A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer

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Primary Objectives(1) To evaluate the overall survival (OS) of subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy (recurrent/progressive metastatic...

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

Summary

ID

NL-OMON44766

Source
ToetsingOnline

Brief title
MK-3475 vs. paclitaxel, Docetaxel or vinflunine in urothelial cancer

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Urothelial Cancer; Bladder Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Industrie

Intervention

Keyword: MK3475, Pembrolizumab, Urothelial Cancer

Outcome measures

Primary outcome

- Overall Survival

- Progression Free Survival

Secondary outcome

- PD-L1 expression in tumor tissue.

Study description

Background summary

Urothelial (transitional cell) cancer describes a range of tumors that arise from the urothelial endothelium, which includes the bladder, renal pelvis, ureter, and urethra. The worldwide incidence of bladder cancer exceeds 300,000 cases annually, ranking it as the seventh most common cancer worldwide. Urothelial carcinoma is the predominant histologic type of bladder cancer in the United States and Western Europe, where it accounts for approximately 90 percent of bladder cancers. In other areas of the world, nonurothelial histologies are more frequent.

Subjects with metastatic urothelial cancer that has recurred or progressed following platinum-based chemotherapy present a challenge. Although a variety of chemotherapeutic agents are used in this setting, the prognosis of subjects with recurrent/progressive urothelial cancer is generally poor despite these therapies. The median survival in most series is 7 to 9 months, and the median PFS is 3 to 5 months, with limited treatment options and substantial morbidity. Single agent or combination therapy using conventional cytotoxic chemotherapy, combined with best supportive care, is palliative for subjects with recurrent/ progressive urothelial cancer. The most widely used agents include taxanes (paclitaxel, docetaxel), pemetrexed, and, in the EU,

vinflunine. There are no approved therapies for recurrent/progressive urothelial cancer in the US, while vinflunine is approved in the EU for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

After failure of first-line platinum-containing chemotherapy, objective responses to second-line cytotoxic chemotherapy are uncommon, particularly when contemporary response criteria are applied. Objective response rates of 5% to 28% have been reported with agents such as paclitaxel, docetaxel, pemetrexed and ifosfamide, but few randomized, controlled studies have been conducted in the second-line setting. In single-arm studies, PFS and OS have been reported as 4 months and 9 months, respectively, with docetaxel; and 2-3 months and 7 months, respectively with paclitaxel. In a Phase III trial, 370 previously treated patients were randomly assigned to either vinflunine or best supportive care. Compared to best supportive care, treatment with vinflunine resulted in a 9% objective response rate and a trend towards increased overall survival that did not reach statistical significance in the ITT population (6.9 versus 4.6 months, hazard ratio 0.88, 95% CI 0.69-1.12).

Study objective

Primary Objectives

(1) To evaluate the overall survival (OS) of subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy (recurrent/progressive metastatic urothelial cancer), when treated with pembrolizumab (MK-3475) compared to paclitaxel or vinflunine.

(2) To evaluate progression-free survival (PFS) per RECIST 1.1 by independent radiologists* review of subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475)compared to paclitaxel or vinflunine.

Study design

This is a randomized, active-controlled, multi-site, open-label trial

Intervention

Patients are randomly assigned to one of two groups (randomisatieverhouding 1: 1).

Patients in groep 1 will receive 200 mg pembrolizumab every 3 weeks. Patients in groep 2 will receive paclitax, vinflunine, or docetaxel every 3 weeks,

depending on the choice of the physician.

Study burden and risks

The patient will receive the study drug every 3 weeks for up to 24 months. Additional treatment is possible (under certain conditions) for an extra year.

The patient will visit the doctor every 3 weeks. The first visit a tumor biopsy will take place (if necessary). Each visit, a physical examination will be performed, and blood samples will be taken. Volume will range from 6 - 44 ml per visit. The patient will also fill in two questionnaires each visit, namely a 'quality-of-life questionnaire' (EORTC QLQ-C30) and a questionnaire which asked about the health of the patient (eEuroQoL EQ-5D).

The patient may experience physical and / or psychological discomfort with some of the procedures performed during a visit, such as blood sampling, the IV line, ECG, CT scan, MRI and tumor biopsy.

The main side effect reported with the use of MK3475 are fatigue, itching, rash, frequent or excessive bowel movements, joint pain and nausea.
For Vinflunine, Paclitaxel and Docetaxel some of the most common side effects are decreased amount of red and white blood cells; diarrhea, fatigue, hair loss, nausea and vomiting.

