A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Cabozantinib (XL184) in Subjects with Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed after Prior VEGFR-Targeted Therapy

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The objective of this study is to evaluate the effect of cabozantinib compared with placebo on PFS and ORR in subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Endocrine neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52807

Source
ToetsingOnline

Brief title
XL184-311

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
Radioiodine-Refractory Differentiated Thyroid Cancer; thyroid 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, Placebo-controlled, Thyroid Cancer

Outcome measures

Primary outcome

Primary endpoints:

• Progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by blinded independent radiology committee (BIRC)

• Objective response rate (ORR) per RECIST 1.1 by BIRC

Secondary outcome

Additional endpoints:

• Overall survival (OS)

• Duration of objective tumor response

• Safety and tolerability

• Pharmacokinetics (PK) of cabozantinib

• Relationship of baseline and postbaseline changes in biomarkers, serum thyroglobulin (Tg), and circulating tumor cells (CTCs) and/or circulating DNA (ctDNA) with treatment and/or clinical outcome assessments may be performed

• Change in mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health as assessed by the EuroQol Health questionnaire instrument (EQ-5D-5L)

• Health care resource utilization

Study description

Background summary

Cabozantinib is an oral anticancer agent which is approved in the United States and in other countries including those in the European Union and other regions of the world, to treat patients with certain types of advanced kidney cancer (renal cell carcinoma), liver cancer (hepatocellular carcinoma), and thyroid cancer (medullary thyroid cancer). Cabozantinib is currently being studied to treat patients with multiple cancer types including your type of cancer. Cabozantinib is considered as an investigational drug for use in radioiodine refractory DTC because it has not been approved by any regulatory authorities for that purpose. To date, cabozantinib has been generally well tolerated in thyroid cancer patients at the doses used in this study.

Study objective

The objective of this study is to evaluate the effect of cabozantinib compared with placebo on PFS and ORR in subjects with RAI-refractory DTC who have progressed after prior VEGFR-targeted therapy.

Study design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of cabozantinib. Best supportive care (BSC) will be provided for subjects on both treatment arms. PFS and ORR (the co-primary efficacy endpoints) will be evaluated by BIRC. Approximately 300 eligible
subjects will be randomized in a 2:1 ratio to receive either cabozantinib or placebo.

Subjects* trial participation will consist of the following periods:
Pretreatment 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 ratio to the following treatment arms:
• Cabozantinib arm: Oral cabozantinib (60 mg) daily (qd)
• Placebo arm: Oral cabozantinib-matched placebo qd
Randomization will be stratified by:
- Receipt of prior Lenvatinib (yes vs no)
- Age at informed consent (<= 65 years vs > 65 years)

Subjects on both arms will be treated with BSC. This excludes nonprotocol anticancer therapy (NPACT).

Crossover Phase: As subjects in the study population have limited treatment options, and to minimize the potential for differential dropout among subjects randomized to placebo with respect to the PFS endpoint as assessed by BIRC, the study will allow eligible subjects randomized to placebo to crossover to receive cabozantinib upon experiencing radiographic disease progression (PD) per RECIST 1.1 that is confirmed by the BIRC. To facilitate this:
• A real-time dual-reader adjudicated BIRC review of radiographic images per RECIST 1.1 will be employed to document objective radiographic PD contemporaneously with subject study participation.
• At the time of investigator-determined radiographic progression per RECIST 1.1, investigators may request from the Sponsor medical monitor (or designee) confirmation of BIRC-determined radiographic PD.
• For subjects with BIRC-confirmed radiographic PD:
• Upon authorization from the Sponsor medical monitor (or designee), investigators may unblind individual subjects via the Interactive Response Technology (IRT) system.
• Unblinded subjects randomized to placebo have the following options:
• Such subjects may be provided by the Investigator the opportunity, if eligible (see Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Appendix B.
• Such subjects who are ineligible or opt not to crossover to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
• Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per Appendix A.
• Subjects without radiographic progression per BIRC will not be unblinded and are to continue to receive blinded study treatment and undergo study assessments according to the schedule in Appendix A.

End of Study Treatment: Subjects will receive blinded study treatment or unblinded treatment with cabozantinib as long as they continue to experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for nonprotocol systemic anticancer treatment. Treatment may continue after radiographic progression as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risk.

Post-Treatment Period: The final safety assessment will occur at the post-treatment follow-up visit 30 (+14) days after the date of the decision to discontinue study treatment unless a Grade 3/4 AE or a serious AE (SAE) is determined to be ongoing (the event would be followed until resolution).

Radiographic tumor assessments and HRQOL (EQ-5D-5L) assessments will continue on the protocol-defined schedule (Appendix A) relative to the date of randomization regardless of whether study treatment is given, reduced, interrupted, or discontinued, including for subjects randomized to placebo who cross over to receive cabozantinib (Appendix B). Consequently these assessments may be required in the Post-Treatment Period, including after the final safety assessment, for some subjects.

In addition, subjects will be contacted approximately every 12 weeks after the Post-Treatment Follow-Up Visit to assess survival status and to document receipt of NPACT and subsequent progression status. Every effort must be made to collect these protocol-specific evaluations unless consent for non-interventional study assessments is withdrawn.

