allowed to dose escalate cabozantinib from 40 qd to 60 mg qd. Crossover from the control to experimental therapy will not be allowed unless study transitions to a Crossover Phase (see below).

Crossover Phase: The study may transition to a Crossover Phase if the analysis of the multiple primary endpoint of OS for the global ITT population (ie, not including subjects enrolled in the Mainland China Extension Phase) shows statistically significant and clinically meaningful evidence of improvement.

The Crossover Phase will only be implemented upon decision by the Sponsor and following any required discussion with regulatory authorities following review of the data. Crossover may be implemented independently and at different points in time for study sites and subjects in mainland China compared to other sites and subjects in the global study. If the decision is made to enter the Crossover Phase, study sites will have 8 weeks to determine eligibility and begin administration of crossover treatment (cabozantinib + atezolizumab combination) to eligible subjects randomized to the control arm (sorafenib) or the single-agent cabozantinib arm; subsequently no further crossover will be

allowed.
• Subjects randomized to the sorafenib control arm or the single-agent cabozantinib arm will have the option to cross over to receive the cabozantinib + atezolizumab combination if they meet predefined eligibility criteria.
• Subjects randomized to the cabozantinib + atezolizumab experimental arm who are still receiving study treatment and subjects randomized to the sorafenib control arm or the singleagent cabozantinib arm who are still receiving study treatment and do not cross over to the combination treatment (cabozantinib + atezolizumab) may continue on their originally assigned study treatment until a criterion for protocol-defined discontinuation has been met.
• Subjects randomized to the cabozantinib + atezolizumab experimental arm who are in the Post-Treatment Period and subjects randomized to the sorafenib control arm or the single-agent cabozantinib arm who do not cross over to cabozantinib + atezolizumab and are in the Post-Treatment Period will continue with post treatment assessments.

The study is expected to have completed enrollment in the global enrollment phase at the time of transitioning to the Crossover Phase for those subjects, but accrual of subjects in the Mainland China Extension Phase may still be ongoing at that point. In the Crossover Phase safety assessments and efficacy assessments will be performed per the schedule of assessments in Appendix B; PK, biomarker, health-related quality of life (HRQOL), and healthcare resource utilization assessments will be discontinued.
Post-Treatment Period: A first Post-Treatment Follow-up visit (FU-1) for safety evaluation (including subjects in the Maintenance Phase [below]) is to occur 30 (+14) days after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to permanently discontinue study treatment or the date of the last dose of study treatment). A second Post-Treatment Follow-up visit (FU-2) for safety evaluation will be conducted approximately 100 days (±14 days) after the date of the decision to permanently discontinue study treatment. Further details for follow-up and data collection requirements for AEs, SAEs, and AESIs are summarized in Appendix L.
Radiographic tumor and HRQOL assessments are to continue, regardless of whether study treatment is given, reduced, held, or discontinued until a protocol-defined criterion for ending radiographic assessments is met (see Section 5.7.6.2). Consequently these assessments may be required in the Post-Treatment Follow-up Period for some subjects.
In addition, subjects are to be contacted every 12 weeks (± 14 days) after FU-2 to assess survival status and document receipt of subsequent anticancer therapy. This follow-up will continue until the subject expires or the Sponsor decides to discontinue collection of these data; however, these assessments are not required in the Maintenance Phase (below). Every effort must be made to perform these evaluations unless consent for non-interventional study assessment is withdrawn.

Mainland China Extension Phase: After completion of the global enrollment phase, additional subjects (up to 148) may be enrolled in a Mainland China

Extension Phase at sites in mainland China for evaluation in a China subpopulation. The Pre-Treatment, Treatment, and Post-Treatment Periods of the study will be conducted in the same manner in the Mainland China Extension Phase as for subjects who were enrolled in the global enrollment phase.

Study Completion: The study will be considered complete if the null hypothesis is rejected for the primary endpoint of OS (experimental vs control arm) in either of the planned interim analyses or if the final planned analysis for OS has been conducted (irrespective of the results) and any required supportive analyses for China are completed.