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

Male and Female subjects of at least 18 years of age with recurrent/progressive metastatic urothelial cancer will be enrolled in this trial.
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 urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies are allowed, but transitional cell carcinoma must be the predominant histology. Subjects with non-urothelial cancer of the urinary tract are not allowed.
4. Have had progression or recurrence of urothelial cancer following receipt of a first-line platinum-containing regimen (cisplatin or carboplatin):
a. Received a first-line platinum-containing regimen in the metastatic setting or for inoperable locally advanced disease;
b. Received adjuvant platinum-containing therapy following cystectomy for localized muscle-invasive urothelial cancer, with recurrence/progression *12 months following completion of therapy.
c. Received neoadjuvant platinum-containing therapy prior to cystectomy for localized muscle-invasive urothelial cancer, with recurrence *12 months following completion of therapy.
5. Have received no more than two prior lines of systemic chemotherapy for urothelial cancer. Subjects for whom the most recent therapy has been a non-platinum-based regimen following progression/recurrence on platinum-based therapy (i.e. third-line patients) are eligible if they have progressed/recurred on their most recent therapy.
6. Have provided tissue for biomarker 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. Adequacy of the archived or freshly-obtained biopsy specimen must be confirmed by the central laboratory during the screening period prior to enrollment.
7. Have measureable disease based on RECIST 1.1 as assessed by the investigator/site radiologist. 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. Subjects with an ECOG performance status of 2 must have a hemoglobin *10 g/dL, must not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen *3 months (90 days) prior to enrollment.
9. Demonstrate adequate organ function as defined in Table 1 of the protocol, all screening labs should be performed within 10 days of treatment initiation
10. Female subjects 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 through120 days after the last dose of pembrolizumab or 180 days after the last dose of paclitaxel, docetaxel or vinflunine (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.
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 pembrolizumab (MK-3475) or 180 days after the last dose of paclitaxel, docetaxel or vinflunine.;Crossover from Control Arm to Pembrolizumab
- Have been randomized to the control arm, taken at least one dose and subsequently discontinued treatment with paclitaxel, docetaxel or vinflunine.
- Experienced an investigator-determined confirmed radiographic disease progression per RECIST 1.1 after stopping their initial treatment.
- A scan must be performed within 30 days prior to starting treatment with pembrolizumab.
- Did not receive any anti-PD1 / PD-L1, anti-CTLA4 or other checkpoint inhibitor since the last dose of chemotherapy.
- Have a performance status of 0 to 2 on the ECOG Performance Scale.
- Subjects with known and treated brain metastasis are eligible provided they are clinically stable, and brain metastases have been treated.
- Have adequately recovered froma dverse events of previous anti-cancer therapy.
- Female and male subjects should agree to use adequate methods of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Exclusion criteria

1.Has disease that is suitable for local therapy administered with curative intent.
2.Currently participating/ has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose.
3.Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose. The use of physiologic doses of corticosteroids may be approved.
4.Has had a prior anti-cancer 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.

5.Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered from adverse events due to a previously administered agent.
Note: Subjects with * Grade 2 neuropathy or * Grade 2 alopecia may qualify for the study.
Note: If subject received major surgery, they must have recovered adequately.
6.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; Gleason score * 6, PSA undetectable.
7.Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable, 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.
8.Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents. Subjects with vitiligo, diabetes Type I, or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjøgren*s syndrome will not be excluded from the study.
9.Has active cardiac disease, defined as:
a. Myocardial infarction or unstable angina pectoris within 6 months of the first date of study therapy
b. History of serious ventricular arrhythmia, high-grade AV block, or other cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled); history of QT interval prolongation
c. NYHA Class III or greater congestive heart failure, or left ventricular ejection fraction of < 40%
10.Has evidence of interstitial lung disease or active non-infectious pneumonitis.
11.Has an active infection requiring systemic therapy.
12.Has a history of severe hypersensitivity reaction to paclitaxel or to other drugs formulated with polyoxyethylated castor oil, to docetaxel or other drugs formulated with polysorbate 80,or to vinflunine or other vinca alkaloids.
13.Requires ongoing therapy with a medication that is a strong inhibitor of the CYP3A4 enzymes.
14.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.
15.Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16.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.
17.Has received prior therapy with an anti-PD-1 or anti-PD-L1 agent, or with an agent

directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).
18.Has received prior chemotherapy for urothelial cancer with all available study therapies in the control arm (i.e both prior paclitaxel and docetaxel in regions where vinflunine is not an approved therapy, or prior paclitaxel, docetaxel and vinflunine in regions where vinflunine is an approved therapy).
19.Has a known history of HIV.
20.Has known active Hepatitis B or C.
21.Has received a live virus vaccine within 30 days of planned start of trial treatment.
22.Is/ has an immediate family member who is investigational site or sponsor staff directly involved with this trial.;Crossover from Control Arm to Pembrolizumab
- Has discontinued from study MK-3475-045.
- Has active pneumonitis of Grade 2 or greater or history of pneumonitis requiring systemic steroid therapy.
- Has received thoracic radiation therapy of > 30 Gy within 6 months have active and untreated brain metastasis.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-01-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Javlor
Generic name:	Vinflunine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Pembrolizumab

Ethics review

Approved WMO Date:	01-10-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-12-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-05-2015
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	21-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2018
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:	16-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2021
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	EUCTR2014-002009-40-NL
CCMO	NL50307.056.14