A Phase III, Randomized, Open-label, Controlled, Multi-Center, Global Study of First-Line MEDI4736 Monotherapy and MEDI4736 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer

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To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS in patients with UC.

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

Summary

ID

NL-OMON50230

Source
ToetsingOnline

Brief title
DANUBE

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
urothelial cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Opdrachtgever/ sponsor Astrazeneca

Intervention

Keyword: immuno therapy, PDL-1 inhibitor, tremelimumab, urothelial cancer

Outcome measures

Primary outcome

To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS in patients with unresectable Stage IV UC

To assess the efficacy of MEDI4736 monotherapy versus SoC in terms of OS in patients with unresectable Stage IV PD L1 High UC

Secondary outcome

To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of PFS in patients with UC.

To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of PFS in patients with PD-L1-High UC.

To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of ORR.

To further assess the efficacy of MEDI4736 monotherapy compared to SoC in terms

of ORR.

To assess disease-related symptoms and HRQoL in UC patients treated with MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared with SoC and each other using the FACTBL questionnaire.

To assess the PK of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy.

To investigate the immunogenicity of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy.

To assess the efficacy profile of MEDI4736 monotherapy in patients who are not cisplatin-eligible.

Study description

Background summary

Urothelial Cancer is the most common tumor of the entire urinary tract and is the ninth most common cancer diagnosis worldwide, with more than 330000 new cases each year and more than 130000 deaths per year. Despite the high rate of disease control (above 80%) in the first-line setting, disease progression invariably occurs after discontinuing chemotherapy, even in patients who initially respond to chemotherapy. Approximately 40% of patients are unfit for cisplatin-containing chemotherapy due to a poor PS, impaired renal function, or comorbidity. Carboplatin containing chemotherapy is less effective than cisplatin-based chemotherapy in terms of CR and survival and should not be considered interchangeable or standard. To date, no standard therapy has been established for patients who recur or are refractory to first-line therapy, or in the maintenance setting. The limited number of treatment options reflects

the poor outcome. There is still a significant unmet medical need in urothelial cancer (UC).

In this study the new investigational product MEDI4736 as monotherapy or as combinationtherapy with tremelimumab will be compared to SoC treatment for UC. MEDI4736 is a human mAb of the immunoglobulin G 1 kappa subclass that inhibits the binding of PD-L1 and tremelimumab is a mAB which binds to the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Both PD-L1 and CTLA-4 proteins play a role in the suppression on the immune system which the tumor uses in order to escape the immune system.

Study objective

To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS in patients with UC.

Study design

This is a randomized, open-label, controlled, multi-center, global Phase III study
The patients will be randomized in a 1:1:1 ratio to receive treatment with

- MEDI4736 monotherapy
- MEDI4736 + tremelimumab combination therapy
- SoC

Patients will be stratified according to cisplatin eligibility (eligible or ineligible), programmed
cell death ligand 1 (PD-L1) status (positive or negative and visceral metastasis

Intervention

MEDI4736 monotherapy:
MEDI4736 1.5 g via IV infusion q4w, starting on Week 0

MEDI4736 + tremelimumab combination therapy:
MEDI4736 1.5 g via IV infusion q4w, starting on Week 0.*
Tremelimumab 75 mg via IV infusion q4w, starting on Week 0, for up to 4 months (4 doses/cycles).

Standard of care

Study burden and risks

Patients will be assessed on the following assessments during the study:

Patienten worden tijdens het onderzoek op verschillende dagen onderworpen aan de volgende handelingen:
- Medical History
- Physical examniation
- Performance status
- Vital signs (BP, pulse, temperature, RR)
- Height
- CT/MRI
- ECG
- Tumor biopsy for PDL-1 status
- Blood and urine samples
- Questionnaires
- Pregnancy testing (if applicable)

Contacts

Public
Astra Zeneca

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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. Age *18 years at the time of screening.
2. Written informed consent
3. Patients with histologically or cytologically documented, unresectable, Stage IV transitional
cell carcinoma of the urothelium who have not been previously treated with first-line chemotherapy.
4. At least 1 lesion, not previously irradiated, that can be accurately measured at
baseline as *10 mm in the longest diameter with a computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements as per
Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) guidelines.
5. Eastern Cooperative Oncology Group (ECOG) PS 0 or 1
6. Life expectancy *12 weeks (in the opinion of the Investigator)
7. Patients eligible or ineligible for cisplatin-based chemotherapy.
8. Tumor PD-L1 status, with IHC assay confirmed by a reference laboratory, must be
known prior to randomization.
9. Adequate organ and marrow function

Exclusion criteria

1. Involvement in the planning and/or conduct of the study
2. Previous IP assignment in the present study
3. Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study
4. Prior exposure to immune-mediated therapy (with exclusion of Bacillus Calmette Guerin), including but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including therapeutic anticancer vaccines. Prior local intervesical chemotherapy or immunotherapy is allowed if completed at least 28 days prior to the initiation of study treatment
5. Any unresolved toxicity NCI CTCAE Grade *2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
6. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.
7. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 28 days of the first dose of study drug.
8. Major surgical procedure (as defined by the Investigator) within 28 days

prior to the first dose of IP.
9. History of allogenic organ transplantation that requires use of immunosuppressive agents.
10. Active or prior documented autoimmune or inflammatory disorders
11. Uncontrolled intercurrent illnesses.
12. Other malignancy within 5 years before first dose of IP, except for the following pending a discussion with AstraZeneca: Patients with a history of prostate cancer and patients who have been adequately treated for a malignancy with a low potential risk for recurrence.
13. History of leptomeningeal carcinomatosis
14. Brain metastases or spinal cord compression.
15. QT interval corrected for heart rate *470 ms calculated from 3 ECGs.
16. History of active primary immunodeficiency
17. Active infection, including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus.
18. Current or prior use of immunosuppressive medication within 14 days before the
first dose of IP.
19. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP.
20. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy
21. Known allergy or hypersensitivity to IP or any IP excipient, or to other humanized mAbs
22. Any medical contraindication to platinum (cisplatin or carboplatin)-based doublet chemotherapy
23. Patient <30 kg in weight

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:	Recruitment stopped
Start date (anticipated):	23-12-2015
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Durvalumab
Product type:	Medicine
Brand name:	NA
Generic name:	Tremelimumab

Ethics review

Approved WMO Date:	08-09-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-11-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	12-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	15-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2015-001633-24-NL
ClinicalTrials.gov	NCT02516241
CCMO	NL54581.029.15