Maintenance Phase/Treatment after Study Completion: The purpose of the Maintenance Phase is to continue to provide long-term access to study drug(s) to subjects who are deriving clinical benefit even after evaluation of the study objectives has been completed (Study Completion, see above). When sufficient data have been collected to adequately evaluate all study endpoints, subjects who continue study treatment may enter the study Maintenance Phase. Upon initiation of the Maintenance Phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established and data analyses required for regulatory purposes to have been completed. If a Crossover Phase has been implemented, the Maintenance Phase may not begin before the Week 9 Day 1 (W9D1) visit has elapsed in the Crossover Phase for the last subject randomized to sorafenib or single-agent cabozantinib who crossed over to receive cabozantinib + atezolizumab. The Sponsor is to notify the sites if or when the study will enter the Maintenance Phase or if an alternative post-Study Completion option will be implemented (Section 6.3).
In the Maintenance Phase, subjects will continue to receive study treatment until they meet the protocol-required criteria for treatment discontinuation. Subjects are to undergo periodic safety assessments (including local laboratory tests) and tumor assessments. The nature and frequency of these assessments during the Maintenance phase are to be performed per institutional standard of care and guidance from the Sponsor. It is the Investigator*s responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.
In order to continue to collect important safety information for subjects enrolled in the study during the Maintenance Phase, reporting of SAEs; certain AEs (including irAEs and other AESIs [whether serious or not], and AEs leading to dose modifications or treatment discontinuation); and other reportable events (DILI, pregnancy, and medication errors with sequelae) is to continue per protocol requirements specific to the Maintenance Phase.
The study clinical database will be closed upon initiation of the Maintenance Phase. Important safety information (noted above) collected in the Maintenance Phase will be captured in the safety database. Only data collected prior to implementation of Maintenance Phase will be

reported in a clinical study report.
End of Trial: End of trial is defined as the last scheduled visit or scheduled procedure for the last
subject (including Maintenance Phase assessments).

Intervention

Subjects in the experimental arm will take oral study medication (40 mg of cabozantinib: 2 tablets containing 20 mg each of cabozantinib) once daily.
Atezolizumab will be administered IV every 3 weeks at 1200 mg dose.
Dose reduction levels of cabozantinib will be allowed in the experimental arm (20 mg qd and 20 mg every other day [qod]). Dose reductions for atezolizumab will not be allowed and AEs will be managed by dose delays. Escalation of cabozantinib from 40 mg qd to 60 mg qd is allowed after Sponsor approval for subjects who are tolerating the 40 mg cabozantinib dose level well and have been treated on this dose level for at least 4 weeks. In general, subjects who develop clinically relevant adverse events (eg, Grade 3 or 4 AEs) are not allowed to dose escalate cabozantinib from 40 qd to 60 mg qd.
Subjects in the control arm will take sorafenib orally (2 tablets containing 200 mg each of sorafenib) twice daily. Dose interruptions and reductions will be allowed as per local prescribing information.
Subjects in the single-agent cabozantinib arm will take 60 mg of cabozantinib qd (1 tablet of 60 mg of cabozantinib). Two dose reduction levels of cabozantinib will be allowed in this arm (40 mg daily and 20 mg daily).
Subjects may be allowed to re-escalate following a dose reduction according to the guidance provided in Section 6.6.1.
Subjects will continue study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator or until unacceptable toxicity, the need for alternative anticancer treatment, or other reasons for treatment discontinuation. Continuation of one component of the combination study in the experimental arm (cabozantinib and atezolizumab) while discontinuing the other will be allowed as per protocol defined guidelines.

Study burden and risks

Please see the schedule of events in the protocol, on page 157-161 for a detailed overview of visits, tests and examinations.
The risks associated with this study are described in the informed consent form, chapter 6 and appendix D.

Contacts

Public
Exelixis, Inc.

