A Randomized, Double-Blind, Controlled Phase 3 Study of Cabozantinib in Combination with Nivolumab and Ipilimumab versus Nivolumab and Ipilimumab in Subjects with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma of Intermediate or Poor Risk

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

Summary

ID

NL-OMON49041

Source
ToetsingOnline

Brief title
COSMIC-313

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Hypernephroma, Renal Cell Cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cabozantinib Nivolumab Ipilimumab, Intermediate or Poor Risk, Renal Cell Carcinoma, with Previously Untreated Advanced or Metastatic

Outcome measures

Primary outcome

Duration of PFS, per Response Evaluation Criteria in Solid Tumors version 1.1

(RECIST 1.1), by Blinded Independent Radiology Committee (BIRC)

Secondary outcome

Secondary efficacy endpoint:

• Duration of OS

Additional endpoints:

• ORR per RECIST 1.1 by BIRC

• PFS and ORR per RECIST 1.1 by BIRC according to PD-L1 status

• PFS and ORR per RECIST 1.1 as assessed by the Investigator

• Duration of radiographic response as assessed by the Investigator and by

BIRC

• Safety through the evaluation of AEs, including immune-related AEs (irAEs),

and other safety assessments.

• Pharmacokinetics (PK) of cabozantinib given in combination with nivolumab and

ipilimumab

• Immunogenicity of nivolumab and ipilimumab given in combination with

cabozantinib

• Correlation of biomarker analyses with clinical outcomes

• Health-related quality of life (HRQoL) as assessed by the EuroQol Health

questionnaire instruments (EQ 5D 5L)

• Health care resource utilization

Study description

Background summary

Renal cell carcinoma (RCC) is the eighth most common cancer in the world. RCC accounts for 90% to 95% of malignant neoplasms arising from the kidney. Globally, over 330,000 cases of RCC are reported each year with over 100,000 deaths occurring as a result of progression of metastatic disease (Znaor et al 2015). In the United States, there are approximately 65,000 new cases each year and about 15,000 deaths from RCC annually (Siegel et al 2018). Recent advances in surgical and systemic therapies have significantly changed the management of RCC. However, the rate of RCC-related mortality has increased despite earlier detection of smaller kidney tumors (Sun et al 2011; Hollingsworth et al 2006). Over the last decade, an increased understanding of the biology of RCC has led to development of multiple agents that target specific growth pathways. The vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways have been found to be important targets in RCC disease. Multiple drugs targeting these pathways have been approved, including cabozantinib which targets the VEGF pathway and other receptor tyrosine kinases (RTKs; Banumathy and Cairns 2010). More recently treating cancer with immunotherapies has also expanded treatment options. Nivolumab, a programmed death receptor 1 (PD-1) antibody, is the only immune checkpoint inhibitor (ICI) indicated for the treatment of relapsed disease (Opdivo* US PI). Recently, the results of the Checkmate-214 trial (Motzer et al 2018) led to approval in the US and other regions of nivolumab in combination with ipilimumab for patients with intermediate- or poor-risk, previously untreated advanced RCC, which

constitutes the control arm of this study.

Study objective

The objective of this study is to evaluate the efficacy and safety of cabozantinib in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab in previously untreated subjects with intermediate- and poor-risk advanced or metastatic RCC.

Study design

This is a multicenter, randomized, double-blinded, controlled Phase 3 trial of cabozantinib in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab in combination with matched placebo. Approximately 840 eligible subjects with intermediate- or poor-risk advanced or metastatic RCC by IMDC criteria will be randomized in a 1:1 ratio (420 per treatment arm) at approximately 180 sites.
The study was originally designed to enroll 676 subjects; the sample size was increased to accommodate new, external data about the expected median OS in the control arm (see Protocol Section 9.5)

Intervention

Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 fashion to receive double-blinded study treatment as follows:

Experimental arm:
Cabozantinib (40 mg oral, once daily [qd]) + nivolumab (3 mg/kg infusion, once every 3 weeks [q3w]) x 4 doses + ipilimumab (1 mg/kg infusion, q3w) x 4 doses, followed by cabozantinib (40 mg oral qd) + nivolumab infusion (480 mg flat dose q4w). Nivolumab will be administered for a maximum of 2 years.

