A Phase II Clinical Trial of Pembrolizumab (MK-3475) in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer

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Primary Objective:To evaluate the anti-tumor activity of pembrolizumab (MK-3475) (200 mg Q3W) as 1L therapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who are ineligible for cisplatin-based therapy. Objective...

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

Summary

ID

NL-OMON46877

Source
ToetsingOnline

Brief title
A Phase II Trial of MK-3475 in Subjects with Bladder Cancer

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder cancer, urothelial cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)

Source(s) of monetary or material Support: Industrie

Intervention

Keyword: Bladder carcinoma, Pembrolizumab

Outcome measures

Primary outcome

The primary efficacy objective of this trial is to evaluate the anti-tumor activity of pembrolizumab (MK-3475) (200 mg Q3W) as 1L therapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who are ineligible for cisplatin-based therapy.

Secondary outcome

PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between tumor PD-L1 expression and response to treatment with pembrolizumab (MK-3475).

Study description

Background summary

The worldwide incidence of bladder cancer exceeds 300,000 cases annually, ranking it as the seventh most common cancer worldwide.
Cisplatin-based combination chemotherapy is standard first-line treatment for patients with advanced bladder cancer based on randomized trials. The median survival with these regimens is 13 to 15 months, and 5% to 15% of patients attain long-term survival. However, cisplatin ineligibility is common.

In light of the relatively limited benefit from cytotoxic chemotherapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who cannot receive cisplatin, and the promising results with pembrolizumab (MK-3475) and other anti-PD-1 pathway agents, pembrolizumab (MK-3475) will be evaluated as monotherapy in this population.

Study objective

Primary Objective:
To evaluate the anti-tumor activity of pembrolizumab (MK-3475) (200 mg Q3W) as 1L therapy in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who are ineligible for cisplatin-based therapy. Objective response rate (ORR) based on RECIST 1.1 as assessed by independent radiology review will be used as the primary efficacy endpoint. The requirement that subjects have measurable disease will be assessed by the central vendor.

See section 3.2 of the protocol for Secondary Objectives.

Study design

This is a non-randomized, multi-site, open-label trial of pembrolizumab (MK-3475) in subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer, who have not received prior systemic chemotherapy (i.e., first line, 1L) and who are not eligible to receive cisplatin, to be conducted in conformance with Good Clinical Practices. PD-L1 will be determined by immunohistochemistry (IHC).

Intervention

All patients will receive pembrolizumab 200 mg IV every three weeks.

Study burden and risks

Patients receive the study medication every 3 weeks for a maximum of 24 months. After achieving complete response and subsequent discontinuation of the first treatment period, an additional treatment with MK3475 may be allowed for up to 1 year for patients who showed progression (under certain conditions).

Patients will visit the study doctor every 3 weeks. A tumor biopsy will be performed at the first visit. A physical exam will be performed and blood samples will be taken at each visit (6-45 ml per visit). Patients will receive a CT- or MRI-scan at cycle 4 and every 6 weeks thereafter during the first year (every 12 weeks after the first year). Patients will be asked to complete electronic questionnaires (EuroQol EQ-5D en EORTC QLQ-C30) at cycle 1 to 5 and every other visit thereafter.

Patients may experience physical and/or psychological discomfort during the study procedures, such as blood sampling, biopsy, IV line, ECG, CT/MRI scan.

The most important side effects reported for MK3475 are fatigue, itching, rash, frequent or excessive bowel movements, joint pain and nausea.

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

In order to be eligible for participation in this trial, the subject must:;1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.;2. Be *18 years of age on day of signing informed consent.;3. 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 cell histologies are allowed. Subjects with non-urothelial cancer of the urinary tract are not allowed.;4. Be considered cisplatin-ineligible to receive cisplatin-based combination therapy, based on having at least one of the following criteria: ;a. ECOG performance status of 2 (the proportion of ECOG 2 subjects will be limited to approximately 50% of the total population);b. 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.;c. CTCAE v.4, Grade >2 audiometric hearing loss (25dB in two consecutive wave ranges);d. CTCAE v.4, Grade >2 peripheral neuropathy;e. NYHA Class III heart failure (Appendix 12.6);Note: In the event that subjects are enrolled for the purposes of determining the biomarker cut-point prior to the start of the main body of this study, these subjects are not required to be cisplatin-ineligible and the above criteria does not apply. However, such subjects are required to have bladder cancer which is refractory to available therapy or for which no effective standard therapy exists.;5. Have received no prior systemic chemotherapy for advanced/unresectable (inoperable) or metastatic urothelial cancer;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.;6.Have provided tissue for biomarker analysis from a newly obtained core or excisional biopsy of a tumor lesion not previously irradiated (mandatory). Adequacy of the biopsy specimen for PD-L1 biomarker analysis must be confirmed by the central laboratory.;7.Have measureable disease based on RECIST 1.1 as determined by central review. Tumor lesions situated in a previously irradiated area are considered measureable if progression has been demonstrated in such lesions.;8. Have a performance status of 0, 1 or 2 on the ECOG Performance Scale, as assessed within 10 days prior to treatment initiation. ;9. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 10 days of treatment initiation.;10. Female subject of childbearing potential must have a negative urine or serum pregnancy test 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.;11. Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.;Note: Abstinence is acceptable if this is the established and preferred contraception for the subject.;12. Male subjects must agree to use an adequate method of 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 established and preferred contraception for the subjec

Exclusion criteria

The subject must be excluded from participating in the trial if the subject:;1. Has disease that is suitable for local therapy administered with curative intent.;2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to the first dose of treatment.;3. Has had a prior anti-cancer monoclonal antibody (mAb) for direct anti-neoplastic treatment 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.;4. 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 neuropathy

or * Grade 2 alopecia 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.;5. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. A history of prostate cancer that was identified incidentally following cystoprostatectomy for bladder cancer is acceptable, provided that the following criteria are met: stage T2N0M0 or lower; and Gleason score * 6, and undetectable PSA. ;6. 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 (confirmed by CT scan if CT used at prior imaging, or confirmed by MRI if MRI was used at prior 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 steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.;7. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. ;8. Has evidence of interstitial lung disease or active non-infectious pneumonitis.;9. Has an active infection requiring systemic therapy.;10. 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.;11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.;12. 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 trial treatment.;13. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).;14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).;15. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).;16. Has received a live virus vaccine within 30 days of planned start of trial treatment.;17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

Study design

Design

Study phase: 2

Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-02-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Keytruda
Generic name:	pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-09-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	19-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	02-12-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	12-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2018

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-002206-20-NL
ClinicalTrials.gov	NCT02335424
CCMO	NL54417.078.15