AVELUMAB SHORT MAINTENANCE

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24701

Source
NTR

Brief title
Ave-short-trial

Health condition

Urothelial Cancer

Sponsors and support

Primary sponsor: Erasmus MC
Source(s) of monetary or material Support: Stichting DUOS

Intervention

Outcome measures

Primary outcome

18 months overall survival (OS)

Secondary outcome

OS in PD-L1 positive and PD-L1 negative tumors, in patients with visceral versus non-visceral metastases, in patients with CR/PR as best response to chemotherapy versus SD, and in retreated patients. PFS in PD-L1 positive and PD-L1 negative tumors, and in re-treated

patients. ORR per RECIST 1.1 in retreated patients. Duration of response. Disease control (defined as complete response, partial response, non–complete response or non–progressive disease, or stable disease at 24 weeks after initiation of avelumab and prior to disease progression or death due to any cause, according to RECIST 1.1). Study avelumab pharmacokinetics.

Study description

Background summary

Rationale: Urothelial cancer (UC) is a relatively frequent cancer worldwide with locally advanced and metastatic muscle invasive UC of the bladder leading to approximately 150.000 deaths annually worldwide. In advanced and metastatic UCC, current standard of care with cisplatin-containing chemotherapy in 1st line results in a median overall survival of approximately 14 months. Since 2016, the FDA has approved five different PDL1/PD1 inhibitors for the treatment of metastatic UCC in second line treatment. However, only 25-55% of patients may receive 2nd line treatment and in case of PD-L1/PD-1 inhibitors only around 20% of patients will derive benefit in 2nd line. Immediate initiation of PD-L1/PD-1 inhibition in patients with at least stable disease following 1st line platinum-based chemotherapy instead of waiting for progressive disease is a compelling strategy which has been proven to be effective in the Javelin Bladder 100 trial (NCT02603432). After completion of chemotherapy (with stable disease (SD), partial or complete response (PR, CR) as best response) patients received maintenance avelumab treatment until progressive disease, unacceptable toxicity or patient withdrawal. As a consequence of this design a proportion of the patients were treated beyond 2 years (up to 4 years at the time of the report). However, the optimal duration of immunotherapy in this context of maintenance therapy is unknown.

Objective: To demonstrate the benefit of maintenance treatment with a maximum of six months avelumab in increasing the overall survival (OS) at 18 months in patients with unresectable locally advanced or metastatic UC whose disease did not progress on or following completion of first-line platinum-containing chemotherapy

Study design: Prospective single arm multicentre nationwide study

Study population: Patients with advanced/metastatic urothelial cancer who have obtained at least SD after a minimum of 4 cycles of (first-line) platinum-based chemotherapy.
Patients can be retreated with checkpoint inhibition (CPI) in case of disease progression after the completion of six months treatment of avelumab, excluding those patients with progressive disease during the maintenance phase and without limiting toxicity.
Evaluation CT scans will be performed 12 and 24 weeks post-initiation of avelumab.
Pharmacokinetics sampling will be done in 20 patients within 24h prior to each avelumab.
Mandatory plasma samples will be collected for isolation of circulating tumor DNA (ctDNA) at baseline and 6 weeks from baseline in all patients to support investigation and, as appropriate, clinical validation of ctDNA biomarkers that may predict response to treatment.

Patient-reported outcomes will be evaluated using a diary at baseline, and at week 12, 24, 36 and 2 years post-initiation of avelumab.
Follow-up from initiation of maintenance avelumab will be 2 years; CT scans will be performed every 12 weeks. Follow-up from initiation of re-treatment phase will be 2 years; CT scans will be performed every 12 weeks.

Main study parameters/endpoints:
Primary endpoint: 18 months overall survival (OS).
Secondary endpoints: OS in PD-L1 positive and PD-L1 negative tumors, in patients with visceral versus non-visceral metastases, in patients with CR/PR as best response to chemotherapy versus SD, and in retreated patients. PFS in PD-L1 positive and PD-L1 negative tumors, and in re-treated patients. ORR per RECIST 1.1 in retreated patients. Duration of response. Disease control (defined as complete response, partial response, non–complete response or non–progressive disease, or stable disease at 24 weeks after initiation of avelumab and prior to disease progression or death due to any cause, according to RECIST 1.1). Study avelumab pharmacokinetics.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients will be treated with intravenous (i.v.) avelumab for six months every two weeks (q2w) at a dose of 10 mg/kg. Directly preceding every infusion of avelumab, patients will be seen by their treating physician. Overall performance status and vital signs will be checked. Additional physical examinations will be performed if indicated. Blood and regular urine sampling to check for therapy-related toxicity or disease-related problems will be performed. This is not different from standard of care in patients treated with systemic immunotherapy. CT scans will be performed to evaluate disease status every 12 weeks.

