A Phase III Randomized, Open-Label, Multicenter Study to Determine the Efficacy and Safety of Durvalumab in Combination With Tremelimumab and Enfortumab Vedotin or Durvalumab in Combination With Enfortumab Vedotin for Perioperative Treatment in Patients Ineligible for Cisplatin or Who Refuse Cisplatin Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer (VOLGA)

Published: 08-07-2021
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This study has been transitioned to CTIS with ID 2023-507342-84-00 check the CTIS register for the current data. (1) Main objective:Safety Run-In (SRI):To assess the safety and tolerability of durvalumab + tremelimumab + EV in participants with MIBC...

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

Summary

ID

NL-OMON54296

Source
ToetsingOnline

Brief title
VOLGA

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
Muscle Invasive Bladder Cancer, Radical Cystectomy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Durvalumab, enfortumab vedotin, Muscle Invasive Bladder Cancer, Tremelimumab

Outcome measures

Primary outcome

(1) Primary objectives Safety Run-In (SRI):

Safety and tolerability of durvalumab + tremelimumab + EV in participants with

MIBC who are ineligible for cisplatin.

Endpoints SRI: Safety and tolerability will be evaluated in terms of AEs, vital

signs, clinical laboratory assessments, ECGs, and WHO/ECOG performance status.

(2) Primary objectives Main Study:

Compare efficacy of durvalumab + tremelimumab + EV relative to cystectomy alone

on pCR rate and EFS.

Endpoints Main Study:

- Pathologic complete response (pCR) rate is defined as the number of participants whose pathological staging was T0N0M0 as assessed per central pathological review using specimens obtained via cystectomy.
- Event-free survival (EFS;) is defined as the time from randomization to the first occurrence of any of the following events: recurrence of disease post-radical cystectomy, the first documented progression in participants who did not receive radical cystectomy, failure to undergo radical cystectomy in participants with residual disease, or death due to any cause.

More details see Study Protocol v2, par 3.1 and 3.2.

Secondary outcome

Secondary objectives Safety Run-In (SRI):

To evaluate the efficacy of durvalumab + tremelimumab + EV on pCR rate and EFS

Endpoints SRI:

- Pathologic complete response (pCR) rates at time of cystectomy in Arm 2 vs Arm 3
- Event-free survival (EFS) defined as time from randomization to event in Arm 2 vs Arm 3

Secondary objectives Main Study:

- To compare the efficacy of durvalumab + EV relative to cystectomy on pCR rate, EFS, OS, EFS24, OS5, DFS, pDS rate, and DSS

- To assess disease-related symptoms, functioning, and global health status/quality of life (QoL) in participants treated with durvalumab + tremelimumab + EV compared with cystectomy, durvalumab + EV compared with cystectomy

- To assess the pharmacokinetics (PK) of durvalumab and tremelimumab

- To investigate the immunogenicity of durvalumab and tremelimumab

Endpoints Main Study:

- Pathologic complete response (pCR) rates at time of cystectomy in Arm 2 vs Arm 3

- Event-free survival (EFS) defined as time from randomization to event in Arm 2 vs Arm 3

- Overall survival defined as length of time from randomization until the date of death due to any cause

- EFS at 24 months (EFS24) defined as proportion of participants alive and event-free at 24 months

- Overall survival rate at 5 years

- Disease-free survival (DFS) defined as time from radical cystectomy to recurrence or death

- Pathologic down staging (pDS) rate-to < pT2

- Disease-specific survival (DSS) defined as time from randomization until death due to bladder cancer

- QoL in all arms

- Immunogenicity of Durvalumab when used in combination with Tremelimumab as measured by presence of antidrug antibodies (ADA)

- Assess the pharmacokinetics (PK) of Durvalumab and Tremelimumab

More details see Study Protocol v2, par 3.1 and 3.2.

