A phase III randomized, open-label, multi-centre, global study of Durvalumab and Bacillus Calmette-Guerin (BCG) administered as combination therapy versus BCG alone in high-risk, BCG-naive non-muscle-invasive bladder cancer patients

Published: 12-07-2018
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-505341-23-00 check the CTIS register for the current data. To assess the efficacy of durvalumab + BCG (induction and maintenance) combination therapy compared to BCG (induction and maintenance)...

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

Summary

ID

NL-OMON50693

Source
ToetsingOnline

Brief title
POTOMAC

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder cancer, non-muscle-invasive bladder cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: opdrachtgever / sponsor AstraZeneca

Intervention

Keyword: Durvalumab, Non-muscle-invasive bladder cancer, Standard of care BCG

Outcome measures

Primary outcome

To assess the efficacy of durvalumab + BCG (induction and maintenance)

combination therapy compared to BCG (induction and maintenance) alone measured

by disease-free survival

Secondary outcome

- To assess the efficacy of durvalumab + BCG (induction and maintenance)

combination therapy compared to BCG (induction and maintenance) alone

- To assess the efficacy of durvalumab + BCG (induction only) combination

therapy compared to BCG (induction and maintenance) alone

- To assess the efficacy of durvalumab + BCG (induction and maintenance)

combination therapy compared to durvalumab + BCG (induction only) alone

- To assess the efficacy of durvalumab + BCG combination therapy compared to

BCG (induction and maintenance) for patients with CIS prior to study entry or

at baseline cystoscopy

- To assess disease-related symptoms and HRQoL in patients with NMBIC treated

with durvalumab + BCG (induction and maintenance) combination therapy and

durvalumab + BCG (induction only) combination therapy compared to BCG

(induction and maintenance) alone and compared to each other using the EORTC

QLQ-C30 questionnaire and the EORTC QLQ-NMIBC24 questionnaire

- To assess patient-reported treatment tolerability directly using specific

PRO-AE symptoms

- To assess the PK of durvalumab when used in combination with BCG treatment

- To investigate the immunogenicity of durvalumab when used in combination with

BCG treatment

- To assess the safety and tolerability of durvalumab + BCG (induction and

maintenance) combination therapy and durvalumab + BCG (induction only)

combination therapy compared to BCG (induction and maintenance) alone

Study description

Background summary

Mortality and morbidity due to bladder represents an important public health issue worldwide. Intravesical BCG continues to be the standard adjuvant treatment for NMIBC completely resected after TURBT. However, the rates of recurrence in this clinical scenario are still very high (50%). Additionally, episodic worldwide shortages of BCG have compromised access to treatment.

Taken together, there is a significant unmet medical need and innovative treatment options are essential for this patient population.

In this study the efficacy (disease-free survival) of durvalumab + BCG (induction and maintenance) combination therapy compared to BCG (induction and maintenance) alone is assessed in patients with non-muscle-invasive bladder cancer.

Study objective

This study has been transitioned to CTIS with ID 2023-505341-23-00 check the CTIS register for the current data.

To assess the efficacy of durvalumab + BCG (induction and maintenance) combination therapy compared to BCG (induction and maintenance) alone in high-risk non-muscle-invasive bladder cancer patients.

Study design

A phase III, open-label study to assess the efficacy (disease-free survival) of durvalumab + BCG combination therapy compared to BCG (induction and maintenance) alone in high-risk non-muscle-invasive bladder cancer patients.

Randomization 1:1:1 stratified to higher risk papillary disease and carcinoma in situ

- Durvalumab + BCG (induction and maintenance)

- Durvalumab + BCG (induction)

- BCG (induction and maintenance)

Study burden and risks

On several days during the study patients will undergo the following assessments:

- Anamnesis (at screening also medical history)
- Physical examination
- Vital signs (blood pressure, pulse, temperature, respiration rate)
- Weight and height
- ECG
- Blood- and urine assessments
- Pregnacy test (if applicable)
- WHO performance status
- AE/SAE assessment
- Disease assessment (cystoscopy, urine cytology, CT urography, pathology testing)
- Questionnaires (EORTC QLQ-C30, EORTC-NMIBC24, EQ-5D-5L, PRO-CTCAE)
- Tumorbiopsy (at screening and at recurrence or disease progression)

Durvalumab may cause side effects. The side effects that are known are reported in previous studies.
Probable risks are: enterocolitis, dermatitis, hepatitis/hepatoxicity, endocrinopathy, pneumonia, neuropathy and neurological incidents.
Other risks are: hypersensitivity, anaphylaxis or severe allergic reactions
In previous studies with durvalumab the following side effects were reported mostly:
Fatigue, diarrhea, anorexia, rash, vomitin, itching, dyspnea, influenza,

hypothyroidism, elevated ALT and AST, coughing, muscle pain, stomach pain, dizziness

