An Open-label, Randomized, Phase 3 Study of MK-6482 in Combination with Lenvatinib (MK-7902) vs Cabozantinib for Treatment in Participants with Advanced Renal Cell Carcinoma Who Have Progressed After Prior Anti-PD-1/L1 Therapy

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This study has been transitioned to CTIS with ID 2024-510620-39-00 check the CTIS register for the current data. To compare belzutifan+lenvatinib to cabozantinib with respect to PFS per Response Criteria in Solid Tumors (RECIST) 1.1 as assessedby...

Ethical review	Approved WMO
Status	Completed
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON52328

Source
ToetsingOnline

Brief title
MK6482-011

Condition

- Renal disorders (excl nephropathies)

Synonym
renal cell cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Industrie

Intervention

Keyword: Advanced renal cell carcinoma, Cabozatinib, Lenvatinib, MK-6482

Outcome measures

Primary outcome

PFS: the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

OS: the time from randomization to death due to any cause.

Secondary outcome

- Objective response (OR): complete response (CR) or partial response (PR).

- DOR: the time from first documented evidence of CR or PR until either disease progression or death due to any cause, whichever occurs first.

- Adverse events (AEs).

- Study intervention discontinuation due to AEs.

Study description

Background summary

The hypoxia-inducible factor, HIF-2α, is believed to play a critical role in tumorigenesis and tumor progression in RCC. MK-6482 is an orally available, small molecule inhibitor of HIF-2α, that selectively disrupts the heterodimerization of HIF-2α with HIF-1β. The safety profile of MK-6482 in 55 heavily pretreated advanced RCC participants (median 3 prior regimens) in Study MK-6482-001 (also known as PT2977-101), together with the ORR of

24% suggest that MK-6482 may be a treatment option for participants with advanced RCC who have progressed after prior therapy [Jonasch, E., et al 2019].

Lenvatinib (also known as E7080 or MK 7902) inhibits the kinase activities of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including FGF receptors FGFR1, 2, 3, and 4; PDGFRα, KIT, and RET. Lenvatinib also showed antiproliferative activity in cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α phosphorylation.

The combination of the VEGFR TKI, lenvatinib, with MK-6482, a HIF-2α antagonist, may enhance therapeutic benefit in patients with kidney cancer for 3 reasons. First, as HIF-2α drives tumor cell expression of several oncogenes in ccRCC, VEGF being just one of them, the combination could inhibit multiple oncogenic signaling pathways involved in initiation, progression and metastasis. Second, the combination will provide enhanced VEGF inhibition through orthogonal mechanisms. HIF-2α is the major regulator of VEGF gene expression in ccRCC, but HIF-1α plays a role in the activation of VEGF in certain tissues [Hu, C. J., et al 2003] [Keith, B., et al 2012]. Treatment with MK-6482, which is highly selective for HIF-2α, will block HIF-2α driven VEGF gene expression, but HIF-1α may also activate VEGF expression in some tumor cells as well as in stromal and immune cells. By combining MK-6482 and lenvatinib, VEGF production regulated by HIF-2α will be repressed at the level of transcription by MK-6482, and production of VEGF downstream of HIF-1α will be inhibited by lenvatinib at the growth factor receptor level. The HIF-2α activation also represents a resistance pathway for anti-VEGF therapy. Therefore, the combination of lenvatinib plus MK-6482 is an attractive therapeutic intervention for patients with advanced RCC [Hu, C. J.,et al 2003] [Keith, B., et al 2012] [Zhao, D., et al 2014] [Blagosklonny, M. V. 2004].

Study objective

This study has been transitioned to CTIS with ID 2024-510620-39-00 check the CTIS register for the current data.

To compare belzutifan+lenvatinib to cabozantinib with respect to PFS per Response Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR).

Study design

This is a Phase 3, open-label, multicenter, randomized, active-controlled study to compare the efficacy and safety of belzutifan+lenvatinib with that of

cabozantinib in participants with advanced RCC with clear cell component who have experienced disease progression on or after first- or second-line systemic treatment with an anti-PD-1/L1 therapy (monotherapy or combination therapy) for locally advanced or metastatic RCC. The immediately preceding line of treatment has to have been an anti-PD-1/L1 therapy. Approximately 708 eligible participants who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned in a 1:1 ratio to receive either belzutifan+lenvatinib or cabozantinib (~354 participants in each arm).

