A Phase 3, Randomized, Double-blind, Placebo-controlled Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Chemoradiotherapy (CRT) versus CRT Alone in Participants with Muscle-invasive Bladder Cancer (MIBC) (KEYNOTE-992)

Published: 04-02-2020
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This study has been transitioned to CTIS with ID 2023-503500-87-00 check the CTIS register for the current data. This study is designed to assess the antitumor efficacy and safety of pembrolizumab + CRT following maximal TURBT compared with placebo...

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

Summary

ID

NL-OMON55121

Source
ToetsingOnline

Brief title
MK3475-992

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Bladder and bladder neck disorders (excl calculi)

Synonym
Muscle-invasive bladder cancer, Urothelial carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme;soms samenwerkende studies

Intervention

Keyword: Bladder Cancer, Intervention, Phase 3, Treatment

Outcome measures

Primary outcome

To compare bladder intact event free survival in participants from Arm A (pembrolizumab + chemoradiotherapy) and Arm B (placebo + chemoradiotherapy), based on cystoscopy, biopsy with central pathology review (if applicable), urine cytology and radiographic assessment by blinded independent central review.

Secondary outcome

1. To compare overall survival between Arm A (pembrolizumab + chemoradiotherapy) and Arm B (placebo + chemoradiotherapy).

2. To evaluate rate of metastasis-free survival.

3. To evaluate time to occurrence of non-muscle-invasive bladder cancer (NMIBC).

4. To evaluate the safety and tolerability of pembrolizumab + chemoradiotherapy.

5. To evaluate changes from baseline in health-related quality of life and time to deterioration (TTD), using 2 general instruments and one disease-specific instrument.

6. To evaluate time to cystectomy.

Study description

Background summary

Urothelial carcinoma (UC) is cancer arising from the urothelial endothelium, which lines organs including the bladder, renal pelvis, ureter, and urethra. UC is the predominant histologic type of bladder cancer in the US and Western Europe. The worldwide incidence of bladder cancer exceeds 549,000 cases annually and 199,000 deaths [Bray, F., et al 2018]. According to Surveillance, Epidemiology, and End Results Program estimates, there will be approximately 80,470 new cases of bladder cancer in the US alone in 2019 with an estimated 17,670 associated deaths [National Cancer Institute 2019]. These statistics remain similar to those reported previously and have been largely unchanged over approximately 25 years [Kaufman, D. S., et al 2009].
Of these patients with bladder cancer, approximately 25%-30% are diagnosed with MIBC at presentation [Cumberbatch, M. G. K., et al 2018]. MIBC is a heterogeneous disease ranging from T2 tumors (which invade the muscularis propria) to T4 tumors (which have grown beyond the bladder wall and may invade the prostate, uterus, vagina, bowel, or abdominal wall), and many patients with MIBC may harbor occult metastases [Chang, S. S., et al 2017].

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD 1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications.
The PURE-01 study evaluated 3 cycles of neoadjuvant pembrolizumab prior to RC in 50 patients with clinical stage T2-T3N0M0 MIBC; 42% of all study participants demonstrated a pathological T0 stage [Necchi, A., et al 2018]. This pCR rate is comparable compared with the historical pCR rates of cisplatin-based combination chemotherapy (~25%-40%) [Zargar, H., et al 2018] [Flaig, T. W., et al 2019]. This study demonstrated the activity of pembrolizumab as a potentially safe and effective monotherapy in MIBC. A similarly designed study of another PD-1/PD-L1 inhibitor, atezolizumab, as neoadjuvant treatment of MIBC (ABACUS) demonstrated a 29% pathological T0 stage after 2 cycles of atezolizumab [Powles, T., et al 2018].
The clinical need for improved therapies for patients with MIBC and evidence of the clinical activity of pembrolizumab across the spectrum of disease states of urothelial carcinoma - including metastatic UC, MIBC and NMIBC - provide a robust rationale for investigating the addition of pembrolizumab to CRT for

bladder-sparing therapy.

