A Phase III, Randomized, Open-Label, Multi-Center, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination with Gemcitabine+Cisplatin for Neoadjuvant Treatment Followed by Durvalumab Alone for Adjuvant Treatment in Patients with Muscle-Invasive Bladder Cancer

Published: 19-11-2018
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-510015-19-00 check the CTIS register for the current data. The treatment options currently available for MIBC- patients remain limited, current standard therapy is likely to result in modest...

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

Summary

ID

NL-OMON52537

Source
ToetsingOnline

Brief title
NIAGARA

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder cancer, Muscle-invasive bladder cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: adjuvant treatment, durvalumab, Gemcitabine + Cisplatin, Muscle-Invasive Bladder Cancer

Outcome measures

Primary outcome

To assess the efficacy of durvalumab + G+C combination therapy

(neoadjuvant)/durvalumab alone (adjuvant) (Arm 1) compared to G+C combination

therapy (neoadjuvant)/no adjuvant treatment (Arm 2) in terms of pCR and EFS in

MIBC patients with adequate renal function.

Secondary outcome

Proportion of patients who achieve
to 6 months]

EFS at 24 months (EFS24) defined as time from randomization to event [Time

Frame: Up to 24 months]

Proportion of patients who undergo cystectomy [Time Frame: Up to 6 months]

Overall survival rate at 5 years [Time Frame: Up to 60 months]

PFS2 defined as time from randomization to event following subsequent therapy [

Time Frame: Up to 84 months]

Safety and Tolerability as evaluated by adverse events occurring throughout the

study [Time Frame: Up to 84 months]

Immunogenicity of durvalumab when used in combination with

gemcitabine/cisplatin as measured by presence of antidrug antibodies (ADA) [

Time Frame: Up to 12 months]

Study description

Background summary

The standard management for patients with muscle-invasive bladder cancer (MIBC) involves radical cystectomy and pelvic lymph node dissection.
Despite improvements of pCR and survival rates with neoadjuvant chemotherapy, many patients will still develop recurrence and will ultimately die of metastatic bladder cancer.
The rationale for the present study is that PD-L1 inhibition through exposure to durvalumab, in combination with chemotherapeutics such as G+C, may increase both the long-term response rate and the frequency of response by preventing the MIBC tumor cells from evading immune-mediated anti-tumor response. Administering durvalumab may provide a benefit to patients by averting intrinsic resistance. Adjuvant durvalumab monotherapy may further improve time to disease relapse in patients.

Study objective

This study has been transitioned to CTIS with ID 2023-510015-19-00 check the CTIS register for the current data.

The treatment options currently available for MIBC- patients remain limited, current standard therapy is likely to result in modest improvements in long-term survival, and additional and alternative therapies are required for patients with MIBC. Therefore, there remains an unmet medical need for this patient population. In this study, gemcitabine and cisplatin will be combined with the PD-L1 inhibitor durvalumab to broaden the therapeutic effect of durvalumab monotherapy for the treatment of patients with MIBC.

Study design

Approximately 1050 patients globally will be randomized to receive durvalumab + G+C combination therapy (Arm1) or G+C combination therapy (Arm2) of neoadjuvant chemotherapy prior to radical cystectomy. Following radical cystectomy and during adjuvant therapy, patients in Arm 1 will receive durvalumab monotherapy

, and patients in Arm 2 will receive no adjuvant treatment.

Intervention

Neo-adjuvant treatment
Patients randomized to the 2treatment arms, Arm 1 or Arm 2, will be treated according to their renal function. Recruitment for patients with borderline renal function will be limited to up to 20% of the targeted global population.

Patients with adequate renal function (creatinine clearance [CrCl]>=60 mL/min):
- Arm 1: Day 1: durvalumab 1500 mg intravenous (IV), cisplatin 70 mg/m2, gemcitabine 1000 mg/m2; Day8: gemcitabine 1000mg/m2; every 21 days for 4 cycles.
- Arm 2: Day 1: cisplatin 70 mg/m2, gemcitabine 1000mg/m2; Day8:gemcitabine 1000mg/m2; every 21 days for 4 cycles.

Patients with borderline renal function (CrCl >=40 mL/min to <60 mL/min):
- Arm 1: Day 1: durvalumab 1500 mg IV, cisplatin 35mg/m2, gemcitabine 1000 mg/m2; Day 8: gemcitabine 1000 mg/m2, cisplatin 35 mg/m2; every 21 daysfor 4 cycles.
- Arm 2: Day 1: cisplatin 35 mg/m2, gemcitabine 1000mg/m2; Day8:gemcitabine 1000mg/m2, cisplatin 35 mg/m2; every 21 days for 4 cycles.

Adjuvant therapy (regardless of renal status)
- Arm 1: Day 1: durvalumab 1500 mg IV; every 28 days for 8 cycles.
- Arm 2: No adjuvant treatment.

Study burden and risks

Study subject will visit the hospital appr. 20 times for screening and treatment visits. On several visits the subject will have the following assessments done:
- Physical exam
- urine and blood tests
- ECG
- CT or MRI scan
- medical history, race and ethnicity, concomitant medication
- AE/SAE
- biopsy
- questionnaires (EORTC QLQ-C30, PGIS, and EQ-5D-5)
- ECOG performance status
- pregnancy test

Durvalumab and some of the study procedures may cause side effects. Most common side effects with durvalumab are:
Diarrhea, rash/dry itchy skin, liver problems, feeling tired, nausea, vomiting,

abdominal pain, accumulation of fluid causing swelling, upper respiratory tract infections, decreased appetite, shortness of breath, cough, pain in muscles and joints and, fever.

Contacts

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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

Patient resectable muscle-invasive bladder cancer with clinical stage T2-T4aN0/1M0 with transitional and mixed transitional cell histology;
Patients must be planning to undergo a radical cystectomy at the time of randomization;
Patients who have not received prior systemic chemotherapy or immunotherapy for treatment of MIBC;
ECOG performance status of 0 or 1 at enrollment.

Availability of tumor sample prior to study entry;
Must have a life expectancy of at least 12 weeks at randomization.

Exclusion criteria

Evidence of lymph node involvement or metastatic disease at the time of screening., Contra-indication to any of the study drugs, Requires immunosuppression medication for a concomitant condition, Active or prior documented autoimmune or inflammatory disorders

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):	19-05-2019
Enrollment:	52
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	durvalumab
Generic name:	durvalumab

Ethics review

Approved WMO Date:	12-10-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-11-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-04-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-05-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-11-2023
Application type:	Amendment
Review commission:	METC NedMec

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	CTIS2023-510015-19-00
EudraCT	EUCTR2018-001811-59-NL
CCMO	NL67613.031.18