A Phase 2 clinical study to assess efficacy of Induction ipilimumab/nivolumab to spare the Bladder in urothelial bladder cancer (IndiBlade)

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This study has been transitioned to CTIS with ID 2024-512211-41-00 check the CTIS register for the current data. In this study, we investigate whether induction with immunotherapy, followed by chemoradiation as consolidative therapy is an effective...

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

Summary

ID

NL-OMON52087

Source
ToetsingOnline

Brief title
Checkpoint inhibition and CRT as bladder sparing treatment in UC

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Urothelial carcinoma of the bladder and bladder cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis

Source(s) of monetary or material Support: Bristol-Myers Squibb,KWF,KWF en Farmaceutisch bedrijf

Intervention

Keyword: Chemoradiotherapies [Mesh], Immunotherapy [Mesh], organ [Mesh], Sparing treatment, Urinary bladder neoplasms [Mesh]

Outcome measures

Primary outcome

Efficacy defined as bladder-intact event-free survival (BI-EFS)

Primary endpoint readout will be BI-EFS. Events are defined as death by any cause, muscle-invasive recurrence in the bladder or in the ureter, distal of the crossing with the common iliac artery, nodal or distant recurrencee, cystectomy, or switch to cisplatin-based chemotherapy.

BI-EFS will be determined starting from the initiation of the study drug by CT-imaging, mpMRI of the bladder and cystoscopy. At the time of analysis, patients without an event will be censored at the time point of their last CT, mpMRI of the bladder or cystoscopy assessment.

Secondary outcome

Efficacy : other efficacy endpoints such as

- Recurrence-free survival (RFS), defined as time from start of therapy until the following events: muscle-invasive recurrence in the bladder or in the ureter, distal of the crossing with the common iliac artery, nodal or distant recurrence, switch to cisplatin-based chemotherapy or death by any cause. A decision to switch to cystectomy is not an event, as RFS is meant to provide a measurement of induction therapy efficacy.

- Overall survival (OS), defined as the time between the date of enrollment and

the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

- The rate of NMIBC recurrence-free survival (RFS), overall survival (OS), and the rate of NMIBC will be established.

Safety

- Feasibility to proceed to CRT: assessed by CT-scanning and mpMRI of the bladder after finalizing treatment with checkpoint inhibition, combined with clinical evaluation by the treating physician. When there is no progressive disease detected on imaging and there are no medical contraindications to proceed with CRT, we consider CRT feasibile.
- Safety of CRT
- Safety of ipi/nivo
- Safety of CRT as consolidative therapy after induction ipi/nivo

All grade AEs both treatment- and non-treatment related will be provided as measured according to CTCAE 5.0.

Diagnostic value of mpMRI of the bladder

Tumor evaluation by AI based radiological assessment of pre- and on-treatment mpMRI will be established to identify nonresponding patients

Translational

Biomarkers - PD-L1, TMB, molecular subtypes, predictive value of ctDNA (in urine and plasma) and imaging biomarkers (AI) will be assessed for correlation

with outcome (recurrence and OS)

Subjective measures

QoL and bladder function

Study description

Background summary

Although muscle-invasive urothelial bladder cancer can be cured by surgery, recurrence rates are high. To improve outcome, patients can be treated with neo-adjuvant cisplatin-based chemotherapy. However, cystectomy is a procedure with a high risk of morbidity and even mortality. Loss of the bladder has a major impact on a patient*s quality of life (QoL). Concurrent chemoradiotherapy is recognized as an alternative to cystectomy in selected patients .

Immunotherapy is developed to encourage the immune system to attack tumor cells. Ipilumumab and nivolumab are examples of immunotherapy.
In a previous study, twenty-four patients with urothelial bladder cancer were treated with ipilumumab and nivolumab. In this study, all patients could undergo surgery after pre-treatment with immunotherapy. In 23 out of 24 patients, surgery was performed within 12 weeks. In one patient, surgery had a delay of one month due to adverse events. After treatment with ipilimumab and nivolumab, a reduction of the tumor size (or even no remaining disease) was observed in 19 out of 24 patients.

Based on promising results of immunotherapy, we here propose to study induction ipilimumab + nivolumab, followed by bladder-sparing consolidative therapy using MMC in combination with fluoropyrimidines + radiotherapy to the bladder. By this sequential approach, we aim to reduce the risk of recurrence. In case this treatment schedule appears to be effective, this may lead to less cystectomies in urothelial bladder cancer patients.

Study objective

This study has been transitioned to CTIS with ID 2024-512211-41-00 check the CTIS register for the current data.

In this study, we investigate whether induction with immunotherapy, followed by chemoradiation as consolidative therapy is an effective bladder-sparing

therapy.

