A PHASE II, MULTICENTRE, OPEN-LABEL STUDY OF CABOZANTINIB AS 2ND LINE TREATMENT IN SUBJECTS WITH UNRESECTABLE, LOCALLY ADVANCED OR METASTATIC RENAL CELL CARCINOMA WITH A CLEAR-CELL COMPONENT WHO PROGRESSED AFTER 1ST LINE TREATMENT WITH CHECKPOINT INHIBITORS

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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-OMON52966

Source
ToetsingOnline

Brief title
Ipsen Cabopoint

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
kidney cancer, RCC

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cabozantinib, Metastatic, Phase II, Renal Cell Canrcinoma

Outcome measures

Primary outcome

Primary Study Objective:

• To assess the efficacy of cabozantinib by the objective response rate (ORR)

per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 evaluated by

independent central review in cohort A.

Secondary outcome

Secondary Study Objectives:

• To assess other efficacy criteria of cabozantinib such as time to response

(TTR), duration of response (DOR), disease control rate (DCR), progression-free

survival (PFS) by independent and Investigator*s review;

• To assess objective response rate (ORR) by independent central review and

Investigator's review in cohort B;

• To assess objective response rate (ORR) by Investigator*s review in cohort A;

• To assess overall survival (OS);

• To assess the ORR and PFS by Investigator's review and OS in overall

population (cohorts A+B);

• To assess the change in disease-related symptoms as assessed by the

Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-DRS)

questionnaire;

• To assess the safety and tolerability of cabozantinib.

Study description

Background summary

Renal cell carcinoma (RCC) comprises a heterogeneous group of kidney cancers and is one of the ten most common cancers worldwide, with more than 300,000 new cases each year. The most common subtypes (>=5% incidence) include clear-cell RCC (ccRCC), papillary RCC (pRCC) and chromophobe RCC (chRCC). The other subtypes are either very rare (each with <=1% total incidence) or designated as unclassified RCC (uRCC, approximately 4% total incidence) when it is not possible to diagnose the tumour according to any other subtype. The ccRCC subtype is associated with most kidney cancer deaths and is predominant in metastatic disease (83-88%). It is estimated that around 25 50% of subjects with localised disease eventually develop metastatic RCC and that up to 30% of subjects considered disease-free after curative treatment for localised RCC will relapse.

The purpose of this study is to find out how safe and effective cabozantinib is for the treatment of unresectable, locally advanced metastatic RCC, after cancer progression with CPI treatment combined or not, with anti-VEGF therapy. The new drug used in this study is cabozantinib (known with the brand name Cabometyx®), which will be referred to as the *study drug* in the remainder of the document. The study drug belongs to a drug class that targets specific proteins that blocks the cancer growth. This drug class has become the standard of care for the treatment of patients with advanced RCC.

Study objective

The overall objective of this study is to evaluate the efficacy and safety of cabozantinib as 2nd line treatment in subjects with unresectable, locally

advanced or metastatic renal cell carcinoma (RCC) with a clear-cell component, who progressed after prior checkpoint inhibitors (CPI) therapy with ipilimumab and nivolumab in combination or CPI combined with vascular endothelial growth factor (VEGF)-targeted therapy.

Study design

This is a Phase II, multicentre, open-label study to evaluate the efficacy and safety of cabozantinib 60 mg once daily (q.d.) in adults with unresectable, locally advanced or metastatic RCC with a clear-cell component that progressed, according to Investigator*s judgement, after prior CPI therapy (ipilimumab and nivolumab) alone or CPI combined with VEGF-targeted therapy. Approximately 250 eligible subjects will receive cabozantinib (two independent cohorts with 125 subjects each).

Intervention

All subjects will be treated with oral cabozantinib 60 mg q.d. In case of treatment-emergent toxicity, the Investigator may decide to reduce the dose to 40 mg or 20 mg according to the instructions specified in this protocol.
The date of the first dose of cabozantinib is defined as baseline (Day 1, Visit 2) and should occur within 15 days after the Screening visit. Doses will be self-administered at home by taking cabozantinib q.d. at the same time each day (preferably at bedtime). Cabozantinib should not be taken with food. The subject should not eat anything for at least 2 hours before and 1 hour after taking cabozantinib.
If a dose is missed, the missed dose should not be taken less than 12 hours before the next one.

Study burden and risks

WHAT PARTICIPATION INVOLVES

If you participate, your participation will last a total of approximately 42 months.
You will come to the study center for 4 visits during the first month of the study, after which you will have one visit per month until the end of your treatment with the study medication. After the end of your treatment period, you will receive a follow-up phone call every 12 weeks, up to the end of the study. There may be additional unscheduled study visits based on your study doctor*s decision of your medical needs. For a clear overview of the visits and procedures done, please see appendix C in the ICF.

