A Phase 3, Randomized, Double-blind Study to Compare the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Lenvatinib (E7080/MK-7902) Versus Pembrolizumab and Placebo as First Line Treatment for Locally Advanced or Metastatic Urothelial Carcinoma in Cisplatin-ineligible Participants Whose Tumors Express PD-L1, and in Participants Ineligible for Any Platinum-containing Chemotherapy Regardless of PD-L1 Expression (LEAP-011)

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The current study is designed to evaluate the safety and efficacy of combination therapy with pembrolizumab + lenvatinib versus pembrolizumab + placebo in cisplatin-ineligible participants whose tumors express PD-L1 (CPS >=10) and participants...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON54684

Source
ToetsingOnline

Brief title
MK7902-011

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
metastatic bladder cancer, Metastatic Urothelial Carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: chemotherapy ineligible, Pembrolizumab, Urothelial Carcinoma

Outcome measures

Primary outcome

Progression Free Survival, defined as the time from randomization to the first documented progressive disease (PD) or death from any cause, whichever occurs first.

Overall Survival, defined as the time from randomization to the date of death from any cause.

As per protocol amendment 03 dated 24September 2021 lenvatinib and placebo have been removed from the study. No further analyses of efficacy endpoints/ exploratory objectives may not be pursued.

Secondary outcome

Objective response (OR), defined as a confirmed complete response (CR) or partial response (PR).

Adverse events (AEs) and discontinuations due to AEs.

duration of response (DOR), defined as the time from the first documented evidence of CR or PR to the earliest date of PD or death due to any cause, whichever comes first, for individuals with a confirmed CR or PR.

Disease control, defined as a confirmed response of CR or PR or stable disease (SD).

EORTC QLQ-C30 global health status/QoL score.

TTD, defined as the time from baseline to the first onset of PRO deterioration in EORTC QLQ-C30 global health status/QoL score.

As per protocol amendment 03 dated 24September 2021 lenvatinib and placebo have been removed from the study. No further analyses of efficacy endpoints/ exploratory objectives may not be pursued.

Study description

Background summary

Urothelial carcinoma (UC), also referred to as transitional cell carcinoma, is a range of tumors that arise from the urothelial endothelium, including the bladder, renal pelvis, ureter, and urethra. The worldwide incidence of bladder cancer exceeds 300,000 cases annually. UC is the predominant histologic type of bladder cancer in the United States and western Europe, where it accounts for approximately 90% of bladder cancers.
UC disproportionately affects the elderly, who often have coexisting, impactful illnesses such as cardiovascular disease and impaired renal function. Such

coexisting illnesses are important factors limiting treatment options for these patients.
the first-line standard of care treatment for patients with locally advanced or metastatic UC has been cisplatin-containing combination chemotherapy, including either gemcitabine or methotrexate/vinblastine/doxorubicin. Chemotherapy, particularly with cisplatin, is toxic, and it has been estimated that only approximately 21% of patients are treated with cisplatin-based chemotherapy. There is no standard of care chemotherapy for patients unable to tolerate cisplatin. Because of the frailty of this population with advanced UC and the toxicity associated with chemotherapy, it has been estimated that 48% of UC patients cannot be treated with any platinum chemotherapy at all.
Recently, pembrolizumab has shown efficacy in first line (1L) and second line (2L) treatment of metastatic bladder cancer . Pembrolizumab is indicated for the treatment of previously untreated patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1. Lenvatinib is a multi-receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) and its family of receptors (VEGFRs 1-3). Lenvatinib also inhibits other receptor tyrosine kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression. Lenvatinib is not currently indicated for bladder cancer.
Advanced/metastatic UC presents unique challenges and represents a clinical area in need of novel therapeutic approaches.

Study objective

The current study is designed to evaluate the safety and efficacy of combination therapy with pembrolizumab + lenvatinib versus pembrolizumab + placebo in cisplatin-ineligible participants whose tumors express PD-L1 (CPS >=10) and participants ineligible for any platinum chemotherapy (eg, ineligible for cisplatin and carboplatin by virtue of comorbidities, advanced age, and clinical judgment), with pembrolizumab monotherapy as a treatment option.

As per protocol amendment 03 dated 24September 2021 lenvatinib and placebo have been removed from the study. No further analyses of efficacy endpoints/ exploratory objectives may not be pursued.

