# A Phase 3 Randomized, Double-Blind Trial of Pembrolizumab (MK-3475) in Combination with Epacadostat (INCB024360) or Placebo in Participants with Cisplatin-ineligible Urothelial Carcinoma (KEYNOTE-672/ECHO-307)

Published: 12-10-2017
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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-OMON44517

**Source**
ToetsingOnline

**Brief title**
MK3475-672

### Condition

- Renal and urinary tract neoplasms malignant and unspecified

**Synonym**
bladder cancer, urothelial carcinoma

**Research involving**

Human

## Sponsors and support

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

## Intervention

**Keyword:** pembrolizumab, urothelial carcinoma

## Outcome measures

### Primary outcome

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

PFS is defined as the time from date of randomization until the earliest date of disease progression or death due to any cause, whichever occurs first.

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

### 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 complete response (CR) or partial response (PR).

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 cytotoxic chemotherapy in participants with advanced/unresectable (inoperable) or metastatic urothelial cancer who are cisplatin-ineligible, 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 cisplatin-ineligible urothelial carcinoma.

### Study design

This is a randomised, double blind, placebo controlled phase 3 trial of pembrolizumab in combination with epacadostat or placebo.

### Intervention

There are two treatment groups:

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, ECGs 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 frequently 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 or cytologically-confirmed diagnosis of advanced/unresectable (inoperable) or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional (predominantly transitional) cell histologies are allowed. Participants with non-urothelial cancer of the urinary tract are not allowed.;2. Have measureable disease based on RECIST 1.1 as assessed by the local site investigator/radiology. Tumor lesions situated in a previously irradiated area are considered measureable if progression has been demonstrated in such lesions.;3. Be considered ineligible to receive cisplatin-based combination therapy, based on having at least one of the following criteria:;a. ECOG PS of 2 within 14 days prior to randomization (the proportion of participants with an ECOG PS of 2 will be limited to approximately 50% of the total population);b. CrCl (calculated or measured) <60 mL/min but *30 mL/min;c. CTCAE v.4.0, Grade *2 audiometric hearing loss (25 dB in two consecutive wave ranges);d. CTCAE v.4.0, Grade *2 peripheral neuropathy;e. New York Heart Association (NYHA) Class III heart failure ;4. Have provided tissue for PD-L1 analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. 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. 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 received no prior systemic chemotherapy for advanced/unresectable (inoperable) or metastatic urothelial cancer;a. Adjuvant platinum based chemotherapy, following radical cystectomy, with recurrence >12 months from completion of therapy is permitted.;OR;b. Neoadjuvant platinum based chemotherapy, with recurrence >12 months since completion of therapy is permitted.;6. Be *18 years of age on day of signing informed consent.;7. Have a PS of 0, 1 or 2 within 14 days prior to randomization on the ECOG Performance Scale.;8. A male participant must agree to use a

contraception as detailed in the protocol 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.;9. 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 follow the contraceptive guidance 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.;10. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.;11. Demonstrate adequate organ function as defined in the protocol. All screening labs must be collected within 14 days prior to randomization.

## Exclusion criteria

1. Has disease that is suitable for local therapy administered with curative intent.;2. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.;3. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. ;4. 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.;5. 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.;6. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.;7. Has an active infection requiring systemic therapy.;8. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.;9. Has known history of or is positive for active Hepatitis B (Hepatitis B surface antigen [HBsAg] reactive) or has active Hepatitis C (HCV RNA). ;10. Has a history of a gastrointestinal condition or procedure that in the opinion of the Investigator may affect oral drug absorption.;11. 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 milliseconds is excluded (corrected by Fridericia 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.;12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.;13. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.;14. A WOCBP who has a positive urine pregnancy test within 72 hours before randomization. If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.;15. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of

pembrolizumab and epacadostat/matching placebo.;16. 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.;17. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to randomization.;18. Has received prior radiotherapy within 2 weeks of start of trial treatment. Participants must have recovered from all radiation-related toxicities, and not require corticosteroids. A 1-week washout is permitted for palliative radiation (*2 weeks of radiotherapy) to non- CNS disease.;19. Has received a live vaccine within 30 days prior to the first dose of trial drug. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.;20. 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. ;21. Has any history of Serotonin Syndrome after receiving serotonergic drugs.;22. Has severe hypersensitivity (*Grade 3) to study treatment (pembrolizumab and epacadostat) and/or any of its excipients.;23. Is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment.

# Study design

## Design

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| 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

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 06-02-2018 |
| Enrollment: | 31 |
| Type: | Actual |

## Medical products/devices used

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| 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

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| Approved WMO Date: | 12-10-2017 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 07-12-2017 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 23-02-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 26-03-2018 |
| 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) |

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| Approved WMO Date: | 02-07-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-08-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 14-09-2018 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 15-01-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 09-09-2019 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 07-11-2019 |
| 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 | EUCTR2017-002311-34-NL |
| CCMO | NL62920.056.17 |