Study Completion by Country or by Site: At the time the Maintenance Phase is initiated, the study will be considered complete at sites and in countries where all subjects have completed post-treatment safety follow-up.

Maintenance Phase: After the primary efficacy endpoints have been analyzed and upon determination by the Sponsor that sufficient data have been collected to adequately evaluate all study endpoints to establish, for regulatory purposes, the safety and efficacy profile of the experimental drug within this study, the study will begin to transition to the Maintenance Phase.
As a transitional step prior to initiation of the Maintenance Phase, all blinded study subjects will be unblinded, and study sites will be notified of their randomized treatment assignments.
• Unblinded subjects randomized to placebo have the following options:
o Such subjects may be provided by the Investigator the opportunity, if eligible (see Appendix B), to enter the Crossover Phase to receive cabozantinib and undergo study assessments per Appendix B.
o Such subjects who are ineligible or opt not to cross over to receive cabozantinib are to have study treatment discontinued and proceed with post-treatment assessments as described in Appendix A.
• Unblinded subjects randomized to cabozantinib may continue on study treatment if the investigator believes the subject is still deriving clinical benefit. Study assessments are to continue per Appendix A.
After the date the entire study is unblinded, study sites will have 8 weeks to determine eligibility and begin administration of crossover cabozantinib treatment to eligible subjects randomized to placebo; subsequently no further crossover will be allowed.
Once the Week 9 Day 1 (W9D1) visit has elapsed in the Crossover Phase for the last placebo subject who crossed over to receive cabozantinib, and upon site notification by the Sponsor, the transition period will end, and the study will enter the study Maintenance Phase.
In the Maintenance Phase, subjects are to be followed as described in Appendix C. Subjects remaining on study treatment will continue to receive it until a criterion for protocol-defined discontinuation has been met. Subjects are to

undergo periodic safety assessments (including local laboratory tests) and tumor assessments; the nature and frequency of these assessments are to be performed per standard of care. It is the Investigator*s responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.
Subjects who discontinue study treatment in the Maintenance Phase, or who had previously discontinued study treatment but had not yet completed the Post-Treatment Follow-Up Visit at the time the transition to the Maintenance Phase, will undergo the final safety assessment at the post-treatment follow-up visit. Upon initiation of the Maintenance Phase, no further follow-up is required for any subject who has completed the Post-Treatment Follow-Up Visit.
The study clinical database will be closed upon initiation of the Maintenance Phase. Only data collected prior to implementation of Maintenance Phase will be reported in a clinical study report.

Intervention

Subjects will take study medication (tablets containing 60-mg or 20-mg cabozantinib or placebo equivalent) once daily orally. 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 nonprotocol systemic anticancer, or other reasons for treatment discontinuation.
The assigned (and highest allowed) dose is 60 mg qd. Two dose reduction levels of the oral study medication (cabozantinib or placebo equivalent) will be allowed (40 mg qd and 20 mg qd).
Placebo tablets that match cabozantinib tablets will be used as the comparator.

Study burden and risks

Please see the schedule of events in the protocol Appendix A (pages 133-137). 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
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria
1. Histologically or cytologically confirmed diagnosis of DTC, including the following subtypes
(Note: results of a previous biopsy will be accepted):
a. Papillary thyroid carcinoma (PTC) including histological variants of PTC such as
follicular variant, tall cell, columnar cell, cribriform-morular, solid, oxyphil,
Warthin-like, trabecular, tumor with nodular fasciitis-like stroma, Hürthle cell variant of
papillary carcinoma, poorly differentiated
b. Follicular thyroid carcinoma (FTC) including histological variants of FTC such as
Hürthle cell, clear cell, insular, and poorly differentiated
2. Measurable disease according to RECIST 1.1 on computed tomography/magnetic resonance
imaging (CT/MRI) performed within 28 days prior to randomization
3. Must have been previously treated with or deemed ineligible for treatment with Iodine-131
for DTC
4. Must have been previously treated with at least one of the following

