A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs Placebo in Subjects with Hepatocellular Carcinoma Who Have Received Prior Sorafenib

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The objective of this study is to evaluate the effect of cabozantinib compared with placebo on overall survival in subjects with advanced HCC previously treated with sorafenib.

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

Summary

ID

NL-OMON47199

Source
ToetsingOnline

Brief title
XL184-309

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
livercell cancer, malignant hepatoma

Research involving
Human

Sponsors and support

Primary sponsor: Exelixis Inc
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Cabozantinib, Hepatocellular Carcinoma, Sorafenib

Outcome measures

Primary outcome

Primary endpoint: Overall survival (OS)

Secondary outcome

Secondary endpoints:

* Objective response rate (ORR) per RECIST 1.1

* Progression-free survival (PFS) per RECIST 1.1

Additional endpoints:

* Safety and tolerability

* Pharmacokinetics (PK)

* Relationship of baseline and changes in biomarkers with treatment and/or clinical outcome

* Health-related quality of life (HRQOL) as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)

Study description

Background summary

Hepatocellular carcinoma (HCC) is the second highest cause of cancer-related

deaths globally, behind only lung cancer. HCC is usually resistant to systemic chemotherapy. Sorafenib, a small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR) and other protein kinases, has been shown to improve the time to progression and overall survival in patients with HCC, who eventually progress and succumb to their disease despite treatment (Llovet 2008). At the present time, no drug has demonstrated efficacy in patients with inoperable or metastatic HCC that has progressed after treatment with sorafenib.

MET and VEGF signaling have been implicated in tumor neo-angiogenesis, invasion, and dissemination, and in osteoblast and osteoclast function, while dysregulation of MET and VEGF pathway components has been associated with poor prognosis in multiple tumor types. Resistance to VEGF-targeted therapies may arise from the up-regulation of alternative pro-angiogenic and pro-invasive signaling pathways, including the MET pathway. Consistent with this, combined inhibition of the VEGF receptor (VEGFR) and MET results in efficacy enhanced over that achieved via inhibition of either pathway alone in some tumor models.

Cabozantinib is an orally bioavailable tyrosine kinase inhibitor with potent activity against MET and VEGFR2, as well as a number of other receptor tyrosine kinases that have also been implicated in tumor pathobiology, including RET, KIT, AXL, 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 prolonged survival in a MET-driven transgenic mouse model of HCC. In clinical studies, cabozantinib has demonstrated promising activity in multiple tumor types and in 2012 was approved by the US FDA for the treatment of progressive metastatic medullary thyroid cancer.

A cohort of 41 subjects with HCC was enrolled in a Phase 2 randomized discontinuation study evaluating cabozantinib (Study XL184-203). The majority of subjects (80%) had received prior systemic therapy for the disease; over half (51%) had received prior sorafenib. Extrahepatic spread was present in 73% of subjects, consistent with a relatively poor prognosis. Within the first 12 weeks, 2 subjects had a confirmed partial response (PR) and 32 subjects had stable disease; the Week-12 disease control rate (PR plus stable disease) was 66%. Tumor regression appeared independent of prior sorafenib exposure. Based on the most recent survival data which included 38 deaths among the 41 subjects, the median OS from the initial cabozantinib dose as estimated by the Kaplan-Meier method was 11.5 months (95% CI: 7.3, 15.6) (data on file). Among sorafenib-pretreated subjects, the median OS was 12.9 months (95% CI: 10.8, 16.8). The safety profile was similar to that of other tyrosine kinase inhibitors such as sorafenib, with manageable adverse events (AEs) during treatment.

Study objective

The objective of this study is to evaluate the effect of cabozantinib compared

with placebo on overall survival in subjects with advanced HCC previously treated with sorafenib.

Study design

This is a Phase 3 multicenter, randomized, double-blinded, controlled trial of cabozantinib vs placebo, both with best supportive care.

Intervention

Subjects will take blinded study medication (tablets containing 60 mg of cabozantinib or placebo equivalent) once daily orally at bedtime. Required dose reductions will be in decrements of 20 mg cabozantinib or placebo equivalent. Subjects will continue blinded study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity, the need for subsequent systemic anticancer therapy or liver-directed local anticancer therapy, or other reasons for treatment discontinuation.

Study burden and risks

With an estimated treatment period of 4 months and a study prticipation of 1 year, patients will undergo the following study procedures, during 12-13 study visits (incl. 2-3 phone contacts):
- 9x physical exam and vital signs
- 9x ECOG score
- 5-6x ECG
- 9x blood samples
- 4x urinalysis
- 5x serum pregnancy test (only women who can get pregnant)
- 4x CT/MRI-scan
- 1x bone scan (4x for subjects with bone lesions at screening)
- 7x questionnaire
- 1x tumor biopsy (optional and only if no archival biopsy is available)

Side Effects That Occurred in More Than 20% of Cancer Patients Treated with Cabozantinib:
- Fatigue (tiredness)
- Diarrhea
- Loss of appetite
- Nausea
- Blisters, rash or pain in hands or feet
- Weight loss
- Vomiting
- High blood pressure
- Changes to the way things taste

- Change in voice

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologische of cytologische diagnose van HCC (resultaten van een voorafgaand biopt wordt geaccepteerd)
2. De proefpersoon heeft een ziekte die niet ontvankelijk is voor een curatieve behandelingsmethode (bv. transplantatie, operatie, radiofrequente ablatie)
3. Eerder behandeld met sorafenib
4. Progressie volgend op tenminste 1 eerdere systemische behandeling voor HCC
5. Herstel tot * graad 1 van toxische effecten van eerdere behandelingen, tenzij de bijwerkingen klinisch niet significant zijn en/of stabiel zijn bij ondersteunende behandeling
6. Leeftijd * 18 jaar op de dag van toestemming

