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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Immunotherapy combined with chemoradiation for localized bladder cancer may exhibit improved efficacy with an acceptable toxicity profile.

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON28813

Bron
NTR

Verkorte titel
CRIMI

Aandoening

Muscle invasive bladder cancer

MIBC

Blaaskanker, spier-invasief blaascarcinoom

Ondersteuning

Primaire sponsor: Amsterdam UMC, AMC
Overige ondersteuning: Amsterdam UMC
Bristol-Myers Squibb

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

In the phase Ib study: toxicity scored with CTCAE v 4.03; incidence of dose limiting toxicity (DLT) during the first 6 weeks after start of the combination treatment

In the phase II study: disease free survival (DFS) and disease free survival-rate (DFS-rate)

Toelichting onderzoek

Achtergrond van het onderzoek

This is a Phase 1b/2, two stage, open label study of MMC/Capecitabine chemoradiotherapy combined with nivolumab monotherapy or nivolumab and ipilimumab combination therapy in adult (>18 years) subjects with non-metastatic muscle invasive bladder cancer that qualify for chemoradiotherapy 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.

The treatment consists of radiotherapy combined with Mitomycin-C (MMC) 12mg/m2 single dose, combined with capecitabine 750mg/m2 bi-daily on days of radiation, combined with either:
• Regimen-A (N=10 patients): immunotherapy (week(w)1-w12) consists of nivolumab 480mg (fixed dose), on day(d)1, d29 and d57 (w1, w5,w9).
• Regimen-B (N= 10 patients): immunotherapy (w1-w12) consists of ipilimumab 1 mg/kg together with Nivolumab 3mg/kg on d1, d22, d43 and d65 (w1, w4, w7, w10)
• Regimen-C (N= 10 patients): immunotherapy (w1-w12) consists of ipilimumab 3 mg/kg and nivolumab 1 mg/kg on d1, d22, d43 and d65 (w1, w4, w7, w10).

All study participants can opt for an additional 10 administrations of nivolumab 480mg fixed dose at intervals of 4 weeks, from week 13 to week 52.

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 (DLT). Before the start of the following regimen the number of patients experiencing dose limiting toxicities determines whether the regimen is considered to have a favorable or unfavorable toxicity.

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.

Doel van het onderzoek

Immunotherapy combined with chemoradiation for localized bladder cancer may exhibit improved efficacy with an acceptable toxicity profile.

Onderzoeksopzet

The DLT-evaluation period is defined as the time period from the first dose of investigational product through 42 days (6 weeks) after the first dose.

Response rate: cystoscopy at week 12 and week 24 will be performed. From week 12 onward 3-montly CT scans will be done in the context of the current standard of care.

Overall survival up to five years

Onderzoeksproduct en/of interventie

Radiotherapy combined with Mitomycin-C (MMC) 12mg/m2 single dose, combined with capecitabine 750mg/m2 bi-daily on days of radiation, combined with either:
• Regimen-A: immunotherapy (week(w)1-w12) consists of nivolumab 480mg (fixed dose), on day(d)1, d29 and d57 (w1, w5,w9).
• Regimen-B: immunotherapy (w1-w12) consists of ipilimumab 1 mg/kg together with Nivolumab 3mg/kg on d1, d22, d43 and d65 (w1, w4, w7, w10)
• Regimen-C: immunotherapy (w1-w12) consists of ipilimumab 3 mg/kg and nivolumab 1 mg/kg on d1, d22, d43 and d65 (w1, w4, w7, w10).

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

-Be willing and able to provide written informed consent for the trial.

-Be ≥ 18 years of age on day of signing informed consent.

-Wish to preserve their bladder function or be ineligible for cystectomy.

-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.

-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.

-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.

-Have planned for chemoradiotherapy as definitive treatment.

-Have a performance status of 0 or 1 on the ECOG Performance Scale

-Have a bladder function that is accessible for cystoscopical follow up.

-Demonstrate adequate organ function. All screening labs should be performed within 28 days of registering the patient on the trial.

-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.

-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.

-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.

-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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

-Has DPD deficiency.

-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.

-Extensive or multifocal bladder carcinoma in situ (CIS) precluding curative chemoradiotherapy.

-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 lymphnodes in the pelvis (below the common iliac arteries) are allowed, if these can be incorporated in the radiotherapy field.

-Prior pelvic lymph-adenectomy

-Prior pelvic radiotherapy

-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 permissible.

-Unsuitable for concurrent MMC / capecitabine based ChRT based on pre-existing medical conditions.

-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.

-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.

-Has a known history of active TB (Bacillus Tuberculosis)

-Hypersensitivity to nivolumab and/or ipilimumab or any of its excipients.

-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)

-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

-Has known history of, or any evidence of active, non-infectious pneumonitis.

-Has an active infection requiring systemic therapy.

-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.

-Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

-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.

-Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

-Has an Human Immunodeficiency Virus (HIV) infection with a PCR detectable viral load.

-Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

-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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	Niet-gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	07-01-2019
Aantal proefpersonen:	50
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	07-02-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 55840
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL7506
CCMO	NL64149.018.18
OMON	NL-OMON55840

Resultaten