A Multi-center, Double-Blind, Randomized Phase 3 Study to Compare the Efficacy and Safety of Belzutifan (MK-6482) plus Pembrolizumab (MK-3475) Versus Placebo plus Pembrolizumab, in the Adjuvant Treatment of Clear Cell Renal Cell Carcinoma (ccRCC) Post Nephrectomy (6482-022)

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This study has been transitioned to CTIS with ID 2023-505023-31-00 check the CTIS register for the current data. 1) To compare disease-free survival (DFS) as assessed by investigator for participants treated with belzutifan plus pembrolizumab versus...

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

Summary

ID

NL-OMON53680

Source
ToetsingOnline

Brief title
MK6482-022

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Kidney cancer, Renal Cell Carcinoma

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: Belzutifan, Clear Cell Renal Cell Carcinoma, Pembrolizumab, Phase 3

Outcome measures

Primary outcome

1) To compare disease-free survival (DFS) as assessed by investigator for

participants treated with belzutifan plus pembrolizumab versus those receiving

placebo plus pembrolizumab

Secondary outcome

- To compare overall survival (OS)

- To compare the safety and tolerability profiles

- To compare measures of disease recurrence-specific survival (DRSS)

- To evaluate change from baseline in health-related quality of life (HRQoL)

and symptoms

Study description

Background summary

40% of patients with locally advanced (T2-T4) RCC experience recurrence after surgery. In addition, These patients have a higher incidence of metastasis at the time of disease recurrence and the estimated 5-year survival of patients with localized low-, intermediate-, and highrisk RCC is approximately 92%, 67%, and 44% (respectively), and decreases to 12% in metastatic RCC patients. As such, effective adjuvant therapy for RCC is an unmet medical need for patients with features that confer a high risk of recurrence. The success of targeted therapies and combination therapies in the treatment of advanced/metastatic RCC led to the interest in testing their efficacy in the adjuvant setting as well.

Results of previous studies (KY564) demonstrated a direct evidence of clinical benefit for pembrolizumab monotherapy in the adjuvant setting in patients with RCC following nephrectomy. Based on these findings and the positive risk-benefit profile, pembrolizumab monotherapy offers an effective and tolerable new therapeutic option for these patients. However, there is still an unmet need to further optimize threatment strategies. The combination of pembrolizumab with belzutifan, a HIF 2-alfa inhibitor, is likely to enhance the therapeutic benefit providing increased activity over the pembrolizumab alone treatment in patients with ccRCC

Pembrolizumab is a potent humanized IgG4 monoclonal antibody (mAb) with high specificity of binding to the programmed
cell death 1 (PD-1) receptor, thus inhibiting its interaction with ligand PD-L1 and ligand PD-L2.The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T- cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. As a consequence, the PD-1/PD-L1 pathway is an attractive target for adjuvant treatment for clear cell renal cell carcinoma post nephrectomy.

Patients with RCC have a defective VHL protein. As a result, HIF-2α cannot bind to VHL and there is no degradation of HIF-2α . Instead, HIF-2α stabilizes and binds with HIF-1β in the cell nucleus. This activates various oncogenes such as cell proliferation, cell survival and angiogenesis. Belzutifan is a molecule that can bind to HIF-2α with high specificity . Consequently, Belzutifan blocks the heterodimerization with HIF-1β. The connection between Belzutifan and HIF-2α thereby inhibits the transcription of these oncogenes.

Study objective

This study has been transitioned to CTIS with ID 2023-505023-31-00 check the CTIS register for the current data.

1) To compare disease-free survival (DFS) as assessed by investigator for participants treated with belzutifan plus pembrolizumab versus those receiving

placebo plus pembrolizumab

Study design

This is a multicenter, double-blind, randomized Phase 3 study to evaluate the efficacy and safety of Belzutifan (MK-6482) plus pembrolizumab (MK-3475) versus Placebo plus pembrolizumab, in the adjuvant treatment of clear cell renal cell carcinoma (ccRCC) Post-nephrectomy. to investigate.

Worldwide, approximately 1600 patients will be included. In the Netherlands this will be 60 patients. Screening procedures must be completed within 42 days prior to treatment. After this screening period, the patient will be randomized 1:1 into one of two treatment groups:
1) Belzutifan + pembrolizumab
2) Placebo + pembrolizumab
A cycle lasts 42 days (6 weeks). A patient can receive up to 9 doses of pembrolizumab (9 cycle, 54 weeks). Belzutifan is used daily. After the end of treatment, each patient will be monitored for pregnancy and adverse events. All patients are followed up until death, withdrawal of consent or the end of the study.

