A phase 3, randomized, double-blind trial of nivolumab in combination with intravesical BCG versus standard of care BCG alone in participants with high-risk non-muscle invasive bladder cancer that is persistent or recurrent after treatment with BCG

Published: 13-01-2020
Last updated: 17-01-2025

Primary objectiveTo compare the event free survival per pathological review committee (PRC) of nivolumab plus BCG vs BCG alone in all randomized ParticipantsEFS, defined as the time from randomization until any of the following events: recurrence (...

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

Summary

ID

NL-OMON50043

Source
ToetsingOnline

Brief title
CA209-7G8

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Bladder cancer

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Bristol Myers Squibb International Corporation;Pharmaceutical company

Intervention

Keyword: BCG, Bladder cancer, Nivolumab

Outcome measures

Primary outcome

• To compare the EFS per PRC of nivolumab plus BCG vs BCG alone in all randomized participants.

EFS, defined as the time from randomization until any of the following events: recurrence (TaHG, T1 or CIS) or progression of disease, or death from any cause. For participants with CIS (+/- papillary disease) at study entry, a lack of complete response of the CIS component at the 13-week assessment will be considered an event.

Secondary outcome

1. To compare the WFS of nivolumab plus BCG vs BCG alone in all randomized participants

WFS, defined as the time from randomization to progression to muscle invasive disease, cystectomy,systemic chemotherapy, radiotherapy, or death from any cause.

2. To compare the OS of nivolumab plus BCG vs BCG alone in all randomized participants

OS, defined as the time from randomization to death from any cause.

3. To evaluate the CRR at first disease assessment (Week 13) in all randomized participants with CIS (+/- papillary disease) at study entry by treatment arm (nivolumab plus BCG and BCG alone)

CRR, defined as the proportion of participants with CIS (+/- papillary disease) at study entry who are disease free at the first disease assessment.

4. To evaluate the duration of response (DoR) in all randomized participants with CIS (+/- papillary disease) at study entry who achieved CRR at first disease assessment by treatment arm (nivolumab plus BCG and BCG alone)

DoR is restricted to participants with CIS (+/- papillary disease) at study entry who are disease free at the first disease assessment and is defined as the time between the date of the first CR to the date of first documented recurrence, progression, or death due to any cause.

5. To describe the safety and tolerability of nivolumab plus BCG and BCG alone in all treated participants

Overall safety and tolerability will be measured by the incidence of AEs, SAEs,

AEs leading to discontinuation, IMAEs, deaths, and laboratory abnormalities and

changes from baseline.

Study description

Background summary

Bladder cancer is the ninth most common cancer worldwide.
Approximately 75% to 80% of all bladder cancers present as superficial, non-muscle-invasive disease, while the remaining 20% to 25% are muscle-invasive or metastatic at the time of presentation. Initial treatment for patients with non-muscle invasive bladder cancer (NMIBC) includes transurethral resection of the bladder tumour (TURBT). During this procedure the surgeon removes the tumour in the bladder through the urethra. The urethra is the tube that carries urine from the bladder to the outside of the body.
Intravesical BCG has become the standard of care (SOC) as adjuvant treatment for patients with high-risk NMIBC after TURBT. With intravesical therapy, the doctor puts the liquid drug (in this case, BCG) right into the bladder rather than giving it by mouth or injecting it into the blood. Despite the recognized benefit of BCG treatment in this patient population, tumour recurrence (when the cancer comes back) and progression (when the cancer gets worse) within 5 years following BCG induction and maintenance is not uncommon. While some patients will respond to a second induction course, treatment with BCG beyond 2 induction courses does not have any additional clinical benefit.

There is significant unmet need in patients who have persistence or recurrence of high-risk NMIBC that is not BCG unresponsive. New therapies are required to reduce the rate of recurrence,cystectomy (removal of the bladder entirely), and progression to metastatic disease.

There is evidence for the efficacy of nivolumab in UC and proof of concept for PD-1 inhibition in NMIBC:
• In metastatic UC, nivolumab as monotherapy has received accelerated approval in the US for the treatment of patients with locally advanced or metastatic UC who have had disease progression during or following platinum-containing chemotherapy or who have had disease
progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. It has received approval in the EU for the treatment of locally advanced unresectable or metastatic UC in adults after failure of prior platinum-containing therapy. See the current prescribing information for nivolumab (Opdivo*) for more information.

• In NMIBC, preliminary evidence of clinical activity of PD-1 inhibition comes from study Keynote-057, a single-arm study of pembrolizumab in BCG-unresponsive NMIBC. In the interim analysis of this study, the response rate of CIS (carcinoma in situ) participants treated with pembrolizumab monotherapy was 39% at Month 3, with 80.2% of participants having a complete duration of > 6 month.3. The safety profile was consistent with the profile of pembrolizumab across tumour types. These data are clinically significant in a group of participants for whom there are no effective intravesical or systemic treatment options, and cystectomy is the SOC.

Intravesical BCG results in tumour inflammation and nivolumab enhances T-cell activity within the tumour; combining BCG with nivolumab therefore offers the potential for improved response of the tumour to immunotherapy. This study aims to demonstrate that treatment with nivolumab in combination with intravesical BCG will improve event-free survival (EFS) vs intravesical BCG alone.