Contacts

Public
Astra Zeneca

Pr. Beatrixlaan 582
Den Haag 2595 BM
NL
Scientific
Astra Zeneca

Pr. Beatrixlaan 582
Den Haag 2595 BM
NL

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. BCG-naïve (patients who have not received prior intravesical BCG or who previously received but stopped BCG more than 3 years before study entry are eligible).
4. Local histological confirmation (based on pathology report) of high-risk transitional
cell carcinoma of the urothelium of the urinary bladder confined to the mucosa

or
submucosa. A high-risk tumor is defined as one of the following:
- T1 tumor
- High grade/G3 tumor
- CIS
- Multiple and recurrent and large (with diameter of largest tumor >=3 cm) tumors (all conditions must be met in this point)
5. Complete resection of all Ta/T1 papillary disease prior to randomization, with the TURBT removing high-risk NMIBC performed not more than 4 months before randomization in the study. Patients with residual CIS after TURBT are eligible.
6. No prior radiotherapy for bladder cancer.
7. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.
8. Body weight >30 kg.
9. Must have a life expectancy of at least 12 weeks.
10. No prior exposure to immune-mediated therapy of cancer including, but not limited
to, other anti CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 antibodies. Patients who have been treated with anticancer vaccines will
be excluded.
11. Must be a candidate for BCG treatment.
12. Adequate organ and marrow function as defined below:
- Hemoglobin >=9.0 g/dL
- Absolute neutrophil count >=1.0 × 109/L
- Platelet count >=75 × 109/L
- Serum bilirubin <=1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert*s syndrome, who will be allowed in consultation with their physician.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=2.5 × ULN
- Measured creatinine clearance (CL) >40 mL/min or calculated creatinine CL >40 mL/min as determined by Cockcroft-Gault (using actual body weight)
Males
Creatinine CL (mL/min) = Weight (kg) × (140 - Age) / 72 × serum creatinine (mg/dL)
Females:
Creatinine CL (mL/min) = Weight (kg) × (140 - Age) × 0.85 / 72 × serum creatinine (mg/dL)
13. Postmenopausal or negative pregnancy test.
14 . At screening, provision of a tumor biopsy that is formalin-fixed and paraffin-embedded (FFPE) is mandatory. Tumor sample should be relevant to the high-risk NMIBC which is the reason for inclusion in the study, preferably, from TURBT removing this tumor.

Exclusion criteria

1. Evidence of muscle-invasive, locally advanced, metastatic, and/or extra-vesical bladder cancer (ie, T2, T3, T4, and / or stage IV).
2. Predominantly variant histology such as micropapillary, plasmocytoid, nested, sarcomatoid, microcystic, squamous and adeno variants of urothelial carcinoma representing more than 50% of tumor tissue or other than urothelial tumors as assessed by pathology
3. Evidence of lymphovascular invasion of bladder tumor.
4. Immediate cystectomy is indicated.
5. Known or documented absolute and/or relative contraindication of adjuvant intravesical BCG treatment.
6. Concurrent extravesical (ie, urethra, ureter, or renal pelvis), non-muscle-invasive transitional cell carcinoma of the urothelium.
7. Involvement in the planning and/or conduct of the study.
8. Previous investigational product (IP) assignment in the present study.
9. Concurrent enrollment in another clinical study.
10. Participation in another clinical study with an IP during the last 28 days or 5 half-lives of the respective Investigational Product, whichever is longer prior to study enrollment.
11. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Chemotherapy for previous instances of NMIBC is acceptable. Patients who have received a single instillation of Mitomycin C or equivalent chemotherapy agent immediately after TURBT can be enrolled in the study.
12. Previous or concurrent treatment with potent systemic immunostimulatory agents (i.e systemic use of interleukins, interferons, glatiramer or similar agents).
13. Major surgical procedure within 28 days prior to randomization.
14. History of allogenic organ transplantation.
15. Active or prior documented autoimmune or inflammatory disorders, diverticulitis, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome.
16. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, serious chronic GI conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs, or compromise the ability of the patient to give written informed consent.
17. History of another primary malignancy.
18. History of active primary immunodeficiency.
19. Intentionally Omitted.
20. Active infection including TB, hepatitis B, hepatitis C or HIV.
21. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab.
22. Receipt of live attenuated vaccine within 90 days (approximately 5

half-lives) prior to the first dose of IP.
23. 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 durvalumab.
24. Known allergy or hypersensitivity to any of the study drugs or any of the study
drug excipients.
25. Prior randomization or treatment in a previous durvalumab clinical study regardless of treatment group assignment.
26. Signs or symptoms of localized bladder infection or urinary tract infection within 2 weeks prior to the first dose of study treatment.
27. Treatment with therapeutic oral or IV antibiotics within 1 week prior to the start of treatment with BCG..
28. Judgment by the Investigator that the patient is unsuitable to participate in the study.

Study design

Design

Study phase:	3
Study type:	Observational invasive
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):	14-05-2019
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Medac
Product type:	Medicine
Brand name:	n.v.t.
Generic name:	Durvalumab
Product type:	Medicine
Brand name:	OncoTice

Ethics review

Approved WMO Date:	12-07-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	28-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	17-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	28-04-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	01-11-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	08-12-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	CTIS2023-505341-23-00
EudraCT	EUCTR2017-002979-26-NL
ClinicalTrials.gov	NCT03528694
CCMO	NL65884.018.18