# A Phase 1b-2 study of Mitomycin-C / Capecitabine chemoradiotherapy combined with Ipilumimab and Nivolumab or Nivolumab monotherapy as bladder sparing curative treatment for muscle Invasive bladder Cancer: the CRIMI study.

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This study has been transitioned to CTIS with ID 2023-509460-19-00 check the CTIS register for the current data. *In the phase Ib study: to assess the feasibility and safety of the addition of nivolumab and/or ipilimumab to MMC/capecitabine...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Miscellaneous and site unspecified neoplasms benign |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON55840

**Source**
ToetsingOnline

**Brief title**
CRIMI

### Condition

- Miscellaneous and site unspecified neoplasms benign
- Bladder and bladder neck disorders (excl calculi)

**Synonym**

1 - A Phase 1b-2 study of Mitomycin-C / Capecitabine chemoradiotherapy combined wit ... 7-05-2025

Muscle invasive bladder cancer, T2-4M0 urothelial carcinoma

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum
**Source(s) of monetary or material Support:** Ministerie van OC&W,afdeling oncologie;afdeling radiololgie;stichtging 1973,Bristol-Myers Squibb

## Intervention

**Keyword:** bladdersparing, chemoradiation, immunotherapy, muscle invasive bladdercancer

## Outcome measures

### Primary outcome

Toxicity (CTCAE 4.0)

### Secondary outcome

overall survival (OS)

overall survival-rate (OS-rate)

response rate (RR)

# Study description

### Background summary

Muscle invasive urothelial cell carcinoma of the bladder is the most common malignancy of the urinary tract, but the treatment algorithms have hardly evolved over the last 30 years. Recently, curative organ sparing treatment has replaced radical resection for most cancers where surgery results in mutilation and functional loss. As an example, chemoradiation (ChRT) has largely replaced radical surgery in breastcancer, head and neck tumors, anal canal cancer, cervical cancer and lung cancer. Studies for organ preservation with ChRT in rectal cancer and esophageal cancer are running. The bladder is one of the last functional organs where radical surgery for invasive cancer is still advocated as the treatment of first choice, even though surgery results in mutilation and functional loss. Although there are no randomized studies comparing bladder sparing treatment (BST) based on ChRT with a radical

cystectomy, a large number of comparative studies show similar survival and locoregional control rates of both modalities, with 75% of patients preserving a functional bladder after BST.
Several developments have led to the improved results of BST. Firstly, combining concurrent chemotherapy with radiotherapy has significantly improved locoregional control rates. Secondly, improved radiation techniques have resulted in decreased toxicity and have facilitated cystectomy as a salvage treatment in case of a local recurrence after BST. Thirdly, the main cause of failure after cystectomy or BST is still the presence of undetectable micrometastatic disease at the time of treatment, leading to the occurrence of distant metastases a few years later. Based on these facts it can be debated whether BST should replace surgical resection as first treatment of choice, leaving the cystectomy as a salvage option in case of local recurrence.
Urothelial cell carcinoma of the bladder cancer is an immunogenic tumor. Immunotherapy with Bacillus Calmette-Guerin(BCG) in patients with superficial urothelial carcinoma reduces the risk of local recurrence by 60% and can lead to 5-year survival rates of 90% in patients with unifocal tumors16. In muscle-invasive urothelial carcinoma, CD8 tumor-infiltrating lymphocytes (TILs) have shown to predictive of survival. A recent study showed that patients with advanced urothelial cancer (pT2, pT3, or pT4) and higher numbers of CD8 TILs within the tumor (> 8) had better disease-free survival ($P < 0.001$) and overall survival ($P = 0.018$) than did patients with similar-staged urothelial carcinoma and fewer intratumoral CD8 TILs. Active immunotherapeutic strategies have been investigated for metastatic bladder cancer showing that immune and antitumor responses are induced.
Recently, several preclinical studies have demonstrated that the combination of RT and targeted PD-1/PD-L1 therapy activates cytotoxic T-cells, reduces myeloid-derived suppressor cells and induces an abscopal response. Based on these results, numerous on-going clinical trials are testing the combination of immune checkpoint inhibition and RT. In addition, immunotherapy by anti PD-(L)1 inhibition has resulted in promising response rates in patients with metastatic bladder cancer. Based on all of the above, we hypothesize that combining concurrent chemoradiation and immune checkpoint inhibition therapy may further improve locoregional control rates of ChRT.
Moreover, several large phase-3 trials testing adjuvant immune checkpoint inhibition after cystectomy are expected to report in the coming 5-10 years. However, preclinical reports point out that immunotherapy in the adjuvant setting may be suboptimal compared to a setting where the primary tumor is still in place. Hence, concurrent immuno-chemo radiation may also lead to improved distant metastases free survival rates of bladder cancer compared to adjuvant immunotherapy after tumor resection. Notably, by the time that the adjuvant studies will report, organ sparing chemoradiation may be the new standard of care for bladder cancer.
Based on all of the above, the phase-2 part of this study is intended to make a preliminary assessment of the efficacy in a phase-2 extension cohort, preceded by a dose escalation phase 1b part. In order to minimize toxicity the radiosensitization will be mediated by Mitomycin-C (MMC) / capecitabine (CAPE)

chemotherapy rather than platinum based chemotherapy. This chemotherapy backbone combines efficacy with an excellent safety profile and allows patients with renal dysfunction to be eligible for ChRT.