Study objective

Primary objective
To compare the event free survival per pathological review committee (PRC) of nivolumab plus BCG vs BCG alone in all randomized Participants
EFS, defined as the time from randomization until any of the following events: recurrence (TaHG, T1 or CIS) or progression of disease, or death from any cause. For participants with carcinoma in situ (+/- papillary disease) at study entry, a lack of complete response of the CIS component at the 13-week assessment will be considered an event.

Additional clinical endpoints include worsening-free survival (WFS), complete response rate (CRR) in patients with carcinoma in situ (CIS), and overall survival (OS). Additional objectives of the study include characterization of safety and tolerability, pharmacokinetics,
potential predictive biomarkers, and changes in patient-reported outcomes for quality of life assessment.

Study design

This is a Phase 3, randomized, double-blind, international, multicentre study of nivolumab in combination with BCG vs nivolumab-placebo with BCG in adult participants with high-riskNMIBC that is persistent or recurrent after treatment with BCG and does not qualify as BCG unresponsive.
Participants are assigned to 1 of 2 treatment groups (Arm A and Arm B).
Treatment assignment is based on 3 stratification factors used in randomization:
1. Disease status per PRC:
2. Time from last dose of BCG until NMIBC high risk recurrence per investigator.:

3. Intended BCG strain:
It is expected that approximately 700 participants will be randomized in a 1:1 ratio to 1 of 2 treatment arms. Assuming a 20% screen failure rate, it is estimated that approximately 875 participants with persistent or recurrent high-risk NMIBC after prior BCG treatment will be enrolled.
Participants will receive:
• Arm A: Nivolumab at a flat dose of 480 mg intravenous (IV) every 4 weeks for up to 24
months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months
• Arm B: Nivolumab-placebo IV Q4W for up to 24 months (104 weeks) and intravesical BCG (induction) weekly for 6 weeks followed by maintenance intravesical BCG weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months

The dose of BCG used for each weekly intravesical treatment will be based on current prescribing information for the particular BCG strain and preparation administered. This may vary as BCG strain and/or preparation administered may vary based on geographic region. BCG will be given at full dose.

The treatment period will end when the participant is discontinued from the last dose of study treatment (nivolumab/nivolumab-placebo or BCG) or completes 3 years of study treatment.

Intervention

The medical interventions include treatment with nivolumab, nivolumab-placebo and BCG. Nivolumab will be supplied by the sponsor but not placebo nor BCG.
Patients will be randomly assigned to one of the following treatments:
• Treatment A: Nivolumab at a flat dose of 480 mg intravenous (IV) every 4 weeks for up to 24
months (104 weeks)
• Treatment B: Matching-placebo every 4 weeks for up to 24 months (104 weeks)

BCG will be given weekly for the first 6 weeks of treatment (induction) and then weekly for 3 weeks at 3, 6, 12, 18, 24, 30, and 36 months from the first treatment (maintenance).

The dose of BCG used for each weekly intravesical treatment will be based on current prescribing information for the particular BCG strain and preparation administered. This may vary as BCG strain and/or preparation administered may vary based on geographic region. BCG will be given at full dose.

The treatment period will end when the participant is discontinued from the last dose of study treatment (nivolumab/nivolumab-placebo or BCG) or completes 3 years of study treatment.

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. Patients will be asked to complete questionnaires about their quality of life. Blood will also be collected at certain visits for research purposes (PK and biomarker studies).
If there is no archive tumour tissue available or the sample was taken too long ago (more than 3 months ago), patients will be required to have a biopsy in order to participate. Cystoscopy of the bladder will be done at screening and every 13 weeks (~ 3 months) for 5 years. Thereafter they will be performed every year. Bladder biopsies are also performed during treatment at week 26 and again at disease progression or recurrence. Patients will undergo radiographic assessment of their tumors by CT or MRI at screening and thereafter on a yearly basis.
The frequency of visits and number of procedures carried out during this trial would typically be 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 participants 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 participants enrolled in the study.
BMS will conduct a rigorous safety monitoring to ensure participants* safety by regularly and systematically reviewing safety data; the reported safety events will be closely followed-up; sites and study investigators will receive an intensive 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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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

_Signed Written Informed Consent;
_Histologically confirmed persistent or recurrent high-risk non-muscle-invasive UC (TaHG and/or T1 and/or CIS);
_Treated with at least 1 adequate course of induction BCG therapy (at least 5 out of 6 doses);
_Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2;
_Males and females, ages 18 or age of majority, and older;

Exclusion criteria

_Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured or not requiring treatment;
_Patients with serious or uncontrolled medical disorders;
_Participants with an active, known, or suspected autoimmune disease;
_Recurrent high-risk NMIBC that is classified as BCG unresponsive;
_Has any contraindication to intravesical BCG therapy, including evidence of active tuberculosis;

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	26-02-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bacillus Calumette-Guerin (BCG)
Product type:	Medicine
Brand name:	Bacillus Calumette-Guerin (BCG) several names
Product type:	Medicine
Brand name:	Opdivo 100 mg / 10 ml
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	13-01-2020
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-03-2021
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
EudraCT	EUCTR2019-002567-96-NL
ClinicalTrials.gov	NCT04149574
CCMO	NL71560.056.19

Study results

Date completed:	28-05-2021
Results posted:	15-10-2024

Summary results
Trial ended prematurely

First publication
01-01-1900