A Phase 3, Randomized, Study of Neoadjuvant Chemotherapy alone versus Neoadjuvant Chemotherapy plus Nivolumab or Nivolumab and BMS-986205, Followed by Continued Post-Surgery Therapy with Nivolumab or Nivolumab and BMS-986205 in Participants with Muscle-Invasive Bladder Cancer

Published: 19-12-2018
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This study has been transitioned to CTIS with ID 2024-512158-12-00 check the CTIS register for the current data. Primary Objectives: - To compare the pCR rate of neoadjuvant nivolumab/BMS-986205 + GC to neoadjuvant GC alone in all randomized...

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

Summary

ID

NL-OMON52608

Source
ToetsingOnline

Brief title
CA017-078

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Muscle invastive bladder cancer

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: BMS-986205, Chemotherapy, Muscle invasive bladder cancer, Nivolumab

Outcome measures

Primary outcome

- pCR rate, defined by the proportion of randomized participants with absence

of any cancer (T0, N0, M0) in pathology specimens after RC, based on

blinded pathology review.

- EFS, defined as the time from randomization to any of the following events:

progression of disease that precludes RC surgery, local or distant

recurrence, based on BIRC assessments, or death due to any cause.

- pCR rate, defined by the proportion of randomized participants with absence

of any cancer (T0, N0,M0) in pathology specimens after RC, based on

blinded pathology review.

- EFS, defined as the time from randomization to any of the following events:

progression of disease that precludes RC surgery, local or distant

recurrence based on BIRC assessments, or death due to any cause.

Secondary outcome

- OS, defined as the time between the date of randomization and the date of

death from any cause.

- Incidence of adverse events (AEs), serious AEs, deaths and laboratory

abnormalities in participants who received at least one dose of study

treatment.

Study description

Background summary

Urothelial cancer of the bladder is the ninth most common cancer in the world. In 2012, approximately 430,000 new cases of bladder cancer were diagnosed worldwide, accounting for 165,000 deaths.

Neoadjuvant chemotherapy prolongs EFS and OS in cisplatin-eligible patients and is the current
SOC for this patient population. OS is closely associated with achieving a pCR1 after NAC, however pCR occurs in a minority of treated patients; patients who have residual MIBC after RC have a high likelihood of relapse and death from metastatic bladder cancer. Furthermore, there is currently no neoadjuvant SOC for patients who are not eligible to receive cisplatin-based chemotherapy, defining an unmet medical need. Therefore, novel therapies are needed to increase the number of patients who qualify to receive neoadjuvant therapy and subsequently achieve a pCR.

Individually targeting immune checkpoint receptors such as CTLA-4 and PD-1 has been successful across multiple tumor types. It is likely, however, that combination therapies could potentially lead to greater depth of response and OS as has been noted with the combination of anti-PD-1 and anti-CTLA-4 in advanced melanoma patients and in NSCLC patients.2 In addition, targeting the

immunosuppressive properties of the cancer cells and tumor-infiltrating inflammatory cells, such as by targeting IDO1, is considered a promising approach. IDO1 inhibitors in combination with checkpoint-targeting immunotherapy, have the potential to achieve improved efficacy similar to PD-1/CTLA-4 targeting combinations with potentially less toxicity.

This study aims to demonstrate that a neoadjuvant regimen consisting of nivolumab plus BMS-986205 or nivolumab plus BMS-986205 Placebo added to SOC chemotherapy pre-surgically, followed by continued IO therapy after RC, will significantly increase the rate of pCR and prolong
EFS in participants with previously untreated MIBC. Additional objectives of the study include
OS, characterization of the safety and tolerability of the treatment regimens, and to determine if the addition of IO therapy to SOC NAC delays time to RC or increases the toxicity associated with this operation. Pharmacokinetic parameters, potential predictive biomarkers of efficacy and toxicity, and changes in patient-reported outcomes for quality of life assessments will also be characterized.

Study objective

This study has been transitioned to CTIS with ID 2024-512158-12-00 check the CTIS register for the current data.

Primary Objectives:

- To compare the pCR rate of neoadjuvant nivolumab/BMS-986205 + GC to neoadjuvant GC alone in all randomized participants.

- To compare EFS of neoadjuvant nivolumab/BMS-986205 +GC followed by continued nivolumab/BMS-986205 after RC versus SOC GC followed by
RC in all randomized participants.

- To compare the pCR rate of neoadjuvant nivolumab + GC to neoadjuvant GC alone in all randomized participants.

- To compare EFS of neoadjuvant nivolumab + GC followed by continued nivolumab after RC versus neoadjuvant SOC GC followed by RC in all randomized participants

Secondary Objectives:

- To compare overall survival (OS) of neoadjuvant nivolumab/BMS-986205 + GC or nivolumab + GC followed by continued IO therapy after RC versus neoadjuvant SOC GC followed by RC in all randomized participants (Arm C vs Arm A and Arm B vs Arm A).