Study design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind study of pembrolizumab + lenvatinib in cisplatin-ineligible participants whose tumors express PD-L1 (CPS >=10), and in participants ineligible for any platinum-containing chemotherapy, with advanced/unresectable or metastatic UC.

As per protocol amendment 03 dated 24September 2021 lenvatinib and placebo have

been removed from the study. All patients remaining on study will continue on open-label pembrolizumab momotherapy.

Intervention

Original groups:
Group 1:
Pembrolizumab 200 mg intravenous (IV) every 3 weeks in combination with once daily 20mg lenvatinib oraly
Groep 2:
Pembrolizumab 200 mg intravenous (IV) every 3 weeks in combination with once daily placebo oraly

As per protocol amendment 03 dated 24September 2021 lenvatinib and placebo have been removed from the study. All patients remaining on study will continue on open-label pembrolizumab momotherapy.

Study burden and risks

Treatment cycles will take three weeks, of which pembrolizumab will be administered on day 1 of the cycles en lenvatinib will be taken once daily. At every visit, a physical examination will be performed, vital signs will be measured and blood samples will be 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 psychologiclal discomfort with some of the study procedures, such as blood sampling, administration of the IV line and tumor biopsy.
It cannot be guaranteed that participants will directly benefit from taking part in clinical research from the study intervention.
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.

Serious side effects of Lenvatinib are:
- Stroke, mini-stroke or bleeding in the brain
- Blood clot in the legs or lungs (pulmonary embolism)
- Heart problems, heart palpitations or heart attack -
- Fistula formation or bowel perforation
- Bleeding inside the body particularly from the gut
- Dehydration and kidney failure
- Heart failure
- Liver damage or failure
- Hepatic encephalopathy
- Posterior reversible encephalopathy syndrome (PRES)
- Pneumothorax

- Aortic dissection

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Have a histologically or cytologically confirmed diagnosis of advanced/unresectable or metastatic urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/nontransitional cell histology are allowed, but transitional cell carcinoma must be the predominant histology, 2. Have at least 1 measurable target lesion per RECIST 1.1 as assessed by the local site investigator/radiologist, per the criteria defined in the protocol, 3. Have provided an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated and adequate for PD-L1 evaluation. , 4. Have received no prior systemic chemotherapy for advanced or

metastatic UC with the following exceptions:, - Neoadjuvant platinum-based chemotherapy for treatment of muscle-invasive bladder cancer with recurrence >12 months from completion of the therapy is permitted, - Adjuvant platinum-based chemotherapy following radical cystectomy, with recurrence >12 months from completion of the therapy, is permitted, 5. Meet criteria for either option a or option b:, a. Have a tumor(s) with PD-L1 CPS >=10 and be considered ineligible to receive cisplatin-based combination therapy, based on 1 of the following:, - ECOG PS 2 within 7 days prior to randomization, - CrCl (calculated or measured using the institutional standard) >=30 to <=60 mL/min, - NCI CTCAE Version 4.0 Grade >=2 audiometric hearing loss, - NCI CTCAE Version 4.0 Grade >=2 peripheral neuropathy, OR, b. In the opinion of the investigator, be considered ineligible to receive any platinum-based chemotherapy (ie, ineligible for cisplatin and carboplatin) based on:, - ECOG PS 2 within 7 days prior to randomization, and at least 1 of the following:, - Documented visceral metastatic disease, - CrCl >=30 to <=60 mL/min, - NCI CTCAE Version 4.0 Grade >=2 audiometric hearing loss, - NCI CTCAE Version 4.0 Grade >=2 peripheral neuropathy, - Other reason, identified on the case report form, for the participant being unable to receive both cisplatin and carboplatin safely. Additional criteria for platinum ineligibility will be considered and allowed on a case-by-case basis, following consultation with the Sponsor, 6. Be male or female and >=18 years of age and considered an adult per local regulations on the day of signing the informed consent, 7. Have ECOG PS 0, 1, or 2 within 7 days prior to randomization and a life expectancy of >=3 months, 8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 30 days after the last dose of pembrolizumab or lenvatinib/placebo:, - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle and agree to remain abstinent, OR, - Must agree to use contraception unless confirmed to be azoospermic 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 low user dependency, or be abstinent from heterosexual intercourse as her preferred and usual lifestyle, during the intervention period and for at least 120 days post pembrolizumab or 30 days post lenvatinib/placebo, - A WOCBP must have a negative highly sensitive pregnancy test within 72 hours before the first dose of study intervention, - If a urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive, - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk of including a woman with an early undetected pregnancy, 10. The participant (or legally acceptable representative if applicable) provides written informed consent for the study, 11. Have adequately controlled BP with or without antihypertensive medications, defined as BP <=150/90 mm Hg at screening and no change in antihypertensive

medications within 1 week prior to randomization, 12. Have adequate organ function

