Phase 3 Randomized, Double-Blind Clinical Study of Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo as a Treatment for Recurrent or Progressive Metastatic Urothelial Carcinoma in Patients who have Failed a First-Line Platinum-containing Chemotherapy Regimen for Advanced/Metastatic Disease (KEYNOTE-698/ECHO-303)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON44435

Source
ToetsingOnline

Brief title
MK3475-698

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder cancer, urothelelial carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: epacadostat, pembrolizumab, urothelial carcinoma

Outcome measures

Primary outcome

The dual primary endpoints are PFS (progression free survival) and OS (overall survival).

* OS is defined as the time from the date of randomization to the date of death due to any cause.

* PFS is defined as the time from the date of randomization until disease progression, or death from any cause, whichever occurs first based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by Investigator determination.

Secondary outcome

The secondary endpoints include safety and tolerability, Overall Response Rate (ORR), time to true deterioration (TTD) in global health status / quality of life (QoL).

ORR is defined as the proportion of participants in the analysis population who have a best response of complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by Investigator determination.

TTD is defined as the time from baseline to first onset of Patient Reported Outcome (PRO) deterioration.

Study description

Background summary

The worldwide incidence of bladder cancer exceeds 300,000 cases annually. Urothelial carcinoma is the predominant histologic type of bladder cancer in the United States and Western Europe, where it accounts for approximately 90% of bladder cancers. Approximately 25% of patients with muscle-invasive disease either present with or later develop metastases. Systemic chemotherapy is the standard approach for the initial treatment of patients with inoperable locally advanced or metastatic urothelial malignancies. The median survival with multi-agent chemotherapy is approximately 14 to 15 months.

While this is superior to the estimated 6-month survival with metastatic disease prior to the development of modern chemotherapy regimens, the 5-year survival rate is approximately 15% with contemporary regimens. More effective and less toxic treatments are greatly needed in this patient population, and immunotherapy offers additional options for patients progressing after their initial systemic therapy.

In light of the relatively limited benefit from second-line chemotherapy in this patient population (at best 6.9 months increase in OS), and the promising results with pembrolizumab and IDO1, pembrolizumab and epacadostat versus pembrolizumab plus placebo will be compared in this participant population. Pembrolizumab is a potent and highly selective monoclonal antibody that directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Epacadostat represents a novel, potent, and selective inhibitor of the enzyme IDO1 in both tumor cells and dendritic cells.

It is expected that combined inhibition of the IDO1 and the PD-1 pathway will

have a complimentary therapeutic effect and will lead to a greater suppression of antitumor immunity.

Study objective

The objective of this study is to test the safety, tolerability and anti-tumor activity of the combination of the investigational products epacadostat and pembrolizumab, compared to pembrolizumab as mono therapy, in patients with advanced/unresectable or metastatic urothelial carcinoma (UC) that has recurred or progressed following one prior line of platinum-containing chemotherapy for advanced/metastatic disease.

Study design

This is a Randomized, Double-Blind, placebo-controlled phase 3 trial of pembrolizumab in combination with epacadostat or placebo.

Intervention

1. Pembrolizumab 200 mg IV every 3 weeks (Q3W) + epacadostat 100 mg PO BID continuously
2. Pembrolizumab 200 mg IV Q3W + placebo PO BID continuously

Study burden and risks

Treatment cycles will take three weeks, of which pembrolizumab will be administered on Day 1 and epacadostat will be taken orally twice daily. At every visit, a physical examination will be performed, vital signs will be measured, ECG made and blood samples will be collected.

Subjects will also be asked to complete questionnaires on their health and symptoms (EuroQol q-5D-3L [Health], and EORTC QLQ-C30 [Quality of Life]. There will be a tumor biopsy at screening (may be omitted in case adequate tumor tissue from a previous biopsy is available). At several timepoints during the study, tumor imaging will be performed.

Subjects may experience physical and/or psychological discomfort with some of the study procedures, such as blood sampling, administration of the IV line, ECGs, CT/MRI scans and tumor biopsy. The most frequent reported side effects with the trial medication include itching, frequent or irregular bowel movements, cough, fatigue, nausea, headache, shortness of breath and rash.