Control arm:
Cabozantinib-matched placebo (oral, qd) + nivolumab (3 mg/kg infusion, q3w) x 4 doses + ipilimumab (1 mg/kg infusion, q3w) x 4 doses,
followed by cabozantinib-matched placebo (oral, qd) + nivolumab infusion (480 mg flat dose q4w). Nivolumab will be administered for a maximum of 2 years.

Study burden and risks

There are 10 visits during the first 14 to 17 weeks and then once every 4 weeks.The following study procedures will be performed: A pharmacokinetic (PK) tests, an anti-drug antibody (or immunogenicity) tests, a biomarker tests, a CT or MRI scan, blood will be drawn, and a Quality of Life questionnaire will be completed.

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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. Histologically confirmed advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) renal cell carcinoma with a clear-cell component, including subjects who also have a sarcomatoid feature.
2. Intermediate- or poor-risk RCC as defined by IMDC criteria.
3. Measurable disease per RECIST 1.1 as determined by the Investigator. Measurable disease must be outside the radiation field if radiation therapy was previously administered.
4. Shipment of archival tumor tissue (unstained slides or paraffin block to the study central laboratory prior to randomization. The tumor tissue can be obtained from any organ except brain or bone and must have been biopsied no more than 2 years prior to the date of informed consent. Alternatively, a fresh tumor sample must be obtained and shipped to the study central laboratory prior

to randomization if archival tumor tissue is unavailable or inadequate.
5. Recovery to baseline or <= Grade 1 CTCAE v5 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy. Examples of exceptions are subjects with Grade 2 neuropathy or alopecia who are allowed for trial participation.
6. Age eighteen years or meeting country definition of adult, whichever is older, on the day of consent.
7. Karnofsky Performance Status (KPS) >= 70%.
8. Adequate organ and marrow function, based upon meeting all of the following laboratory criteria within 14 days prior to randomization:
a. Absolute neutrophil count (ANC) >= 1500/µL (>= 1.5 GI/L) without granulocyte colony stimulating factor support within 2 weeks before screening laboratory sample collection.
b. Criterion intentionally left blank.
c. Platelets >= 100,000/µL (>= 100 GI/L) without transfusion within 2 weeks before screening laboratory sample collection.
d. Hemoglobin >= 8 g/dL (>= 80 g/L) without transfusion within 1 week before screening laboratory sample collection and no clinical evidence of bleeding.
e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <= 3 x ULN.
f. Total bilirubin <= 1.5 x ULN (with the exception that total bilirubin for subjects with Gilbert*s disease <= 3 x ULN).
g. Serum creatinine <= 1.5 x ULN or calculated creatinine clearance >= 40 mL/min (>= 0.67 mL/sec) using the Cockcroft-Gault equation.
h. Urine protein-to-creatinine ratio (UPCR) <= 1 mg/mg (<= 113.2 mg/mmol), or 24-h urine protein <= 1
9. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document prior to any screening assessments except those procedures performed as standard of care within the screening window.
10. Sexually active fertile subjects and their partners must agree to use highly effective methods of contraception during the course of the study and for 5 months for women, and 7 months for men, after the last dose of study treatment. A barrier contraceptive method (eg, condom) is also required.
11. 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 are met: documented permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman > 45 years-of-age in the absence of other biological or physiological causes. In addition, females < 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

