A Phase 1/2 Open-Label Rolling-Arm Umbrella Platform Study of Investigational Agents With or Without Pembrolizumab in Participants with PD-1/L1 Refractory Locally Advanced or Metastatic Urothelial Carcinoma (KEYMAKER-U04): Substudy 04A

Published: 12-10-2022
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2023-506384-34-00 check the CTIS register for the current data. Primary:- To assess the safety and tolerability of MK2140- To evaluate objective response rate (ORR) of MK2140 as assessed by BICR per...

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

Summary

ID

NL-OMON51831

Source
ToetsingOnline

Brief title
MK3475-04A

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: MK-2140, Phase 1/2, Urothelial Carcinoma

Outcome measures

Primary outcome

- Adverse Events (AEs)

- Study intervention discontinuations due to AEs.

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

Secondary outcome

Duration of response (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.

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

Anti-PD-1/L1 agents are approved for the adjuvant treatment of high-risk muscle-invasive bladder cancer and for the treatment of locally advanced and mUC in the 1L setting for cisplatin-ineligible patients with PD-L1 CPS >=10; for patients who are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status, and as maintenance therapy for a subset of patients that have received platinum-based chemotherapy. Anti-PD-1/L1 agents are also

approved in the 2L setting in patients deemed platinum refractory UC. Despite the durable clinical benefits from the use of these agents, a large portion of patients have disease that either shows no clinical response or response followed by progression requiring subsequent therapies.

The patients who respond best to anti-PD-1/L1 therapies have a longer OS, but those with no response quickly develop progressive disease. The Society for Immunotherapy of Cancer taskforce has generated clinical definitions for resistance to PD-1/L1 inhibitors in 3 distinct scenarios: 1) primary resistance, 2) secondary resistance, and 3) disease progression after discontinuation or halting of PD-1/L1 inhibitors. This patient population resistant to immunotherapy represents a significant unmet medical need because of very limited available treatment options and therefore necessitates the development of new therapies.

The study drug MK2140 in this study may improve responsiveness in tumors that are resistant or refractory to anti-PD-1/L1 therapy.

Study objective

This study has been transitioned to CTIS with ID 2023-506384-34-00 check the CTIS register for the current data.

Primary:

- To assess the safety and tolerability of MK2140
- To evaluate objective response rate (ORR) of MK2140 as assessed by BICR per RECIST 1.1

Secondary:

-To evaluate the duration of response (DOR) of MK2140 as assessed by BICR per RECIST 1.1

Study design

This is a Phase 1/2 Substudy of MK2140 in PD-1/L1 Refractory Locally Advanced or mUC.
The study will be perfomed in individuals at least 18 years of age with PD-1/L1 refractory locally advanced/unresectable or metastatic UC receiving MK2140.

This substudy protocol employs a design in which new investigational treatment arms will be open for enrollment on a rolling basis to evaluate new investigational treatments with or without pembrolizumab. Therefore, the total number of participants will depend on the number of investigational treatment

arms open for enrollment

Approximately 40 participants will be enrolled in this study.

The total number of investigational treatment arms will depend on the number of investigational agents evaluated.

In this current first arm A all subjects will receive MK2140 as an IV infusion in 3-weekly cycles where MK2140 is given on day 1 and 8 of each cycle.

Intervention

The total number of investigational treatment arms will depend on the number of investigational agents evaluated. This study protocol will include a minimum of 1 investigational treatment arm (arm A).

In arm A the interventional agent is MK2140 which is given on day 1 and day 8 of each Q3W cycle. (please refer to protocol section 10.6.2.2)

MK2140 is a solution for infusion in a unit dose of 10 mg/ml given at 2 mg/kg as IV infusion

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 IMP on day 1 and 8 of three-week cycles. 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.