Exclusion criteria

1. Has disease that is suitable for local therapy administered with curative intent (eg, chemotherapy and radiation for Stage 3 disease). , 2. Has tumor with any neuroendocrine or small cell component., 3. Has a history of a gastrointestinal condition or procedure (eg, gastric bypass, malabsorption) that, in the opinion of the investigator, may affect oral drug absorption., 4. Has had major surgery within 3 weeks prior to the first dose of study intervention., 5. Has a pre-existing Grade >=3 gastrointestinal or non-gastrointestinal fistula., 6. Has radiographic evidence of major blood vessel invasion/infiltration, or has had clinically significant hemoptysis (at least 0.5 teaspoon of bright red blood) or tumor bleeding within 2 weeks prior to the first dose of study intervention. The degree of tumor invasion/infiltration of major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy., 7. Has had significant cardiovascular impairment within 12 months of the first dose of study intervention, such as history of NYHA >Class II congestive heart failure, unstable angina, myocardial infarction or cerebrovascular accident (CVA)/stroke, cardiac revascularization procedure, or cardiac arrhythmia associated with hemodynamic instability., 8. Has known intolerance or severe hypersensitivity (Grade >=3) to pembrolizumab or lenvatinib or any of their excipients , 9. Has received lenvatinib as monotherapy or in combination with a PD-1/PD-L1 inhibitor or has previously been enrolled in a clinical study evaluating lenvatinib for bladder cancer, regardless of the treatment received., 10. Is a WOCBP who has a positive urine pregnancy test within 24 hours before randomization , 11. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 inhibitor, indoleamine-pyrrole 2,3 dioxygenase (IDO1) inhibitor, or agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137), or any other antibody or drug targeting T-cell costimulatory pathways in the adjuvant or advanced/metastatic setting., 12. Has received prior radiotherapy to a metastatic site without the use of chemotherapy radiosensitization within 3 weeks of the first dose of study intervention, with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks before the start of study intervention. Participants must have recovered from all radiation-related toxicities, and must not require corticosteroids. , 13. Has received a live vaccine within 30 days prior to the first dose of study intervention, 14. In the investigator*s judgment, has not recovered from toxicity or other complications from any major surgery prior to starting study intervention., 15. Is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study

intervention., 16. Has an LVEF below the institutional normal range, as determined by MUGA or ECHO, 17. Has history or presence of an abnormal ECG that, in the investigator*s opinion, is clinically meaningful. , 18. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (at a dose exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization, 19. Has had an active malignancy (except locally advanced or metastatic UC) within the past 36 months, 20. Has central nervous system (CNS) metastases, unless the participant has completed local therapy and has discontinued use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs or symptoms of CNS metastases must be stable for at least 4 weeks before starting study intervention, 21. Has an active autoimmune disease that has required systemic treatment in the past 2 years., 22. Has a history of (non-infectious) pneumonitis that required systemic steroids, or current pneumonitis, 23. Has an active infection requiring systemic therapy, 24. Has a known history of human immunodeficiency virus (HIV) infection, 25. Has a known history of or is positive for active hepatitis B or has active hepatitis C, 26. Has active tuberculosis, 27. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant*s participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator., 28. Has a known psychiatric or substance abuse disorder that would interfere with the participant*s ability to cooperate with the requirements of the study., 29. Is receiving hemodialysis., 30. A participant with >1+ proteinuria on urinalysis at screening will undergo 24-hour urine collection for quantitative assessment of proteinuria. A participant with urine protein >=1 g/24 h will be excluded. , 31. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of pembrolizumab and lenvatinib/placebo, 32. Has had an allogeneic tissue/solid organ transplantation

Study design

Design

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

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-11-2019
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-04-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-05-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	30-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-12-2019
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:	27-01-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	08-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-05-2021
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:	01-08-2021
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:	24-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	02-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-11-2023
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
Other	141237
EudraCT	EUCTR2018-003752-21-NL
CCMO	NL69118.028.19