A Phase II Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Subjects with High Risk Non-muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG) Therapy

Published: 29-02-2016
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This study has been transitioned to CTIS with ID 2022-502526-41-00 check the CTIS register for the current data. Objective- To evaluate anti-tumor activity of pembrolizumab (MK-3475) by evaluating the absence of high risk NMIBC or progressive...

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

Summary

ID

NL-OMON46995

Source
ToetsingOnline

Brief title
Pembrolizumab (MK-3475) in high risk NMIBC patients unresponsive to BCG

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Bladder Cancer

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Bladder Cancer, Pembrolizumab (MK-3475)

Outcome measures

Primary outcome

Complete response (CR) for patients in cohort A and disease free survival (DFS)

of high risk NMIBC for patients in cohort B, as assessed by central pathology

and radiology review, will be used as the primary efficacy endpoints.

Secondary outcome

Apart from complete response / disease free survival:

- Response duration

- PD-L1 expression

- Overall Survival

- Progression free survival (PFS)

Study description

Background summary

Bladder cancer represents 4.4% of all new cancer diagnoses in the United States; it is the fourth most common cancer in men, the tenth most common in women, and the tenth leading cause of cancer death overall. Notably, bladder cancer is associated with the highest cost per patient from diagnosis to death of all malignancies, largely owing to the frequent procedures required for disease monitoring and treatment. Bladder cancer can be categorized as NMIBC, which represents 75% of primary diagnoses and is characterized by frequent

recurrence and high morbidity but a low risk of mortality, or muscle-invasive bladder cancer, which represents the other 25% of primary diagnoses and is potentially lethal in approximately 50% of patients. Standard therapy for high-risk NMIBC patients includes TURBT augmented by intravesical administration of BCG. BCG is a bovine mycoplasma derived agent which creates a profound immunologic/inflammatory reaction in the bladder epithelium, and thereby, reduces tumor recurrences. While BCG therapy is successful at preventing early tumor recurrences, most patients do not maintain sustained remissions. With 5-year follow-up, recurrent bladder tumors requiring repetitive TURBT and further cystoscopic surveillance are observed in 66% of patients. Given the high-rate of progression to muscle-invasive stages, both the American Urological Association (AUA) and the European Association of Urology have advocated for cystectomy as a standard option for BCG-refractory urothelial carcinoma (UC) patients. However, due to the 28% morbidity and 3% mortality rates associated with cystectomy, many patients either have comorbidities precluding surgical intervention or electively seek nonsurgical alternative therapy options. Additional intravesical therapy with non-BCG agents has been extensively evaluated both in the front-line and post-BCG settings. While 6-month complete response rates have been encouraging, once therapy is stopped 1-year relapse free survival rates have only been sustained in 10-15% of patients. Recently, novel immune checkpoint inhibitors have been developed which block both the programmed cell death 1 protein (PD-1) and/or the programmed cell death 1 protein ligand (PD-L1) mediated pathways. In normal physiology, the PD-1/PD-L1 pathway functions to dampen inflammatory immune responses as a checkpoint balance preventing unregulated destructive inflammation. A strong rationale exists to study pembrolizumab (MK-3475) in patients with NMIBC unresponsive to BCG, based upon the following:
1) NMIBC represents a population amenable to immunotherapies;
2) A recent public workshop held by the Food and Drug Administration (FDA) and AUA recognized BCG unresponsive NMIBC as an important unmet medical need for development of new therapies, as these patients have few available non-surgical options [50];
3) Expression of PD-L1 is frequent in bladder cancer;
4) Activation of the PD-1/PD-L1 pathway could be implicated in resistance to BCG therapy;
5) Pembrolizumab (MK-3475) has shown significant activity in a pre-treated population with metastatic urinary tract cancer.

Study objective

This study has been transitioned to CTIS with ID 2022-502526-41-00 check the CTIS register for the current data.

Objective
- To evaluate anti-tumor activity of pembrolizumab (MK-3475) by evaluating the absence of high risk NMIBC or progressive disease in subjects with CIS at baseline (cohort A) and subjects without CIS at baseline (cohort B).