Harbor Bay Parkway 1851
Alameda CA94502
US
Scientific
Exelixis, Inc.

Harbor Bay Parkway 1851
Alameda CA94502
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria 1. Histological or cytological diagnosis of HCC or clinical diagnosis of HCC in cirrhotic patients by multiphase imaging using CT or MRI per the American Association for the Study of Liver Diseases (AASLD) (Marrero et al 2018) or European Association for the Study of the Liver (EASL 2018) guidelines. Note: Sites must receive Sponsor accreditation for imaging-based diagnosis of HCC prior to implementing this methodology. In addition, subjects who do not meet the AASLD or EASL guidelines for imaging diagnosis of HCC or who do not have cirrhosis must have histological or cytological diagnosis of HCC. 2. The subject has disease that is not amenable to a curative treatment approach (eg, transplant, surgery, ablation therapy) or locoregional therapy (eg, TACE). 3. The subject is receiving antiviral therapy per local standard of care if the subject has active HBV infection (defined by HBsAg positive); the subject must have HBV DNA < 500 IU/mL. 4. Measurable disease per RECIST 1.1 as determined by the Investigator. 5. Barcelona Clinic Liver Cancer (BCLC) stage Category B or C. 6. Child-Pugh Score of A. 7. Recovery to baseline or <= Grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy as determined by the

Investigator. 8. Age eighteen years or older on the day of consent. 9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 10. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days prior to randomization: a. Absolute neutrophil count (ANC) >= 1500/µL (>= 1.5 × 10 9/L) without granulocyte colony-stimulating factor support within 2 weeks before screening laboratory sample collection. b. White blood cell (WBC) count >= 2000/µL (>= 2.0 × 10 9/L). c. Platelets >= 60,000/µL (>= 60 × 10 9/L) without transfusion within 2 weeks before screening laboratory sample collection. d. Hemoglobin >= 9 g/dL (>= 90 g/L) without transfusion within 2 weeks before screening laboratory sample collection. e. Hemoglobin A1c (HbA1c) <= 8% within 28 days before randomization (if HbA1c results are unavailable [eg, hemoglobin variant], a fasting serum glucose <= 160 mg/dL) f. Alanine aminotransferase (ALT), AST, and alkaline phosphatase (ALP) <= 5 × upper limit of normal (ULN). g. Total bilirubin <= 2 mg/dL (<= 34.2 µmol/L). h. Serum albumin >= 2.8 g/dL (>= 28 g/L). i. Serum creatinine <= 1.5 × ULN or calculated creatinine clearance >= 40 mL/min (>= 0.67 mL/sec) using the Cockcroft-Gault equation. j. Urine protein/creatinine ratio (UPCR) <= 1 mg/mg (<= 113.2 mg/mmol), or 24-h protein <= 1 g. 11. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document prior to any screening assessment except those procedures performed as standard of care within the screening window. 12. Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly (see Appendix I) during the course of the study and for 5 months after the last dose of study treatment. A barrier method (eg, condom) is also required. 13. Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria is met: documented permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman > 45 years-of-age in the absence of other biological or physiological causes. In addition, females < 55 years-of-age must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause). Note: Documentation may include review of medical records, medical examination, or medical history interview by study site staff.

Exclusion criteria

Exclusion Criteria 1. Known fibrolamellar carcinoma, sarcomatoid HCC or mixed hepatocellular cholangiocarcinoma. 2. Prior systemic anticancer therapy for advanced HCC including but not limited to chemotherapy, small molecule kinase inhibitors, and ICIs. Subjects who have received local intratumoral or arterial chemotherapy are eligible. 3. Documented hepatic encephalopathy (HE) within 6 months before randomization. 4. Clinically meaningful ascites (ie, ascites requiring paracentesis or escalation in diuretics) within 6 months before

