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

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This study has been transitioned to CTIS with ID 2023-506838-68-00 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	Pending
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56282

Source
ToetsingOnline

Brief title
MK3475-03A

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: Clear Cell Renal Cell Carcinoma, Multiple combination therapies, No prior systemic therapy for advanced RCC, 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, the recommended systemic therapy for 1L ccRCC in patients with good risk is axitinib in combination with pembrolizumab. Alternative therapies include sunitinib, pazopanib or tivozanib monotherapy. For patients with intermediate or poor risk, pembrolizumab in combination with axitinib, or ipilimumab in combination with nivolumab are recommended. Alternative therapies for intermediate or poor risk patients include sunitinib, pazopanib or cabozantinib monotherapy.
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.
Advanced 1L RCC has historically been resistant to anticancer therapies; however, with the arrival of new therapies including immune-checkpoint-based immunotherapy (CTLA-4 and
PD-[L]1 inhibitors) in combination with a VEGF-TKI, OS in this population has significantly improved. Although several mechanisms have been proposed to explain resistance to PD-1 inhibition including insufficient antitumor T-cell generation, inadequate antitumor T-cell effector function, or impaired T-cell memory, the exact mechanism remains unknown. Thus, the goal of evaluating combination strategies in this setting is to improve the overall outcome of patients with 1L RCC.

Study objective

This study has been transitioned to CTIS with ID 2023-506838-68-00 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 MK3475-03A 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 not received prior systemic therapy for advanced RCC. This substudy is composed of a specific set of treatment arms, and these arms are composed of combinations 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 receive 1 of these IV (intravenous infusion) treatments: pembrolizumab or MK-1308A (quavonlimab + pembrolizumab) or MK-7684A (vibostolimab + pembrolizumab) for up to 2 years, either 3-weekly or 6-weekly. The subjects 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

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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 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).
Not received prior systemic therapy for advanced RCC (first line). Prior neoadjuvant/adjuvant therapy for RCC is acceptable if completed >=12 months before randomization/allocation.
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.
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

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 protocol.
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

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-03-2023
Enrollment:	5

Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	23-01-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	17-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	13-04-2023
Application type:	Amendment
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:	18-07-2023
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	CTIS2023-506838-68-00
EudraCT	EUCTR2019-003609-84-NL
ClinicalTrials.gov	NCT04626479
CCMO	NL82980.056.22