# A Phase 1b/2 Study of Immune and Targeted Combination Therapies in Participants With RCC (KEYMAKER-U03): Substudy 03B

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This study has been transitioned to CTIS with ID 2023-506839-15-00 check the CTIS register for the current data. Primary objectives:# Safety Lead-in Phase: To assess the safety and tolerability, and to establish an RP2D if applicable, of treatment...

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

## Summary

### ID

NL-OMON55940

**Source**
ToetsingOnline

**Brief title**
MK3475-03B

### Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Renal disorders (excl nephropathies)

**Synonym**
Advanced Clear Cell Renal Cell Carcinoma, kidney cancer

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** Advanced RCC in second line plus (2L+) treatment, Clear Cell Renal Cell Carcinoma, Multiple combination therapies, Phase 1b/2

## Outcome measures

### Primary outcome

Occurrence of Dose-Limiting Toxicity (DLT), Adverse Events (AE), and

discontinuation of study intervention due to an AE.

Objective Response (OR): Complete response (CR) or partial response (PR).

### Secondary outcome

# DOR: For participants who demonstrate CR or PR, DOR is defined as the time

from the first documented evidence of CR or PR until disease progression or

death due to any cause, whichever occurs first.

# PFS: The time from the date of randomization to the date of the first

documented PD per RECIST 1.1 by BICR, or death from any cause, whichever occurs

first.

# OS: The time from the date of randomization to the date of death.

# CBR: The percentage of participants who have achieved stable disease (SD) >= 6

months or CR or PR based on assessments by BICR per RECIST 1.1.

# Study description

### Background summary

There were > 400.000 new cases of kidney cancer and > 175.000 deaths due to the disease reported in 2018 worldwide. Approximately 85% of kidney tumors are renal cell carcinoma (RCC), RCC comprises approximately 3,8% of all cancers, and approximately 70% of these have a clear cell (cc) histology.
Since 2005, targeted therapy using VEGF-TKIs and/or anti-VEGF antibodies have been the mainstay for the treatment of advanced RCC, and agents targeting mTOR are also used in this setting. More recently, immune checkpoint inhibitors have become the new revolution in treatment options.
In the EU, for the treatment of 2L ccRCC after 1L treatment with a TKI, monotherapy with nivolumab or cabozantinib is standard. If 1L treatment is with nivolumab in combination with ipilimumab, 2L options include any TKI or lenvatinib in combination with everolimus.
There have been recent advances in the treatment of 1L advanced RCC combining immunomodulators and/or VEGF-TKI(s), and multiple agents are now available for the treatment of patients with 2L RCC. However, existing data shows that few patients experience CR with these agents and nearly all progress. Although these significant advances have led to a change in the treatment paradigm of these patients, there remains an unmet need to improve outcomes for both 1L and 2L+ advanced RCC populations. Currently there is no SOC for post PD-(L)1 inhibitors /post VEGF-TKI 2L+ advanced RCC.
There are several drugs currently available for 2L+ therapy in patients with advanced RCC including nivolumab, cabozantinib, and lenvatinib in combination with everolimus. These agents have shown benefit in terms of outcome compared with single agent everolimus, which had previously been the standard 2L treatment for advanced RCC since the 2008 RECORD 1 study. It is notable that these studies were all conducted when the SOC for 1L advanced ccRCC were VEGF-TKIs. No clinical studies have so far been conducted to investigate subsequent treatment options after 1L treatment with IO/VEGF-TKI either in combination or in sequence. As a result, there is no SOC for patients with 2L+ post PD-(L)1 inhibitors/post VEGF-TKIs advanced RCC, and there remains an unmet need to improve treatment outcomes in this population.

**Study objective**

This study has been transitioned to CTIS with ID 2023-506839-15-00 check the CTIS register for the current data.

Primary objectives:
# Safety Lead-in Phase: To assess the safety and tolerability, and to establish an RP2D if applicable, of treatment combinations that have not been evaluated in a separate study.
# Efficacy Phase: To assess the safety and tolerability of each treatment arm based on the proportion of participants with AEs.
# Efficacy Phase: To evaluate objective response rate (ORR) of each treatment arm as assessed by Blinded Independent Central Review (BICR) per RECIST 1.1.

Secondary objectives (all in Efficacy Phase):

# To evaluate the duration of response (DOR) as assessed by BICR per RECIST 1.1.
# To evaluate progression free survival (PFS) as assessed by BICR per RECIST 1.1.
# To evaluate overall survival (OS).
# To evaluate clinical benefit rate (CBR) per RECIST 1.1 as assessed by BICR.

## Study design

Substudy MK3475-03B from Umbrella research protocol MK3475-U03 is a phase 1b/2, rolling arm, multicenter, open-label adaptive design study that evaluates the safety and efficacy of multiple experimental arms for the treatment of advanced ccRCC in subjects who have previously received at least 1 systemic therapy for advanced RCC.
This substudy is composed of a specific set of treatment arms, and these arms are composed of investigational products (IPs). More IP(s) will be added to the Efficacy Phase of this study after an initial evaluation of safety and tolerability of the IP(s) has been completed in a separate study or in the Safety Lead-in Phase of this study.

## Intervention

This study has 4 intervention groups with different IP combinations. The subjects may receive 1 of these IV (intravenous infusion) treatments: *pembrolizumab or *MK-1308A (quavonlimab + pembrolizumab), 6-weekly for up to 2 years. The subjects may also receive oral treatment (daily) with lenvatinib and/or belzutifan until disease progression or unacceptable toxicity.

