A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR).

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal and urinary tract neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON54767

Source
ToetsingOnline

Brief title
CLEAR - E7080-G000-307

Condition

- Renal and urinary tract neoplasms benign

Synonym
Advanced Renal Cell Carcinoma, Kindney Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: First-Line, open-label, Renal cel Carcinoma

Outcome measures

Primary outcome

• Progression-free survival (PFS) by independent review is defined as the time from the date of randomization to the date of the first documentation of disease progression or death (whichever occurs first) as determined by IIR using RECIST 1.1. PFS censoring rules will follow the FDA guidance of 2007; specifics of this will be detailed in the Statistical Analysis Plan.

Secondary outcome

• Objective response rate (ORR) is defined as the proportion of subjects who have best overall response of CR or PR as determined by IIR using RECIST 1.1.

• Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cut-off will be censored at the date the subject was last known alive, or date of data cut-off, whichever occurs first.

• Safety will be assessed summarizing the incidence of treatmentemergent adverse events (TEAEs) and SAEs together with all other safety parameters.

• Proportion of subjects who discontinued treatment due to toxicity is defined

as the proportion of subjects who discontinue study treatment due to

treatment-emergent adverse events (TEAEs).

• Time to treatment failure due to toxicity is defined as the time from the

date of first dose to the date that a subject discontinues study treatment due

to TEAEs.

• Health-Related Quality of Life (HRQoL) will be assessed using the Functional

Assessment of Cancer Therapy Kidney Syndrome Index- Disease-Related Symptom

(FKSI-DRS), the European Organization for the Research and Treatment of Cancer

(EORTC) QLQ-C30 and the European Quality of Life (EuroQOL) EQ-5D-3L instruments.

• PFS on next-line of therapy (PFS2) is defined as the time from randomization

to disease progression on next-line of treatment, or death from any cause,

(whichever occurs first).

Study description

Background summary

Renal cell carcinoma (RCC), which originates within the renal cortex from the proximal
renal tubular epithelium, is the most common kidney cancer, constituting 80 to 85 percent of primary renal neoplasms. An estimated 365,943 new cases of kidney (renal) cancer are expected to be diagnosed in 2015, and an estimated 155,520 deaths
from kidney cancer are expected to occur in 2015.
The current treatment approach for patients with metastatic RCC consists of sequential
administration of single-agent therapies that target either the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) or mammalian target of rapamycin (mTOR)
pathways First-line therapy consists of treatment with anti-VEGF agents, typically sunitinib or pazopanib, however, all patients ultimately progress after therapy and will need further treatment.

Study objective

The primary objective of the study is to demonstrate that lenvatinib in combination with everolimus (Arm A) or pembrolizumab (Arm B) is superior compared to sunitinib alone (Arm C) in improving progressionfree survival (PFS) (by independent imaging review [IIR] using Response Evaluation Criteria In Solid Tumors [RECIST 1.1]) as first-line
treatment in subjects with advanced renal cell carcinoma (RCC).

Study design

This is a multicenter, randomized, open-label, Phase 3 study to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line treatment in subjects with advanced RCC.

Intervention

Test Arm (Arm A): Lenvatinib is provided as 4-mg and 10-mg capsules. Everolimus is provided as 5-mg tablets. Lenvatinib 18 mg (one 10-mg plus two 4-mg capsules) plus everolimus 5 mg will be taken orally once daily in each 21-day cycle.
Test Arm (Arm B): Lenvatinib is provided as 4-mg and 10-mg capsules. Lenvatinib 20 mg (two 10-mg capsules) once daily will be taken orally in each 21-day cycle. Pembrolizumab is provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab Pembrolizumab will be administered at a dose of 200 mg IV over 30 minutes on Day 1 of each 21-day cycle.
Comparator Arm (Arm C): Sunitinib malate will be provided as 12.5-mg and 25-mg capsules.
Sunitinib 50 mg once daily will be administered orally for 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) in each 21-day cycle.

Study burden and risks

Based on the available data to date for the two investigational treatment arms (ie, Arms A and B), the benefit/risk profile for subjects who participate in Study 307 is positive. With the measures contained within the protocol, the safety will continue to be assessed moving forward.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Histological or cytological confirmation of RCC with a clear-cell component (original tissue diagnosis of RCC is acceptable).
2. Documented evidence of advanced RCC.
3. At least 1 measurable target lesion according to RECIST 1.1 meeting the following criteria:
• Lymph node (LN) lesion that measures at least 1 dimension as >=1.5 cm in the short axis
• Non-nodal lesion that measures >=1.0 cm in the longest diameter
•The lesion is suitable for repeat measurement using computerized tomography/magnetic resonance imaging (CT/MRI). Lesions that have had external beam radiotherapy (EBRT) or locoregional therapy must show radiographic evidence of disease progression based on RECIST 1.1 to be deemed a target lesion.

