A Phase 3, Randomized, Comparator-controlled Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Bacillus Calmette-Guerin (BCG) in Participants with High-risk Non-muscle Invasive Bladder Cancer (HR NMIBC) that is Persistent or Recurrent Following BCG Induction (KEYNOTE-676)

Published: 19-12-2018
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This study has been transitioned to CTIS with ID 2022-501817-29-00 check the CTIS register for the current data. Cohort ATo compare the CRR for the combination of pembrolizumab + BCG versus BCG alone in participants with CIS.Cohort B- To compare the...

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

Summary

ID

NL-OMON55727

Source
ToetsingOnline

Brief title
MK3475-676

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: Industrie

Intervention

Keyword: Bacillus Calmette-Guerin (BCG), Bladder Cancer, High-Risk Non-muscle Invasive, Pembrolizumab

Outcome measures

Primary outcome

Cohort A:

Complete response among CIS participants

Cohort B:

Event-free survival (EFS)

Secondary outcome

Cohort A: EFS

Cohort B: None

Study description

Background summary

Bladder cancer is more common in men than women; global incidence of bladder cancer among men and women is 36 and 9 per 100,000 person-years, respectively. In 2017, it was expected to be the fourth most common cancer and the eighth leading cause of cancer death in men. Bladder cancer becomes more common with age and is the fourth leading causing of cancer death in men aged >=80 years. Age, smoking, occupational exposure to carcinogens, certain medical treatments (including pelvic radiation and cyclophosphamide), and genetic predisposition are risk factors for bladder cancer. 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.
Approximately 70% of newly diagnosed urothelial bladder cancer cases are classified as non-muscle invasive. NMIBC includes Ta (noninvasive papillary), T1 (submucosal invasive) tumors, and CIS, which account for approximately 70%, 20%, and 10% of non-muscle invasive cancers, respectively. NMIBC is characterized by frequent recurrence and high morbidity but a low risk of mortality. Muscle-invasive bladder cancer represents 20% of primary diagnoses and is potentially lethal in approximately 50% of patients [National Comprehensive Cancer Network 2015].
According to the International Bladder Cancer Group (IBCG) classification, NMIBC is stratified as low, intermediate, and high-risk disease. Low-risk NMIBC is defined as solitary Ta, low grade, and < 3 cm. High risk is defined as the presence of any T1, high-grade Ta, or CIS.

Standard therapy for high-risk NMIBC patients includes TURBT followed by BCG induction and maintenance. For patients with HG Ta, CIS, or recurrent T1 disease that have not responded to the first induction, a second induction may be given.
While BCG therapy may be successful at preventing early tumor recurrences, most patients do not maintain sustained remissions. Despite TURBT and intravesical treatments including BCG, approximately 40% of patients progress to muscle invasive disease. Progression to metastatic disease occurs in 20-30% of these individuals with death due to bladder cancer in nearly all of these patients.
Standard treatment for muscle invasive bladder cancer is radical cystectomy with intestinal diversion or neobladder. Radical cystectomy is associated with significant morbidity and mortality and has a negative impact on quality of life. After radical cystectomy, patients require lifelong care and monitoring.
There is an urgent need for novel treatments to preserve the bladder and minimize the risk of recurrent and progressive disease.

Study objective

This study has been transitioned to CTIS with ID 2022-501817-29-00 check the CTIS register for the current data.

Cohort A
To compare the CRR for the combination of pembrolizumab + BCG versus BCG alone in participants with CIS.

Cohort B
- To compare the EFS between participants who receive pembrolizumab + BCG (reduced maintenance) versus BCG alone
- To compare the EFS between participants who receive pembrolizumab + BCG (full maintenance) versus BCG alone

Study design

This is a randomized, comparator-controlled, parallel-group, multi-site, open-label study of pembrolizumab in combination with BCG in participants with HR NMIBC that is persistent or recurrent following BCG induction.

Intervention

Arm 1:
Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W) for 35 doses (about 2 years)
BCG Induction (once a week for 6 weeks) and Maintenance (once a week for 3 weeks at Weeks 13, 25, 49, 73, 97, 121, and 145)

Arm 2:
BCG Induction (once a week for 6 weeks) and Maintenance (once a week for 3 weeks at Weeks 13, 25, 49, 73, 97, 121 and 145)

Study burden and risks

Treatment cycles will take three weeks, of which pembrolizumab will be administered on day 1, en on day 1, 8 en 15 BCG. At every visit, a physical examination will be performed, vital signs will be measured and blood samples will collected.
The subjects will also be asked to complete questionnaires on their health and symptoms.
There will be a tumor biopsy at screening (this can be omitted in case there is adequate tumor tissue available).
Trial subjects may experience physical and/or psychological discomfort with some of the study procedures, such as blood sampling, administration of the IV line, cystoscopy, and tumor biopsy.
The main side effects reported with the trial medication pembrolizumab are itchy skin, thin or watery stools, cough, joint pain, skin rash, fever, back pain, abdominal pain, skin patches that have lost their color.
The main side effects reported of the trial medication BCG are cystitis, pain when urinating, frequent urination, blood in the urine, fever, fatigue, less

energy, discomfort.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Cohort A-BCG Post-induction Cohort:
1. Male/female participants who are at least 18 years of age on the day of providing documented informed consent will be enrolled in this study.
2. Have locally and BICR-confirmed histological diagnosis of high-risk non-muscle invasive (T1, high-grade Ta and/or CIS) UC of the bladder.
3. Have been treated with one adequate course of BCG induction therapy for the treatment of HR NMIBC defined as at least 5 intravesical instillations of BCG within a 10 week period of time.
4. Following adequate BCG induction therapy, must have persistent or recurrent HR NMIBC.