Intervention

Group 1: MK-6482 (120 mg, orally, 1x daily) + Lenvatinib (20 mg, orally, 1x daily)
Group 2: Cabozantinib (60 mg, orally, 1x daily)

Study burden and risks

For this study, patients will be subjected to invasive procedures such as blood collection, CT/MRI/bone scans, physical examinations, any confrontational questionnaires and patients will be asked to visit the hospital regularly.

Patients should take belzutifan with Lenvatinib once a day or take Cabozantinib once a day. Patients continue to take the medication until they show progression.

It cannot be ensured that clinical trial participants will benefit directly from treatment during participation, as clinical trials are designed to gather information on the safety and effectiveness of an experimental drug.

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. Must have a histologically confirmed diagnosis of unresectable, locally advanced/metastatic RCC with clear cell component (with or without sarcomatoid features) ie, Stage IV RCC per AJCC (8th Edition). Previous nephrectomy or metastasectomy is allowed.
2. Has experienced disease progression on or after an anti-PD-1/L1 therapy as either first- or second-line treatment for locally advanced/metastatic RCC or as adjuvant or neoadjuvant/adjuvant treatment with progression on or within 6 months of last dose. The anti-PD-1/L1 therapy may have been monotherapy or in combination with other agent(s) such as anti- CTLA4 or VEGFtargeted-TKI. The immediately preceding line of treatment has to have been an anti-PD-1/L1 therapy.
- Treatment progression is defined by meeting ALL of the following criteria:
o Has received at least 2 doses of an anti-PD-1/L1 mAb.
o Has shown radiographic disease progression during or after an anti-PD-1/L1 mAb as assessed by investigator.
3. Has measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.
4. Has a KPS >=70% assessed within 10 days before randomization.
5. Has received no more than 2 prior systemic regimens including:
- One anti-PD-1/L1 containing adjuvant or neoadjuvant/adjuvant regimens with progression on or within 6 months from the last dose of that regimen
OR
-One or 2 regimens for locoregional/advanced disease
6. Has received only 1 prior anti-PD-1/L1 therapy for adjuvant, neoadjuvant/adjuvant or locally advanced/metastatic RCC.
7. Has recovered from all AEs due to previous therapies to <=Grade 1 or baseline. Participants with <=Grade 2 neuropathy may be eligible.

Participants with endocrine-related AEs Grade <=2 requiring treatment or hormone replacement may be eligible.
8. If participants received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
9. Is male or female, at least 18 years of age, at the time of signing the informed consent.
10. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of belzutifan or lenvatinib in the belzutifan+lenvatinib arm, whichever occurs last, and 23 days after the last dose of cabozantinib:
• Be abstinent from heterosexual intercourse as their preferred and usual lifestyle and agree to remain abstinent
OR
•Must agree to use contraception unless confirmed to be azoospermic.
-Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
-If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.
11. A female participant is eligible to participate if they are not pregnant or breastfeeding, and at least 1 of the following conditions applies:
• Is not a WOCBP.
OR
• Is a WOCBP and using a contraceptive method that is highly effective during the treatment period and for at least 120 days after the last dose of cabozantinib for participants in the cabozantinib arm, or during the treatment period and for at least 30 days after the last dose of belzutifan or lenvatinib (whichever occurs last) for participants in the belzutifan +lenvatinib arm.
- A WOCBP must have a negative highly sensitive pregnancy test within 24 hours (urine) of 72 hours (serum) before the first dose of study intervention.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.
12. The participant (or legally acceptable representative if applicable) has provided documented informed consent for the study.
13. Participants must have adequately controlled BP with or without antihypertensive medication, defined as BP <=150/90 mm Hg with no change in antihypertensive medications within 1 week before randomization.
14. Has adequate organ function; all screening laboratory tests will be performed within 10 days before randomization.

