Phase 2 Study of MK-6482 in Participants With Advanced Renal Cell Carcinoma

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This study has been transitioned to CTIS with ID 2022-502123-21-00 check the CTIS register for the current data. To compare the 120 mg once daily (QD) dose and 200 mg QD dose of MK*6482with respect to objective response rate (ORR) based on Response...

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

Summary

ID

NL-OMON56267

Source
ToetsingOnline

Brief title
MK6482-013

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: MSD/ Merck Sharp & Dohme

Intervention

Keyword: clear cell, MK6482, Renal Cell Carcinoma

Outcome measures

Primary outcome

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

Secondary outcome

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

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

• Clinical benefit (CB): stable disease >=6 months or CR or PR based on assessments by BICR per RECIST 1.1.

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

• Adverse events (AEs).

• Study intervention discontinuation due to AEs.

• Maximum concentration (Cmax), trough concentration (Ctrough).

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]. The rationale

for this study is to compare efficacy and safety between the 120 mg and 200 mg doses. If 200 mg shows significant and relevant efficacy and an acceptable safety profile, it may be considered for further development.
Refer to paragraph 2 for more detailed backgound information regarding the study

Study objective

This study has been transitioned to CTIS with ID 2022-502123-21-00 check the CTIS register for the current data.

To compare the 120 mg once daily (QD) dose and 200 mg QD dose of MK*6482with respect to objective response rate (ORR) based on Response Criteria in Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR).

Study design

This is a Phase 2, open-label, multicenter, randomized, study to compare the safety and efficacy of the 120 mg QD dose and the 200 mg QD dose of MK*6482 in participants with advanced RCC that has progressed after a maximum of 3 prior systemic therapies.

Approximately 150 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 120 mg QD or 200 mg QD of MK*6482 (~75 participants in each arm).

Intervention

once daile intake of MK6482 120 mg OR MK6482 200 mg

Study burden and risks

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.
The proposed study will enroll participants with advanced RCC who have progressed after prior therapy. As described in Section 2.2.3, MK*6482 is a potent and selective inhibitor of HIF-2α in preclinical studies and clinical data as described in Section 2.2.4 demonstrate antitumor activity of MK*6482, which warrants further investigation. In MK*6482-001 (PT2977-101), the ORR for 55 heavily pretreated advanced RCC participants (62% having received >=3 prior lines of therapy) was 24% (95% CI: 13, 37), with median duration of response not yet reached, a median PFS of 11 months (95% CI: 6, 17) and clinical activity seen across IMDC risk categories [Choueiri, T. K., et al 2020]. This

compares favorably to the ORR seen with nivolumab in Checkmate 25 (25%, 95% CI: 3.68, 9.72) and cabozantinib in METEOR (17%, 95% CI: 13, 22)-both studies in advanced RCC participants with at least 2 prior lines of therapy including post TKI treatment [Motzer, R. J., et al 2015] [Choueiri, T. K., et al 2017]. While there are no data on the efficacy of 200 mg, as described in Section 2.2.4 and 4.3.1, there is potential for benefit at least equal if not exceeding that seen for the 120 mg QD dose. The safety profile seen in MK*6482-006 (PT2977-104) at the 200 mg dose was similar to that seen previously for the 120 mg dosing, with the limitations that it was a single-dose study. Given the high risk of progression of disease in patients with advanced RCC, there is an unmet medical need for more effective and tolerable treatment, and as MK*6482 has been shown to be well tolerated across various tumor types, a positive benefit/risk profile is expected.

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 locally advanced/metastatic RCC with clear cell component (with or without sarcomatoid features) 2. Has measurable disease per RECIST 1.1 as assessed by BICR. 3. Submit an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. 4. Has experienced disease progression on or after having received first-line systemic treatment for locally advanced or metastatic RCC with prior anti-PD-1/L1 + anti-CTLA4 combination or anti-PD-1/L1 + VEGF-targeted TKI combination. - PD-1/L1 checkpoint inhibitor-based combination regimens (with either VEGFtargeted TKI or anti-CTLA-4) 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 demonstrated radiographic disease progression during or after an anti-PD- 1/L1 mAb as assessed by investigator. - If the participant has received >1 prior regimen, there must have been demonstrated radiographic disease progression after the most recently received regimen. 5. Has received no more than 3 prior systemic regimens for locally advanced or metastatic RCC. 6. Is male or female, who is at least 18 years of age at the time of signing the informed consent. 7. Has a KPS score of at least 70% [Karnofsky, D. A., et al 1948] assessed within 10 days prior to the first dose of study intervention. 8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 5 days after the last dose of study intervention: • Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent OR • Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause) as detailed below: - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. • Male participants must also agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex. • Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. 9. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: • Is not a WOCBP OR • Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), during the intervention period and for at least 30 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. • A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. • If a urine test

cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. • Additional requirements for pregnancy testing during and after study intervention • The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. • Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. 10. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the main study without participating in FBR. 11. Has adequate organ function, all screening laboratory tests should be performed within 10 days prior to the first dose of study intervention.

Exclusion criteria

1. A WOCBP who has a positive urine pregnancy test within 24 hours prior to randomization (see Appendix 5). 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: - Hypoxia as defined by 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 cardiac disease, including unstable angina, acute myocardial infarction <=6 months from Day 1 of study drug administration, or New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted. 6. Has moderate to severe hepatic impairment (Child-Pugh B or C). 7. Received colony-stimulating factors (eg, G-CSF, GM-CSF or recombinant EPO) <=28 days prior to the first dose of study intervention. 8. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study. 9. Is unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption (eg, gastrectomy, partial bowel obstruction, malabsorption). 10. Has known hypersensitivity or allergy to the active pharmaceutical ingredient or any component of the study intervention (MK-6482) formulations. 11. Has received prior treatment with MK-6482 or another HIF-2α inhibitor. 12. Has received any type of small molecule kinase inhibitor (including investigational kinase inhibitor) <=2 weeks before randomization. 13. Has received any type of systemic anticancer antibody (including investigational antibody) <=4 weeks before randomization. 14. Has received prior radiotherapy <=2 weeks prior to first dose of study intervention. Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout

is required for palliative radiation (<=2 weeks of radiotherapy) to non-CNS disease. 15. Has had major surgery <=3 weeks prior to first dose of study intervention. 16. Is currently receiving either strong (phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John*s Wort) or moderate (eg, bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study. 17. Is currently participating in a study of an investigational agent or is currently using an investigational device. 18. Has an active infection requiring systemic therapy. 19. Has active TB. 20. Has a diagnosis of immunodeficiency. 21. Has a known history of HIV infection. 22. Has a known history of HBV (defined as HBsAg reactive) or known active HCV (defined as HCV RNA [qualitative] is detected) infection. 23. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant*s participation for the full duration of the study, or is not the best interest of the participant to participate, in the opinion of the treating investigator.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-12-2020
Enrollment:	19
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MK6482

Generic name:	NA

Ethics review

Approved WMO Date:	17-08-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-09-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-11-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	26-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-12-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-08-2023
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	CTIS2022-502123-21-00
EudraCT	EUCTR2020-001907-18-NL
ClinicalTrials.gov	NCT04489771
CCMO	NL74544.028.20