## Study objective

This study has been transitioned to CTIS with ID 2023-509460-19-00 check the CTIS register for the current data.

*In the phase Ib study: to assess the feasibility and safety of the addition of nivolumab and/or ipilimumab to MMC/capecitabine chemoradiation of the bladder.
*In the phase II study: to assess the impact of the addition of the addition of nivolumab and/or ipilimumab to MMC/capecitabine chemoradiation of the bladder on disease free survival (DFS) and disease free survival rate (DFS-rate).
*to assess toxicity

## Study design

This is a multicenter Phase 1b/2, two stage, open label study of MMC/Capecitabine ChRT combined with nivolumab monotherapy or nivolumab an ipilimumab combination therapy in adult (>18 years) subjects with non-metastatic muscle invasive bladder cancer that qualify for ChRT with curative intent.
The study will enroll patients with non-metastatic histologically confirmed muscle invasive bladder cancer, who either wish to preserve their bladder function or are ineligible for cystectomy. Patients have to be staged with CT imaging of the thorax, abdomen and pelvis. FDG PET/CT may be used instead of CT. In case of uncertainty about potential metastatic sites additional imaging or tissue sampling may be performed according to local guidelines. In case staging by FDG-PET/CT up to 3 metastatic pelvic lymph nodes are allowed, provided that distant metastases are absent and the suspect nodes are located below the common iliac arteries and can safely be incorporated in the radiation field. Patients must have adequate organ function and performance status WHO 0-1 to receive ChRT . Patients who received neo-adjuvant chemotherapy are excluded
In the Phase-1b part of the study we will enroll a maximum of 30 patients with a maximum of 10 patients per treatment regimen, in order to determine optimal regimen based on the occurrence of dose limiting toxicities. In the Phase-2 part of the study we will enroll an additional 20 subjects at the regimen determined to be optimal in the phase-1b part.

## Intervention

In the Phase-1b part of the study we will enroll a maximum of 30 patients with a maximum of 10 patients per treatment regimen, in order to determine optimal

regimen based on the occurrence of dose limiting toxicities.
• Regimen-A: immunotherapy (week(w)1-w12) consists of nivolumab 480mg (fixed dose), on day(d)1, d29 and d57 (w1, w4,w8).
• Regimen-B: immunotherapy (w1-w12) consists of ipilimumab 1 mg/kg together with Nivolumab 3mg/kg on d1, d22, d43 and d64 (w1, w3, w6, w9)
• Regimen-C: immunotherapy (w1-w12) consists of ipilimumab 3 mg/kg and nivolumab 1 mg/kg on d1, d22, d43 and d64 (w1, w3, w6, w9).

All patients will be treated with a radiation dose of 40Gy in 20 fractions of 2 Gy to the whole bladder and the pelvic lymph nodes, with a simultaneously integrated boost of 15 Gy in 20 fractions of 0.75 Gy to the primary tumor area. All patients will receive MMC 12mg/m2 IV on day 1 of radiation therapy and capecitabine 750mg/m2 bid on each day of radiation therapy as radiosensitizers. This standard ChRT backbone is combined with one of three immunotherapy regimens from week 1 through week 12. All patients receive adjuvant immunotherapy from week 5-12. For all patients it is optional to continue adjuvant nivolumab 480mg fixed dose every 4 weeks after the cystoscopy up to 1 year.

In the Phase-2 part of the study we will enroll an additional 20 subjects at the regimen determined to be optimal in the phase-1b part.

**Study burden and risks**

The additional risks for study participants compared to standard of care consist of exposure to nivolumab and ipililumab, resulting in auto-immune side-effects. These side-effects are managable with a short treatment course of high dose corticosteroids. The benefit is the potential of nivolumab and ipilimumab combined with radiotherapy to generte a systemic immue response , that may decrease the micrometastatic load in these patients and thereby may decrease the chance of distant metastasis formation.

