A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of MK-1484 as a Monotherapy and in Combination with Pembrolizumab in Participants with Advanced or Metastatic Solid Tumors

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This study has been transitioned to CTIS with ID 2023-505067-36-00 check the CTIS register for the current data. Primary objective: To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of MK-1484...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON51516

Source
ToetsingOnline

Brief title
MK1484-001

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced or Metastatic Solid Tumors / Terminal 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 or Metastatic Solid Tumors, Combination with pembrolizumab, MK-1484 monotherapy, Phase I First-in-Human

Outcome measures

Primary outcome

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

discontinuation of study intervention due to an AE.

Secondary outcome

PK parameters of MK-1484, including area under the curve (AUC), minimum

concentration (Cmin), and maximum concentration (Cmax).

Study description

Background summary

The usefulness of Interleukin-2 (IL-2) as a therapeutic is hampered by its short half-life and toxicity profile, which often leaves patients hospitalized due to adverse events. As a result of these toxicities, it is rarely used. Thus, the key features to improve on for an IL-2 based therapeutic are safety profile and the half-life, which would enable more convenient administration. MK-1484 is an agonistic analog of IL-2 with PEGylation for half-life extension. In preclinical studies, MK-1484 showed antitumor activity in a mouse tumor model and induced tumor growth inhibition. In these preclinical studies MK-1484 appeared to be well tolerated and showed limited elevation of eosinophils, a known toxicity biomarker for aldesleukin (also a form of IL-2, used for treatment of metastatic renal cell carcinoma). The favorable tolerability and pharmacology profile in nonhuman primates validate the hypothesis and supports selection of MK-1484 as a clinical candidate.

In this study, MK-1484 is further explored for the treatment of advanced/metastatic solid tumors as monotherapy and as combination therapy with pembrolizumab.

Study objective

This study has been transitioned to CTIS with ID 2023-505067-36-00 check the CTIS register for the current data.

Primary objective: To determine the safety and tolerability and to establish a preliminary recommended Phase 2 dose (RP2D) of MK-1484 administered as monotherapy and in combination with pembrolizumab infusion.
Secondary objective: To evaluate the PK of MK-1484 administered as monotherapy and in combination with pembrolizumab.

Study design

MK1484-001 is a first-in-human, phase 1, multicenter, 2-arm, open-label, dose escalation and dose confirmation study using an ATD, followed by mTPI design strategy, to evaluate the safety and tolerability of MK-1484 as monotherapy and in combination with pembrolizumab in adult participants with advanced or metastatic solid tumors.

Intervention

This study has 2 intervention groups: participants in Arm 1 receive MK-1484 monotherapy and participants in Arm 2 receive MK-1484 in combination with pembrolizumab. Each participant will receive assigned intervention for approximately 2 years (35 cycles). MK-1484 is administered by subcutaneous injection Q3W and pembrolizumab is administered by intravenous infusion Q3W. If participants in Arm 1 experience disease progression, they may be eligible for crossover to Arm 2 (criteria per protocol and upon sponsor approval). Participants who crossover to combination treatment will be eligible to receive a maximum of 35 cycles of combination treatment irrespective of the number of cycles or dose of MK-1484 received in monotherapy.

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 unknown and potentially serious side effects. It is unsure if the participants will directly benefit from the study intervention. There are however no (approved) treatments left to confer clinical benefit for this patient population.
MK-1484 has never been administered to humans. Similar drugs that work like

MK-1484 (e.g. next generation engineered IL-2 molecules NKTR-214, THOR-707 and ALKS-4230) are known to have the following most common side effects: rash, pruritus, fatigue, arthralgia, enlarged abdomen, nausea, malaise, chills, fever, and changes in liver and kidney function (elevated transaminase and blood urea nitrogen).
Pembrolizumab has been administered to a large number of oncology patients (various indications) with a known safety profile. Pembrolizumab has been approved for treatment of different types of cancer. Overall, pembrolizumab is well tolerated with most common side effects being itchy skin, loose/watery stools and coughing.
Participants are 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 of at least 18 years at the time of signing the informed consent form.
Histologically- or cytologically-confirmed advanced/metastatic solid tumor by pathology report and received, or intolerant to, all treatment known to confer clinical benefit.
Measurable disease by RECIST 1.1.
Performance status of 0 or 1 on the ECOG Performance Scale (within 7 days before the start of study intervention).
Normal cardiac function based on TTE or MUGA.
Presence of an evaluable archival or newly obtained tumor tissue sample for biomarker analysis.
Adequate organ function (within 7 days before the start of study intervention).
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

Chemotherapy, definitive radiation or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) before the first dose of study intervention.
Not recovered to CTCAE Grade 1 or better from any AEs that were due to cancer therapeutics administered more than 4 weeks earlier.
Currently participating and receiving study intervention in a study of an investigational agent, or participated and received study intervention in a study of an investigational agent, or used an investigational device within 28 days of administration of MK-1484.
Received any prior IL-2 based therapy.
Allogeneic tissue/solid organ transplant in the last 5 years or evidence of graft-versus-host disease.
History of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years.
Clinically active CNS metastases and/or carcinomatous meningitis (exceptions per protocol).
History of severe hypersensitivity reaction to treatment with a monoclonal antibody and/or components of the study intervention(s).
Active infection requiring therapy.
Active autoimmune disease that required systemic treatment in the past 2

years (details per protocol).
History of interstitial lung disease, history of (noninfectious) pneumonitis that required steroids, or current pneumonitis.
Known HIV and/or hepatitis B or C infections, or known to be positive for HBsAg/HBV DNA or hepatitis C Antibody or RNA.
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, make administration of the study drugs hazardous, or make it difficult to monitor adverse effects such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-07-2022
Enrollment:	30
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	25-04-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-04-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2023
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	CTIS2023-505067-36-00
EudraCT	EUCTR2021-005220-38-NL
CCMO	NL80286.056.22