Screening
First, we determine whether you can participate. The following assessment and procedures will take place during screening:

• The study doctor will review the entry criteria with you, to find out whether or not you qualify to be in this study.
• You will be asked to sign this consent form if you agree to take part in this study. You will read, review, and sign this ICF if you choose to take part in this study.
• You will be asked about your demographic data (age, sex).
• You will be asked about your medical history and any medications you use/have used.
• You will be asked about your RCC history and any surgery, radiotherapy, chemotherapy, or medications related to the same.
• You will have a physical examination, your weight, height and vital signs (blood pressure and heart rate) will be measured.
• You will have an Eastern Cooperative Oncology Group (ECOG) performance status assessment to see how your cancer is progressing and to determine your level of functioning in terms of your ability to take care of yourself, daily activities and physical ability (walking, working, etc.).
• You will have an electrocardiogram (ECG). This is a painless, non-invasive test that shows how your heart works (takes a picture of the electrical activity of your heart).
• You will be asked to give blood and urine samples which will be tested to assess your general well-being (including thyroid function and clotting of blood) and to assess for any medical abnormalities.
• If you are a female and can get pregnant, you will have a blood test or a urine pregnancy test to confirm that you are not pregnant. You will not have this pregnancy test, if you had a previous hysterectomy (removal of your uterus), bilateral oophorectomy (removal of both your ovaries), or your hormone test (follicular stimulating hormone) indicates that you are post-menopausal.
• You will have a CT scan or a MRI scan within 28 days before you receive first dose of study drug. These scans are performed to confirm and assess your cancer. During the MRI scan, you may be asked to lie down on your back on a table and you will need to stay still until the scan is over. Each MRI scan will take less than 1 hour.
• You may have a brain CT or MRI scan and/or a bone scan, if your study doctor suspects that you have developed brain and/or bone metastases, 28 days before you receive first dose of the study drug. A bone scan is used to detect bone tumors or cancer that has spread to the bone. For the bone scan, a radioactive material is injected into the bloodstream. After a few hours, the radioactive material collects in the bones and is detected by a scanner.
Sometimes we find something during the scans that requires further medical investigation. We will always tell you. Further investigation is carried out by the primary care physician or specialist. The cost of this will be borne by your own insurance. You will be monitored for any side effects or symptoms after signing of the ICF until the end of the study.
If you are found eligible and agree to be in this study, depending on the duration of your first line treatment, you may not be included in the study, if the maximum number of patients is reached. If applicable, your study doctor will discuss this situation with you.

Treatment
We will treat you approximately 8 months with the study drug. The exact duration will depend on the course of your disease. You will be given bottles containing tablets of the study drug. This contains daily doses until your next visit. You will start taking the study drug on the day of Visit 2 at home as per the study doctor*s instructions. You will take 1 tablet daily with a full glass of water 2 hours after your meal (e.g., your evening meal), at around the same time every day. You cannot take the study drug with food; thus, you must not have food 2 hours before and 1 hour after taking study drug. The tablet must be taken whole, so you should not crush or chew the tablet. If you miss a dose, you should not take additional tablets to make up for it, and you should not take the missed dose if the next dose is to be taken in less than 12 hours. During the study, your study doctor may reduce your dosage of study drug according to your situation. In case of any uncertainties regarding dosage please do not hesitate to contact your study doctor.
This study is *open label*, which means that both you and the study doctor will know that you will receive cabozantinib.

Visits and tests
For the study, during the treatment period, you have to visit the hospital every month except during the first month (then you need to visit the hospital every2 weeks). A visit will take app 2.5 hours.
During these visits, most of the procedures from the screening will be repeated. In addition, the following will take place:
• You will be asked about any medications you have taken since the last visit or are currently taking.
• You will be asked if you have experienced new or worsening of any illness, side effects or injury since your last visit.
• You will also be asked to complete a quality of life questionnaire before being given the first dose of the study drug, which is a 9 item questionnaire that includes questions related to your energy levels, general pain, weight loss, bone pain, fatigue, shortness of breath, if you have been coughing, if you are bothered by fevers, and if you have had blood in your urine. The questionnaire will take approximately 10 minutes of your time.
• You will be given the bottle of study drug (30 tablets per bottle) and you will be advised to take the study drug 60 mg (one tablet) once daily by yourself at home. In case of any side effects, the study doctor may reduce the study drug dose to 40 mg or 20 mg once daily.
• At some Visits, you will be asked to return any unused study drug and then be given a fresh stock of study drug. You will be asked if you are taking the study drug regularly and as instructed by the study doctor.

End of Study Treatment Visit
The End of Study Treatment visit will be carried out 30 days to 45 days after you have received the last dose of the study drug and also for subjects who have discontinued study treatment whatever the reason (e.g., disease progression, unacceptable toxicity or withdrawal of consent).