randomization. 5. Subjects who have received any local anticancer therapy including surgery, PEI, RFA, MWA, transarterial chemoembolization (TACE), or transarterial radioembolization (TARE)within 28 days prior to randomization 6. Radiation therapy for bone metastasis within 2 weeks, any other external beam radiation therapy within 8 weeks prior to randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible. 7. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 8 weeks prior to randomization. Subjects who are neurologically symptomatic or are receiving systemic corticosteroid treatment at the planned time of randomization are not eligible. 8. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel), except for the following allowed anticoagulants: • Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH) 9. Administration of a live, attenuated vaccine within 30 days prior to randomization. 10. Any subject who cannot be evaluated by either triphasic liver computed tomography (CT) or triphasic liver magnetic resonance imaging (MRI) because of allergy or other contraindication to both CT and MRI contrast agents. 11. The subject has uncontrolled, significant intercurrent or recent (within the last 3 months before randomization [unless otherwise specified below]) illness including, but not limited to, the following conditions: a. Cardiovascular and cardiac disorders: i. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias. ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment. iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event or thromboembolic event (eg, deep vein thrombosis [DVT], pulmonary embolism) within 6 months before randomization. iv. History of risk factors for torsades de pointes (eg, long QT syndrome). b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation: i. Tumors invading the GI-tract, active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction. ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months prior to randomization. Complete healing of an intra-abdominal abscess must be confirmed prior to randomization. iii. Gastric or esophageal varices that are untreated or incompletely treated with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (according to institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months before randomization are eligible. c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 3 months before randomization. d. Cavitating pulmonary lesion(s) or known endobronchial disease

manifestation. e. Lesions invading major blood vessel, including, but not limited to: inferior vena cava, pulmonary artery, or aorta. Subjects with lesions invading the intrahepatic vasculature, including portal vein, hepatic vein, and hepatic artery, are eligible. f. Other clinically significant disorders such as: i. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjo*gren*s syndrome, Guillain-Barre* syndrome, or multiple sclerosis (see Appendix E for a more comprehensive list of autoimmune diseases and immune deficiencies). Subjects with the following conditions are eligible for the study: • A history of autoimmune-related hypothyroidism and on thyroid replacement hormone • Controlled Type 1 diabetes mellitus and on an insulin regimen • Asthma that requires intermittent use of bronchodilators • Eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only provided all of following are true: o Rash covers < 10% of body surface area o Disease is well controlled at baseline and requires only low-potency topical corticosteroids o No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months ii. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days before randomization. Note: Inhaled, intranasal, intra-articular, and topical corticosteroids and mineralocorticoids are permitted. Transient use of systemic corticosteroids for allergic conditions such as contrast allergy is allowed. iii. Active infection requiring systemic treatment, known history of infection with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or a known positive test for tuberculosis due to tuberculosis infection. Subjects with active hepatitis B virus infection controlled with antiviral therapy are eligible (see Inclusion Criterion 3). Subjects with active, uncontrolled hepatitis C virus infection are eligible provided liver function meets eligibility criteria and are receiving management of the disease per local institutional practice (note: antiviral treatment for HCV is allowed with Sponsor approval). Subjects with history of COVID-19 must have recovered from the disease at least 30 days prior to randomization. iv. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan v. Serious non-healing wound/ulcer/bone fracture. vi. Malabsorption syndrome. vii. Symptoms of thyroid dysfunction with thyroid function test corroboration (Note: asymptomatic subjects with an isolated abnormal free thyroxine [FT4] are eligible) viii. Moderate to severe hepatic impairment (Child-Pugh B or C). ix. Requirement for hemodialysis or peritoneal dialysis. x. History of solid organ transplant including liver transplant, or allogeneic stem cell transplant. See section J. for the remainder of criteria.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-08-2019
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cabometyx
Generic name:	cabozantinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nexavar
Generic name:	sorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tecentriq
Generic name:	atezolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-09-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	10-07-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-003354-24-NL
ClinicalTrials.gov	NCT03755791
CCMO	NL68454.018.19