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. Have histologically-confirmed diagnosis of UC of the renal pelvis, ureter, bladder, or urethra, that is transitional cell, or mixed transitional/non-transitional (predominantly transitional) cell type.;2. Have progression or recurrence of UC following one prior platinum containing chemotherapy regimen for metastatic or unresectable locally advanced disease. No additional lines of systemic treatment are allowed.;3. Have the presence of at least one measurable lesion by computed tomography (CT) or Magnetic Resonance Imaging (MRI) per RECIST 1.1 as determined by the investigator/local radiology assessment.;a. If participants have only 1 measurable lesion per RECIST 1.1, any biopsy specimen should be obtained from the non-target lesion or archival tissue.;b. If participants have only 1 measurable lesion per RECIST 1.1, this lesion should not have been in the field of prior irradiation unless there is documented progression of the lesion(s).;4. Have provided an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated for PD-

L1 analysis. A newly obtained biopsy is strongly preferred but not required if archival tissue is adequate for analysis. If submitting unstained cut slides, freshly cut slides should be submitted to the central laboratory within 14 days from when the slides are cut. Refer to Section 9.8.1 in the protocol for an explanation. PD-L1 status (CPS *10 or CPS<10) must be determined by the central laboratory prior to randomization. Participants will be excluded if PD-L1 status cannot be determined.;5. Have resolution of all toxicities and any toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia). Participants with *Grade 2 neuropathy are an exception and may enroll.;6. Be *18 years of age on day of signing informed consent.;7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 within 14 days prior to randomization.;Male participants:;8. A male participant must agree to use a contraception during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.;Female participants:;A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:;a.) Not a woman of childbearing potential (WOCBP);OR;b.) A WOCBP who agrees to use contraception during the treatment period and for at least 120 days (corresponding to time needed to eliminate any study treatments (MK-3475 and epacadostat) after the last dose of study treatment.;9. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.;10. Have adequate organ function as defined in the protocol. Specimens must be collected within 14 days prior to randomization.

Exclusion criteria

1. Has urothelial carcinoma that is suitable for local therapy with curative intent.;2. Has presence of a gastrointestinal condition that in the opinion of the Investigator may affect drug absorption.;3. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, or New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.;4. Has a history or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening corrected QT interval (QTc) interval >480 msec is excluded (corrected by Fridericia formula or Bazett formula). In the event that a single QTc is >480 milliseconds, the participant may enroll if the average QTc for the 3 ECGs is <480 milliseconds.;5. Has 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.;6. Has 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 treatment.;7. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.;8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging, (note that repeat imaging should be performed during the study screening), clinically stable and without requirement of steroid treatment for at least

14 days prior to first dose of study treatment.;9. Has severe hypersensitivity (*Grade 3) to study treatment (pembrolizumab and epacadostat) and/or any of its excipients.;10. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.;11. Has known history of or is positive for active Hepatitis B (HBsAg reactive) or has active Hepatitis C (HCV RNA).;12. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.;13. Has an active infection requiring systemic therapy.;14. Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is not required unless mandated by local health authority.;15. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.;16. A WOCBP who has a positive urine pregnancy test within 72 hours before randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.;17. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti PD-L2 agent, IDO1 inhibitor, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137), or any other antibody or drug targeting T-cell costimulatory pathways in the adjuvant or advanced/metastatic setting.;18. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to randomization.;19. Has received prior radiotherapy within 2 weeks of randomization. Participants must have recovered from all radiation-related toxicities (to Grade *1), and not require corticosteroids. A 1-week washout is permitted for palliative radiation (* 2 weeks of radiotherapy) to non-CNS disease.;20. Has received a live vaccine within 30 days prior to the first dose of study treatment. ;21. Has received therapy with a MAOI, melatonin supplement, or UGT1A9 inhibitor within 21 days prior to starting treatment, or anticipates requiring one of these prohibited medications during the treatment phase.;22. Has any history of SS after receiving serotonergic drugs.;23. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.;24. 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 treatment.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-04-2018
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INCB024360
Generic name:	epacadostat
Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	31-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	06-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2018
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
EudraCT	EUCTR2017-002310-31-NL
CCMO	NL62921.056.17