# 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 Be willing and able to provide written informed consent for the trial.
2 Be >= 18 years of age on day of signing informed consent.
3 Wish to preserve their bladder function or be ineligible for cystectomy.
4 Must have undergone transurethral biopsy of the bladder tumor, within 35 days of planned treatment commencement. The patient should have a histologically-confirmed diagnosis of muscle-invasive T2-T4a, N0-1M0 urothelial cell carcinoma of the bladder.
5 Must have undergone maximal transurethral resection of the bladder tumour, to an extent that is judged as safe by the urologist performing the resection, within 35 days of planned treatment commencement.
6 Subjects with tumors of mixed urothelial/non-urothelial cell histology are allowed, but urothelial cell carcinoma must be the predominant histology (>50%). Subjects with predominant or exclusively non-urothelial cell histology are not allowed.
7 Have planned for chemoradiotherapy as definitive treatment.
8 Have a performance status of 0 or 1 on the ECOG Performance Scale
9 Have a bladder function that is accessible for cystoscopical follow up.
10 Demonstrate adequate organ function as defined below. All screening labs should be performed within 28 days of registering the patient on the trial.
11 Female participants of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to registering the patient. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
12 Female participants of childbearing potential should be willing to one highly effective method of birth control or be surgically sterile, or abstain

from heterosexual activity for the course of the study through 5 month after the last dose of study medication Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
13 Male participants should agree to use condoms starting with the first dose of study therapy through 7 month after the last dose of study therapy.
14 Willing to consent to the use of their collected tumor specimen, blood and urine as detailed in the protocol for future scientific research including but not limited to DNA, RNA and protein based biomarker detection.

## Exclusion criteria

1 Has DPD deficiency.
2 Has concurrent extra-vesical (i.e. urethra, ureter or renal pelvis) urothelial cell carcinoma of the urothelium. Patients who have involvement of the prostatic urethra with urothelial cell cancer may be included if the location can be safely incorporated in the radiation field.
3 Extensive or multifocal bladder carcinoma in situ (CIS) precluding curative chemoradiotherapy.
4 Evidence of distant metastatic disease on a CT or FDG PET/CT chest/abdomen/pelvis performed within 28 days prior to study entry. Up to 3 metastatic lymph nodes in the pelvis (below the common iliac arteries) are allowed, if these can be incorporated in the radiotherapy field.
5 Prior pelvic lymph-adenectomy
6 Prior pelvic radiotherapy
7 Has had prior intravenous chemotherapy, targeted small molecule therapy, or radiation therapy for treatment of bladder cancer. Prior intravesical use of BCG and MMC is permittedssible.
8 Unsuitable for concurrent MMC / capecitabine based ChRT based on pre-existing medical conditions.
9 Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to the first dose of treatment. An exception is fiducials that are aimed at improving positional stability during the radiotherapy treatment course. These are allowed.
10 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy over 10mg daily prednisone (or equivalent) or any other form of immunosuppressive therapy within 14 days prior to registering the patient. Patients with adrenal insufficiency receiving replacement dose steroids are allowed on the trial.
11 Has a known history of active TB (Bacillus Tuberculosis)
12 Hypersensitivity to nivolumab and/or ipilimumab or any of its excipients.
13 Prior or concurrent known additional malignancy of any site unless disease free for 5 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative

therapy or in situ cervical cancer, Stage T1a well differentiated prostatic carcinoma in men (Gleason = 3+3, PSA <5)
14 Has any history of active autoimmune disease, Stevens-Johnson syndrome or Guillain-Barre. Exceptions to this are:
a. Patients with autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
b. Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen
15 Has known history of, or any evidence of active, non-infectious pneumonitis.
16 Has an active infection requiring systemic therapy.
17 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient*s participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
18 Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
19 Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
20 Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
21 Has an Human Immunodeficiency Virus (HIV) infection with a PCR detectable viral load. Note: HIV 1/2 seropositivity without a PCR detectable viral load is no exclusion criterion
22 Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
23 Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed

# Study design

## Design

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

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 21-01-2019 |
| Enrollment: | 50 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Mitomycin-C |
| Generic name: | Mitomycin-C |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Opdivo |
| Generic name: | Nivolumab |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Xeloda |
| Generic name: | Capecitabine |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Yervoy |
| Generic name: | Ipilimumab |
| Registration: | Yes - NL outside intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 23-05-2018 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 05-11-2018 |
| Application type: | First submission |

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|---|---|
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 23-04-2019 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 20-05-2019 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 24-05-2019 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 17-06-2019 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 19-08-2019 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 18-01-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 25-02-2021 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

ID: 28813
Source: NTR
Title:

## In other registers

| Register | ID |
|---|---|
| EU-CTR | CTIS2023-509460-19-00 |
| EudraCT | EUCTR2017-004751-23-NL |
| ClinicalTrials.gov | NCT03844256 |
| CCMO | NL64149.018.18 |