Exclusion criteria

1. A WOCBP who has a positive urine pregnancy test within 24 hours before first dose of study intervention. If the urine test is positive or
cannot be confirmed as negative, a serum pregnancy test will be required.
2. Has any of the following:
- A pulse oximeter reading <92% at rest, or
- Requires intermittent supplemental oxygen, or
- Requires chronic supplemental oxygen.
3. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
4. Has known CNS metastases and/or carcinomatous meningitis.
5. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including but not limited to New York Heart Association
Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia.
6. Prolongation of QTc interval to >480 ms.
7. Has a LVEF below the institutional (or local laboratory) normal range as determined by MUGA or ECHO.
8. Has urine protein >=1 g/24 hours.
9. Has symptomatic pleural effusion (for example cough, dyspnea, pleuritic chest pain). A participant who is clinically stable after treatment
for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
10. Has pre-existing >=Grade 3 gastrointestinal or nongastrointestinal fistula.
11. Has moderate to severe hepatic impairment (Child-Pugh B or C).
12. Has clinically significant hematuria, hematemesis or hemoptysis (>2.5 ml) of red blood, or other history of significant bleeding (eg,
pulmonary hemorrhage) within 3 months before randomization.
13. Has other clinically significant disorders such as:
a. Serious active nonhealing wound/ulcer/bone fracture
b. Requirement for hemodialysis or peritoneal dialysis
c. History of solid organ transplantation
14. Received colony-stimulating factors (eg, G-CSF, GMCSF or recombinant EPO) within 28 days before randomization.
15. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.
16. Is unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption (eg, gastrectomy, partial bowel obstruction, malabsorption).
17. Has known hypersensitivity or allergy to the active pharmaceutical ingredient or any component of the study intervention (belzutifan, lenvatinib, or cabozantinib) formulations.
18. Has received prior treatment with belzutifan or another HIF-2α inhibitor.
19. Has received prior treatment with lenvatinib.

20. Has received prior treatment with cabozantinib.
21. Has received any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomization.
22. Has received any type of systemic anticancer antibody (including investigational antibody) <=28 days before randomization.
23. Has received prior radiotherapy within 2 weeks before randomization. Participants must have recovered from all radiationrelated toxicities and not require corticosteroids. A 1-week washout is required for palliative radiation (<=2 weeks of radiotherapy) to non-CNS disease.
24. Has had major surgery within 3 weeks before randomization.
25. Is receiving concomitant treatment, in therapeutic doses, with anticoagulants such as heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (eg, clopidogrel).
26. Is currently receiving strong inhibitors of CYP3A4 (eg, boceprevir, cobicistat, itraconazole, ketoconazole, clarithromycin, idelalisib, nefazodone, nelfinavir, and ritonavir in combination with protease inhibitors that cannot be discontinued for the duration of the study.
27. Is currently receiving strong inducers of CYP3A4 (mitotane, phenytoin, rifampin, carbamazepine and St John's Wort) that cannot be discontinued for the duration of the study.
28. Is currently participating in a study of an investigational agent or is currently using an investigational device.
29. Has an active infection requiring systemic therapy.
30. Has a known history of HIV infection.
31. Has a known history of HBV (defined as HBsAg reactive) or known active HCV (defined as HCV RNA [qualitative] is detected) infection.
32. Had medically significant hemorrhage within prior 3 months before randomization.
33. Has a history or current evidence of any condition, therapy, or laboratory abnormality or other circumstance that might confound the results of the study or
interfere with the participant's participation for the full duration of the study, sucht that it or is not the best interest of the participant to participate, in the
opinion of the treating investigator.

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:	Completed
Start date (anticipated):	30-07-2021
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Belzutifan
Generic name:	Belzutifan
Product type:	Medicine
Brand name:	Cabozantinib
Generic name:	Cabozantinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lenvatinib
Generic name:	Lenvatinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-10-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-12-2020

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-12-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-07-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-02-2022

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-10-2023

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-11-2023
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
EU-CTR	CTIS2024-510620-39-00
EudraCT	EUCTR2020-002075-35-NL
ClinicalTrials.gov	NCT04586231
CCMO	NL75425.028.20