- To describe the safety and tolerability of nivolumab and nivolumab/BMS-986205 in combination with GC chemotherapy.

Study design

Phase 3, Randomized, Study of Neoadjuvant Chemotherapy alone versus Neoadjuvant Chemotherapy plus Nivolumab or Nivolumab and BMS-986205, Followed by Continued Post- Surgery Therapy with Nivolumab or Nivolumab and BMS-986205 in Participants with Muscle- Invasive Bladder Cancer

Approximately 1200 patients will be enrolled for this study, of which 954 will be treated.

Safety-Lead In
CA017078 will start with a safety lead-in for the combination of BMS-986205 with nivolumab plus Gemcitabine & Cisplatin chemotherapy at the same dosages and frequencies as described in Arm C. After the regimen is determined safe, the study will begin randomization.
Randomization:

Participants will be randomized in a 1:1:1 ratio to either Arm A, B, or C.

- Treatment Arm A: Gemcitabine & Cisplatin infusions every 3 weeks for 4 cycles followed by radical cystectomy within 6 weeks of completing neo-adjuvant treatment. No further study therapy.

- Treatment Arm B: Gemcitabine & Cisplatin + Nivolumab (360mg) infusions every 3 weeks for 4 cycles + BMS-986205 Placebo (100mg) daily followed by radical cystectomy within 6 weeks of completing neo-adjuvant treatment. Post-surgery Nivolumab (480mg) every 4 weeks + BMS-986205 Placebo (100mg) daily for 9 cycles.

- Treatment Arm C: Gemcitabine & Cisplatin + Nivolumab (360mg) infusions every 3 weeks for 4 cycles + BMS-986205 Blinded (100mg) daily followed by radical cystectomy within 6 weeks of completing neo-adjuvant treatment. Post-surgery Nivolumab (480mg) every 4 weeks + BMS-986205 Blinded (100mg) daily for 9 cycles.

Note: Dosing for chemotherapy for all arms listed above:
• GFR >= 60 mL/min: standard GC (cisplatin 70 mg/m2 D1, gemcitabine 1000 mg/m2 D1, D8, 21D cycles
• GFR < 60 mL/min: split-dose GC (cisplatin 35 mg/m2 D1, D8, gemcitabine 1000 mg/m2 D1, D8, 21D cycles

Patients will undergo screening procedures prior to the first treatment to

assess if they are eligible to participate in the study.

Nivolumab will be given intravenously via infusion. Patients, who will receive BMS-986205, will take a pill of BMS-986205 every day after a meal. Patients will complete a diary to document the BMS-986205 administration. Gemcitabine & Cisplatin will be given as per local standard.

All patients will receive treatment as per scheduled cycle until progression, recurrence, unacceptable toxicity, withdrawal of consent by the participant, completion of treatment, or the study ends, whichever occurs first.

Intervention

The medical interventions include treatment with Gemcitabine/Cisplatin, Gemcitabine/Cisplatin plus Nivolumab & BMS-986205 pre-surgery and Nivolumab & BMS-986205 post-surgery.

Patients will be randomly assigned to one of the following treatment arms:
- Treatment Arm A: Gemcitabine & Cisplatin infusions every 3 weeks for 4 cycles followed by radical cystectomy within 6 weeks of completing neo-adjuvant treatment. No further study therapy.

- Treatment Arm B: Gemcitabine & Cisplatin + Nivolumab (360mg) infusions every 3 weeks for 4 cycles + BMS-986205 Placebo (100mg) daily
followed by radical cystectomy within 6 weeks of completing neo-adjuvant treatment. Post-surgery Nivolumab (480mg) every 4 weeks + BMS-986205 Placebo (100mg) daily for 9 cycles.

- Treatment Arm C: Gemcitabine & Cisplatin + Nivolumab (360mg) infusions every 3 weeks for 4 cycles + BMS-986205 Blinded (100mg) daily f
followed by radical cystectomy within 6 weeks of completing neo-adjuvant treatment. Post-surgery Nivolumab (480mg) every 4 weeks + BMS-986205 Blinded (100mg) daily for 9 cycles.

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• GFR < 60 mL/min: split-dose GC (cisplatin 35 mg/m2 D1, D8, gemcitabine 1000 mg/m2 D1, D8, 21D cycles

Patients will receive treatment until progression, recurrence, unacceptable toxicity, withdrawal of consent by the participant, completion of treatment, or the study ends, whichever occurs first.