Hypotheses:
- Intravenous administration of single agent pembrolizumab (MK-3475) to subjects with high risk NMIBC and underlying CIS at baseline who are unresponsive to BCG, and either are ineligible for radical cystectomy or elect not to undergo the procedure, will result in a complete response (CR) rate in high risk NMIBC that is greater than 20%
- Intravenous administration of single agent pembrolizumab (MK-3475) to subjects will result in a 12-month disease free survival (DFS) rate of high risk NMIBC that is greater than 20%.

Study design

This is a single arm, multi-site, open-label trial of pembrolizumab (MK-3475) in subjects with high risk non-muscle-invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette Guerin (BCG), who are considered ineligible for radical cystectomy or have elected not to undergo the procedure.

Intervention

Subjects will receive pembrolizumab (MK-3475) 200 mg every three weeks. Treatment with pembrolizumab (MK-3475) will continue until high risk recurrence or documented disease progression (by grade or stage as determined by the investigator/site urologist, central pathologist and/or central radiologist), unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, the investigator*s decision to withdraw the subject, the subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with pembrolizumab (MK-3475), or administrative reasons.

Study burden and risks

Treatment cycles will take three weeks, and pembrolizumab will be administered on day 1. At every visit, a physical examination will be performed, vital signs measured, and blood samples will be collected (see additional comments). The subject will also be asked to complete questionnaires about health and symptoms (EuroQoL EQ-5D, FACT-B1, CLSS/Core Lower Urinary Tract Symptom Score). There will be a tumor biopsy at screening if needed. Cytoscopy is done at the screening visit as well as in cycles 4 and 8, and in the follow up phase.

The patient may experience physical and/or psychological discomfort with some of the procedures performed during a visit, such as blood sampling, administration of the IV line, ECG, CT/MRI scans, cytoscopy and tumor biopsy. The main side effects reports with the use of 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

1. Have a histologically-confirmed diagnosis of high risk non-muscle-invasive (T1, High Grade Ta and/or CIS) transitional cell carcinoma of the bladder.
2. In subjects who have papillary tumors (Ta and T1), a complete TURBT must have been performed, as per protocol.
3. Have been treated with adequate BCG therapy and have developed high risk NMBIC that is unresponsive to BCG therapy.
4. Have elected not to undergo, or are considered ineligible for radical cystectomy, as determined by the treating surgeon.
5. Have provided tissue for biomarker analysis from the most recent cystoscopy/TURBT

procedures, from which tumor sample is available.
6. Have a performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale. (Max of 5% ECOG of 2.)
7. Demonstrate adequate organ function.
8. 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 and be willing to use contraception in accordance with Section 5.7.2 of Protocol.

Exclusion criteria

1. Has muscle invasive (i.e. T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma.
2. Has concurrent extra-vesical (i.e. urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium.
3. 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 of the first dose of treatment.
4. Has undergone any intervening intravesical chemotherapy or immunotherapy from the time of most recent cystoscopy/TURBT to starting trial treatment.
5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Cycle 1, Day 1 or who has not recovered (i.e., <= Grade 1 or at baseline) from adverse events due to a previously administered agent.
6. Has a known additional malignancy that is progressing or requires active treatment.
7. Has an active autoimmune disease that has required systemic treatment in past 2 years.
8. Has a diagnosis of immunidefiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the planned first dose of the study. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
9. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
10. Has an active infection requiring systemic therapy, including active or intractable urinary tract infection (UTI) in the last month.
11. Is pregnant or breastfeeding, or expecting to conceive within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
12. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).
13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).
14. Has known active Hepatitis B or Hepatitis C.
15. Has received a live virus vaccine within 30 days of planned start of trial treatment.
16. Has had an allogenic tissue/solid organ transplant.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-10-2016
Enrollment:	20
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:	29-02-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-07-2016
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-09-2016
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:	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:	18-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	19-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2018
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:	22-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-12-2018
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:	18-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	18-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2023
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
EU-CTR	CTIS2022-502526-41-00
EudraCT	EUCTR2014-004026-17-NL
CCMO	NL55403.056.16