A Randomized, Double-blind Study To Evaluate the Efficacy and Safety of Cabozantinib (XL184) at 60 mg/Day Compared to 140 mg/Day in Progressive, Metastatic Medullary Thyroid Cancer Patients

Published: 01-12-2014
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The objective of this study is to evaluate the efficacy of oral cabozantinib at adaily dose of 60 mg compared with 140 mg in subjects with progressive,metastatic MTC.

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

Summary

ID

NL-OMON47076

Source
ToetsingOnline

Brief title
XL184-401

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Medullary Thyroid Cancer, Thyroid Cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cabozantinib, Medullary Thyroid Cancer, Metastatic

Outcome measures

Primary outcome

Primary efficacy endpoint:

* Progression-free survival (PFS) per RECIST 1.1 (Eisenhauer, 2009) per

independent radiology review

Secondary outcome

Secondary efficacy endpoint:

* Objective response rate (ORR) per RECIST 1.1 per independent radiology

review

Study description

Background summary

Previous research has shown that cabozantinib 140 mg / day significantly improved progression-free survival in patients with progressive, metastatic medullary thyroid cancer. However, many patients had a dose reduction to 100 or 60 mg / day due to side effects. This study aims to compare the efficacy of oral cabozantinib 60 mg once daily (the second dose reduction in the Phase 3 study) versus 140 mg once daily, using a non-inferiority design with a primary endpoint of progression-free survival (PFS, progression-free survival). For more information, see the rationale of the protocol.

Study objective

The objective of this study is to evaluate the efficacy of oral cabozantinib at a
daily dose of 60 mg compared with 140 mg in subjects with progressive, metastatic MTC.

Study design

This is a multicenter, randomized, double-blind non-inferiority trial of cabozantinib at 60 mg versus 140 mg once daily, with PFS as the primary efficacy endpoint. Approximately 188 subjects enrolled at up to 100 sites will be randomized in a 1:1 ratio to receive cabozantinib at 60 or 140 mg once daily (qd)
(~94 subjects each).

Intervention

Subjects randomized to the 140 mg treatment arm will receive active capsules and placebo tablet. Subjects randomized to the 60 mg treatment arm will receive active tablet and placebo capsules. Subjects will take blinded study medication once daily (qd) orally.

Study burden and risks

Subjects randomized to the 140 mg treatment arm will receive active capsules and placebo tablet. Subjects randomized to the 60 mg treatment arm will receive active tablet and placebo capsules. Subjects will take blinded study medication once daily (qd) orally.

Patients will be asked to complete worksheets for medication and they will receive additional information about the IP by means of a document.

Side Effects that Occurred in More Than 20% of Cancer Patients Treated with Cabozantinib Given Alone
* Blisters, rash, or pain in hands or feet
* Change in voice
* Changes to the way things taste
* Diarrhea
* Fatigue * High blood pressure
* Loss of appetite
* Nausea
* Vomiting
* Weight loss

Contacts

Public
Exelixis, Inc.

Harbor Bay Parkway 1851
Alameda, CA 94502
US
Scientific
Exelixis, Inc.

Harbor Bay Parkway 1851
Alameda, CA 94502
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. The subject has a histologically confirmed diagnosis of MTC.
2. Availability of tumor tissue for shipment to the central laboratory according to prior determination of RET mutation status:
a. For subjects lacking evidence of a RET of RAS mutation, a recent tumor tissue sample (defined as collected within 6 months prior to randomization) will be required. Tissue shall come from a progressive tumor location, preferably from the most recently progressed metastatic site if feasible. If a recent tumor sample is not available, a tumor biopsy will be obtained during screening.
b. Subjects with documentation of a RET or RAS mutation found in tumor tissue will not be required to submit a recent tumor tissue sample; however, the report demonstrating the subject's RET or RAS mutation must be reviewed

