A Phase 1/2 Randomized, Umbrella Study to Evaluate the Safety and Efficacy of Pembrolizumab Plus Enfortumab Vedotin (EV) in Combination With Investigational Agents Versus Pembrolizumab Plus EV, as First-Line Treatment for Participants With Advanced Urothelial Carcinoma (KEYMAKER-U04): Substudy 04B

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This study has been transitioned to CTIS with ID 2023-506385-30-00 check the CTIS register for the current data. Primary Part 1:-To evaluate ORR in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus…

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

Summary

ID

NL-OMON53800

Source
ToetsingOnline

Brief title
MK3475-04B

Condition

- Miscellaneous and site unspecified neoplasms benign
- Bladder and bladder neck disorders (excl calculi)

Synonym
bladder cancer, inoperable or metastatic UC

Research involving
Human

Sponsors and support

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

Intervention

Keyword: investigational agents, Phase 1/2, Urothelial Carcinoma

Outcome measures

Primary outcome

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

- AEs.

- Discontinuations of study interventions due to an AE.

- Dose-limiting toxicity (DLT).

- Progression Free Survival (PFS): The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

Secondary outcome

- PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

- Overall Survival (OS): The time from randomization to death due to any cause.

- OR: CR or PR.

- AEs.

- Discontinuations of study interventions due to an AE.

- Dose-limiting toxicity (DLT).

- Duration of Response (DOR): For participants who show 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.

- Change from baseline in:

• The global health status/quality of life of the EORTC QLC-C30 (Items 29 and 30).

• The physical functioning scale of the EORTC QLQ-C30.

• EQ-5D-5L visual analog score (VAS).

The time-to-deterioration, defined as the time from baseline to first onset of patient reported outcome deterioration based on established minimal important differences threshold, in:

• The global health status/quality of life of the EORTC QLQ-C30 (Items 29 and 30).

• The physical functioning scale of the EORTC QLQ-C30.

• EQ-5D-5L VAS.

Study description

Background summary

Locally advanced or mUC is a serious and incurable condition with poor long-term survival and a high unmet medical need.

Pembrolizumab is approved for the 1L treatment of patients with la/mUC who are not eligible for chemotherapy.
EV was approved for la/mUC who have previously received a PD-1 or PD-L1

inhibitor and platinum-containing chemotherapy and
for cisplatin-ineligible patients who have received one or more prior lines of therapy.

The preliminary results with the combination of pembrolizumab and EV show a better tumor response and survival in patients with la/mUC but there is still a need to further improve outcomes for patients with this aggressive disease.
The aim of substudy 04B is to build upon the efficacy of the combination of pembrolizumab and EV, with the addition of novel immunotherapy agents (MK-4280 and MK-7684)

Study objective

This study has been transitioned to CTIS with ID 2023-506385-30-00 check the CTIS register for the current data.

Primary

Part 1:

-To evaluate ORR in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by BICR.
- To evaluate the safety and tolerability in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C).

Part 2:

-To compare EV plus MK-4280A (Arm A) and/or EV plus MK-7684A (Arm B) to EV plus pembrolizumab (Arm C) with respect to PFS per RECIST 1.1 by BICR.
- Hypothesis (H1): EV plus MK- 4280A (Arm A) and/or EV plus MK-7684A (Arm B) are superior to EV plus pembrolizumab (Arm C) with respect to PFS per RECIST 1.1 by BICR.

Secondary

Part 1:

-To evaluate PFS in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by BICR.
- To evaluate DOR in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by BICR
- To evaluate changes in patient-reported outcomes from baseline and TTD using the EORTC QLQ-C30 instrument and EQ-5D-5L in participants treated with MK-4280A plus EV (Arm A), MK- 7684A plus EV (Arm B) and pembrolizumab plus EV (Arm C).

Part 2:

-To compare EV plus MK-4280A (Arm A) and/or EV plus MK-7684A (Arm B) versus EV plus pembrolizumab (Arm C) with respect to OS.
- Hypothesis (H2) EV plus MK-4280A (Arm A) and/or EV plus MK-7684A (Arm B) are superior to EV plus pembrolizumab (Arm C) with respect to OS
- To evaluate ORR in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by BICR.
- To evaluate the safety and tolerability in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C).
- To evaluate DOR in participants treated with MK-4280A plus EV (Arm A), MK-7684A plus EV (Arm B), and pembrolizumab plus EV (Arm C) per RECIST 1.1 by BICR
- To evaluate changes in patient-reported outcomes from baseline and TTD using the EORTC QLQ-C30 instrument and EQ-5D-5L in participants treated with MK-4280A plus EV (Arm A), MK- 7684A plus EV (Arm B) and pembrolizumab plus EV (Arm C).