Study description

Background summary

Bladder cancer is the ninth most common cancer diagnosed worldwide. Bladder cancer is generally divided into muscle-invasive (MIBC) and non muscle-invasive disease (NMIBC). The standard management for patients with MIBC involves cisplatin-based neoadjuvant chemotherapy, in addition to radical cystectomy and pelvic lymph node dissection. Approximately 40% of MIBC patients are deemed ineligible for cisplatin-based chemotherapy based on renal function. This percentage might be even higher based on other ciplatin eligibility criteria.
For these patients straight radical cystectomy is the only curative option.
This has a suboptimal long-term benefit as compared to patients who are fit to receive cisplatincontaining neoadjuvant treatment. Furthermore, patients with MBIC still have high rates of disease recurrence and possible development of advanced cancer, with most recurrences occuring within the first 2 to 3 years after cystectomy. There is clearly still a significant unmet medical need for additional treatment options to improve survival in this patient population, especially in patients who cannot tolerate cisplatin-containing neoadjuvant regimens.
Preliminary data with pembrolizumab and atezolizumab demonstrate that neoadjuvant treatment with anti-PD-(L)1 therapy results in clinically relevant pCR rates in cisplatin ineligible MIBC. Furthermore, durvalumab + tremelimumab combine non-redundant mechanisms of action of anti-PD-L1 and anti-CTLA-4 agents that have the potential to result in synergistic activity as demonstrated by encouraging data in metastatic UC. Enfortumab vedotin is an ADC composed of an anti-Nectin-4 monoclonal antibody attached to a synthetic cell killing (microtubule-disrupting) agent, MMAE.
The rationale for the present study is that PD-L1 and CTLA-4 inhibition (through respective exposure to durvalumab and tremelimumab), in combination with EV may increase both the durability and the frequency of response by preventing the MIBC tumor cells from evading immune-mediated antitumor response.

Study objective

This study has been transitioned to CTIS with ID 2023-507342-84-00 check the CTIS register for the current data.

(1) Main objective:

Safety Run-In (SRI):
To assess the safety and tolerability of durvalumab + tremelimumab + EV in participants with MIBC who are ineligible for cisplatin or who refuse cisplatin

Main Study:
To compare the efficacy of durvalumab + tremelimumab + EV relative to cystectomy on pCR rate and EFS

(2) Secondary objective:

Safety Run-In (SRI):
To evaluate the efficacy of durvalumab + tremelimumab + EV on pCR rate and EFS

Main Study:
To compare the efficacy of durvalumab + EV relative to cystectomy on pCR rate, EFS, OS, EFS24, OS5, DFS, pDS rate, and DSS

Study design

This is a Phase III, parallel, randomized, open-label, 3-arm, multicenter, international study assessing the efficacy and safety of perioperative treatment with durvalumab + tremelimumab + EV (Arm 1) or durvalumab + EV (Arm 2) compared with cystectomy alone (Arm 3) in participants with MIBC who are ineligible for cisplatin and who are undergoing radical cystectomy.

Intervention

Safety Run in:
3 cycli with Durvalumab + Tremelimumab and Enfortumab Vedotin, followed by radical cystectomy and then 9 cycli with Durvalumab and Tremelimumab

Main:
Arm 1 - 3 cylci with Durvalumab + Tremelimumab and Enfortumab Vedotin, followed by radical cystectomy and then 9 cycli with Durvalumab and Tremelimumab

Arm 2 - 3 cycli with Durvalumab + Enfortumab Vedotin, followed by radical cystectomy and then 9 cycli with Durvalumab

Arm 3 - directly to radical cystectomy and then observation only

Study burden and risks

Taking into account the measures to minimize risk to participants in this study, the potential risks identified in association with a stand-alone monotherapy consisting solely of cystectomy, the potential risks of EV used in tandem with durvalumab or in a triple combination with durvalumab and tremelimumab are justified by the benefits (improved time to disease relapse that may be afforded to the study participants).

Contacts

Public
Astra Zeneca

- -
Södertälje SE 151 85
SE
Scientific
Astra Zeneca

- -
Södertälje SE 151 85
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1 Participant must be >= 18 years
2 Histologically or cytologically documented muscle-invasive TCC of the bladder with clinical stage of T2-4aN0-N1M0
3 Medically fit for cystectomy and able to receive neoadjuvant therapy
4 ECOG performance status of 0 to 2 with no deterioration over the previous 2 weeks prior to baseline or day of first dosing.
5 Provision of the most recent tissue sample from MIBC to assess the PD L1 status/expression prior to randomization.
6 Cisplatin-ineligible, determined by protocol OR Refuse cisplatin-based chemotherapy
7 Adequate organ and marrow function, determined by protocol
8 Minimum life expectancy of 12 weeks at randomization per the opinion of the investigator.
9 Body weight > 30 kg.
10 Negative pregnancy test (serum) for women of childbearing potential.
11 Female participants must be 1 year post-menopausal, surgically sterile, or using one highly effective form of birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly.) Women of childbearing potential must agree to use one highly effective method of birth control. They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study to 90 days after the last dose of durvalumab, 180 days after the last dose of durvalumab + tremelimumab, or 2 months after the last dose of EV, whichever is longer. Non sterilized male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period.
12 Non-sterilized male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (per protocol) from the time of screening throughout the total duration of the study and the drug washout period (90 days after the last dose of durvalumab, 180 days after the last dose of durvalumab + tremelimumab, or 4 months after the last dose of EV, whichever is longer) to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period.
13 Capable of giving signed informed consent as described in protocol Appendix A 3, which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.
14 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of sample for optional genetic research that supports Genomic Initiative.