4. Male or female subjects age >=18 years (or any age greater than 18 years of age if that age is considered to be an adult per the local jurisdiction) at the time of informed consent
5. Karnofsky Performance Status (KPS) of >=70.
6. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP <=150/90 mmHg at Screening and no change in antihypertensive medications within 1 week before the Cycle 1/Day 1.
7. Adequate renal function as creatinine <=1.5× upper limit of normal (ULN); or for subjects with creatinine >1.5×ULN, the calculated creatinine clearance >=30 mL/min (per the Cockcroft-Gault formula) is acceptable.
8. Adequate bone marrow function defined by:
• Absolute neutrophil count (ANC) >=1500/mm3
• Platelets >=100,000/mm3
• Hemoglobin >=9 g/dL.
9. Adequate blood coagulation function defined by International Normalized ratio (INR) <=1.5 unless participant is receiving anticoagulant therapy, as long as INR is within therapeutic range of intended use of anticoagulants
10. Adequate liver function defined by:
• Total bilirubin <=1.5 x ULN except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
• Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) <=3×ULN (in the case of liver metastases <=5×ULN), unless there are bone metastases. Subjects with ALP values >3xULN and known to have bone metastases can be included.
11. Provide written informed consent.
12. Willing and able to comply with all aspects of the protocol.

Exclusion criteria

1. Subjects who have received any systemic anticancer therapy for RCC, including anti-VEGF therapy, or any systemic investigational anticancer agent. Prior adjuvant treatment with an investigational anticancer agent is not allowed unless the investigator can provide evidence of subject's randomization to placebo arm.
2. Subjects with CNS metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.
3. Active malignancy (except for RCC, definitively treated basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix or bladder) within the past 24 months. Subjects with history of localized & low risk prostate cancer are allowed in the study if they were treated with curative intent and there is no PSA recurrence within the past 5 years.

4. Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start.
5. Subjects who are using other investigational agents or who had received investigational drugs <=4 weeks prior to study treatment start.
6. Received a live vaccine within 30 days of planned start of study treatment (Cycle 1/Day 1). Examples of live vaccines include, measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed within 30 days of C1D1.
7. Subjects with proteinuria >1+ on urine dipstick testing will undergo 24-h urine collection for quantitative assessment of proteinuria.
Subjects with urine protein >=1 g/24 h will be ineligible
8. Fasting total cholesterol >300 mg/dL (or >7.75 mmol/L) and/or fasting triglycerides level >2.5 x ULN. NOTE: these subjects can be included after initiation or adjustment of lipid-lowering medication.
9. Uncontrolled diabetes as defined by fasting glucose >1.5 times the ULN. Note: these subjects can be included after initiation or adjustment of glucose-lowering medication.
10. Prolongation of QTc interval to >480 ms.
11. Subjects who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.
12. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib, everolimus, and/or sunitinib.
13. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (eg, carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor
shrinkage/necrosis following lenvatinib therapy.
14. Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.
15. Significant cardiovascular impairment within 12 months of the first dose of study drug: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke, cerebrovascular accident (CVA), or cardiac arrhythmia associated with hemodynamic instability.
The following is also excluded:
Left ventricular ejection fraction (LVEF) below the institutional normal range as determined by MUGA or echocardiogram.
16. Active infection (any infection requiring systemic treatment).
17. Subjects known to be positive for Human Immunodeficiency Virus (HIV).
18. Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).
19. Known history of, or any evidence of, interstitial lung disease or active

non-infectious pneumonitis.
20. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
20.Has a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
22. Subjects with a diagnosis of immunodeficiency or who are receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
23. Active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years.
24. Females who are breastfeeding or pregnant at Screening or Baseline.
25. Females of childbearing potential who do not agree to use a highly effective method of contraception for the entire study period and for 120 days after study discontinuation.
27. Males who have not had a successful vasectomy and do not agree to use condom + spermicide OR have a female partner who does not meet the criteria above.

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:	Recruiting
Start date (anticipated):	06-08-2018
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	everolimus
Generic name:	Afinitor
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	lenvatinib (E7080)
Generic name:	Kisplyx
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	pembrolizumab
Generic name:	Keytruda
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	sunitinib
Generic name:	Sutent
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-04-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-09-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2021
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:	27-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2023

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2016-000916-14-NL
ClinicalTrials.gov	NCT02811861
CCMO	NL64847.029.18