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Study design

This is a Phase 1/2 randomized, parallel-group, multi-site, open-label substudy of MK-4280A plus EV (Arm A) and MK-7684A plus EV (Arm B) versus pembrolizumab plus EV (Arm C) in participants with la/mUC previously untreated for their advanced disease.

This substudy will consist of 2 parts. Part 1 will evaluate the efficacy and safety of Arms A and B relative to Arm C. Based on results from Part 1, the Sponsor may consider further development of the treatment arm(s) of interest under Part 2 of the substudy.

Participants in Arm A will receive EV at 1.25 mg/kg, administered as an IV infusion over approximately 30 minutes on Days 1 and 8 of every 3-week cycle, and MK-4280A (800 mg MK-4280/200 mg pembrolizumab) as an IV infusion on Day 1 of every 3-week cycle (Q3W), after completion of the EV infusion.

Participants in Arm B will receive EV at 1.25 mg/kg, administered as an IV infusion on Days 1 and 8 of every 3-week cycle, and MK-7684A (200 mg MK-7684/200 mg pembrolizumab) as an IV infusion on Day 1 of every 3-week cycle (Q3W), after completion of the EV infusion.

Participants in Arm C will receive EV at 1.25 mg/kg, administered as an IV infusion on Days 1 and 8 of every 3-week cycle, and pembrolizumab 200 mg as an IV infusion on Day 1 of every 3-week cycle (Q3W), after completion of the EV

infusion

In Part 1, a total of 120 participants will be randomized in a 1:1:1 ratio to arm A, B and C.
If the Sponsor considers further development of the treatment arm(s) of interest is warranted, Part 2 will be conducted. In Part 2, a maximum of approximately 270 participants (approximately 90 participants per arm) will be randomized in a 1:1:1 ratio to Arms A, B, and C or in a 1:1 ratio to Arms A and C or B and C, depending on the treatment Arm(s) that are expanded in Part 2.Therefore, the total sample size may vary from approximately 120 participants if only Part 1 is conducted, approximately 300 participants if Part 1 and Part 2 are conducted with the expansion of 2 treatment arms (Arms A/B and C) or approximately 390 participants if Part 1 and Part 2 are conducted with the expansion of all 3 Arms (Arms A,
B and C).
No treatment crossover is planned for the substudy.

Intervention

Arm A:
EV at 1.25 mg/kg, administered as an IV infusion over approximately 30 minutes on Days 1 and 8 of every 3-week cycle, and MK-4280A (800 mg MK-4280/200 mg pembrolizumab) as an IV infusion on Day 1 of every 3-week cycle (Q3W), after completion of the EV infusion.

Arm B:
EV at 1.25 mg/kg, administered as an IV infusion on Days 1 and 8 of every 3-week cycle, and MK-7684A (200 mg MK-7684/200 mg pembrolizumab) as an IV infusion on Day 1 of every 3-week cycle (Q3W), after completion of the EV infusion.

Arm C:
EV at 1.25 mg/kg, administered as an IV infusion on Days 1 and 8 of every 3-week cycle, and pembrolizumab 200 mg as an IV infusion on Day 1 of every 3-week cycle (Q3W), after completion of the EV infusion

Please refer to table 4 in the protocol

Study burden and risks

For this study, subjects will be exposed to invasive procedures such as biopsy, blood collection, IV infusions, CT-MRI or bone scans, physical exams and patients will be asked to visit the hospital regularly.

Patients will receive EV with 1 other IMP: MK-4280A, MK-7684A or pembrolizumab.

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/investigational medicines.

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

1. The participants must have histologically documented, la/mUC (ie, cancer of the bladder, renal pelvis, ureter, or urethra). Histology will be confirmed locally.
2. Participants must have measurable disease by investigator assessment according to RECIST 1.1.
3. Participants must not have received prior systemic therapy for la/mUC. The