Exclusion criteria

1 Evidence of multiple lymph node (N2+) or metastatic TCC/UC, extravesical TCC/UC that invades the pelvic and/or abdominal wall for bladder cancer (T4b), or primary non bladder (ie, ureter, urethral, or renal pelvis) TCC/UC of the urothelium.
2 Nephroureterectomy required per investigator at the time of randomization for tumor of the mid ureter, renal pelvis, or collecting system.
3 Ureterectomy required if a ureteral tumor is present proximal to common iliacs in addition to planned cystectomy.
4 History of allogeneic organ transplantation that requires use of immunosuppressive agents. Participants with a history of allogenic stem cell transplantation are also excluded.
5 Active or prior documented autoimmune or inflammatory disorders (eg. Given per protocol). The following are exceptions to this criterion:
* Participants with vitiligo or alopecia
* Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
* Any chronic skin condition that does not require systemic therapy
* Participants without active disease in the last 5 years may be included but only after consultation with the Study Physician
* Participants with celiac disease controlled by diet alone may be included but only after consultation with the Study Physician
6 Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease, serious chronic gastrointestinal 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 participant to give written informed consent
7 Ongoing sensor or motor neuropathy of CTCAE Grade 2 or higher
8 Active keratitis or corneal ulcerations. Participants with superficial punctate keratitis are allowed if the disorder is being adequately treated in the opinion of the investigator.
9 History of another primary malignancy except for
* Prostate cancer of pathologic stage <= T2cN0M0 that has been previously treated without evidence of biochemical recurrence at time of study entry and who in the opinion of the investigator are not deemed to require active intervention at the present time, or participants with incidental histologic findings of prostate cancer that has not been treated prior to the study and who do not require specific therapy for prostate cancer beyond the surgery described in the protocol and also are considered to be at low risk for recurrence per the investigator
* Malignancy treated with curative intent and with no known active disease >= 5 years before the first dose of IP and of low potential risk for recurrence

* Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
* Adequately treated carcinoma in situ without evidence of disease
10 History of active primary immunodeficiency
11 Active infection including tuberculosis , hepatitis B, hepatitis C, or human immunodeficiency virus. Participants with a past or resolved hepatitis B infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of hepatitis B surface antigen) are eligible. Participants positive for hepatitis C antibody are eligible only if polymerase chain reaction is negative for hepatitis C RNA.
12 Mean QT interval corrected for heart rate using Fridericia*s formula (QTcF) >= 470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart)
13 Known allergy or hypersensitivity to any of the study interventions or any of the study intervention excipients
14 NYHA Class IV Heart Failure
15 Baseline hemoglobin A1C >= 8%
16 Prior exposure to immune-mediated therapy (with exclusion of Bacillus-Calmette Guerin [BCG]), including but not limited to other anti-CTLA-4, anti-PD-1, anti PD L1, or anti PD-L2 antibodies.
17 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Participants, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
18 Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
19 Prior pelvic radiotherapy treatment within 6 months of randomization to study.
20 Any prior radiotherapy for bladder cancer.
21 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab with exceptions described in the protocol.
22 Any concurrent anticancer treatment. Concurrent use of hormonal therapy for non cancer related conditions (eg, hormone replacement therapy) is allowed.
23 Participation in another clinical study with an IP administered in the last 30 days
24 Previous IP assignment in the present study (Participants in the safety run-in will not be permitted to participate in the main study.)
25 Concurrent enrollment in another clinical study, unless it is an observational (non interventional) clinical study or during the follow-up period of an interventional study
26 Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.
27 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
28 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

29 Currently pregnant (confirmed with positive pregnancy test) or breast feeding.

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:	Recruiting
Start date (anticipated):	24-05-2022
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Imfinzi
Generic name:	Durvalumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Padcev
Generic name:	enfortumab vedotin
Product type:	Medicine
Brand name:	Tremelimumab
Generic name:	Tremelimumab

Ethics review

Approved WMO Date:	08-07-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-10-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-11-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-12-2022

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-04-2023
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Approved WMO Date:	25-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-12-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	CTIS2023-507342-84-00
EudraCT	EUCTR2020-005452-38-NL
CCMO	NL77859.042.21