Study design

Patients will be treated with immunotherapy in three cycles:
- Day 1: ipilimumab 3 mg/kg
- Day 22: ipilimumab 1 mg/kg + nivolumab 3 mg/kg
- Day 43: nivolumab 3 mg/kg
After induction therapy, the first response evaluation will be performed by cystoscopy, CT- and mpMRI of the bladder. When there is no progressive disease, patients will proceed to chemoradiotherapy (CRT). This is a standard approach in which radiation is executed regarding the local protocol. Probably, this will be 4-5 consecutive weeks from monday-friday.
The schedule for chemotherapy is as follows:
- A single dose of mitomycin C on day 1 of the radiation period
- Either 5-FU intraveniously for 5 days in week 1 and 4 of the radiation period, or capecitabin tablets during the radiation period.
The second response evaluation with an mpMRI in selected centers, cystoscopy, CT scanning of the thorax and abdomen will take place three months after CRT. Follow-up takes place 6, 12, 18, 24, 30 en 36 months after completing CRT.

Intervention

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- Day 1: ipilimumab 3 mg/kg
- Day 22: ipilimumab 1 mg/kg + nivolumab 3 mg/kg
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After induction therapy, tumor evaluation will be performed by cystoscopy, CT- and mpMRI of the bladder. When there is no progressive disease, patients will proceed to chemoradiotherapy (CRT).
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Study burden and risks

Participating in this study requires extra time. Patients need to visit the the hospital three times to receive immunotherapy. Furthermore, patients are schedules for additional controls during the study. For response evaluation after immunotherapy, patients require a cystoscopy, a CT-scan and a mpMRI of the bladder. The CT-scan and mpMRI can be unpleasant for claustrofobic patients, A cystoscopy could be painfull afterwards and could result in mild hematuria.

Several times, blood will be drawn and urine will be collected. Two ECGs will

be performed. We expect patients not to experience these examinations to be unpleasant.
Women with childbearing potential should have a negative pregnancy test.

By participating in this study, patients could experience immune related adverse events, which may require treatment with steroids or hospitalization. It may even be necessary to postpone CRT due to adverse events

Questionnaires regarding QoL and bladder function will be provided several times during this study, which could be confrontational for some patients. A subset of patients will be able to join focus groups in order to expand the QoL research in the study.

Contacts

Public
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066CX
NL
Scientific
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Willing and able to provide informed consent
2. Age >= 18 years
3. Patients with cT2-4aN0-2M0 urothelial bladder cancer, seeking an alternative to radical cystectomy and/or patients who are medically unfit for surgery. Patients with suspected metastatic disease are not eligible.
4. Lymph nodes should be amenable for inclusion into the radiation field according to the multidisciplinary tumor board and/or follow-up consultations between the treating physician and the radiation oncologist.
5. World Health Organization (WHO) performance Status 0 or 1.
6. Urothelial cancer is the dominant histology (>70%). %). A small cell component is not allowed.
7. Formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks from diagnostic TUR available.
8. Screening laboratory values must meet the following criteria: WBC >= 2.0x109/L, Neutrophils >=1.0x109/L, Platelets >=100 x109/L, Hemoglobin >=5.5 mmol/L, GFR>30 ml/min as per Cockcroft-Gault formula, AST <= 2.5 x ULN, ALT <=2.5 x ULN, Bilirubin <=1.5 X ULN
9. Negative pregnancy test (βHCG in urine or blood) for female patients of childbearing potential within 2 weeks prior to day 1 of start immunotherapy.
10. Highly effective contraception for both male and female subjects if the risk of conception exists. Female patients of childbearing potential must comply with contraception methods as requested by the study protocol

Exclusion criteria

1. Previous pelvic irradiation
2. Upper tract urothelial cancer
3. Extensive CIS of the bladder
4. Bilateral hydronephrosis
5. Previous intravenous chemotherapy for bladder cancer
6. Contra-indication to one of the study treatment components, or mpMRI
7. Subjects with active autoimmune disease in the past 2 years. Patients with diabetes mellitus, properly controlled hypothyroidism or hyperthyroidism, vitiligo, psoriasis or other mild skin disease can still be included
8. Documented history of severe autoimmune disease (e.g. inflammatory bowel disease, myasthenia gravis)
9. Prior CTLA-4 or PD-(L)1 -targeting immunotherapy
10. Known history of Human Immunodeficiency Virus, active tuberculosis, or other active infection requiring therapy at the time of inclusion
11. Positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA)
12. Underlying medical conditions that, in the investigator's opinion, will

make the administration of study drug hazardous or obscure the interpretation of adverse events
13. Medical condition requiring the use of immunosuppressive medications, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) will be allowed
14. Use of other investigational drugs four weeks or five half lifes before study drug administration
15. Malignancy, other than urothelial cancer, in the previous 2 years, with a high chance of recurrence (estimated >10%). Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score <= 6, and PSA <= 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible
16. Pregnant and lactating female patients
17. Major pelvic surgical procedure within 4 weeks prior to enrolment or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis
18. Severe infections within 2 weeks prior to enrolment in the study including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-03-2022
Enrollment:	50
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-10-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-11-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2023

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	CTIS2024-512211-41-00
EudraCT	EUCTR2021-004420-15-NL
ClinicalTrials.gov	NCT05200988
CCMO	NL78855.031.21