following therapies in earlier disease settings (eg, MIUC) are permitted:
• Participants that received neoadjuvant or adjuvant chemotherapy are permitted.
• Participants who received anti-PD-1 or PD-L1 therapy for an earlier disease stage (eg, NMIBC, MIUC) with progression/recurrence >12 months from completion of therapy are permitted.
4. Participants must provide an archival tumor tissue sample or newly obtained core or
excisional biopsy of a tumor lesion demonstrating UC, not previously irradiated, and
adequate for biomarker evaluation. A newly obtained biopsy is strongly preferred, but not
required if archival tissue is evaluable.
5.Participants who have AEs due to previous anticancer therapies must have recovered to <=Grade 1 or baseline. Participants with endocrine-related AEs who are adequately treated with hormone replacement or participants who have 2 neuropathy are eligible.
6. Is male or female, and >=18 years at the time the participant (or their legally acceptable
representative) provides documented informed consent for the study.
7. If male, agrees to the following during the intervention period and for at least 180 days
after the last dose of EV:
Refrains from donating sperm
PLUS either:
• Abstains from heterosexual intercourse as their preferred and usual lifestyle (abstinent on
a long-term and persistent basis) and agrees to remain abstinent
OR
• Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to
medical cause, documented from the site personnel*s review of the participant*s medical
records, medical examination, or medical history interview) as per protocol.
8. 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 (Refer to Appendix 5 for definition of WOCBP)
OR
• A WOCBP and
-Uses a contraceptive method that is highly effective as er protocol.
-Has a negative highly sensitive pregnancy test (urine or serum as required by local
regulations) within 24 hours before the first dose of study intervention.
-Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention (for MK-4280A, MK-7684A, or pembrolizumab) or 180 days (EV) days after the last dose of 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.
9. Provides documented informed consent/assent for the study.
10. An ECOG performance status of 0 to 1 assessed within 7 days prior to randomization.
11. Adequate organ function as defined in Table 3 of the protocol.

Exclusion criteria

1. Known additional malignancy, except if the participant has undergone potentially curative therapy with no evidence of that disease recurrence for at least 3 years since initiation of that therapy.
2. Participants with treated CNS metastases are permitted on-study if all of the following are true: a) CNS metastases have been clinically stable for at least 4 weeks prior to screening and baseline scans show no evidence of new or enlarged metastasis; b) the participant is on a stable dose of <=10 mg/day of prednisone or equivalent for at least 2 weeks (if requiring steroid treatment); c) participant does not have leptomeningeal disease.
3. Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, LAG3, TIGIT, OX-40, CD137). Exception includes participants who received neo-adjuvant or adjuvant anti-PD-1 or PD-L1 therapy for an earlier disease stage (eg, MIUC) with recurrence >12 months from completion of therapy.
4. Received therapy with hematopoietic growth factor such as G-CSF or GM-CSF within 14 days prior to randomization.
5. Received prior systemic anticancer therapy including investigational agents (including EV or other MMAE-based ADCs) within 3 years prior to randomization. Exception includes participants that received neoadjuvant or adjuvant chemotherapy or anti-PD-1/L1 therapy for an earlier disease stage (eg, MIUC).
6. Received a live or live-attenuated vaccine within 30 days prior to the first dose of study
intervention.
7. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.
8. Ongoing sensory or motor neuropathy Grade 2 or higher.
9. A diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study intervention. Inhaled or topical steroids are permitted in the absence of active autoimmune disease. Physiologic replacement doses of corticosteroids are permitted for participants with adrenal insufficiency.

10. Severe hypersensitivity (>=Grade 3) to mAb (including pembrolizumab) and/or any of their excipients.
11. Known severe hypersensitivity (>=Grade 3) to any excipient contained in the drug formulation of EV (including histidine, trehalose dihydrate, and polysorbate 20).
12. Active keratitis or corneal ulcerations. Participants with superficial punctate keratitis are allowed if the disorder is being adequately treated in the opinion of the investigator.
13. Active autoimmune disease that has required systemic treatment in past 2 years except
replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid).
14. A history of uncontrolled diabetes. Uncontrolled diabetes is defined as HbA1c >=8% or HbA1c 7% to < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.
15. A history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
16. An active infection (viral, bacterial, or fungal) requiring systemic therapy. Participant
may be rescreened after resolution of the infection.
17. A known history of HIV infection. No HIV testing is required unless mandated by local
health authority.
18. Hepatitis B (defined as HBsAg reactive) or hepatitis C virus (defined as HCV RNA
qualitative is detected) infection.
19. A 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.
20. A known psychiatric or substance abuse disorder that would interfere with the participant*s ability to cooperate with the requirements of the study.
21. Had major surgery within 4 weeks prior to first dose of study intervention.
22. Has had an allogenic tissue/solid organ transplant.

Study design

Design

Study phase:	2
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-06-2023
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MK-4280A
Generic name:	favezelimab+ pembrolizumab
Product type:	Medicine
Brand name:	MK7684A
Generic name:	vibostolimab +pembrolizumab
Product type:	Medicine
Brand name:	Padcev
Generic name:	enfortumab vedotin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	08-02-2023
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-03-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-09-2023
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	CTIS2023-506385-30-00
EudraCT	EUCTR2022-001371-14-NL
Other	IND 152.554
CCMO	NL83032.056.23