Appendix C in the ICF states which procedures will take place at each of the visits.

Post-Treatment Follow-up Period
If you discontinue study treatment you will enter the Post-Treatment Follow-Up period. You will be contacted every 12 weeks after the End of Study Treatment Visit and you will be asked about your other cancer treatments, and your health status will be assessed. You may have a chest abdomen pelvic and/or a brain CT or MRI scan and/or a bone scan based on your study doctor*s decision. You will also be asked if you have experienced any side effects or symptoms after the last dose of the study drug.

Early Study Withdrawal Visit
If you prematurely discontinue from the study during the Study Treatment period, you will be invited to attend the Early Study Withdrawal Visit. All the procedures applicable to End of Study Treatment Visit will be performed during this visit.

Unscheduled visits
If an unexpected or unwanted event happens during the study, you may be asked to come to the study center for more tests or procedures. Some of the tests or procedures done during the study may have to be repeated at no extra cost, if the results are not usable or are not normal. If additional visits are required during your participation in this study, your study doctor may perform some procedures and evaluations (see appendix C of the ICF for an overview).

POSSIBLE SIDE EFFECTS

The study drug and study procedures may involve unknown risks. Any medication can have temporary and permanent side effects and can cause unforeseen adverse reactions, although not everybody gets them. Results from completed clinical studies suggest that cabozantinib is generally well tolerated.
If you have any side effects, your study doctor may tell you to take the study drug at a lower dose. Your study doctor may also prescribe other medicines to help control your side effects.

Tell your doctor straight away if you notice any of the following side effects - you may need urgent medical treatment:
• Symptoms including pain in the abdomen, nausea (feeling sick), vomiting, constipation, or fever. These may be signs of a gastrointestinal perforation, a hole that develops in your stomach or intestine that could be life-threatening.
• Severe or uncontrollable bleeding with symptoms such as: vomiting blood, black stools, bloody urine, headache, coughing up blood.
• Swelling, pain in your hands and feet, or shortness of breath.
• A wound that does not heal.
• Fits, headaches, confusion, or finding it difficult to concentrate. These may

be signs of a condition called reversible posterior leukoencephalopathy syndrome (RPLS) and is also known as Posterior Reversible Encephalopathy Syndrome (PRES). RPLS (or PRES) is rare (it affects less than 1 in 1000 people).
• Feeling drowsy, confused or loss of consciousness. This may be due to liver problems.

Side Effects
These side effects are very common (Occurs in 1 in 10 people or more):
• Stomach upset, including diarrhoea, nausea, vomiting, constipation, indigestion, abdominal pain
• Blisters, pain in the hands or soles of the feet, rash or redness of the skin
• Decreased appetite, weight loss, altered sense of taste
• Fatigue, weakness, headache, dizziness
• Hypertension (increase in blood pressure)
• Anaemia (low levels of red blood cells)
• Redness, swelling or pain in the mouth or throat, difficulty in speaking, hoarseness, cough
• Shortness of breath
• Changes in blood tests used to monitor general health and function of your organs (including the liver and kidney), low levels of electrolytes (like magnesium or potassium)
• Reduced thyroid activity; symptoms can include: tiredness, weight gain, constipation, feeling cold and dry skin
• Swelling in your legs and arms
Common and less common side effects and discomforts from tests performed during the study, are described in Appendix D of the ICF.

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) Subjects must provide a signed informed consent prior to any study-related procedures;
(2) Male or female subjects must be aged >=18 years on the day the informed consent is signed;
(3) Subjects must have histologically confirmed unresectable, locally advanced (defined as disease not eligible for curative surgery or radiation therapy) or metastatic RCC with a clear-cell carcinoma component;
(4) Subjects must have radiographic disease progression, according to Investigator*s judgement, following 1st line treatment with CPI (ipilimumab plus nivolumab) (Cohort A) or CPI in combination with VEGF-targeted therapy (Cohort B);
(5) Subjects present >=1 target lesion according to RECIST 1.1 per investigator;
(6) Subjects should have Eastern Cooperative Oncology Group (ECOG) status 0-1;
(7) Subjects with treated brain metastases are eligible if metastases have been shown to be stable as per Investigator*s judgement;
(8) Subjects must have adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 15 days before baseline:
(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) Serum creatinine <= 2.0 × upper limit of normal or calculated creatinine clearance >= 30 mL/min (>= 0.5 mL/sec) using the Cockcroft-Gault equation

(h) Urine protein-to-creatinine ratio (UPCR) <= 1 mg/mg (<= 113.2 mg/mmol) creatinine or 24-hour urine protein < 1 g.
(9) Subject must have recovered 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;
(10) Subjects must have completed a steroid taper, if he/she experienced an immune-related adverse event associated with previous CPI treatment;
(11) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) must provide a negative pregnancy test within 7 days prior to the start of study treatment. If a urine test cannot be confirmed as negative, a negative serum pregnancy test is required;
(12) Female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile) 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;
(13) All male participants must agree to refrain from donating sperm and unprotected sexual intercourse with female partners during the study and for 120 days after the last dose of study treatment;
(14) Subjects must be willing and able to comply with study requirements, remain at the investigational site for the required duration of each study visit and be willing to return to the investigational site for the follow up evaluation, as specified in the protocol.
(15) Subjects must be covered by social security or be the beneficiary of such a system (only applicable for French subjects).