Intervention

2 treatment groups

1) Belzutifan (120 mg oral, every day for 54 weeks) + Pembrolizumab (400 mg infusion, every 6 weeks up to a maximum of 9 doses)
2) Placebo (0 mg, every day for 54 weeks) + Pembrolizumab (400 mg, every 6 weeks up to a maximum of 9 doses)

Study burden and risks

For this study, patients will be subjected to invasive procedures such as blood collection, CT-MRI or bone scans, physical exams, possibly confrontational questionnaires, and patients will be asked to visit the hospital regularly. Patients will be administered with different medicines, during six-week cycles up to a maximum of 9 treatments with pembrolizumab and 1 daily dosis of pemrbolizumab (up to 54 weeks).

It cannot be guaranteed that participants in clinical studies will directly benefit from study intervention during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. Pembrolizumab and Belzutifan have been administered in a large number of cancer participants with a well characterized safety profile and pemrbolizumab has received
regulatory approval for multiple malignancies. Overall, pembrolizumab and

belzutifan are well tolerated in previous studies. However, potential risks of this novel combination may beincreased toxicity, intolerability, or unanticipated adverse drug reactions

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The below mentioned inclusion criteria are the most important ones. A complete list of specific inlcusion criteria can be found in the protocol.
1. Has a histologically or cytologically confirmed diagnosis of RCC with clear cell component per AJCC (8th Edition), with or without sarcomatoid features.
2. Has intermediate-high risk, high risk, or M1 NED RCC
3. Has undergone complete resection of the primary tumor (partial or radical nephrectomy) and complete resection of solid, isolated, soft tissue metastatic

lesion(s) in M1 NED participants.
4. Must have undergone a nephrectomy and/or metastasectomy <=12 weeks prior to randomization
5. Must be tumor-free before randomization as assessed by the investigator and verified by BICR
6. Must have provided tissue per any of the following:
• Nephrectomy only: tissue from nephrectomy (required).
• Synchronous M1 NED: tissue from nephrectomy (required) and tissue from metastasectomy (if available).
• Metachronous M1 NED: tissue from metastasectomy (required) and tissue from nephrectomy (if available).
7. Is male or female, at least 18 years of age, at the time of signing the informed consent.
8. Has ECOG performance status of 0 to 1 within 10 days before randomization.
9. Agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for the study intervention is as follows:
- Belzutifan/placebo - at least 7 days after the last dose
• Abstains from heterosexual intercourse as their preferred and usual lifestyle and agree to remain abstinent OR
• Uses contraception unless confirmed to be azoospermic as detailed
10. A female participant is eligible to participate if she is not pregnant or breastfeeding
11. The participant has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR.
12. Has adequate organ function.

Exclusion criteria

The below mentioned exclusion criteria are the most important ones. A complete list of specific inlcusion criteria can be found in the protocol.
1. Has had a major surgery, other than nephrectomy plus resection of preexisting metastases for M1 NED participants, within 4 weeks prior to randomization.
2. 2. Has residual thrombus post nephrectomy in the vena renalis or vena cava.
3. 3. Has any of the following:
• Pulse oximeter reading <92% at rest, or
• Requires intermittent supplemental oxygen, or
• Requires chronic supplemental oxygen.
4. Has clinically significant cardiovascular disease within 6 months from first dose of study intervention,
5. Has other clinically significant disorders such as:
• Serious active nonhealing wound/ulcer/bone fracture
• Requirement for hemodialysis or peritoneal dialysis

6. Has preexisting brain or bone metastatic lesions.
7. Has received colony-stimulating factors (eg, G-CSF, GM-CSF) or recombinant EPO or transfusion within 28 days before study intervention initiation.
8. Is unable to swallow orally administered medication or has a history or current evidence of a GI condition or impaired liver function or diseases that in the opinion of the investigator may significantly alter the absorption or metabolism of oral study intervention.
9. Has a severe hypersensitivity (Grade >=3) reaction to belzutifan/placebo or pembrolizumab and/or any of their excipients
10. Has received prior systemic therapy for RCC
11. Has received prior radiotherapy for RCC.
12. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention.
13. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention
14. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior the first dose of study intervention
15. Has a known additional malignancy (other than RCC treated with nephrectomy and/or metastasectomy) that is progressing or has required active treatment within the past 3 years.
16. Has an active autoimmune disease that has required systemic treatment in past 2 years
17. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
18. Has an active infection, requiring systemic therapy.
19. Has a known history of HIV infection, a known history of Hepatitis B or known active Hepatitis C virus infection
20. Has a history or current evidence of any condition, therapy, 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.
21. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study
22. Has had an allogenic tissue/solid organ transplant.

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:	Recruiting
Start date (anticipated):	10-06-2022
Enrollment:	67
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Belzutifan
Generic name:	Belzutifan
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-12-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-03-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-07-2022

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:	10-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-10-2022
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:	21-01-2023
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:	11-07-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-09-2023

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	CTIS2023-505023-31-00
EudraCT	EUCTR2021-003436-92-NL
CCMO	NL79608.028.21