A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy

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

Summary

ID

NL-OMON40334

Source
ToetsingOnline

Brief title
XL184-308

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Grawitz' tumour, Renal cell cancer

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Cabozantinib, Everolimus, Metastatic Renal Cell Carcinoma, VEGFR Tyrosine Kinase Inhibitor Therapy

Outcome measures

Primary outcome

Progression-free survival, per RECIST 1.1, per independent radiology committee

(IRC)

Secondary outcome

Secondary efficacy endpoints

• Overall survival

• Objective response rate (ORR) per RECIST 1.1, per IRC

Additional endpoints

• Duration of radiographic response

• Changes in bone scans

• Safety and tolerability

• Characterization of the pharmacokinetics (PK) of cabozantinib

• Change in kidney-cancer related symptoms as assessed by the Functional

Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-19)

• Change in mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression, and global health as assessed by the EuroQol Health

questionnaire instrument (EQ-5D-5L)

• Proportion of subjects with post-randomization skeletal-related events (SREs)

• Relationship of baseline and changes in plasma biomarkers, serum bone

markers, serum calcium, and circulating tumor cells (CTCs) with treatment

and/or clinical outcome

• Health care resource utilization

Study description

Background summary

Renal Cell Carcinoma (RCC) is diagnosed in about 170,000 individuals worldwide each year and results in over 72,000 deaths. Many patients present with advanced or unresectable disease at initial diagnosis. Despite an increasing number of available systemic therapies such as cytokines, VEGFR-inhibitors, and mTOR inhibitors for this malignancy, patients eventually relapse. Therefore, additional, effective therapies are clearly required.

Cabozantinib is an orally bioavailable tyrosine kinase inhibitor (TKI) 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 FLT. Cabozantinib suppresses
MET and VEGFR2 signaling, rapidly inducing apoptosis of endothelial and tumor cells, resulting in tumor regression in a variety of xenograft models. In clinical studies, cabozantinib has demonstrated promising activity in multiple tumor types. Based on the molecular pathophysiology of RCC, there is a strong mechanistic rationale for the evaluation of cabozantinib, with its potent dual inhibition of MET and VEGFR2, for the treatment of RCC.
A recent Phase 1 study enrolled 25 patients with advanced RCC who had at least one prior systemic therapy including VEGFR inhibitors and mTOR inhibitors. In these patients single agent cabozantinib treatment showed substantial antitumor activity. High rates of soft-tissue lesion
reduction and 16-week disease control were observed. Bone scan improvements along with pain alleviation were also reported in individual cases. Median PFS was 14.7 months and median OS had not yet been reached. These clinical observations provide evidence that cabozantinib could be a valuable new treatment option for patients with RCC who experienced disease progression on or after prior VEGFR targeted therapy.

Study objective

The objective of this study is to evaluate the effect of cabozantinib compared with everolimus on progression-free survival (PFS) and overall survival (OS) in subjects with advanced renal cell cancer that has progressed after prior VEGFR tyrosine kinase inhibitor therapy.

Study design

This is a Phase 3 multicenter, randomized, open-label, controlled trial of cabozantinib vs everolimus, with PFS as the primary efficacy endpoint.

Intervention

Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 fashion to receive open-label treatment with either cabozantinib or everolimus as follows:
• Cabozantinib arm: Oral cabozantinib (60 mg) once daily (qd)
• Everolimus arm: Oral everolimus (10 mg) once daily (qd)

Study burden and risks

With an estimated average treatment period of 8 months, a subject*s participation will last approx. 12 months, in which there will be 14 scheduled visits. During these 14 visits the subject will undergo the following assessments:
- 13x physical exam
- 13x vital signs
- 7x ECG
- 13x blood sample
- 12x urine sample
- 11x serum pregnancy test (women of childbearing potential only)
- 1x tumour tissue biopty (optional, only if no archival tissue is available)
- 9x questionnaires
- 6x CT/MRI scan
- 4x bone scan

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

Side Effects That Occurred in More Than 30% of Cancer Patients Treated with Everolimus:
- Mouth sores
- Infections, which can be fatal
- Weakness
- Tiredness
- Cough
- Diarrhea
- Decreased amounts of red blood cells (anemia), which may cause feelings of tiredness or shortness of breath
- Decreased white blood cell counts, which may increase chances of infection
- Increased levels of creatinine in the blood, which may indicate complications with the kidneys
- Increased levels of cholesterol and other fats in the blood.
- Increased levels of sugar in the blood (hyperglycemia)