## Study burden and risks

By participating in this study, participants will be exposed to invasive procedures (e.g. biopsy collection, blood collection and CT- or MRI-scans), are asked to visit the hospital regularly, and receive experimental therapy with potentially serious side effects. It is unsure if the participants will directly benefit from the study intervention.
The treatment depends on the group the participant is assigned to. Some of the treatments have been administered to a large number of oncology patients (various indications) with a known safety profile. Other treatments have recently been developed and were administered to < 1.000 participants in previous studies. All known side effects are included in the written information provided to the participants, including the expected frequency of occurrence.
In general, participants must be informed on the nature and extent of the burden and risks associated with participation, as well as the potential benefit, by means of the patient information sheet and the explanation from the investigator.

# Contacts

**Public**
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL
**Scientific**
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

# The participant has provided documented informed consent for this study.
# Male or female from 18 years to 120 years at the time of signing the informed consent form.
# Histologically confirmed diagnosis of locally advanced/metastatic ccRCC (with or without sarcomatoid features).
# Disease progression on or after systemic treatment for locally advanced or metastatic RCC with a PD-(L)1 checkpoint inhibitor (in sequence or in combination with a VEGF-TKI). Criteria for PD-(L)1 checkpoint inhibitor treatment progression are per protocol.
# Disease progression on or after systemic treatment for locally advanced or metastatic RCC with a VEGF-TKI (in sequence or in combination with a PD-[L]1 checkpoint inhibitor). Criterion for VEGF-TKI treatment progression is per

protocol.
# Measurable disease by RECIST 1.1 (assessed by a Blinded Independent Central Review).
# Karnofsky Performance Status >=70% (within 10 days before randomization/allocation).
# Able to swallow oral medication.
# Presence of an evaluable archival or newly obtained tumor tissue sample for central analysis.
# Adequate organ function (within 10 days before the start of study intervention).
# If on bone resorptive therapy, this must be initiated at least 2 weeks before randomization/allocation.
# Toxic effects of prior therapy are resolved to <= grade 1 (exceptions per protocol) and for systemic steroid therapy due to an irAE the dose should not exceed 10 mg daily of prednisone (or equivalent).
# Adequately controlled blood pressure with or without antihypertensive medications.
# A male participant must agree to use contraception as detailed in the protocol.
# A female participant is eligible to participate if not pregnant or breastfeeding, agrees to follow the contraceptive guidance as detailed in the protocol, or is not of child-bearing potential.

## Exclusion criteria

# Prior treatment with pembrolizumab plus lenvatinib in combination.
# Prior treatment with belzutifan or another HIF-2α inhibitor.
# Treated with more than 4 previous systemic anticancer treatment regimens.
# Previously randomized/allocated to study intervention in any substudy of protocol MK3475-U03.
# Received an investigational product or used an investigational device within 4 weeks before the first dose of study intervention.
# Prior radiotherapy within 2 weeks before the first dose of study intervention or radiation-related toxicities requiring corticosteroids (exceptions per protocol).
# Live or live attenuated vaccine within 30 days before the first dose of study intervention.
# Allogeneic tissue/solid organ transplant.
# Clinically significant cardiovascular disease within 12 months before first dose of study intervention (details per protocol).
# Prolongation of QTcF interval to >480 ms.
# LVEF below the institutional normal range as determined by MUGA or ECHO.
# Major surgery within 3 weeks before first dose of study intervention.
# Urine protein >=1 g/24 hours.
# History of interstitial lung disease, history of (noninfectious) pneumonitis

that required steroids, or current pneumonitis.
# Symptomatic pleural effusion (details per protocol).
# History of inflammatory bowel disease.
# Preexisting grade >=3 GI or non-GI fistula, or malabsorption due to prior GI surgery or GI disease.
# Active hemoptysis within 3 weeks prior to the first dose of study intervention.
# Diagnosis of immunodeficiency or receiving chronic systemic steroid therapy (or any other form of immunosuppressive therapy) within 7 days before the first dose of study intervention.
# Known additional malignancy that is progressing or required active treatment within the past 3 years (exceptions per protocol).
# Known active CNS metastases and/or carcinomatous meningitis (exceptions per protocol).
# Radiographic evidence of encasement or invasion of a major blood vessel, or of intratumoral cavitation.
# History of (severe) hypersensitivity reaction to any of the investigational products included in this study.
# Active autoimmune disease that required systemic treatment in the past 2 years (details and exceptions per protocol).
# Active infection requiring systemic therapy.
# Known history of HIV and/or hepatitis B infection, or known active hepatitis C infection.
# Pulse oximeter reading <92% at rest, or requiring intermittent or chronic supplemental oxygen.
# Known psychiatric or substance abuse disorder that would interfere with the participant*s ability to cooperate with the requirements of the study.
# 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 in the best interest of the participant to participate, in the opinion of the treating investigator.

## Study design

### Design

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

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 31-07-2023 |
| Enrollment: | 9 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Registration: | No |
| Product type: | Medicine |
| Brand name: | Keytruda |
| Generic name: | Pembrolizumab |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Kisplyx, Lenvima |
| Generic name: | Lenvatinib |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | N/A |
| Generic name: | Quavonlimab/Pembrolizumab co-formation |
| Product type: | Medicine |
| Brand name: | Welireg |
| Generic name: | Belzutifan |

# Ethics review

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| Approved WMO Date: | 19-01-2023 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 17-03-2023 |
| Application type: | Amendment |

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| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-04-2023 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 25-04-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-04-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 17-07-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 19-07-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 17-10-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 18-10-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# 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 | CTIS2023-506839-15-00 |
| EudraCT | EUCTR2019-003610-13-NL |
| ClinicalTrials.gov | NCT04626518 |
| CCMO | NL83009.056.22 |