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

1. Has a histologically or cytologically confirmed diagnosis of locally advanced/unresectable or mUC of the renal pelvis, ureter (upper urinary tract), bladder, or urethra. Participants with nonurothelial tumors,including pure squamous cell carcinoma, pure adenocarcinoma including urachal adenocarcinomas, neuroendocrine tumors, and mesenchymal tumors, are not eligible.
2. Has measurable disease as assessed by the site and verified by blinded independent central review (BICR) according to RECIST 1.1.
3. Has PD-1/L1 refractory locally advanced or mUC as evidenced by:
EITHER disease progression while on treatment or after treatment with an anti-PD-1/L1 mAb for locally advanced/unresectable or mUC administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. In these participants, anti-PD-1/L1 mAb treatment is defined by meeting ALL of the following criteria:
a. Has received at least 2 doses of an approved anti-PD-1/L1 mAb.
b. Has demonstrated radiographic disease progression while on treatment or after treatment with an anti-PD-1/L1 mAb by investigator assessment.
c. Disease progression has been documented radiographically by the investigator within 12 weeks from the last dose of anti-PD-1/L1 mAb.
OR
Has experienced disease recurrence while on treatment or after treatment with an anti-PD-1/L1 mAb for muscle-invasive UC (MIUC) administered as monotherapy. In these participants, anti-PD-1/L1 mAb treatment is defined by meeting ALL of the following criteria:

a. Has received at least 2 doses of an approved anti-PD-1/L1 mAb.
b. Has demonstrated radiographic disease recurrence while on treatment with an anti-PD-1/L1 mAb or within 6 months from treatment completion by investigator assessment.
4. Participants who received an anti-PD-1/L1 mAb for the treatment of locally advanced/unresectable or mUC must have demonstrated disease progression while on treatment or after treatment with an anti-PD-1/L1 mAb based on investigator assessment. If available, scans before treatment with an anti-PD-1/L1 or showing nadir during treatment with an anti-PD-1/L1 mAb and scans that document radiographic disease progression within 12 weeks (84 days) from the last dose of an anti-PD-1/L1 mAb should be submitted to the iCRO.
Participants who received an anti-PD-1/L1 mAb for the treatment of MIUC must have demonstrated disease recurrence while on treatment or within 6 months from treatment completion based on investigator assessment. If available, scan before treatment with an anti-PD-1/L1 mAb and scan that documents radiographic recurrence should be submitted to the iCRO.
5. 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.
6. Has an ECOG performance status of 0 to 1 (as assessed within 7 days of the first dose of study intervention).
7. Has resolution of toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia).
8. Has adequate organ function. Specimens must be collected within 7 days before the start of study intervention.
9. Participants are male or female, >=18 years of age at the time of providing documented informed consent.
10. Male participants are eligible to participate if they agree to follow the contraception requirements for the investigational treatment arm to which they are assigned.
• Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.
11. Female participants are eligible to participate if they agree to follow the contraception requirements for the investigational treatment arm to which they are assigned.
12. The participant (or legally acceptable representative) has provided documented informed consent for the study.

Exclusion criteria

1. Has a known additional nonurothelial malignancy that is progressing or has

required active treatment within 3 years prior to study randomization/allocation.
2. Has known active CNS metastases and/or carcinomatous meningitis.
3. Has known hypersensitivity to active substances or any of their excipients including previous clinically significant hypersensitivity reaction to treatment with pembrolizumab or other investigational agents being evaluated within this study.
4. Has received prior systemic anticancer therapy including investigational agents within 4 weeks before randomization/allocation.
5. Has an active infection requiring systemic therapy.
6. Has received prior radiotherapy within 2 weeks of first dose of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
7. Has had major surgery (<3 weeks before first dose of study intervention).
8. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.
9. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention.
10. Has known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies).
11. Has known history of hepatitis B (defined as HBsAg reactive) or known hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
12. Has a history or has current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the 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.
13. Has had an allogeneic tissue/solid organ transplant.

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):	16-01-2023
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Zilovertamab vedotin
Generic name:	MK-2140

Ethics review

Approved WMO Date:	12-10-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-12-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2023
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	CTIS2023-506384-34-00
EudraCT	EUCTR2020-004544-28-NL
Other	IND 152,554
CCMO	NL82488.056.22