5. Have undergone cystoscopy/TURBT to remove all resectable disease within 12 weeks prior to randomization.
6. Have provided tissue for biomarker analysis from the most recent TURBT/biopsy procedures from which tumor sample is available.
7. Have a performance status of 0, 1 or 2 on the ECOG Performance Scale, as assessed within 14 days prior to randomization.
8. Have adequate organ function. Specimens must be collected within 14 days prior to randomization.
9. Male participants are eligible to participate if they agree to the following during the treatment period and for at least 7 days after the last dose of BCG:
•Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
OR
•Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause)
10. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
a) Is not a WOCBP
OR
b) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as
their preferred and usual lifestyle (abstinent on a long term and persistent basis), during the treatment period and for at least 7 days after the last dose of BCG or
120 days after the last dose of pembrolizumab, whichever comes last
11. The participant (or legally acceptable representative) provides documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the main study without participating in FBR

Cohort B-BCG Naïve Cohort
12. Male/female participants who are at least 18 years of age on the day of providing documented informed consent will be enrolled in this study
13. Have locally and BICR-confirmed histological diagnosis of high-risk non-muscle invasive (T1, highgrade Ta and/or CIS) UC of the bladder
14. Have undergone cystoscopy/TURBT to remove all resectable disease within 12 weeks prior to randomization
15. Have provided tissue for biomarker analysis from the most recent TURBT/biopsy procedures from which tumor sample is available
16. Have a performance status of 0, 1 or 2 on the ECOG performance Scale, as assessed within 14 days prior to randomization
17. Have adequate organ function. Specimens must be collected within 14 days prior to randomization
18. Male participants are eligible to participate if they agree to the following during the treatment period and for at least 7 days after the last

dose of BCG
•Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
OR
•Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause)
19. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
a) Is not a WOCBP
OR
b) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), during the treatment period and for at least 7 days after the last dose of BCG or 120 days after the last dose of pembrolizumab, whichever comes last
20. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study. The participant may also provide
consent/assent for FBR. However, the participant may participate in the main study without participating in FBR

Exclusion criteria

Cohort A-BCG Post-induction Cohort
1. Has persistent (remains present or occurs within 3 months [-2 weeks] to 6 months [+4 weeks] after start of BCG induction T1 disease following an induction course of BCG
2. Has a history of or concurrent locally advanced non-resectable (ie, T2, T3, T4) or metastatic UC
3. Has concurrent extra-vesical non-muscle invasive urothelial carcinoma, concurrent upper tract involvement, or invasive prostatic UC including T1 or greater disease, or ductal invasion
4. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD L2 agent or with an agent directed to another stimulatory or co inhibitory T-cell receptor
5. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks of start of study treatment
6. Has received prior radiotherapy within 2 weeks of start of study treatment
7. Has received a live vaccine within 30 days of start of study treatment
8. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks of start of study treatment
9. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid

therapy or any other form of immunosuppressive therapy within 7 days of start of study treatment
10. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years
11. Has hypersensitivity to pembrolizumab and/or any of its excipients
12. Has an active autoimmune disease that has required systemic treatment in past 2 years
13. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis
14. Has 1 or more of the following contraindications to BCG: prior BCG sepsis or systemic infection, total bladder incontinence, or an adverse experience to a previous BCG instillation that resulted in treatment discontinuation and precludes retreating with BCG
15. Has an active infection or diagnosis requiring systemic antimicrobial therapy
16. Has a known history of HIV infection
17. Has a known history of Hepatitis B or known active Hepatitis C virus
18. Has current active tuberculosis
19. Has known psychiatric or substance abuse disorder that would interfere with cooperating with the requirements of the study
20. Has had an allogenic-tissue/solid organ transplant
21. Has any contraindication(s) to IV contrast or is otherwise unable to have screening with IV contrast performed

Cohort B-BCG Naïve Cohort
22. Has a history of or concurrent locally advanced or metastatic UC
23.Has concurrent extra-vesical non-muscle invasiveurothelial UC or a history of extra-vesical non-muscle invasive UC that recurred within 2 years prior.
24. Has any contraindication(s) to IV contrast or is otherwise unable to have screening imaging with IV contrast performed
25. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD L2 agent or with an agent directed to another stimulatory or co inhibitory T-cell receptor
26. Has received any prior treatment with BCG for their NMIBC within the past 2 years prior to study entry
27. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks of start of study treatment
28. Has received prior radiotherapy within 2 weeks of start of study treatment
29. Has received a live vaccine within 30 days of start of study treatment
30. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks of start of study treatment
31. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days of start of study treatment
32. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years

33. Has hypersensitivity to pembrolizumab and/or any of its excipients
34. Has an active autoimmune disease that has required systemic treatment in past 2 years
35. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
36. Has one or more of the following contraindications to BCG: prior BCG sepsis or systemic infection, total bladder incontinence, or an adverse experience to a previous BCG instillation that resulted in treatment discontinuation and precludes retreating with BCG
37. Has an active infection or diagnosis requiring systemic antimicrobial therapy
38. Has a known history of HIV infection.
39. Has a known history of Hepatitis B or known active Hepatitis C virus infection
40. Has current active tuberculosis
41. Has known psychiatric or substance abuse disorder that would interfere with cooperating with the requirements of the study
42. Has had an allogenic-tissue/solid organ transplant

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:	Recruiting
Start date (anticipated):	13-08-2019
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	OncoTICE®
Generic name:	BCG-vaccin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-12-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-12-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-12-2019
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-12-2021
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-02-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	CTIS2022-501817-29-00
EudraCT	EUCTR2018-001967-22-NL
ClinicalTrials.gov	NCT03711032
CCMO	NL67236.028.18