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. Documented histological or cytological diagnosis of renal cell cancer with a clear-cell component.
2. Measurable disease per RECIST 1.1 as determined by the investigator.
3. Must have received at least one VEGFR-targeting TKI (eg, sorafenib, sunitinib, axitinib, pazopanib or tivozanib).
Prior treatment with other anticancer therapies including cytokines (eg, interleukin-2, interferon-alfa), monoclonal antibodies, (eg, bevacizumaband cytotoxic chemotherapy is allowed (except Exclusion Criterion #1).
4. For the most recently received VEGFR-targeting TKI the following criteria must apply:
a. Must have radiographically progressed during treatment, or been treated for at least 4 weeks and radiographically progressed within 6 months after the last dose.
Radiographic progression is defined as unequivocal progression of existing tumor lesions or developing new tumor lesions as assessed by the investigator on CT or MRI scans.
b. The last dose must have been within 6 months before the date of randomization.
5. Recovery to baseline or <= Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.
6. Age eighteen years or older on the day of consent.
7. Karnofsky Performance Status (KPS) score of >= 70%.
8. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 10 days before randomization:
a. Absolute neutrophil count (ANC) >= 1500/mm3 (>= 1.5 GI/L).
b. Platelets >= 100,000/mm3 (>= 100 GI/L).
c. Hemoglobin >= 9 g/dL (>= 90 g/L).
d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × upper limit of normal.
e. Total bilirubin <= 1.5 × the upper limit of normal. For subjects with Gilbert*s disease <= 3 mg/dL (<= 51.3 µmol/L).
f. Fasting serum triglycerides <= 2.5 × upper limit of normal AND total cholesterol <= 300 mg/dL (<= 7.75 mmol/L). Lipid-lowering medication is allowed.
g. HbA1c <= 8%. For subjects with a condition (eg, hemoglobin variant) that affects the interpretation of HBA1c results, a fasting glucose <= 160mg/dL (<=8.9 mmol/L).
h. Serum creatinine <= 2.0 × upper limit of normal or calculated creatinine clearance >= 30 mL/min (>= 0.5 mL/sec) using the Cockroft-Gault equation (see Table 5-2 for Cockroft-Gault formula).
i. Urine protein-to-creatinine ratio (UPCR) <= 1 mg/mg (<= 113.2 mg/mmol) creatinine or 24-hour urine protein < 1 g.

Exclusion criteria

1. Prior treatment with everolimus, or any other specific or selective TORC1/PI3K/AKT inhibitor (eg, temsirolimus), or cabozantinib.
2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomization.
3. Receipt of any type of anticancer antibody (including investigational antibody) within 4 weeks before randomization.
4. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before randomization. Systemic treatment with radionuclides within 6 weeks before randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
5. 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 neurologically asymptomatic and without corticosteroid treatment at the time of randomization.
6. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel).
Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen.
7. Chronic treatment with corticosteroids or other immunosuppressive agents (with the exception of inhaled or topical corticosteroids or corticosteroids with a daily dosage equivalent <= 10 mg prednisone if given for disorders other than renal cell cancer). Subjects with brain metastases requiring systemic corticosteroid are not eligible.
8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
a. Cardiovascular disorders:
i. Congestive heart failure New York Heart Association class 3 or 4, unstable angina pectoris, 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, or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism) within 6 months before randomization.
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, gastrointestinal perforation, bowel obstruction, or intra-abdominal

abscess within 6 months before randomization.
Note: Complete healing of an intra-abdominal abscess must be confirmed before randomization.
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 pulmonary blood vessels.
f. Other clinically significant disorders such as:
i. Active infection requiring systemic treatment, infection with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or chronic hepatitis B or C infection.
ii. Serious non-healing wound/ulcer/bone fracture.
iii. Malabsorption syndrome.
iv. Uncompensated/symptomatic hypothyroidism.
v. Moderate to severe hepatic impairment (Child-Pugh B or C).
vi. Requirement for hemodialysis or peritoneal dialysis.
vii. History of solid organ transplantation.
9. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 2 months before
randomization. Complete wound healing from major surgery must have occurred 1 month before randomization and from minor surgery (eg, simple excision, tooth extraction) at least 10 days before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
10. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 msec within 10 days before randomization (see Section 5.5.4 for Fridericia formula).
Three ECGs must be performed. If the average of these three consecutive results for QTcF is <= 500 msec, the subject meets eligibility in this regard.
11. Pregnant or lactating females.
12. Inability to swallow tablets or capsules.
13. Previously identified allergy or hypersensitivity to components of the study treatment formulations.
14. 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:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-04-2014
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	Everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cabozantinib
Generic name:	-

Ethics review

Approved WMO

Date:	26-06-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	23-12-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	19-06-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-11-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-12-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-10-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-10-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

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	EUCTR2013-001010-14-NL
ClinicalTrials.gov	NCT01865747
CCMO	NL44646.068.13