7. ECOG-performancestatus van 0 of 1
8. Adequate hematologische functie, gebaseerd op het voldoen aan de volgende laboratoriumcriteria binnen 7 dagen voor randomisatie:
a. absolute aantal neutrofielen (ANC) * 1200/mm3 (* 1,2 x 109/l)
b. bloedplaatjes * 60.000/mm3 (* 60 x 109/l)
c. hemoglobine * 8 g/dl (* 80 g/l)
9. Adequate nierfunctie, gebaseerd op het voldoen aan de volgende laboratoriumcriteria binnen 7 dagen voor randomisatie:
a. serumcreatinine * 1,5 x de bovengrens van normaal of een berekende creatinineklaring * 40 ml/min (gebruikmakend van de Cockroft-Gault-vergelijking: (140 * leeftijd) x gewicht (kg)/(serumcreatinine × 72 [mg/dl]) voor mannen. (Voor vrouwen vermenigvuldigen met 0,85.)
EN
b. urinaire eiwit/creatinine-verhouding (*urine protein/creatinine ratio*, UPCR) * 1 mg/mg (* 113,1 mg/mmol) of eiwit in 24-uurs urine < 1 g
10. Child-pughscore A
11. Totaal bilirubine * 2 mg/dl (* 34,2 µmol/l) binnen 7 dagen voor randomisatie
12. Serumalbumine * 2,8 g/dl (* 28 g/l) binnen 7 dagen voor randomisatie
13. Alanineaminotransferase (ALAT) en aspartaataminotransferase (ASAT) < 5,0 x de bovengrens van normaal (*upper limit of normal*, ULN) binnen 7 dagen voor randomisatie
14. Hemoglobine A1c (HbA1c) * 8% binnen 7 dagen voor randomisatie
(als HbA1c resultaten niet beschikbaar zijn [bv, hemoglobine variant], een nuchtere serum glucose * 160 mg/dL)
15. Antivirale therapie volgens de plaatselijke zorgstandaard in geval van actieve infectie met hepatitis B-virus (HBV)

Exclusion criteria

1. Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma
2. Receipt of more than 2 prior systemic therapies for advanced HCC. Additional prior systemic therapies used as adjuvant or local therapy are allowed.
3. Any type of anticancer agent (including investigational) within 2 weeks before randomization
4. Radiation therapy within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment (eg, I-131 or Y-90) within 6 weeks of randomization. Subject is excluded if there are any clinically relevant ongoing complications from prior radiation therapy.
5. Prior cabozantinib treatment
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization. Eligible subjects must be without corticosteroid treatment at the time of randomization.
7. Concomitant anticoagulation, at therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, low molecular weight heparin (LMWH), thrombin or coagulation factor X (FXa) inhibitors, or antiplatelet agents (eg, clopidogrel). Low-dose aspirin for

cardioprotection (per local applicable guidelines), low-dose warfarin (* 1 mg/day), and low-dose LMWH are permitted.
8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
a. Cardiovascular disorders including
i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias
ii. Uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment
iii. Stroke (including TIA), myocardial infarction, or other ischemic event within 6 months before randomization
iv. Thromboembolic event within 3 months before randomization. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor are eligible
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 (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction
ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,
Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization
c. Major surgery within 2 months before randomization. Complete healing from major surgery must have occurred 1 month before randomization. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before randomization. Subjects with clinically relevant complications from prior surgery are not eligible
d. Cavitating pulmonary lesion(s) or endobronchial disease
e. Lesion invading a major blood vessel including but not limited to :
inferior vena cava, pulmonary artery, or aorta). Subjects with lesions
invading the portal vasculature are eligible.
f. Clinically significant bleeding risk including the following within 3 months of randomization: hematuria, hematemesis, hemoptysis of >0.5 teaspoon (>2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors
g. Other clinically significant disorders such as:
i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)-related illness Subjects with active
hepatitis virus infection controlled with antiviral therapy are eligible.
ii. Serious non-healing wound/ulcer/bone fracture
iii. Malabsorption syndrome
iv. Uncompensated/symptomatic hypothyroidism
v. Requirement for hemodialysis or peritoneal dialysis
vi. History of solid organ transplantation

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding are excluded with the following clarification: subjects with history of prior variceal bleeding must have been treated with adequate endoscopic therapy without any evidence of recurrent bleeding for at least 6 months prior to study entry and must be stable on optimal medical management (e.g. non-selective beta blocker, proton pump inhibitor) at study entry.
10. Moderate or severe ascites
11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before randomization
Note: If the QTcF is > 500 ms in first ECG, a total of 3 ECGs should be performed. If the average of these 3 consecutive results for QTcF is * 500 ms, the subject meets eligibility in this regard.
12. Inability to swallow tablets
13. Previously identified allergy or hypersensitivity to components of the study treatment formulations
14. Pregnant or lactating females
15. Diagnosis of another malignancy within 2 years before randomization, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-04-2014
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cabozantinib
Generic name:	-

Ethics review

Approved WMO Date:	04-07-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-01-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-03-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-11-2018
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-04-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2013□001001□91-NL
ClinicalTrials.gov	NCT01908426
CCMO	NL44658.068.13