A Phase 1, Open-label, Multicenter Study of the Safety, Pharmacokinetics, and Pharmacodynamics of MK-4464 as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced / Metastatic Solid Tumors

Published: 21-02-2023
Last updated: 05-10-2024

This study has been transitioned to CTIS with ID 2023-504855-28-00 check the CTIS register for the current data. To determine the safety and tolerability and to establish a preliminary RP2D and/or an MTD or an MAD of MK-4464 administered via IV...

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

Summary

ID

NL-OMON53771

Source
ToetsingOnline

Brief title
MK4464-001

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
advanced or metastatic solid tumors, solid neoplasm

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: advances solid tumors, metastatic solid tumors, MK4464, pembrolizumab

Outcome measures

Primary outcome

To determine the safety and tolerability and to establish a preliminary

"recommended Phase2 dose" (RP2D) and/or an "maximum tolerated dose" (MTD) or an

"maximum administered dose"(MAD) of MK-4464 administered via IV infusion as

monotherapy and in combination with pembrolizumab IV infusion.

Endpoints:

• Dose-limiting toxicity (DLT)

• Adverse event (AE)

• Discontinuing study treatment due to an AE

Secondary outcome

1. To evaluate the PK of MK-4464 administered via IV infusion as monotherapy

and in combination with pembrolizumab IV infusion.

Endpoints:

• Appropriate PK parameters of MK-4464, which may include Cmin, Cmax, and AUC

2. To evaluate ORR as assessed by the investigator per RECIST 1.1. RECIST 1.1

is adjusted to follow a maximum of 10 target lesions and a maximum of 5 target

lesions per organ.

Endpoints:

• Objective response: CR or PR

Study description

Background summary

MK4464 is a TriNKET* (Dragonfly Pharmaceuticals), an antibody-based trifunctional molecule designed to exert dual mechanisms of action in cancer immunotherapy. MK4464 recruits immune cells into tumors and directly activates killing of cancer cells. MK4464 binds to CEACAM5 (on cancer cells) and NKG2D and CD16A (on NK cells). It also engages cytotoxic T cells. MK4464 is under study for the treatment of advanced/metastatic solid tumors as monotherapy and as combination therapy with pembrolizumab. This is a FIH, doseescalation, and dosefinding study to assess the safety and tolerability of MK4464, both as monotherapy and as combination therapy with pembrolizumab.

Study objective

This study has been transitioned to CTIS with ID 2023-504855-28-00 check the CTIS register for the current data.

To determine the safety and tolerability and to establish a preliminary RP2D and/or an MTD or an MAD of MK-4464 administered via IV infusion as monotherapy and in combination with pembrolizumab IV infusion

Study design

This is a multicenter, worldwide, open-label, nonrandomized, Phase 1 study of MK 4464 as a monotherapy and in combination with pembrolizumab in participants with a histologically or cytologically confirmed diagnosis of locally advanced/metastatic solid tumor that has not responded to conventional therapy.

This study will evaluate the safety, tolerability, PK/PD, and preliminary efficacy of MK 4464 monotherapy administration (Arm A), and in combination with pembrolizumab (Arm B).

Intervention

2 Arms:
1) MK4464 (0.25 mg to 750 mg via infusion, once every 3 weeks up to a maximum

of 35 cycles)
2) MK4464 (7.5 mg to 750 mg via infusion, once every 3 weeks up to a maximum of 35 cycles) + Pembrolizumab (200 mg via infusion, once every 3 weeks up to a maximum of 35 cycles)

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.

During the study participation subjects are treated with the experimental therapy that has not been administered to human before. A 7-day delay between participants during Dose Escalation is intended to provide sufficient time for monitoring for and mitigating early-onset treatment-related AEs after MK 4464 administration. Additionally, there will be a 2-dose lag between the monotherapy and combination treatments providing a safety gate.

