A Phase 1b trial in Stage II-III urothelial cancer to explore pre-operative immunotherapy - TURANDOT

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We will assess feasibility of pre-operative nivolumab in PD-L1 positive resectable stage II-III urothelial cancer patients

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

Summary

ID

NL-OMON52369

Source
ToetsingOnline

Brief title
Pre-operative immunotherapy in stage II-III urothelial cancer

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Urothelial carcinoma and urothelial cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: 4SC,Farmaceutische industrie

Intervention

Keyword: Feasibility studies [Mesh], Immunotherapy [Mesh], Neoadjuvant therapy [Mesh], Urinary bladder neoplasms [Mesh]

Outcome measures

Primary outcome

The primary endpoint is feasibility, defined as the number of patients

undergoing cystectomy within 12 weeks after start of the study drug.

Secondary outcome

1. Efficacy: Efficacy will be defined as the percentage of pathological

complete response (pCR), defined as pT0N0 or pTisN0, at cystectomy. Other

efficacy endpoints will include RFS and OS.

2. Safety: We will provide the frequency of treatment-related toxicities as

measured according to CTCAE 5.0.

3. Translational: Effects of immunotherapy on the UC tumor microenvironment

Study description

Background summary

Although muscle-invasive urothelial cancer can be cured by surgery, recurrence rates are high. To improve outcome, patients are treated with neo-adjuvant cisplatin-based chemotherapy, which has a high rate of response. Despite impressive responses, the absolute benefit in terms of overall survival is marginal. Furthermore, cisplatin-based chemotherapy is contra-indicated in a significant number of patients due to comorbidity.

Previous studies with neo-adjuvant ipilimumab and nivolumab have shown tumor regression in the majority of patients with UC.

The effect of immune checkpoint blockade is known to be superior in tumor with high expression of PD-L1. In this trial, we'll investigate feasibility and

efficacy of pre-operative nivolumab in patient with high PD-L1 expression.

Study objective

We will assess feasibility of pre-operative nivolumab in PD-L1 positive resectable stage II-III urothelial cancer patients

Study design

This is a phase 1b safety, feasibility and proof-of-principle study of pre-operative immune checkpoint inhibition in patients with stage II and III urothelial cancer (cT2-4aN0M0 or T1-4aN1-3M0). This study can be adapted/expanded into a phase 2 study based on results obtained in this initial feasibility portion.

Intervention

PD-L1 positive patients (CPS>10%): 3x nivolumab 240 mg, D1, 22 and 43

Study burden and risks

Participation in this triall will be time consuming. Patients will visit the hospital for three times to receive immune therapy intravenously. Furthermore, there are some additional checks after surgery.

When treatment with the study drugs is accomplished, a CT-scan and an optional MRI will be performed to evaluate the response to treatment. Patients who suffer from claustrofobia can experience these investigations as being aggravating.

Before the start of treatment, an ECG will be performed. During this trial, multiple blood examinations will be performed. The burden of these investigations is considered acceptable.

By participating in this study, patients could experience immune related adverse events, which may require treatment with steroids or hospitalization. In case of severe immune related adverse events, surgery may be postponed for safety reasons.

By participating in this study, surgery is scheduled some weeks later compared to patients who do not receive pre-operative therapy. A potential disadvantage is that disease progresses while awaiting surgery. This could lead to a more difficult surgery with an increased risk for complications or disease relapse. In the worst case, surgery may not be appropriate anymore.

Contacts

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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. Resectable muscle-invasive UC (upper urinary tract allowed), defined as: - cT2-4aN0M0 OR - cT1-4aN1-3M0 2. World Health Organization (WHO) performance Status 0 or 1. 3. Urothelial cancer is the dominant histology (>70%). 4. PD-L1 status must be determined using the 22C3 pharmDx test. Combined positivity score (CPS) must be >10 under amendment V3. 5. 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, AST <= 1.5 x ULN, ALT <=1.5 x ULN, Bilirubin <=1.5 X ULN 6. Negative pregnancy test 7. Age >= 18 years

Exclusion criteria

1. 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.
2. Documented history of severe autoimmune disease (e.g. inflammatory bowel disease, myasthenia gravis).
3. Prior CTLA-4 or PD-1/PD-L1-targeting immunotherapy.
4. Known history of Human Immunodeficiency Virus infection, or tuberculosis, or other active infection requiring therapy at the time of inclusion.
5. Positive tests for Hepatitis B or Hepatitis C
6. Underlying medical conditions that, in the investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of adverse events
7. Medical condition requiring the use of immunosuppressive medications
8. Use of other investigational drugs before study drug administration
9. Malignancy, other than urothelial cancer, in the previous 2 years, with a high chance of recurrence (estimated >10%).
10. Pregnant and lactating female patients.
11. Major 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.
12. Severe infections within 2 weeks prior to enrolment in the study
13. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to enrolment, unstable arrhythmias and unstable angina.
14. Previous intravenous chemotherapy for bladder cancer. Prior low-dose sensitizing chemotherapy used for combined modality treatment, or radiation alone, is allowed if patients have recurred after an initial response. Patients with residual disease after (chemo)radiation for bladder cancer are not eligible.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-09-2021
Enrollment:	15
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	17-05-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-06-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-10-2024
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-11-2024
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
EudraCT	EUCTR2021-002033-41-NL
ClinicalTrials.gov	NCT04871594
CCMO	NL77423.031.21