Study objective

This study has been transitioned to CTIS with ID 2023-503500-87-00 check the CTIS register for the current data.

This study is designed to assess the antitumor efficacy and safety of pembrolizumab + CRT following maximal TURBT compared with placebo + CRT following maximal TURBT for participants with newly diagnosed T2 T4aN0M0 MIBC who elect to receive CRT for bladder preservation.

Study design

A Phase 3, Randomized, Double-blind, Placebo-controlled Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Chemoradiotherapy (CRT) versus CRT Alone in Participants with Muscle-invasive Bladder Cancer (MIBC).

Intervention

Parallel.

Study burden and risks

The most reported side effects of the study medication Pembrolizumab are itching skin, thin/watery feces, coughing, joint pain, rash, fever, stomach ache, backpain, loss of skin pigment.

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. Has a histologically confirmed initial diagnosis of MIBC with predominant urothelial histology (histology and presence of muscle invasion to be confirmed by BICR) obtained via a diagnostic or maximal TURBT performed within 90 days before enrollment (signing of ICF).
2. Has clinically non-metastatic bladder cancer (N0M0) determined by imaging (CT of the chest and CTU/MRU of abdomen and pelvis), assessed by the site and verified by BICR.
3. Has provided tumor specimen to the central vendor to determine PDL1 status before randomization.
4. Has planned and is eligible to receive CRT and one of the protocolspecified radiosensitizing chemotherapy regimens.
5. Has an ECOG performance status of 0, 1, or 2 assessed within 14 days before randomization.
6. Demonstrates adequate organ function. All screening laboratory tests should be performed within 14 days before randomization.
7. Is male or female, at least 18 years of age, at the time of signing the informed consent.
8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after
the last dose of CRT treatment.
- Refrain from donating sperm
PLUS either:
- 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) as detailed below:

Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
9. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
- Is not a WOCBP
OR
- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows: MK-3475 [120 days], CRT [180 days].
The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Abstains from breastfeeding during the study intervention period and for at least 120 days (5 half-lives) after study intervention.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.
10. The participant (or legally acceptable representative if applicable) has provided 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 future biomedical research.

Exclusion criteria

1. Has the presence of diffuse CIS (multiple foci [4 or greater] of CIS) throughout the bladder.
2. Has the presence of UC at any site outside of the urinary bladder in the

previous 2 years except for Ta/T1/CIS of the upper tract if the patient has undergone a complete nephroureterectomy.
3. Has the presence of any small cell or neuroendocrine component in the tumor tissue sample.
4. Has a known additional malignancy that is progressing or has required active therapy within the past 3 years.
5. Has the presence of bilateral hydronephrosis during the Screening period.
6. Has limited bladder function with frequency of small amounts of urine (< 30 mL), urinary incontinence, or requires self-catheterization or a permanent indwelling catheter.
7. Has received prior pelvic/local radiation therapy or any antineoplastic treatment for MIBC.
8. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PDL2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX- 40, CD137).
9. Has received a live vaccine within 30 days before the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
10. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention.
11. Has known severe hypersensitivity (>=Grade 3) to the selected chemotherapy regimen, and/or any of their excipients and excipients of pembrolizumab.
12. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study drug.
13. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, 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) is not considered a form of systemic treatment and is allowed.
14. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
15. Has an active infection requiring systemic therapy.
16. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.
17. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
18. Has a known history of active tuberculosis (TB; Bacillus tuberculosis). No TB testing is required unless mandated by local health authority.
19. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the

study, interfere with the participant's participation for the full duration of the study, such that is not in the best interest of the participant to participate, in the opinion of the treating investigator.
20. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
21. 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:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-11-2020
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:	04-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-03-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	24-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-01-2023
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	CTIS2023-503500-87-00

Register	ID
EudraCT	EUCTR2019-004023-20-NL
ClinicalTrials.gov	NCT04241185
CCMO	NL72314.056.20