VEGFR-targeting TKI
agents for DTC: lenvatinib or sorafenib.
(Note: Up to two prior VEGFR-targeting TKI agents are allowed including (but not limited
to) lenvatinib and sorafenib.)
5. Must have experienced documented radiographic progression per RECIST 1.1 per Investigator during or following treatment with a VEGFR-targeting TKI prior to starting the
next anticancer therapy (which may be treatment in this study)
6. Recovery to baseline or <= Grade 1 (Common Terminology Criteria for Adverse Events
Version 5 [CTCAE v5]) from toxicities related to any prior treatments, unless AE(s) are
clinically nonsignificant and/or stable on supportive therapy
7. Age >= 16 years old on the day of consent
8. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
9. Adequate organ and marrow function based upon meeting all of the following laboratory
criteria within 10 days before randomization:
a. Absolute neutrophil count >= 1500/mm3 (>= 1.5 GI/L) without receipt of granulocyte
colony-stimulating factor support within 2 weeks before screening laboratory sample
collection
b. Platelets >= 100,000/mm3 (>= 100 GI/L) without receipt of transfusion within 2 weeks
before screening laboratory sample collection
c. Hemoglobin >= 9 g/dL (>= 90 g/L) without receipt of transfusion within 2 weeks before
screening laboratory sample collection
d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline
phosphatase (ALP) <= 3 × upper limit of normal (ULN). ALP <= 5 × ULN if the subject has
documented bone metastases
e. Bilirubin <= 1.5 × the upper limit of normal (ULN). For subjects with known Gilbert*s
disease <= 3 × ULN
f. Serum creatinine <= 2.0 × ULN or calculated creatinine clearance >= 30 mL/min (>= 0.5 mL/sec) using the Cockcroft-Gault (see Table 5-2 for Cockcroft-Gault formula)
g. Urine protein/creatinine ratio (UPCR) <= 1 mg/mg (<= 113.2 mg/mmol)
10. Must be receiving thyroxine suppression therapy, and TSH must be below the lower cutoff of
the reference range or less than 0.50 mIU/L (< 0.50 µIU/mL), whichever is lower, within 28
days before randomization.

(Note: If hormone replacement therapy is tolerated a TSH level of <= 0.1 mIU/L should be
targeted.)
11. Capable of understanding and complying with the protocol requirements and signed informed
consent (or informed assent and parental/guardian consent for subjects < 18 years of age)
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 during the course of the study and for 4 months after the
last dose of study treatment. For females, such methods include combined hormonal
contraception (oral, intravaginal, dermal), progestogen-only hormonal contraception
associated with inhibition of ovulation (oral, injectable hormonal contraception, implantable
hormonal contraception), placement of an intrauterine device, or placement of an intrauterine
hormone-releasing system. Males must agree to use a barrier method (eg, condom) unless
they have had a vasectomy.
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:
permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or
documented postmenopausal status (defined as 12 months of amenorrhea in a woman over
45 years-of-age in the absence of other biological or physiological causes. In addition,
females under 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. Prior treatment with any of the following:

a. Cabozantinib
b. Selective small-molecule BRAF kinase inhibitor (eg, vemurafenib, dabrafenib)
c. More than 2 VEGFR-targeting TKI agents (eg, lenvatinib, sorafenib, sunitinib, pazopanib, axitinib, vandetanib)
d. More than 1 immune checkpoint inhibitor therapy (eg, PD-1 or PD-L1 targeting agent)
e. More than 1 systemic chemotherapy regimen (given as single agent or in combination
with another chemotherapy agent)
2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase
inhibitor) within 2 weeks or 5 half-lives of the agent, whichever is longer, before
randomization
3. Receipt of any type of anticancer antibody (including investigational antibody) or systemic
chemotherapy within 4 weeks before randomization
4. Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy
within 4 weeks before randomization. Subjects with clinically relevant ongoing complications
from prior radiation therapy that have not completely resolved are not eligible (eg, radiation
esophagitis or other inflammation of the viscera).
5. Known brain metastases or cranial epidural disease unless adequately treated with
radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before
randomization. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of randomization.
6. 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)
• Anticoagulation with therapeutic doses of LMWH in subjects without known brain metastases who are on a stable dose of LMWH for at least 6 weeks before randomization
and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor
7. The subject has uncontrolled, significant intercurrent or recent illness including, but not
limited to, the following conditions:
a. Cardiovascular disorders:

i. Congestive heart failure class 3 or 4 as defined by the New York Heart Association,
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 transient ischemic attack [TIA]), myocardial infarction, or other
ischemic event, or thromboembolic event (eg, deep venous thrombosis [DVT], pulmonary embolism) within 6 months before randomization. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before randomization.
b. Gastrointestinal disorders (eg, malabsorption syndrome or gastric outlet obstruction)
including those associated with a high risk of perforation or fistula formulation:
i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, 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 before randomization
Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization
c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 mL) of red
blood or history of other significant bleeding 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:
• Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic hepatitis B or C infection
• Serious non-healing wound/ulcer/bone fracture
• Malabsorption syndrome
• Moderate to severe hepatic impairment (Child-Pugh B or C)
• Requirement for hemodialysis or peritoneal dialysis
• Uncontrolled diabetes mellitus
• History of solid organ transplantation
8. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 8 weeks before
randomization. Complete wound healing from major surgery must have occurred 4 weeks
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.
9. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 28 days
before randomization
Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs
at intervals of approximately 3 min must be performed within 30 min after the initial ECG,
and the average of these 3 consecutive results for QTcF will be used to determine eligibility.
10. Pregnant or lactating females
11. Inability to swallow tablets
12. Previously identified allergy or hypersensitivity to components of the study treatment
formulations
13. Diagnosis of another malignancy within 3 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:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-12-2019

Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cabometyx 20 mg
Generic name:	cabozantinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Cabometyx 60 mg
Generic name:	cabozantinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	06-03-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	29-10-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	10-01-2020

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	20-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	13-09-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	08-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	16-09-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	13-10-2022

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-12-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	23-01-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.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	EUCTR2018-001771-21-NL
ClinicalTrials.gov	NCT03690388
CCMO	NL68743.058.19