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

A participant will be eligible for inclusion in the study if the participant meets the following
criteria:
1. Have a histologically or cytologically confirmed advanced/metastatic solid tumor by pathology report and have received, or been intolerant to, all treatment known to confer clinical benefit. Only solid tumors of the following types may be included:
• CRC
• Gastric carcinoma
• Esophageal carcinoma
• Pancreatic cancer
• NSCLC
2. Have measurable disease by RECIST 1.1 as assessed by the local site investigator/radiology. Target lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.
3. Must submit a baseline tumor sample for analysis (either a recent or archival tumor sample). Details pertaining to tumor tissue submission can be found in the Laboratory Manual.
4. Arm A (mTPI part): Have 1 or more discrete malignant lesions that are amenable to biopsy.
5. Have a performance status of 0 or 1 on the ECOG Performance Scale.
6. Have adequate organ function as defined in the protocol. Specimens must be collected within 7 days before the start of study intervention.
7. Is male or female, >=18 years of age at the time of providing informed consent.
8. No contraception measures are required for male participants.
9. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
• Not a WOCBP
• A WOCBP and:
- Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), 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 120 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. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- Has a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within [specify time frame eg, 72 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.]
- Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.
- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.
10. The participant (or legally acceptable representative) has provided documented informed
consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.
11. HIV-infected participants must have well controlled HIV on ART meeting all of the criteria below:
a. Participants on ART must have a CD4+ T cell count >350 cells/mm3 at the time of screening
b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening
c. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1).
Please refer to the protocol for the complete list of the inclusion criteria

Exclusion criteria

The participant must be excluded from the study if the participant meets the following criteria:
1. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4 weeks (2 weeks for palliative radiation) before the first dose of study intervention or has not recovered to CTCAE Grade 1 or better from any AEs that were due to cancer therapeutics administered more than 4 weeks earlier (this includes participants with previous immunomodulatory therapy with residual immune-related AEs). Participants receiving ongoing replacement hormone therapy for endocrine immune-related AEs will not be excluded from participation in this study.
2. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years. Note:

Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.
3. Has clinically active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic (without evidence of progression by MRI scan of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks before first study intervention administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks before enrollment.
4. Has an active infection requiring therapy.
5. History of an allogenic stem cell transplant or a solid organ transplant.
6. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
7. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs) except vitiligo or resolved childhood asthma/atopy. Replacement therapy, such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, is not considered a form of systemic treatment and is allowed. Use of nonsystemic steroids is permitted.
8. HIV-infected participants with a history of Kaposi*s sarcoma and/or Multicentric Castleman*s Disease.
9. 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, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
10. Has known psychiatric or substance abuse disorders that would interfere with the participant*s ability to cooperate with the requirements of the study.
11. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study intervention.
12. Has not fully recovered from any effects of major surgery without significant detectable infection. Surgeries that required general anesthesia must be completed at least 2 weeks before first study intervention administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study intervention administration and participants should be recovered.
13. QTc using Fridericia*s QT correction formula >480 msec.
14. Has had a severe hypersensitivity reaction to treatment with a mAb and/or other components of the study intervention.
15. Has had prior treatment with any NK engager/targeting-based therapies.
16. Has received radiation therapy to the lung that is >30 Gy within 6 months of the first dose of study treatment.
17. Received a live or live-attenuated vaccine within 30 days before the first

dose of study intervention. Administration of killed vaccines are allowed. Refer to Section 6.5.2 in the study protocol for information on COVID-19 vaccines.
18. Is currently participating and receiving study intervention in a study of an investigational agent or has participated and received study intervention in a study of an investigational agent or has used an investigational device within 28 days of administration of MK-4464.
Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent.
19. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

Please refer to the protocol for the complete list of the exclusion criteria

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-03-2023
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab

Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	MK4464
Generic name:	MK4464

Ethics review

Approved WMO Date:	21-02-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2023
Application type:	First submission
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	CTIS2023-504855-28-00
EudraCT	EUCTR2021-005882-42-NL
ClinicalTrials.gov	NCT05514444
CCMO	NL81789.056.22