and approved by the sponsor prior to subject randomization.
c. For subjects with documentation of a hereditary RET mutation (ie, pathology report showing presence of a specific RET mutation identified in a blood sample), a tumor sample will not be required. Review and approval of the RET mutation report by the sponsor is required prior to randomization of the subject.
3. The subject has MTC that is metastatic as determined by the investigator based upon computerized tomography (CT), magnetic resonance imaging (MRI), bone scan, PET scan, or X-ray taken within 28 days before randomization.
4. The subject has disease that is measurable per RECIST 1.1 as determined by the investigator based upon CT or MRI images taken within 28 days before randomization.
5. The subject has documented progressive disease (PD) on CT, MRI, PET scan, bone scan, or X-ray as determined by the investigator per RECIST 1.1 on qualifying screening images taken within 4 months prior to randomization as compared to previous images taken within 14 months before the qualifying screening images.
a. PET scan can only be used to establish PD by the presence of new lesions (not to document increases in target or non-target lesions).
b. Bone scan or x-ray, can only be used to establish PD by the presence of new lesions in bone (not to document increases in target or nontarget lesions).
6. The subject has recovered to baseline or CTCAE v4.0 (Common Terminology Criteria for Adverse Events, version 4.0) * Grade 1 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.
7. The subject is * 18 years old on the day of consent.
8. The subject has an ECOG (Eastern Cooperative Oncology Group) status * 1 at screening
9. The subject has adequate organ and marrow function, based upon the following laboratory criteria from assessments performed within 28 days before randomization
a. Absolute neutrophil count (ANC) * 1500/mm3
b. Platelets * 100,000/mm3
c. Hemoglobin * 9 g/dL
d. Total bilirubin * 1.5 x the upper limit of normal (ULN). For subjects with known Gilbert's disease, total bilirubin * 3.0 mg/dL.
e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 x ULN
f. Serum creatinine * 1.5 x ULN or creatinine clearance * 50 mL/min (using the Cockcroft-Gault equation: CrCl (mL/min) <= (140 * age) x wt (kg) / (serum creatinine [mg/dL] x 72); for females multiply by 0.85
g. Urine protein/creatinine ratio (UPCR) * 1 mg/mg (* 113.1 mg/mmol) or 24-hour urine protein < 1 g
h. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test results at screening * 1.3 x the laboratory ULN

10. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document.
11. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (defined in appendix E of the protocol) during the course of the study and for 4 months after the last dose of study treatment
12. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (ie, females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, or ovarian suppression or other reasons.

Exclusion criteria

1. The subject has previously received cabozantinib
2. The subject has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 28 days or five half-lives of the compound or active metabolites, whichever is shorter before randomization or at any time after the date of the qualifying images used to document PD for eligibility
3. The subject has received prior systemic anti-tumor therapy (eg, chemotherapy, biologic modifiers, or anti-angiogenic therapy) within 28 days of randomization (42 days for nitrosoureas or/ mitomycin C) or at any time after the date of the qualifying images used to document PD for eligibility
4. The subject has received any other type of investigational agent within 28 days before randomization or at any time after the date of the qualifying images used to document PD for eligibility
5. The subject has received radiation therapy within 28 days (14 days for radiation for bone metastases) or radionuclide treatment within 42 days of randomization. Subject is ineligible if there are any clinically relevant ongoing complications from prior radiation therapy
6. The subject has untreated and/or active (progressing or requiring anticonvulsants or corticosteroids for symptomatic control) central nervous system (CNS) metastasis. Must have completed radiation therapy * 28 days prior to randomization and stable without corticosteroids or anti-convulsant treatment for * 10 days
7. Concomitant anticoagulation at therapeutic doses with oral anticoagulants or platelet inhibitors

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 transient ischemic attack [TIA]), myocardial infarction, or other ischemic event within 6 months before randomization
iv. Thromboembolic event within 3 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 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 must be confirmed prior to randomization, including radiographic evidence of complete resolution of abdominal abscess
c. Major surgery (eg, open surgery of the chest or abdominal cavity, surgery involving the viscera or removal of a large amount of tissue, removal or biopsy of brain metastasis) within 2 months before randomization. Complete healing from major surgery must have occurred 1 month before randomization. Complete healing from minor surgery 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 (eg, pulmonary artery, aorta, carotid artery, or vena cava)
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
ii. Serious non-healing wound/ulcer/bone fracture
iii. Malabsorption syndrome
iv. Uncompensated/symptomatic hypothyroidism
v. History of solid organ transplantation

9. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days before randomization. Note: If the QTcF is >500 ms in the first ECG, a total of three ECGs should be performed. If the average of these three consecutive results for QTcF is * 500 ms, the subject meets eligibility in this regard.
10. The subject is unable to swallow multiple tablets or capsules
11. The subject has a previously identified allergy or hypersensitivity to components of the study treatment formulation
12. The subject is pregnant or breastfeeding
13. The subject has had a diagnosis of another malignancy within 2 years before randomization, except for superficial scan cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-08-2015
Enrollment:	8
Type:	Actual

Medical products/devices used

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

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-12-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	05-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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□003402□40-NL
ClinicalTrials.gov	NCT01896479
CCMO	NL46204.042.14