1. Prior systemic anticancer therapy for unresectable locally advanced or metastatic RCC including investigational agents.
Note: One prior systemic adjuvant therapy is allowed for completely resected RCC and if recurrence occurred at least 6 months after the last dose of adjuvant therapy.
Note: Adjuvant therapy with a PD1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor is not permitted.
2. Radiation therapy for bone metastasis within 2 weeks, any other radiation therapy within 4 weeks prior to randomization. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
3. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or radiosurgery and stable for at least 4 weeks prior to randomization after radiotherapy, or at least 4 weeks prior to randomization after major surgery (eg, removal or biopsy of brain metastasis). Subjects who are neurologically symptomatic as a result of their CNS disease or are receiving systemic corticosteroid treatment (prednisone equivalent > 10 mg/day) at the planned time of randomization are not eligible.
4. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel).
a. Allowed anticoagulants are:
i. Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH)
ii. Therapeutic doses of LMWH in subjects without known brain metastases who are on a stable dose of LMWH for at least 1 week before randomization without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor
Note: Subjects who switch from an oral anticoagulant to LMWH are allowed if the oral anticoagulant was stopped >= 5 half-lives of the oral anticoagulant prior to planned randomization date.
5. Administration of a live, attenuated vaccine within 30 days prior to randomization. The use of inactivated (killed) vaccines for the prevention of infectious disease is permitted.
6. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
a. Cardiovascular disorders:
i. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, unstable angina pectoris, serious cardiac arrhythmias (eg, ventricular flutter, ventricular fibrillation, Torsades de pointes).
ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment.
iii. Stroke transient ischemic attack (TIA), myocardial infarction, or other symptomatic ischemic event or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism [DVT/PE]) within 6 months before randomization.
Note: Subjects with a diagnosis of DVT within 6 months are allowed if

asymptomatic and stable at screening and treated with LMWH for at least 1 week before randomization.
Note: Non-symptomatic white matter disease in the brain is acceptable.
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, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months prior to randomization. Complete healing of an intra abdominal abscess must be confirmed prior to 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. Autoimmune disease that has been symptomatic or required treatment within the past two years from the date of randomization.
Note: Patients with a history of Crohn*s disease or ulcerative colitis are always excluded.
Note: Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
ii. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization.
Note: Inhaled, intranasal, intra-articular, or topical steroids are permitted. Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted. Transient short-term use of systemic corticosteroids for allergic conditions (eg, contrast allergy) is also allowed.
iii. Active infection requiring systemic treatment. Acute or chronic hepatitis B or C infection, known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or known positive test for tuberculosis infection where there is clinical or radiographic evidence of active mycobacterial infection.
iv. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
v. Serious non-healing wound/ulcer/bone fracture.
vi. Malabsorption syndrome.
vii. Uncompensated/symptomatic hypothyroidism.
viii. Moderate to severe hepatic impairment (Child-Pugh B or C).
ix. Requirement for hemodialysis or peritoneal dialysis.
x. History of solid organ or allogeneic stem cell transplant.

xi. Known history of COVID-19 unless the subject has clinically recovered from the disease at least 30 days prior to randomization.
7. Major surgery (eg, nephrectomy, GI surgery, removal or biopsy of brain metastasis) within 4 weeks prior to randomization. Minor surgeries within 10 days prior to randomization. Subjects must have complete wound healing from major or minor surgery before randomization. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
8. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 14 days before randomization. Furthermore, subjects with a history of additional risk factors for torsades de pointes (eg, long QT syndrome) are also excluded.
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
9. History of neuropsychiatric disorder likely to interfere with ability to comply with protocol requirements or give informed consent.
10. Pregnant or breastfeeding females.
11. Inability to swallow tablets or unwillingness or inability to receive IV administration.
12. Previously identified allergy or hypersensitivity to components of the study treatment formulations or history of severe infusion-related reactions to monoclonal antibodies. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are also excluded.
13. Any other active malignancy at time of randomization or diagnosis of another malignancy within 3 years prior to randomization that requires active treatment, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

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:	Completed
Start date (anticipated):	26-05-2020
Enrollment:	7
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	CABOMETYX®
Generic name:	Cabozantinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	OPDIVO®
Generic name:	Nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	YERVOY®
Generic name:	Ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	26-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2023
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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	EUCTR2018-004567-31-NL
CCMO	NL70854.018.19