Biomarker discovery study to identify patients with advanced urothelial cancer benefitting from pembrolizumab treatment

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To identify potential biomarkers for early identification of clinical benefit during pembrolizumab treatment in patients with advanced urothelial cancer. To identify potential mechanisms of primary and acquired resistance to pembrolizumab.To assess...

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

Summary

ID

NL-OMON53077

Source
ToetsingOnline

Brief title
RESPONDER

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
urinary tract cancer, urothelial carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: bedrijf (Merck),Merck Sharp & Dohme (MSD)

Intervention

Keyword: advanced urothelial cancer, biomarkers, pembrolizumab

Outcome measures

Primary outcome

To early identify patients with clinical benefit, translational data (immune &

molecular profiling) will be explored in relation with best response according

to RECIST 1.1.

Secondary outcome

Secondary endpoints are:

* immune related response criteria .

* duration of response according to RECIST 1.1 and irRC

* duration of clinical benefit (CR, PR & SD) according to RECIST 1.1 and irRC

* progression-free survival

* overall survival

Study description

Background summary

In the current study, the role of the immune evasive mechanisms combined with genomic characterization will be explored in urothelial cancer patients treated with first- second-line treatment with pembrolizumab. Combined profiling of immune and molecular status is novel and may contribute to improved patient stratification and provide rationale for future treatment strategies containing pembrolizumab.

Study objective

To identify potential biomarkers for early identification of clinical benefit

during pembrolizumab treatment in patients with advanced urothelial cancer.

To identify potential mechanisms of primary and acquired resistance to pembrolizumab.

To assess potential correlations between biomarkers and clinical activity according to different definitions and response evaluation criteria.

To collect tissue, blood and urine samples for future translational experiments.

Study design

This is a prospective translational, multi-site, single-arm trial of pembrolizumab as first- or second-line treatment in subjects with advanced or metastatic urothelial cancer to whom the drug is provided until regulatory approval and commercial availability in the Netherlands. The expected number of patients that will be recruited is 80.

Intervention

All patients included in the study will be treated with pembrolizumab on an outpatient basis. Study treatment should begin on the day of inclusion or as close as possible to the date on which treatment is allocated/assigned.

Pembrolizumab will be administered at a flat dose of 200 mg as a 30 minute IV infusion every 3 weeks, see table 2. Study treatment should be administered on Day 1 of each cycle.

Study burden and risks

Please see the Investigator*s Brochure (IB) for a detailed background on and the (pre)clinical data of MK-3475.

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. Should have signed informed consent for CPCT-02
Note: when a safe biopsy of a metastatic or locally advanced lesion is not deemed possible by the treating investigator, subject may be included in the trial without participation in the CPCT-02 trial only upon approval by the central principal investigator.
2. Be willing and able to provide written informed consent for the trial.
3. Be >< = 18 years of age on day of signing informed consent.
4. Have histologically or cytologically-confirmed urothelial cancer that is not amenable to curative treatment with local and/or systemic therapies.
5. Second-line treatment: Have progressive disease after platinum containing chemotherapy as defined by:
a. Disease progression after treatment with a platinum-containing regimen for recurrent (disease not amenable to curative treatment)/metastatic disease
b. Recurrence/progression within 12 months of prior therapy containing platinum
OR
First-line treatment: have received no prior systemic chemotherapy for advanced/ unresectable (inoperable) or metastatic urothelial
a. Adjuvant platinum based chemotherapy, following radial cystectomy, with recurrence > 12 months from completion of therapy is permitted
b. Neoadjuvant platinum based chemotherapy, with recurrence > 12 months since completion of therapy is permitted.
Note: Low-dose chemotherapy (e.g., low dose cisplatin, cisplatin+5FU, mytomycin+5FU, or cisplatin+paclitaxel) given concurrent with radiation to the primary tumor site is not considered as systemic therapy.

And subject must be considered ineligible to receive cisplatin-based combination therapy, based on having at least one of the following criteria:
a. Creatinine clearance (calculated or measured) < 60 mL/min but >30 mL/min
Note: Subjects with a creatinine clearance (calculated or measured) < 30 mL/min or on dialysis are excluded from the trial.
b. CTCAE v.4, Grade >2 audiometric hearing loss (25dB in two consecutive wave ranges)
c. CTCAE v.4, Grade >2 peripheral neuropathy
d. NYHA Class III heart failure (Appendix 13.1)
6. Cisplatin-unfit patients should have a PD-L1 CPS of *10, determined with the use of the commercially available PD-L1 IHC 22C3 pharmDx assay on a DAKO stainer. PD-L1 expression may be determined prior to enrollment or during the screening phase.
7. Have measurable disease based on RECIST 1.1. Tumor lesions located in a previously irradiated area are considered measurable if progression has been demonstrated in these lesions.
8. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.
Note: when a safe biopsy of a metastatic or locally advanced lesion is not deemed possible by the treating investigator, subject may be included in the trial without participation in the CPCT-02 trial only upon approval by the central principal investigator.
9. Have a performance status of 0 or 1 on the ECOG Performance Scale.
10. Demonstrate adequate organ function according to screening labs, which should be performed within 10 days of treatment initiation.
11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
12. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 * Contraception, for the course of the study through 120 days after the last dose of study medication.
Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
13. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.1-
Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.
Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

Exclusion criteria

1. Treamtent with an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving high dose systemic steroid therapy (defined as > 20 mg prednisone or equivalent per day) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has a known history of active TB (Bacillus Tuberculosis).
4. Hypersensitivity to pembrolizumab or any of its excipients.
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., * Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., * Grade 1 or at baseline) from adverse events due to a previously administered agent.
- Note: Subjects with * Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- Note: Radiation therapy to a symptomatic solitary lesion to the brain may be allowed at the investigator's discretion.
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. Diagnosis of prostate carcinoma in cystectomy material is not an exclusion criterium.
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using high dose steroids (defined as > 20 mg prednisone or equivalent per day) for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. 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, etc.) is not considered a form of systemic treatment.
10. Has known history of, or any evidence of active, (non-infectious)

pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.
11. Has an active infection requiring systemic therapy.
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 subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the prescreening or screening visit through 120 days after the last dose of trial treatment.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti- PD-L2 agent.
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
17. Has a known history of or is positive for hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (hepatitis C virus [HCV] RNA [qualitative] is detected). Note: Without known history, testing needs to be performed to determine eligibility. Hepatitis C antibody (Ab) testing is allowed for screening purposes in countries where HCV RNA is not part of standard of care.
18. Has received a live vaccine within 30 days of planned start of study therapy.
Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-08-2017
Enrollment:	80
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	12-07-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-07-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-07-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-01-2019
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:	27-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-04-2022
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	EUCTR2017-000976-27-NL
ClinicalTrials.gov	NCT03263039
CCMO	NL61719.056.17