Exclusion criteria

(1)Inability to swallow tablets;
(2)treated with any other investigational medicinal product (IMP) within the last 30 days before baseline;
(3)previously treated with cabozantinib;
(4)Has a contraindication to Magnetic Resonance Imaging (MRI) or contrast medium used for Contrast Tomography (CT)-scan;
(5)Presents untreated brain or leptomeningeal metastases, or current clinical or radiographic progression of known brain metastases;
(6)diagnosis of a serious cardiovascular disorder:
(a)Congestive heart failure New York Heart Association class 3 or 4, unstable angina pectoris, or serious cardiac arrhythmias;
(b)Uncontrolled hypertension, defined as sustained blood pressure (BP) (>140 mm Hg systolic or>90 mm Hg diastolic pressure) despite optimal antihypertensive treatment;

(c)Stroke (including transient ischaemic attack (TIA)), myocardial infarction (MI) or other ischaemic event, or thromboembolic event (e.g. deep venous thrombosis, pulmonary embolism) within 6 months before screening;
(d)History of risk factors for torsades de pointes (eg, long QT syndrome);
(7)receiving a concomitant anticoagulation with oral anticoagulants (e.g. warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors
Note:Low dose aspirin for cardioprotection (per local applicable guidelines) and low dose LMWH are permitted.
(8)gastrointestinal (GI) disorder including those associated with a high risk of perforation or fistula formation:
(a)Tumours 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;
(b)Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before screening;
Note: Complete healing of an intra-abdominal abscess must have been confirmed before screening.
(9)Presents a corrected QT (QTc) interval calculated by the Fridericia formula (QTcF)>500 msec within 1 month prior to baseline;
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 three consecutive results for QTcF will be used to determine eligibility
(10)clinically significant haematuria, hematemesis, or haemoptysis of >0.5 teaspoon (2.5 mL) of red blood, or other history of significant bleeding within 3 months before screening;
(11)cavitating pulmonary lesion(s) or known endobronchial disease manifestation;
(12)lesions invading major pulmonary blood vessels;
(13)diagnosed with other clinically significant disorders such as:
(a)Serious nonhealing wound/ulcer/bone fracture;
(b)Malabsorption syndrome;
(c)Free thyroxine (FT4) outside the laboratory normal reference range;
(d)Uncompensated/symptomatic hypothyroidism;
(e)Moderate to severe hepatic impairment
(f)Requirement for haemodialysis or peritoneal dialysis
(g)History of solid organ transplantation;
(14)predicted life expectancy of less than 3 months;
(15)prior surgery within 4 weeks prior to baseline. Note: If the subject has undergone major surgery, complete wound healing must have occurred 1 month prior to baseline.
(16)palliative radiation therapy for bone within 2 weeks or for radiation fields including viscera within 4 weeks prior to baseline. Note: Resolution/healing of side effects must be complete prior to baseline;
(17)history of another active malignancy within 3 years from screening except for locally curable cancers that have been apparently cured, such as low-grade thyroid carcinoma, prostate cancer not requiring treatment , basal or squamous

cell skin cancer, superficial bladder cancer, in situ melanoma, in situ prostate, cervix or breast carcinoma or other treated malignancies with <5% chance of relapse according to the Investigator;
(18)history of allergy to study treatment components or agents with a similar chemical structure or any excipient used in the formulation as listed in the SmPC document;
(19)rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption;
(20)serious medical or psychiatric condition that render the subject unable to understand the nature, scope and possible consequences of the study, and/or presents an uncooperative attitude;
(21) pregnant or breastfeeding. A β-human chorionic gonadotrophin (HCG) serum pregnancy test will be performed up to 7 days prior to baseline for all female subjects of childbearing potential (i.e. less than or equal to 2 years post-menopause and not surgically sterile);
(22)likely to require treatment during the study with drugs that are not permitted by the study protocol;
(23)abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the subject*s safety.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-10-2020
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cometriq
Generic name:	Cabozantinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-01-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-04-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-05-2021
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2018-002820-18-NL
ClinicalTrials.gov	NCT03945773
CCMO	NL72371.028.19