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements, blood tests for safety assessment, pregnancy testing (for females of child bearing potential) and monitoring for adverse events & serious adverse events. Patients will be asked to complete questionnaire*s (FACT-G, FACT-BI-Cys & EQ-5Q-3L) about their quality of life. Blood will also be collected at certain visits for research purposes (PK, Biomarker & Immunogenicity). If there is no archival tumour tissue available or the sample was taken too long ago (>=4 months), patients will be required to have a biopsy in order to participate. Radical cystectomy will be performed on patients post completion of neo-adjuvant therapy. Patients who do not undergo radical cystectomy for reasons other than progression, will be surveyed for disease recurrence/progression by cystoscopy, every 3 months for the next two years, then every 6 months for 3 additional years, then once per year for subsequent years. For these patients, maximal TURBT of all visible tumor should be performed on the first on-treatment cystoscopy. Patients will undergo radiographic assessment of their tumors by CT or MRI at screening. Imaging will continue for patients for a maximum of 5 years or until: Investigator assessed disease progression that precludes surgery, Blinded Independent Central Review confirms progression or recurrence, at intervals of every 12 weeks (± 1 week) until Week 96 (from the date of first neoadjuvant dose), then every 16 weeks (± 2 weeks) from Week 96 to Week 160 and finally every 24 weeks (± 3 weeks). The frequency of visits and number of procedures carried out during this trial would be typically considered over and above standard of care. The procedures are carried out by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient. Treatment for cancer often has side effects, including some that are life threatening. To assure an ongoing favourable risk/benefit assessment for patients enrolled onto the study, an Independent Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of patients enrolled in the study.
BMS will conduct rigorous safety monitoring to ensure patients safety by regularly & systematically reviewing safety data; the reported safety events will be closely followed-up; sites and study investigators will receive training on the implementation of the BMS-986205 and Nivolumab toxicity management strategies.
New immune system targeted therapy (immunotherapies) such as Nivolumab could potentially provide clinical benefit and improvements in the outcomes for patients with this disease. However, with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study.

Contacts

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Bristol-Myers Squibb

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Participants with MIBC, clinical stage T2-T4a, N0 (<10 mm on CT or MRI), M0, diagnosed at
TURBT and confirmed by radiographic imaging. Variant histology is acceptable if there is a
predominant urothelial component
- Participant must be deemed eligible for RC by his/her urologist and/or oncologist, and must agree
to undergo RC after completion of neo-adjuvant therapy
- Prior BCG or other intravesical treatment of non-muscle invasive bladder cancer (NMIBC) is
permitted if completed at least 6 weeks prior to initiating study treatment
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1
- Life expectancy >= 6 months

- Documentation of PD-L1 status by immunohistochemistry (IHC) performed by the central lab
during the screening period from the TURBT or biopsy that made the diagnosis of MIBC. No
systemic therapy (eg, adjuvant or neoadjuvant chemotherapy) should be given after the sample
was obtained. PD-L1 results are not required prior to beginning treatment on the safety lead-in.

Exclusion criteria

- Clinical evidence of positive LN (>= 10 mm in short axis) or metastatic bladder cancer
- Prior systemic therapy, radiation therapy, or surgery for bladder cancer other than TURBT or
biopsies is also not permitted
- Ineligible to receive cisplatin due to Grade 2 or higher peripheral neuropathy or audiometric
hearing loss, or calculated (Cockcroft-Gault formula) GFR or measured (24-hour urine) creatinine
clearance (CrCl) < 50 mL/min
- Participants with an active, known or suspected autoimmune disease. Exceptions per protocol
- Participants with conditions known to interfere significantly with the absorption of oral medication,
as per investigator judgement
- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily
prednisone equivalent) or other immunosuppressive medications within 14 days of randomization.
Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone
equivalent, are permitted in the absence of active autoimmune disease
- Participants with uncontrolled adrenal insufficiency
- Participants with a personal or family (i.e., in a first-degree relative) history or presence of
cytochrome b5 reductase deficiency (previously called methemoglobin reductase deficiency) or
other diseases that puts them at risk of methemoglobinemia. All participants will be screened for
methemoglobin levels prior to randomization.
- Participants with a history of G6PD deficiency or other congenital or autoimmune hemolytic
disorders. All participants will be screened for G6PD deficiency prior to randomization.

- Major surgical procedure within 14 days prior to initiating study treatment or anticipation of the
need for a major surgical procedure (other than RC) during the course of the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-03-2020
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abiplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	BMS-986205
Generic name:	BMS-986205
Product type:	Medicine
Brand name:	Gemzar
Generic name:	Gemcitabine

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-12-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-04-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-12-2019
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	01-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	CTIS2024-512158-12-00
EudraCT	EUCTR2017-004692-31-NL
ClinicalTrials.gov	NCT03661320
CCMO	NL68068.056.18