Study objective

In patients with advanced/metastatic urothelial cancer who have obtained at least stable disease after a minimum of 4 cycles of (first-line) platinum-based chemotherapy, subsequent avelumab maintenance treatment with a maximum duration of 6 months is not inferior to avelumab treatment for an undetermined time.

Study design

18 months

Intervention

Avelumab maintenance treatment with a maximum duration of 6 months.

Contacts

Public

Erasmus Medical Center Rotterdam
Debbie Robbrecht

0107041733
Scientific
Erasmus Medical Center Rotterdam
Debbie Robbrecht

0107041733

Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Diagnosis:
a. Histologically confirmed, unresectable locally advanced or metastatic transitional cell carcinoma of the urothelium.
b. Documented Stage IV disease (T4b, N0, M0; any T, N1–N3, M0; any T, any N, M1) at the start of first-line chemotherapy.
c. Measurable disease prior to the start of first-line chemotherapy by RECIST v1.1.

2. Prior first-line chemotherapy must have consisted of at least 4 cycles and no more than 6 cycles of gemcitabine + cisplatin and/or gemcitabine + carboplatin. No other chemotherapy regimens are allowed in this study.

3. Patients without progressive disease as per RECIST v1.1 guidelines (ie, with an ongoing CR, PR, or SD) following completion of 4 to 6 cycles of first-line chemotherapy.

4. Plasma samples: Provision of a baseline plasma sample is mandatory

5. Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative, as allowed by local guideline/practice) has been informed of all pertinent aspects of the study.

6. Patients who are willing and able to comply with scheduled visits, treatment plans,

laboratory tests, and other study procedures.

7. Age; Minimum of 18 years

8. Estimated life expectancy of at least 3 months.

9. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (Appendix 1).

10. Adequate bone marrow function, including:
a. Absolute neutrophil count (ANC) 1,500/mm3 or 1.5 x 109/L;
b. Platelets 100 x 109/L;
c. Hemoglobin 5.6 mmol/L (may have been transfused).

11. Adequate renal function, defined as estimated creatinine clearance 30 mL/min as calculated using the Cockcroft-Gault equation

12. Adequate liver function, including:
a. Total serum bilirubin 1.5 x upper limit of normal (ULN);
b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)2.5 x ULN.

13. Serum pregnancy test (for females of childbearing potential) negative at screening.

14. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception (Section 4.3.1) throughout the study and for at least 60 days after the last dose of assigned treatment.

Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this study:

Patients with any of the following characteristics/conditions will not be included in the study:
1. Patients whose disease progressed by RECIST v1.1 on or after first-line chemotherapy for urothelial cancer.

2. Prior adjuvant or neoadjuvant therapy within 12 months of initiation of avelumab.

3. Prior immunotherapy with IL-2, IFN-ɣ.-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or CTLA-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

4. Major surgery 4 weeks or major radiation therapy 2 weeks prior to initiation of avelumab. Prior palliative radiotherapy (10 fractions) to metastatic lesion(s) is permitted, provided it has been completed at least 48 hours prior to patient initiation.

5. Patients with known symptomatic central nervous system (CNS) metastases requiring

steroids. Patients with previously diagnosed CNS metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to initiation of avelumab, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and are neurologically stable.

6. Persisting toxicity related to prior therapy NCI CTCAE v5.0 Grade >1; however, sensory neuropathy Grade 2 is acceptable.

7. Diagnosis of any other malignancy within 5 years prior to initiation of avelumab, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or low-grade (Gleason 6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration).

8. Participation in other studies involving investigational drug(s) within 4 weeks prior to initiation of avelumab. Observational studies are permitted.

9. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo orhyperthyroid disease not requiring immunosuppressive treatment are eligible.

10. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, deep vein thrombosis, or symptomatic pulmonary embolism.

11. Active infection requiring systemic therapy.

12. Known severe hypersensitivity reactions to monoclonal antibodies (Grade 3), any history of anaphylaxis, or uncontrolled asthma (ie, 3 or more features of asthma symptom control per the Global Initiative for Asthma 2015). 62

13. Known prior or suspected hypersensitivity to study drugs or any component in their formulations.

14. Current or prior use of immunosuppressive medication within 7 days prior to initiation of avelumab, EXCEPT the following:
a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
b. Systemic corticosteroids at (equivalent) doses of maximum 10 mg prednisone
c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

15. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy, or known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

16. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection.

17. Vaccination within 4 weeks of the first dose of study treatment and while on trial is prohibited except for administration of inactivate vaccines (for example, inactivated influenza vaccines).

18. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

19. Pregnant female patients; breastfeeding female patients; male patients able to father children, and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in the protocol for the duration of the study and for at least 60 days after the last dose of avelumab.

20. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, and pneumonitis; psychiatric condition including recent (within the past year) or active suicidal ideation or behaviour; or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2021
Enrollment:	101
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	10-12-2020
Application type:	First submission

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
NTR-new	NL9109
Other	Stichting BEBO : Ave-short-trial

Study results